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Aspirin resistance in children and young adults with splenectomized thalassemia diseases

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ABSTRACT

Aspirin is now recommended for splenectomized thalassemia patients with high platelet counts. However, aspirin resistance defined by arachinodic acid (ACA) induced platelet aggregation ≥20%, has never been reported in this group of patients. In this study, twenty-four splenectomized thalassemia patients (15.7 ± 4.1 years), with platelet counts ≥800x10^9/L, and 21 non-splenectomized severe thalassemia patients (14.3 ± 3.2 years), were enrolled. After taking aspirin (2 mg/kg/day), seven patients (29.2%) displayed aspirin resistance. Serum thromboxane B_2 (TXB_2) levels in the aspirin responsive group decreased significantly [52.6(8.8-174.6) vs 4.0(1.6-7.3) mcg/mL, $p < 0.001$], while no change was demonstrated in the aspirin resistant group. Having increased aspirin to 4 mg/kg/day, three of the seven aspirin resistant patients responded, while one developed upper GI bleeding from esophageal varices and was withdrawn from the study. For the three remaining patients, their doses were increased to the maximum of 300 mg/day, and two of the three responded. Thrombin antithrombin complex and D-dimer levels were significantly decreased after taking aspirin (2 mg/kg/day), although D-dimer level was still significantly higher than that in non-splenectomized group. Therefore, aspirin dosage can be adjusted individually to reach maximum effect of platelet inhibition. In addition, aspirin can reduce the levels of coagulation markers.

Introduction

Thalassemia is an inherited hemolytic disorder common in Southeast Asian countries, including Thailand [1]. The prevalence rates of gene carriers and diseases are around 20-50% and 1% respectively [2–4]. The cause of thalassemia is decreased or abnormal synthesis of α or β globin chains. The most severe form of thalassemia, a transfusion dependent thalassemia, is thalassemia major (TM), namely β^0/β^0 and E/β^0. Thalassemia intermedia (TI), such as hemoglobin H (HbH) and $HbE/\beta^{0/+}$, is a non-transfusion dependent thalassemia [5]. The symptoms of thalassemia are anemia, jaundice, bone change, and hepatosplenomegaly from extramedullary hematopoiesis [6]. The current curative treatment is hematopoietic stem cell transplantation (HSCT). For patients who do not undergo HSCT, regular packed red cell (PRC) transfusion to maintain hemoglobin levels at around 9–10 g/dL is recommended. Splenectomy is considered in patients with hypersplenism, with a markedly enlarged spleen, or who are receiving PRC more than 200–220 ml/kg/year to maintain hemoglobin around 10 g/dL [7,8]. Complications include osteopenia/osteoporosis, endocrine dysfunction and heart failure resulting from chronic anemia, iron overload, immune dysfunction, pulmonary hypertension, and thromboembolism (TE), especially in splenectomized patients.

Hypercoagulable states in thalassemia have been determined by increased levels of thrombin-antithrombin complex (TAT), prothrombin fragment (F1 + 2) and global thrombin generation, especially in splenectomized patients [9–11]. The incidence rate of TE in TM, including splenectomized patients, has been estimated to be between 0.9% to 4% [12]. The mean age at which patients started to experience this complication was at 15.9 years [13]. The mechanisms of TE are platelet and endothelial activation, abnormal red blood cell surface and splenectomy which results in increased platelet counts, platelet activation and abnormal red cells in the circulation.

As a result of the high risk of TE, aspirin is now suggested in thalassemia patients who undergo splenectomy. It has been reported to improve PaO_2 in TM patients, [14] and has been used to prevent TE in splenectomized thalassemia patients with platelet counts higher than 1,000x10^9/L [15]. In splenectomized TI, aspirin has been recommended when platelet counts are higher than 500x10^9/L [16].

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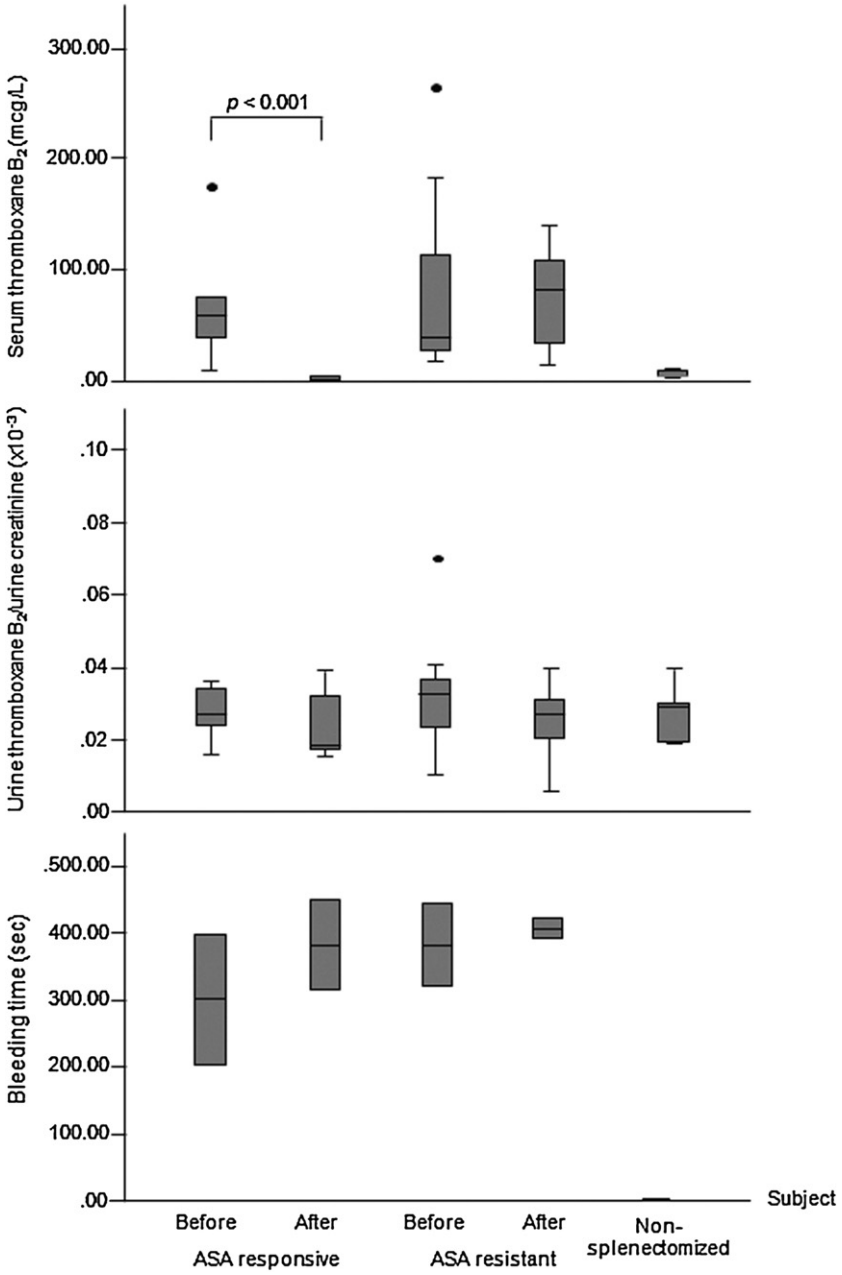

Fig. 1. Serum thromboxane B_2, urine thromboxane B_2/creatinine and bleeding time in responsive and resistant splenectomized thalassemia patients; before and after 2 mg/kg/day of aspirin (ASA) and non-splenectomized thalassemia patients.

Aspirin, an inhibitor of cyclooxygenase-1 (COX-1), decreases the formation of arachidonic acid (ACA) to thromboxane B_2 (TXB_2), resulting in platelet inactivation. However, some patients are aspirin resistance, and fail to respond to aspirin. Aspirin resistance is determined by either clinical TE or laboratory results which do not reveal platelet inactivation, shown by platelet aggregation test, serum, and urine TXB_2 [17]. Aspirin resistance is mostly reported in adult patients with cardiovascular diseases, cerebrovascular diseases and peripheral vascular diseases. The incidence has been reported to be approximately 5.0-60% [18–27]. In addition, patients with aspirin resistance had higher risks of serious events compared to aspirin responsive patients [28]. The incidence of aspirin resistance in splenectomized thalassemia patients is expected to be high due to the increased platelet activation in thalassemia patients [29]. Although the treatment with aspirin has been followed with the guideline, there have been the reports of high incidence of TE in splenectomized thalassemia patients. Therefore, the aim of this study was to identify the incidence of aspirin resistance and levels of coagulation markers in splenectomized thalassemia patients after taking aspirin.

Materials and Methods

Study Populations

The study was performed between February 2012 and October 2015 at the Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, and approved by the Ethics Committee of the Faculty of Medicine.

Inclusion Criteria

Severe thalassemia patients age <25 years who had undergone splenectomy and had at least one recorded platelet count $\geq 800 \times 10^9$/L were