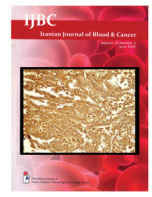
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Review Article

Thromboembolic Events in Severe Thalassemia Syndromes

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ABSTRACT

In the last few decades, the prognosis of patients with β-thalassemia has improved dramatically. However these patients suffer from many serious complications. One of the most important morbidities in patients with thalassemia are thromboembolic events that are mainly observed in thalassemia intermedia. Profound hemostatic changes have been observed in patients with thalassemia intermedia and numerous factors have been attributed to the pathogenesis of hypercoagulable state among patients with thalassemia intermedia. In this review the different mechanisms resulting in hypercoagulability in patients with thalassemia, the clinical importance, prevention and treatment of thromboembolic episodes have been discussed.

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Introduction

Thalassemia syndromes are the most prevalent hereditary quantitative hemoglobinopathy worldwide. The hallmark of β-thalassemia is the complete absence or the reduction of β chain synthesis leading to excess of α chains. In β- TM (β-TM), there is a complete absence of β-chain synthesis, but in patients with thalassemia intermedia (β-TI), the production of β-chain is decreased (1). The prevalence of thalassemia is around 3.6% in Iran and Iran is located on the belt of thalassemia; however, thalassemia prevention programs starting since 1997 have resulted in a significant decrease in the birth rate of children with TM (2, 3).

Due to improvements in transfusion practice and chelation therapies in patients with TM, life expectancy of these patients has improved enormously in recent decades (4). In addition to iron overload and subsequent hemosiderosis of the vital organs (5, 6), one of the major complications of thalassemic syndromes especially in patients with β-TI is thromboembolic events (TEE) (7). Marked hemostatic alterations have been defined in patients with thalassemic. Numerous abnormalities in the platelets, RBCs and coagulation factors have been proposed for the hypercoagulable state of these patients and frequently, a combination of these abnormalities have contribution in these thromboembolic events (8). In the following sections, the contribution of each parameter will be discussed.

Platelets

Numerous reports have suggested that patients with TM have activated platelets. In these patients; especially splenectomized subjects, survival of platelets due to enhanced platelet consumption have been reduced. In addition, expression of CD26p (p-selectin) and CD63 on the platelets of patients with thalassemia have been increased. Therefore, platelet activation and aggregation are enhanced. Due to chronic platelet activation in these

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patients, urinary level of prostacyclin metabolites such as PGI2 and thromboxane A2 are elevated (9).

Red Blood Cells

Oxidation of globin subunits in red blood cells of thalassemic patients results in the production of hemichromes. Due to the binding of the hemichrome to the membrane of RBCs, disintegration of heme occurs and then toxic iron is released into the circulation. The free iron leads to the oxidation of the membrane proteins and formation of RBC antigens such as phosphatidylserine. This phenomenon causes rigidity, deformation and aggregation of the RBCs and premature death in patients with thalassemia. Due to theses alterations, RBCs may be a source of negatively charged phospholipids leading to thrombin generation. Therefore, aggregation and cohesiveness of RBCs of thalassemic patients have been increased (8).

Adhesion Molecules

In patients with thalassemia, level of endothelial adhesion proteins (E-selectin or ELAM-1), intercellular adhesion molecule-1 (ICAM-1), Von Willebrand factor and vascular cell adhesion molecule-1 (VCAM-1) have been increased. This elevation of adhesion molecules suggests an endothelial injury due to the disease itself. Also, enhanced adhesion of RBCs to the cultured endothelial cells of thalassemic patients have been reported (9).

Microparticles

Microparticles are fragments with length of 0.1 to 2 µm which are produced from the remodeling of the plasma membranes of platelets, endothelial cells and circulating RBCs in response to cell activation and apoptosis. The elevated numbers of circulating microparticles may be responsible for the occurrence of thromboembolic episodes in patients with thalassemia. In addition, in other disorders such as; diabetes mellitus, sepsis and preeclampsia, the level of microparticles have also been increased. Youssry and his colleagues found no difference between β-TM and β-TI in terms of the level of the microparticles (10).

Coagulation Factors

Decreased levels of protein C, S and Antithrombin III have been reported in thalassemic patients (11-15). One of the common morbidities in patients with TM is liver dysfunction due to different causes such as hepatic hemosiderosis, viral infections and vitamin and protein deficiency states. Protein C and S are very sensitive to even mild degrees of impairment in liver synthetic functions. High affinity binding of protein C to phosphatidylserine and other negatively charged phospholipids present on the surface of RBCs in patients with TM has been suggested as a hypothesis (16).

Prothrombin fragment 1.2 (F 1.2), a marker of thrombin generation has been reported to be increased in patients with TI (17). Some authors have shown that plasma homocysteine level is elevated in patients with β-TM (18); however, others have commented that hyperhomocysteinemia is not a significant risk factor for development of TEE in thalassemic patients (19, 20).

D-dimer which is a marker of enhanced fibrinolysis is increased in splenectomized thalassemic patients (14, 21). The level of fibrinogen is reported lower among patients with thalassemia compared with healthy control (14, 22). "Thrombin activatable fibrinolysis inhibitor" (TAFI) is a strong fibrinolysis inhibitor which plays an important role in hemostasis (23). Interestingly, the level of TAFI was significantly lower in β-TM (16).

Despite above mentioned factors, alterations in antiphospholipid antibodies, factor V leiden, mutations in prothrombin 20210 and methylene tetrahydrofolate reductase genes do not have reported to have any association with increased risk of thromboembolism (24).

Splenectomy

In splenectomized patients with TI, risk of thromboembolic events is much higher than non-splenectomized patients. The tendency for thrombosis in splenectomized patients is originated from high platelet counts and their aggregation following splenectomy. Also the number of damaged RBC increases after splenectomy (8). Taher et al. have demonstrated that TI patients with NRBC ≥300/100 WBC, platelet count ≥500×10^9/ul, evidence of pulmonary hypertension or transfusion naivety have a greater risk for occurrence of thromboembolic events (25).

Clinical Importance of TEEs

Both venous and arterial TEEs could be detected in patients with β-TM and β-TI, but the incidence of TEE is much higher in TI patients due to lack of regular transfusion. In a study by Taher et al. on 8860 patients with β-TM and β-TI from Iran and Mediterranean region, the incidence of thrombotic events was 0.9% and 4 %, respectively. In other words, risk of TEEs was 4.38 fold higher in patients with β-TI (26). Cappellini and co-workers reported 24 thromboembolic events in 83 splenectomized patients during a 10-year period in patients with β-TI (12).

TEEs could occur in every organ of the body. DVT, pulmonary embolism, portal vein thrombosis and recurrent arterial occlusions are the most important thromboembolic events in thalassemia patients (27). Recently, brain ischemia and infarction resulting in stroke have been reported in these patients. Silent ischemic brain lesions are more prevalent in β-TI; but overt stroke is much more common in β-TM, due to risk factors such as heart failure, cardiomyopathy, arrhythmia and diabetes mellitus which are more common in β-TM (28). Karimi et al. have shown abnormal findings on brain MRI in 28% of patients with β-TI in a study on asymptomatic splenectomized β-TI patients (29). In another study from Lebanon on 30 adult patients with β-TI who have undergone splenectomy, 60% of patients had evidence of one or more lesions on brain MRI mainly involving subcortical white matter. In a multivariate analysis, increasing age and transfusion naivety were associated with a higher incidence of ischemic lesions in MRI (30).

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Prevention and Treatment of Thromboembolic Events

As mentioned before, marked alterations in natural anticoagulants and fibrinolysis pathway could be expected in otherwise healthy patients with β-TI which predisposes them to thromboembolic events. These changes along with thrombocytosis are more significant in splenectomized subjects. In this regard, a group of authors advocate primary prophylaxis in some patients. Another hemostatic abnormality in thalassemia is a profound reduction in TAFI level; therefore even in asymptomatic splenectomized patients, a low grade consumptive coagulopathy with continuous thrombin generation and exaggerated fibrinolysis might be observed. This process may lead to asymptomatic ischemic brain lesions in these subjects (16). In adult splenectomized patients with β-TI who are not receiving regular blood transfusions, mainly in the presence of other risk factors for cerebrovascular accidents, the frequency of brain thrombotic events is expected to be increased. MRI can detect early asymptomatic CNS ischemic/thrombotic lesions in these patients (27). It seems there is an independent association between iron overload and thrombotic disorders; however, role of iron chelators in these conditions has not been investigated (31).

Blood Transfusion

Regular blood transfusion results in the reduction of the exposure of phosphatidylserine on the surface of the erythrocytes leading to both prevention and treatment of thrombotic events (32). In thalassemic patients with symptomatic CNS thrombosis, regular blood transfusion is strongly recommended (28). In patients with β-TI who are scheduled to undergo surgery; regular blood transfusions, hydroxyurea, aspirin and anticoagulants could be considered to have beneficial effects (32).

Hydroxyurea

Hydroxyurea could decrease plasma markers of thrombin generation and coagulation activation factors in patients with β-TI. The mechanism of this phenomenon is reduction of expression of phospholipids on the surface of RBCs (33). Karimi et al. showed that hydroxyurea could prevent silent ischemic brain lesions in 95 patients with β-TI (34).

Aspirin

Aspirin acetylates serine-530 of cyclooxygenase-1(COX-1), thereby blocks thromboxane A2 synthesis in platelets and reduces platelet aggregation. This drug could reduce the conversion of arachidonic acid to thromboxane B2 resulting in platelet inactivation (35). Aspirin could have a protective effect against TEEs in splenectomized β-TI subjects with thrombocytosis. Taher et al. have demonstrated a lower recurrence rate of TEEs after the first episode in subjects who consume aspirin (31). Aspirin has been shown to improve Pao2 in patients with β-TM. Aspirin is indicated by some authors in splenectomized patients with β-TI with platelet counts more than 500×10^9/ul. However, it is not indicated in some patients with cardiovascular and cerebrovascular diseases. In a study on 24 splenectomized and 21 non-splenectomized severe thalassemia patients, the incidence of aspirin resistance (at regular doses) in children and adults who were splenectomized was 29.2%. Aspirin resistance can result in significant TEEs (35).

Anticoagulants

Low-molecular-weight heparins (LMWHs) are a new class of anticoagulants derived from unfractionated heparin (UFH). LMWHs are used routinely for prevention of post-surgery thrombosis. They are often used for a period of 7-14 days (28).

The choice of anticoagulant depends on the site of thromboembolic event. Aspirin has been recommended mostly for arterial thrombosis, but heparins (both the classic UFH and LMWH) and warfarin are usually indicated for venous thromboembolism (24). Also warfarin has been used in patients with cardiac diseases such as dilated cardiomyopathy and atrial fibrillation (36).

Direct Oral Anticoagulants (DOACs)

Nowadays, despite the extensive use of direct oral anticoagulants (DOACs) for coronary arterial disease and also prevention of venous thromboembolism after surgery, there is limited experience regarding the use of DOACs in thalassemia patients. Rivaroxaban was the first of DOACs family which was approved for prevention of TEEs. Apostolou et al. in a study on 8 patients with hemoglobinopathy (4 with sickle cell disease and 4 with β-TM) has reported his experience about the use of rivaroxaban. Five patients had non-valvular atrial fibrillation and received rivaroxaban for prevention of emboli and stroke (primary prophylaxis). The other three patients received rivaroxaban for treatment of DVT and prevention of the recurrence of DVT and pulmonary embolism (secondary prophylaxis). The most significant toxicity of this drug is hepatotoxicity (37). In any patient taking DOACs, special attention to liver function tests is recommended (38). One of the most advantages of DOACs to warfarin is its minimal interactions with other food and drugs. Vitamin K antagonists (warfarin) need multiple phlebotomies and continuous laboratory monitoring of PT and international normalized ratio (INR). Administration of heparin as subcutaneous LMWH may cause local complications at the injection site (39, 40).

Further studies with larger sample size are needed to document the efficacy and safety of DOACs in thalassemic patients.

Discussion

Increased propensity for TEEs in thalassemia has been documented in many published articles, however some conflicts exist on the level of hemostatic parameters and also the differences between splenectomized versus non-splenectomized patients. Reduction of protein C and S levels have been reported in many investigations (11, 13-15). Hashemieh and colleagues have shown that splenectomy had no effect on protein C and S levels. In other words, there was no significant difference in

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protein C and S activity between splenectomized and non-splenectomized patients (11). However, decreased protein C and S levels have been confirmed in numerous studies in splenectomized thalassemic patients (16, 22, 41). Sherief et al. have reported significantly higher homocysteine levels in thalassemic patients compared with healthy subjects (18). In a study from Iran, the homocysteine level did not show any significant difference between thalassemic patients and control group (11).

D-dimer is a marker for enhanced fibrinolysis and there are conflicting results about the level of D-dimer in different studies. In numerous articles, increased D-dimer levels in patients with β-thalassemia has been reported (11, 14, 16, 21). Naithani et al. reported similar D-dimer levels in thalassmic patients and healthy control group (42). In contrast to D-dimer elevation in thalassemia, level of TAFI is reported to be low in these patients. As it was mentioned before, TAFI is a potent fibrinolysis inhibitor and a significant difference in TAFI level was observed between splenctomized and non-splenctomized patients (16). Cappellini et al. have reported higher levels of D-dimer in patients with β-TI especially after splenectomy (12). Many authors have proved that the level of D-dimer in thalassemic patients increases after splenectomy (11, 13, 14).

At last, level of fibrinogen has been reported to be significantly lower in thalassemia intermedia patients (11, 14, 22). However, Fayed et al. in a study on 36 Egyptian children with β-thalassemia and 20 healthy children found no significant difference in fibrinogen levels between the two groups (43).

Conclusion

Hemostatic changes and activation of the coagulation cascade has led to a hypercoagulable state in more severe forms of thalassemia syndromes.

Multiple factors such as reduction of protein C, S and Anti thrombin III activity levels, alterations in composition of RBC's membrane, thrombocytosis following splenectomy and elevation of a group of adhesion molecules have proven to have contribution in the state of thrombophilia in these patients.

There is no standard guideline for prophylaxis of TEEs in thalassemic patients. In patients with β-TI, the best approach is identification of high risk patients and strict monitoring. In patients who are complicated with a thromboembolic event, secondary thromboprophylaxis is recommended to prevent the recurrence. It sounds rational that an individualized approach and an appropriate strategy would be necessary in order to prevent thromboembolic events in thalassemic patients.

Conflict of Interest: None declared.

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