Potential Role of Intravenous Immunoglobulin in the Management of Peripartum Maternal Thrombocytopenia Due to Various Causes

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Severe maternal thrombocytopenia resulting in hemorrhage is often associated with high mortality. Three cases of severe maternal thrombocytopenia in association with heparin-induced thrombocytopenia (HIT), HELLP syndrome, and systemic lupus erythematosus (SLE) were successfully managed using intravenous immunoglobulin (IVIG). IVIG can reduce the severity of thrombocytopenia and hemolysis, stabilize lupus activity, prevent peripartum hemorrhage, and shorten hospitalization, but it may induce reversible interstitial nephritis and membranous glomerulonephritis. IVIG may be beneficial in the management of severe peripartum maternal thrombocytopenia in association with HIT, HELLP syndrome, and SLE. [J Chin Med Assoc 2008;71(5):267–269]

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Introduction

The common causes of maternal thrombocytopenia in pregnancy are gestational thrombocytopenia, pre-eclampsia, immunologic etiologies (including idiopathic thrombocytopenia purpura [ITP], systemic lupus erythematosus [SLE], heparin-induced thrombocytopenia [HIT], and alloimmune thrombocytopenia), viral infection, B12 or folic acid shortage and hypersplenism.1,2 The presence of antiplatelet antibodies may induce platelet aggregation and precipitate destruction of antibody-coated platelets by reticuloendothelial uptake. Intravenous immunoglobulin (IVIG)-induced immunomodulation derived from management of ITP may apply to other immune-induced thrombocytopenia.3–5 Herein, the experience of using IVIG in the management of severe maternal thrombocytopenia in association with heparin administration, HELLP (hemolysis, elevated liver function, low platelets) syndrome, and SLE, is presented. Both the mechanisms and side effects of IVIG are also briefly reviewed.

Case Reports

Case 1

A 24-year-old woman with pulmonary hypertension and suspected postpartum pulmonary embolism on the third postpartum day was treated with unfractionated heparin, urokinase, and extracorporeal membrane oxygenation (ECMO) therapy. After 6 days of heparin administration, severe thrombocytopenia (18,000/mm³) was noted, which did not respond to repeated platelet transfusion. Heparin infusion was stopped due to HIT. Unfortunately, deteriorating pulmonary hypertension with massive bilateral pulmonary hemorrhage subsequently occurred. Platelet transfusion and IVIG (GAMMAR-P I.V., Aventis Behring, USA) were administered (15 g/d for 3 days). Four days after initiation of IVIG therapy, the platelet count increased and was maintained above 77,000/mm³ without further platelet transfusion. The ECMO therapy was continued for 33 days to successfully rescue the patient’s life.
Case 2
A 35-year-old woman with HELLP syndrome and acute postpartum uterine bleeding was treated with platelet transfusion, prostaglandin E1, and IVIG (15 g, single dose; GAMMAR-PL.V., Aventis Behring) because of worsening hemolytic renal failure and thrombocytopenia (23,000/mm³). Platelet counts increased to 110,000/mm³ within 6 hours and were maintained above 65,000/mm³ without further transfusion. Uterine bleeding was under control and hemoglobinuria improved over 2 days despite persistent severe oliguria. Unfortunately, pulmonary edema ensued, then hemodialysis was initiated. The patient’s condition became stable gradually. On postpartum day 14, renal biopsy revealed interstitial nephritis with infiltrating eosinophils and lymphocytes as well as membranous glomerulonephritis (Figure 1). Two weeks later at follow-up, renal function had normalized.

Case 3
A 30-year-old woman with SLE was noted to have rupture of membranes at 37 weeks' gestation. Her prenatal care was notable for unstable lupus activity with fluctuation of platelet level (with nadir of 4,000/mm³), which was managed with immunotherapy (prednisolone and methylprednisolone) and platelet transfusions. At admission, she had no lupus nephritis, but laboratory data were significant for severe thrombocytopenia (8000/mm³). Hydrocortisone (100 mg q6hr), IVIG (40 g, single dose; Gamimune, Bayer, USA) and platelet transfusion (18 units) were administered. Twenty hours later, the platelet count increased to 72,000/mm³ and cesarean section was performed due to breech presentation. Her postpartum course was uneventful. The platelet level was maintained above 70,000/mm³ for 2 weeks without further platelet transfusion.

Discussion
The possible mechanisms of IVIG in clinical use may involve interaction of pathologic antibodies with anti-idiotype antibodies in IVIG, competitive inhibition of autoantibody adsorption to the platelets, prevention of reticuloendothelial uptake of autoantibody-coated platelets through Fc-receptor (FcR) blockade by dimerized aggregates in IVIG, acceleration of catabolism of pathologic antibody by competitive binding to the molecule FcRn, or the presence of anticytokine antibodies and neutralizing antibodies against toxin and pathologic antigen. The side effects of IVIG include anaphylaxis, headache, aseptic meningitis, thrombosis (due to high viscosity), renal toxicity, hemolysis (due to anti-D,A,B dependent on manufacturers), and neutropenia with dyspnea (due to antineutrophil Ab). Most cases of IVIG-associated acute renal failure (ARF) are reversible, with approximately 2-week duration and serum creatinine peaking at day 5. ARF may occur with sucrose-stabilized IVIG, rarely with maltose-stabilized IVIG, but not with d-sorbitol-stabilized IVIG, possibly due in part to osmotic damage to renal tubular cells. IVIG may induce reversible interstitial nephritis and membranous glomerulonephritis. Other risk factors for IVIG-associated ARF include old age, diabetes mellitus, nephrotic agents, hypovolemia, and high dose of IVIG.

HIT type I is a non-immune, mild (rarely <100,000/mm³) and transient thrombocytopenia that develops early (within 2 days of starting heparin) and resolves quickly once the heparin is stopped. HIT type II is a common (incidence of 1–5%) and potential life-threatening condition which usually occurs 5–7 days after initial use of unfractionated heparin. Immunoglobulin G antibodies bound to the heparin-platelet factor 4 complex cause platelet activation via the FcR. Activated platelets release platelet factor 4, thus perpetuating the cycle of heparin-induced platelet activation, which results in thrombocytopenia. Additionally, platelet factor 4 that is bound to endothelial cell surface heparin sulfate may bind to HIT antibodies, possibly precipitating intravascular coagulation and thrombosis. IVIG may have a beneficial effect on HIT. In our case, IVIG appeared effective in facilitating recovery from HIT, possibly due to inhibition of HIT antibody through anti-idiotype antibody, acceleration of HIT antibody catabolism by competitive binding to FcRn on endothelial cells, and
competitive blockade of FcRII on platelets.\textsuperscript{10,11} Further studies are needed to elucidate the potential role of IVIG in management of HIT. Also, using IVIG to inhibit platelet activation prior to clearance of residual heparin helps stabilize pulmonary hemorrhage, thus providing an opportunity to support the patient’s life with intensive care and ECMO therapy.\textsuperscript{12} Furthermore, through inhibition of HIT antibody, IVIG may prevent subsequent fatal thrombosis.

As to management of severe HELLP syndrome associated with postpartum uterine hemorrhage, the major aim is to interrupt cascading thrombocytopenia in order to eliminate further hemorrhage and reduce the requirement for repeated blood transfusions which may exacerbate pulmonary edema in the situation of hemolysis-induced renal failure. In association with platelets transfusion, IVIG seemed to be able to keep platelets count at a safe level in the acute stage of HELLP syndrome. In addition, high-dose steroid may improve laboratory data in HELLP syndrome. Although its exact mechanism remains unknown, IVIG may exert effects through modulation of Fc receptor expression on leukocytes and endothelial cells, and modulation of cytokine release.\textsuperscript{5} Cytokines released by activating leukocytes and lipid peroxide are potential mediators of endothelial dysfunction.\textsuperscript{13}

IVIG has been used to successfully treat active SLE with various manifestations, including thrombocytopenia.\textsuperscript{2,5,14} The possible mechanisms are Fc receptor blockage in reticuloendothelial cells, anti-idiotypic antibody, downregulation of autoantibody production, neutralization of autoantibody, inhibition of complement-mediated damage, and modulation of production of cytokine.\textsuperscript{5} In addition to platelet transfusion and steroid administration, using IVIG may expedite the recovery of thrombocytopenia in SLE during delivery. Besides, IVIG may exert effect on maintaining a safe platelet level for several weeks without further platelet transfusion on account of its long half-life. Other advantages include lessening peripartum bleeding, shortening hospital stay, decreasing risk of infection from using steroid, and allowing more time for steroid to stabilize the lupus activity.

In conclusion, IVIG may be beneficial in the management of severe peripartum maternal thrombocytopenia in association with HIT, HELLP syndrome, and SLE, and it should be a last option.

References