Original Article

Enhancing Hematological Parameters and Alleviating Complaints in Transfusion-Dependent Thalassemic Patients

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Abstract

Objective: To investigate the potential benefits of using supplements, such as folic acid, vitamin E, and calcium, to improve certain hematological parameters and overall well-being in patients with beta-thalassemia.

Methodology: This quasi-experimental study included 277 transfusion-dependent beta thalassemia major patients aged 20-38 from 20th January-30th April 2024. Patients received at least one transfusion per month and presented symptoms like lethargy, fatigue, breathlessness, bone pain, brittle hair and nails. They were prescribed daily oral supplements: Folic Acid (5mg), Vitamin E (200mg), Calcium (500mg) with Vitamin D3 (400IU), and Magnesium (150mg). Patients were monitored every 15 days for symptom improvements. Blood samples were collected before each transfusion. Hematological parameters like hematocrit, hemoglobin levels, White Blood Cells (WBCs), Red Blood Cells (RBCs) and platelets were recorded. Hematological parameters before initiation of supplements and at 3 month follow-up were compared using paired t test.

Results: The results showed a significant increase in hemoglobin, hematocrit, RBCs, and platelets after the intervention. Mean hemoglobin improved from 8.284 to 8.651, with increase of 0.367 units (95% CI: 0.24336 to 0.4904). MCV increased by 0.4224, and MCH by 0.2365, both statistically significant ($p = 0.047$ and $p = 0.007$, respectively). The generalized complaints reduced considerably in these patients.

Conclusion: The study showed that prescribed supplements significantly improved hematological parameters in these patients and reduced their clinical complaints.

Keywords: beta-Thalassemia, Blood transfusion, Hematologic diseases, Hematologic tests, Quality of life.

Introduction

Beta-thalassemia major is a serious genetic disorder that affects the production of red blood cells.[1] People with this condition have chronic anemia and therefore, they need regular blood transfusions. The disorder is caused by defects in the beta-globin gene, which is a gene that helps make hemoglobin, resulting in decreased or no synthesis of Hb chain. It is one of the most common single gene disorders, affecting an estimated 1.5% of the global population.[2] In Pakistan, the frequency of beta-thalassemia major is not low, and ranges from 5.0-7.0% which means that there are more than 10 million carriers suffering from the disorder in the country.[3]

Nutritional deficiencies, particularly of essential vitamins and minerals, exacerbate anemia and complicate treatment outcomes. Globally, malnutrition and communicable diseases have come under better control and patients with β-thalassemia major, who previously used to die at a young age, now live longer to seek medical treatment.[4] On the contrary, life expectancy of a Pakistani thalassemic children is still 10-12 years, which predisposes them to tremendous psychological and physical distress. In economically deprived countries like Pakistan, this creates an increasing stress on existing healthcare services.[5]

Despite advances in blood transfusions and iron chelation therapy, managing low hemoglobin levels and maintaining optimal cell counts remain significantly challenging. The quality of life of these patients is further jeopardized by extreme fatiguability, increasing tendency of bone fractures, skin and hair brittleness, weakened immune system and low self-esteem. These factors collectively impact both their physical and mental well-being. Several studies have explored the role of supplements like folic acid, vitamin E, calcium and others in managing low hemoglobin levels and improving systemic health in transfusion-dependent beta-thalassemia major patients.[6]

Folic acid is essential for red blood cell production and DNA synthesis, making it a common supplement in thalassemia management. It helps reduce the severity of anemia by enhancing red blood cell formation, which can alleviate some of the complications caused by frequent blood transfusions.[7-9] Improved erythropoiesis leads to better oxygenation which can significantly reduce the symptoms associated with anemia such as, easy fatigue, breathlessness, weakness and lethargy.

Calcium supplementation along with vitamin D is important for thalassemic patients, as they are at increased risk for bone disorders like osteoporosis due to iron overload. In a study, several previous studies have been cited showing decreased Parathyroid Hormone (PTH) levels in individuals with thalassemia, caused by iron overload, leading to hypocalcemia. Administering calcium supplements with vitamin D successfully restored normal calcium levels in the body to maintain bone density and strength, improving bone health.[10]

Vitamin E has antioxidant properties which help protect cells from oxidative stress that can be elevated in thalassemia patients due to frequent transfusions and iron overload. Studies suggest that vitamin E may improve the lifespan of red blood cells and reduce hemolysis. Also, it is beneficial for improving immunity and for skin, hair and nails health.[11] Vitamin E deficiency has been often observed in thalassemia patients and so supplementation with vitamin E can help address the nutritional needs of these individuals and potentially improve their overall health.[12]

Given the challenges faced by patients with transfusion-dependent beta thalassemia major, this study aimed to investigate the combined benefits of folic acid, vitamin E and calcium with vitamin D supplements on the hematological parameters and the generalized complaints of these patients. While these supplements cannot cure the disease, they may help improve the hemoglobin levels and primarily the overall wellbeing of the patients. Previous studies in Pakistan have focused on different aspects of thalassemia, but to the best of our knowledge, this is the first to specifically examine the impact of these supplements in mitigating symptoms of this miserable population.

Methodology

This study followed a quasi-experimental design, for which ethical approval was obtained from Baqai Medical University (Reference no. BDC/ERB/2023/051). It included 277 transfusion-dependent beta thalassemia major patients of age 20-38years from Husaini Institute of Hematology, after taking consent. The study was conducted from 20th January-30th April 2024. The patients who underwent at least one transfusion per month (3 per quarter) were made part of the study. Those who had other hemoglobin disorders like thalassemia intermedia with occasional transfusions, non-transfusion dependent were excluded from the study. The primary complaints of these patients were lethargy, general body weakness, easy body fatigue, breathlessness, bone pain and fracture, skin problems and brittle hair and nails. On the basis of these symptoms, they were prescribed a daily dose of folic acid (5mg), vitamin E (200mg) and calcium (500mg, elemental calcium), vitamin D3 (400IU) and magnesium (150mg). Patients were followed up every 15 days to assess their general health and any improvements in their symptoms. Moreover, blood samples were collected before each blood transfusion for complete blood count (CBC) analysis, which was carried out in the same Institute. The numbers of blood transfusions were different for each patient. Blood tests that were done on the first blood transfusion before starting the

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supplements and on the last blood transfusion which occurred three months later, following the use of supplements were recorded. These tests were used to measure changes in hemoglobin concentration and blood counts. SPSS 25 was used for statistical analysis. A paired sample t-test compared the mean difference of hemoglobin concentration, blood counts and red blood cell indices, before and after the intervention. The overall symptoms improved and blood counts and hemoglobin content increased over the period of three months after intervention.

Results

A total of 277 patients were included in this study. Most of the patients were young males. After taking supplements, hemoglobin levels increased in 58% of the patients. However, 12% saw no change in hemoglobin levels, and 30% experienced a decrease despite supplementation.

A paired sample t-test was used to compare the blood parameters, before and after supplements. The results showed statistically significant increase in hemoglobin, hematocrit, red blood cells, and platelets after the intervention. The mean Hb value was 8.284 before intervention which improved to 8.651 after the intervention. The average increase in hemoglobin was 0.3670 units, with a 95% confidence interval ranging from 0.24336 to 0.4904 units. (Table II). However, white blood cell count did not show a significant change. In fact, it was slightly higher before the intervention, suggesting possible infections due to anemia.

People with thalassemia often have red blood cells that are smaller and paler than normal (microcytic hypochromic). A paired sample t-test showed that taking supplements improved the size and hemoglobin content of red blood cells. The average red blood cell volume (MCV) increased by 0.4224, and the average hemoglobin concentration in each cell (MCH) increased by 0.2365. These changes were statistically significant, with p-values of 0.047 and 0.007, respectively. However, the variation in red blood cell size (RDW) did not change significantly after taking supplements. (Table III). In addition to the improvements in blood parameters, patients reported clinicalimprovement.

Discussion

The findings of this study revealed a varied response to the use of supplements in transfusion-dependent thalassemia patients. The data showed that 58% of the patients experienced a notable increase in hemoglobin levels, indicating that for the majority, the supplementation was effective. Not only did the hemoglobin levels increased, but the associated symptoms like tiredness, fatigability and general body weakness were remarkably reduced. These results are consistent with the recognized advantages of hemoglobin-boosting supplements.[13]

However, the absence of an increase in hemoglobin concentration in 12% of the patients might be due to several other possible factors. These may include issues with folic acid absorption, chronic inflammation, gastrointestinal disorders or inadequate supplement dosing.[14-16]

More concerning was the decrease in hemoglobin concentration observed in 30% of the patients, despite taking supplements. This unexpected result might be

Table 1. Effect of Supplements on Hemoglobin

Serum Hemoglobin	Frequency (n=277)	Percentage
Increased	161	58.1%
Decreased	83	30%
Unchanged	33	11.9%

Table 2. Comparison of blood parameters before and after supplements (n=277)

Variables	Before Intervention (Mean±SD)	After Intervention (Mean±SD)	Mean Difference	t-value (n=277)	P-value
Hemoglobin	8.284 ± 0.9765	8.651 ±1.0049	0.3670	5.855	0.00*
Hematocrit	25.996± 3.1488	27.055±3.3414	1.0596	5.202	0.00*
RBCs	3.192± 0.3790	3.304± 0.4247	0.1123	4.577	0.00*
WBCs	10.157±18.7167	9.944±12.3064	0.2134	0.265	0.791
Platelets	237.31±162.304	251.39±154.637	14.072	2.010	0.045*

Paired sample t-test; p-value<0.05, RBCs= red blood cells, WBCs= white blood cells

Table 3. Comparison of red blood cell indices before and after supplements (n=277)

Variables	Before Intervention (Mean+ SD)	After Intervention (Mean+ SD)	Mean Difference	t-value (n=277)	P-value
MCV	81.652±3.9384	82.075±4.0920	0.4224	1.993	0.047*
MCH	26.036±1.5899	26.273±1.5936	0.2365	2.707	0.007*
RDW	26.356±15.2141	27.565±16.3544	1.2094	1.661	0.098

Paired sample t-test; p-value<0.05, MCV=Mean corpuscular volume, MCH= Mean corpuscular hemoglobin, RDW= Red cell distribution width

due to excessive iron overload that can cause to toxicity, resulting in inflammation and reduced erythropoiesis. Inflammatory conditions induced by excess iron, stimulate the production of hepcidin through the IL-6-mediated signaling pathway which inhibits the absorption of iron from the intestines and traps iron in macrophages and liver cells. Reduced availability of iron in the bloodstream limits the iron supply to the bone marrow, where it is needed for hemoglobin synthesis, thus erythropoiesis is impaired.[17] Inflammatory cytokines directly inhibit erythropoietic progenitor cells in the bone marrow, leading to reduced RBCs production.[18] In thalassemia, fragile RBCs are produced that are prone to premature destruction, causing hemolysis, therefore, despite taking folic acid supplements, the high rate of hemolysis outweighs the production, causing a net decrease in hemoglobin levels.[19] Also, some studies indicate that folic acid supplementation might not be necessary due to high serum levels in thalassemia major patients, rather vitamin B12 deficiency has been identified in these patients. Therefore, vitamin B12 supplementation might be more beneficial in improving health and red blood cell production.[20]

The statistically significant increase in hemoglobin, hematocrit, RBCs, and platelets suggests that oral supplementation is associated with improvemenrt in hematological parameters. Other Studies have also shown that folic acid supplementation leads to a rise in RBC count and hematocrit, demonstrating improved erythropoiesis.[21] Several studies mention that adequate calcium levels support the production and function of platelets, enhancing blood clot formation and reducing bleeding risks. A deficiency of calcium lead to impaired bone marrow function, while its supplementation can improve platelet count and hematologic health.[22, 23] Patients with beta-thalassemia major are at a higher risk of developing osteopenia and osteoporosis, which could lead to frequent fractures, as seen in the studied population.[24] Calcium supplements were found to improve the bone strength and reduce the occurrence of fractures in many patients with beta thalassemia major in our study population. This is in line with a review article that highlights the benefits of calcium and vitamin D in improving bone health and preventing the development of osteomalacia in thalassemia patients.[25]

Several studies have shown that vitamin E supplements can improve RBC stability, reduces hemolysis and supports hematocrit levels.[26,27] Additionally, vitamin E is known to boost the immune system and improve hair and nail health.[28] This study supports these findings, as patients reported decreased hair loss, reduced nail brittleness and fewer infections, which together improved the wellness of these patients.

Thalassemia is characterized by smaller-sized RBCs with less hemoglobin content. The results showed that taking supplements significantly improved both the size and hemoglobin content of RBCs which was evidenced by the increase in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH). The reported increase of 0.4224 suggested that the RBCs increased in size after the intervention, indicating enhanced nutritional support and improved cellular development. Consistent with our findings, various researches confirm that folic acid supplementation leads to improved erythropoiesis and results in an increase in MCV.[29] Furthermore, vitamin E supplementation ensures that RBC membranes remain intact and robust, promoting healthier and potentially larger cells.[30]

The increase in MCH by 0.2365 indicated that each red blood cell after intervention contained more hemoglobin. This meant that the RBCs became more effective at oxygen transport, which is critical for maintaining adequate energy levels and metabolic function. A deficiency in folic acid causes impaired RBC production and lower hemoglobin content. Folic acid supplementation enhances the production of hemoglobin within RBCs, increasing MCH.[31]

The findings of the study suggest that the supplements seem beneficial for individuals with thalassemia major. The improved hematologic parameters and enhanced morphology of RBCs, following the intervention led to better oxygen delivery, less fatiguability, improved immunity and bone strength and strengthened hair and nail health. Thus, the intervention appears to be a promising option for managing individuals with thalassemia. Further research is needed to explore the long-term benefits of these supplements on the lifestyle.

As there is no control arm, definitive causal relationship cannot be established. Lack of randomization can

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lead to selection bias. Regular transfusions and lack of spenectomy data can become confounding variables. This study could have been further strengthened by including additional factors such as history of splenectomy and baseline and post-intervention calcium and vitamin D levels. Additionally, tracking the severity of the disease by the frequency of blood transfusions each month, could have provided valuable insights into the impact of supplementation with different disease severities. By incorporating these factors, future studies could offer a more detailed understanding of the long-term benefits of these supplements in thalassemia major patients.

Conclusion

The study demonstrated that oral supplementation with folic acid, vitamin E and calcium, vitamin D3 and magnesium can be beneficial for patients with transfusion-dependent beta-thalassemia. Hematological parameters improved significantly in most patients, with noticeable changes in red blood cell morphology.

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Authors' Contribution Statement

RPA contributed to the conception and acquisition of data. SS* contributed to the conception, design, analysis, and interpretation of data. SS and SA were involved in drafting the manuscript, and AJ approved and reviewed the version. All authors are accountable for their work and ensure the accuracy and integrity of the study.

Confilct of Interest

Authors declared no conflict on interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.