Enoxaparin Plus Ticlopidine: An Effective Combination Therapy for Intracardiac Thrombi in Thalassemia Intermedia

Mohammad Saeed Rahiminejad*1, MD, Pediatric Hematologist; Mohammad Bagher Sharifkazemi2, MD, Cardiologist; Kambiz Sotoudeh3, General Physician

1. Department of Pediatrics, Tehran University of Medical Sciences, IR Iran
2. Department of Cardiology, Shiraz University of Medical Sciences, IR Iran
3. Research Development Center, Tehran University of Medical Sciences, IR Iran

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Abstract

Objective: Patients with thalassemia intermedia have an increased risk of thrombotic events as compared to the general population.

Case Presentation: We describe two cases of thalassemia intermedia with intracardiac thrombi who failed to respond to traditional anticoagulation therapy with Unfractionated Heparin and Aspirin; but thrombolysis occurred following combination therapy with Ticlopidine and Enoxaparin.

Conclusion: Our experience in patients shown combination of Enoxaparin and Ticlopidine is effective for treatment of ventricular thrombus in TI patients.

Key Words: Thalassemia intermedia, Intracardiac Thrombus, Enoxaparin, Ticlopidine

Introduction

Thalassemia intermedia (TI) patients are characterized by a transfusion independent course of intermediate severity between beta-thalassemia major and asymptomatic carriers[1]. Increased tendency of thrombosis has been reported in thalassemia patients suggesting a hypercoagulable state can be present in thalassemia syndromes[2]. In a recent study 4% of 2190 patients with thalassemia intermedia and 0.9% of 6670 patients with thalassemia major experienced a thrombotic event[3]. Recommended treatments in these settings are aspirin and/or low molecular weight heparin (LMWH)[3]. In this paper we have reported two cases of thalassemia intermedia with potentially life threatening heart thrombi in which anticoagulation therapy with aspirin and low molecular weight heparin was insufficient to prevent the thrombosis.

* Correspondence author;
Address: Hematology Devisio, Children’s Medical Center, Dr Gharib Ave, Tehran, IR Iran
E-mail: rahiminms@hotmail.com
molecular weight heparin failed but thrombi disappeared after Ticlopidine was added to LMWH in a short time.

**Case Presentation**

**Case 1:** A 26-year-old female, a diagnosed case of thalassemia intermedia, was admitted in July 2003 with a one day history of chest pain. After a general physical examination and complete paraclinical tests, a pea size thrombus attached to the apex was found by transthoracic echocardiography, indicating it was probably of local origin. In echocardiography, global left ventricle hypokinesia, trivial mitral valve insufficiency, normal pulmonary artery pressure and ejection fraction of 30% also were found. In electrocardiogram a sinus tachycardia was present.

She regularly received one unit packed red blood cell every two months and had no history of thrombotic events. She was splenectomized. Renal and liver function tests as well as serum glucose, cholesterol and triglyceride levels were normal. Prothrombin time, activated partial thromboplastin time, bleeding time, serum fibrinogen, protein S, protein C, factor V and VII were in normal range. Hemoglobin at admission was 8.5 g/dL. Blood cultures were negative for several times. She also denied using any drugs except for iron chelating agents (Deferoxamine) five days a week.

Intravenous infusion of Standard Unfractionated Heparin (UFH) was started intravenously with a dose of 18000 Unit/day, but despite adequate dosage (PTT increased to 1.5 × normal) echocardiography showed an increase in the size of thrombus after 3 days. Aspirin (80 mg/day, oral) was added but severe epistaxis developed, therefore both drugs were discontinued and Enoxaparin (low molecular weight heparin) was started subcutaneously with a dose of 40 mg/day. After two days the size of thrombus was not changed and a new fresh and small thrombus was detected in the right ventricle’s apex.

Evaluation of calf and pelvic veins for source of the thrombosis was not significant. Ticlopidine (250 mg/every 12 hours, oral) was added to Enoxaparin, thereupon the size of thrombi started to decrease and two weeks later no thrombus could be detected by echocardiography. This combination therapy continued (Ticlopidine for two months and Enoxaparin for six months). In follow up study after one, two and six months there was no evidence of thrombus in the heart. She visited us in late August 2006 and her heart was clear.

**Case 2:** In November 2003 a 28-year-old man was admitted for his cardiomyopathy and biventricular heart failure. He was a case of thalassemia intermedia with regular transfusions every 15 days. Four months before admission he underwent splenectomy because of hypersplenism. In admission he had hepatomegaly, moderate pleural effusion, moderate ascites and 2+ pitting edema in lower extremities, increased jugular vein pressure with hemoglobin 8.4 g/dL and platelet count 34000/μL. Total and direct bilirubins were 6.2 and 2.3 mg/dL, respectively. Prothrombin time was 22 sec (control 12 sec) and activated partial thromboplastin time 120 sec (control 35 sec).

Blood culture in several occasions was negative. In electrocardiogram, right bundle branch block, right axis deviation and right ventricular hypertrophy and tachycardia were seen. Echocardiography showed dilated chambers with a globular thrombus (2 cm^2), mild mitral regurgitation and global hypokinesia. Color Doppler sonography of lower limbs was normal. The patient’s present underlying cardiac disease was too risky for surgical intervention, therefore nonsurgical treatment was chosen.

Standard Unfractionated Heparin (20,000 unit/day, injected intravenously) was started. 3 days later an increased size of thrombus was demonstrated in echocardiography. The treatment has been changed to Enoxaparin plus Ticlopidine (250 mg/every 12 hours, oral). After 10 days the size of thrombus decreased to one third. Patient died after two weeks due to his cardiomyopathy and hepatic insufficiency.
**Discussion**

Thalassemia intermedia patients similar to the thalassemia major patients, predispose to thrombotic events\[^{2,4}\]. In thalassemia intermedia patients, these events primarily occurred in the venous system and comprised deep vein thrombosis, portal vein thrombosis, stroke, pulmonary embolism and other symptoms\[^{2-4}\]. Moreover; the risk of thrombosis in splenectomized TI patients is more than in non-splenectomized TI patients\[^{2,4}\]. Although the pathogenesis is uncertain, thrombophilic state in TI patients is attributed to the procoagulant activity of damaged red blood cells (RBC) and the abnormal exposure of phosphatidyl-serin from the RBC remnants. Other hypothesized mechanisms include coinheritance of coagulation defects, endothelial inflammation, depletion of antithrombotic factors, and stressful conditions that increase thrombosis formation\[^{2,3}\].

Spontaneous intracardiac thrombus in the absence of any predisposing cardiac disease that was seen in case one, is a rare event, because the main causes of left ventricular thrombi, namely acute myocardial infarction and dilated cardiomyopathy, were not seen in that patient\[^{5}\]. On the other hand biventricular thrombi in case 1 was an even more rare condition and have been reported to occur in patients with dilated cardiomyopathy, ischemic cardiomyopathy and hypercoagulable state secondary to nephrotic syndrome\[^{6}\]. Despite left ventricular thrombi, thrombi in the right ventricle may develop within the right heart chambers or may be peripheral venous clots that on their way to the lungs, accidentally lodge in right ventricle\[^{7}\].

There is no consensus regarding the optimal treatment of ventricular thrombi. Over the past 30 years, the primary therapeutic options have included surgical removal of thrombi, anticoagulation, or more recently, thrombolysis. Some cases of intravenous thrombolysis have been reported, but risks of bleeding and embolism were too high\[^{8}\]. Similarly the use of tissue plasminogen activator (t-PA) for cardiac thrombus is controversial because it could potentially accelerate break up of the thrombus and cause additional embolies. Some authors have been advocating a surgical approach for patients with mobile and pedunculated thrombi, but such patients are exposed to a high risk of complications of surgery\[^{9}\]. The most common therapeutic approach consists in the administration of intravenous UFH followed by oral anticoagulation therapy\[^{5}\]. Although in many conditions efficacy of LMWHs are equivalent or superior to UFH, UFH has been considered as the treatment of choice for left ventricle thrombus\[^{5,10}\].

LMWH for treatment of left ventricular thrombus was not evaluated before and only one clinical case was reported\[^{11}\]. Recently a preliminary study showed the safety and efficacy of LMWH (Enoxaparin) in disappearance or size reduction of left ventricular thrombi associated with acute myocardial infarction or dilated cardiomyopathy. Aspirin and Clopidogrel in combination with LMWH were used in that study but neither the etiology of cardiac problem nor the different antiaggregant treatments appeared to influence the progression of thrombi on LMWH therapy\[^{5}\].

In this country Ticlopidine has been available for several years, however its use has been limited by the significant risk of neutropenia\[^{12}\]. Ticlopidine inhibits the binding of adenosine 5'-diphosphate (ADP) to its platelet receptor and this ADP receptor blockade leads to direct inhibition of fibrinogen binding to the glycoprotein IIa/IIIb complex. Also Ticlopidine may interfere with von Willebrand factor, resulting in less binding of von Willebrand factor to platelet receptors\[^{13}\].

In our cases, when we added Ticlopidine to LMWH, thrombolysis potency increased and it is suggested that this combination therapy may be more potent than each of them. The mechanism of this additive thrombolysis is not well known. However, it may be due to at least two mechanisms: One is that, addition of Ticlopidine to LMWH improves the antiplatelet activity and leads to dissolving of
thrombus in a process similar to dethrombosis\cite{14,15}. The second one is a particularly thrombolytic action of those drugs in TI patients with an unknown mechanism.

**Conclusion**

Although our experience is limited to the treatment of two patients, we believe that combination of Enoxaparin and Ticlopidine is effective for treatment of ventricular thrombus in TI patients. Whether this combination therapy is specific for TI patients or not, should be further evaluated with more patients.

**References**