


Successful Management of Thrombotic Thrombocytopenic Purpura in a Jehovah's Witness: An Individualized Approach With Joint Decision-Making

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Abstract

The management of thrombotic thrombocytopenic purpura (TTP) presents a unique challenge in individuals who are unable to accept plasma due to religious beliefs, given that therapeutic plasma exchange (TPE) is the standard of care. A 61-year-old Jehovah's Witness woman presented to our hospital with neurological symptoms and laboratory findings suggestive of TTP. On admission, she refused transfusion of blood products, specifically red blood cells, platelets, and plasma but accepted albumin and intravenous immunoglobulin (IVIG); fractions of plasma. She was started on steroids, IVIG, and TPE with albumin as replacement therapy with minimal improvement. After a detailed discussion with the patient and family, they agreed to accept cryosupernatant. The patient started TPE with cryosupernatant for replacement therapy, which resulted in clinical improvement. This case highlights the importance of an individualized approach with joint decision-making given the significant heterogeneity that exists in Jehovah's Witnesses' attitude toward the receipt of blood products.

Keywords

Jehovah's Witness, plasma exchange, cryosupernatant

Introduction

Therapeutic plasma exchange (TPE) is currently the standard of care in the initial management of thrombotic thrombocytopenic purpura (TTP) (1). However, this presents a unique challenge in individuals who are unable to accept plasma due to religious beliefs. With Jehovah's Witnesses, there have been 8 published case reports discussing the successful management of TTP (7 idiopathic, 1 drug related) without the use of TPE (2-9). There is likely a publication bias with only successful cases being reported. Other than the use of high-dose corticosteroids in 7 of the 8 cases, there was no consistency in the management of TTP in these cases. This reflects the lack of consensus on adjunct measures in the management of TTP (10). We report the successful management of TTP in a Jehovah's Witness using TPE, the standard of care, but with cryosupernatant, a fraction of plasma, as replacement therapy.

Case Presentation

A 61-year-old woman from out-of-state was attending a wedding dinner when she developed slurred speech with facial

asymmetry. Her medical history was significant for hypothyroidism on replacement therapy, and poorly controlled hypertension on atenolol-chlorthalidone. On arrival to the emergency department, her neurological symptoms had resolved. She was admitted for stroke workup. Urgent brain computed tomography (CT) showed no acute intracranial pathology.

Laboratory findings revealed hemoglobin of 8.4 g/dL (range: 14.0-18.0), platelet count of $15 \times 10^9/L$ (range: 140-440), and white blood cells of $6.4 \times 10^9/L$ (range: 4.8-10.8). Peripheral blood smear demonstrated 10 to 15 schistocytes per high power field. Renal function and liver enzymes were within normal range. Troponin was elevated at 0.190 ng/mL (range: <0.034), lactate dehydrogenase (LDH) was elevated at 2005 U/L (range: 313-618), and

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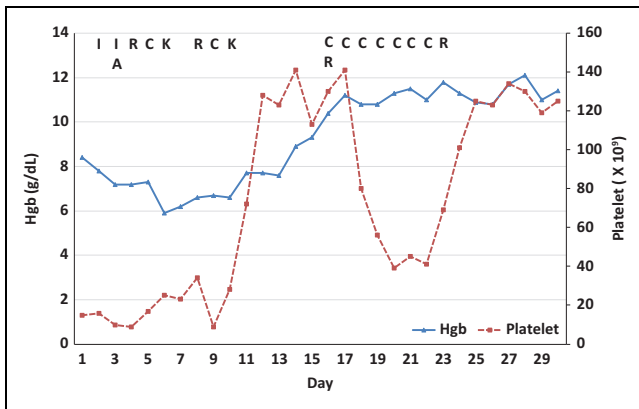


Figure 1. Hemoglobin and platelet response to treatment. The patient received IVIG 1 g/kg on day 2 and 3; plasma exchange with albumin replacement on day 3; rituximab 375 mg/m² on day 4 and 8; rituximab 100 mg on day 16 and 23; Koate 2000 IU on day 6 and 10; and plasma exchange with cryosupernatant on day 5, 9, 16 to 22. The patient also received methylprednisolone 1000 mg on day 1 to 3, followed by prednisone 1 mg/kg daily; folic acid daily; intravenous iron infusion on day 6 to 12 and recombinant human erythropoietin on day 3, 5, 7, 10, 12, and 14 (not shown in graph above due to space constraints). I, IVIG; A, plasma exchange with albumin replacement; R, rituximab; K, Koate; C, plasma exchange with cryosupernatant. IVIG indicates intravenous immunoglobulin.

haptoglobin was undetected at <8 mg/dL (range: 14-258). Reticulocyte count was elevated at 4.9% (range: 0.5%-2.5%). The disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity was <5% with the presence of an inhibitor at 4.8 units (range: <0.4), supporting the diagnosis of TTP.

She was started on methylprednisolone 1000 mg daily and transferred to our institution for emergent TPE. On arrival, we discovered that she was a Jehovah's Witness. The patient stated her refusal of transfusion of blood products, specifically red blood cells, platelets, and plasma. She accepted the following fractions of plasma: albumin and intravenous immunoglobulin (IVIG).

On day 2, IVIG 1 g/kg was given (Figure 1). On day 3, her platelet count decreased to $10 \times 10^9/L$. A second dose of IVIG 1 g/kg was given. Alternative adjunct measures with other fractions of plasma, namely cryoprecipitate, cryosupernatant, fibrinogen concentrate (RiaSTAP) and Koate (Koate-DVI, antihemophilic factor [human]; Kedrion Biopharma, Fort Lee, NJ), were discussed with the patient. As acceptance of "fractions of any primary blood component (cellular blood product and plasma)" must be "conscientiously decided" by each individual Jehovah's Witnesses, the patient was asked about her personal interpretation of what constitutes a blood product (11). A church elder visited with the patient to provide educational and religious support. Despite extensive discussion and written information provided to the patient and her family (husband and 2 sons), she remained indecisive on whether she would accept other fractions of plasma.

Given her ongoing indecisiveness, the option to pursue TPE with albumin replacement was presented to the patient. The increased risk of a cardiovascular event given her anemia and possible coagulopathic event from hypofibrinogenemia, as well as the lack of evidence supporting this approach, was discussed with the patient, who consented to the procedure. Preprocedure, her fibrinogen levels on day 3 were 453 mg/dL (range: 213-486). Postfirst TPE with albumin replacement, her fibrinogen levels decreased to 111 mg/dL. Given the significant drop in fibrinogen, further TPE with albumin replacement were held. Recombinant human erythropoietin (40 000 U subcutaneously 3 times per week) and oral folic acid were also started on day 3.

In the early morning of day 4, the patient developed recurrent neurological symptoms with a seizure lasting 15 seconds. Repeat head CT and CT angiogram of the head and neck were negative for acute hemorrhage. Magnetic resonance imaging of the brain revealed acute infarction within the left insular lobe. She continued to have expressive aphasia and was unable to provide informed consent. Her husband, the next-of-kin, provided written consent for use of fractionated plasma only, as was discussed above. This was in agreement with the patient's 2 sons. Rituximab at 375 mg/m² was given on day 4. Methylprednisolone was switched to prednisone 1 mg/kg on day 4.

On day 5, she underwent TPE with cryosupernatant for replacement therapy, which resulted in resolution of her neurological symptoms. On day 6, her hemoglobin dropped to 5.9 g/dL. Therapeutic plasma exchange was withheld. Koate was given on day 6 at 2000 IU (25 IU/kg). Preinfusion factor VIII (FVIII) activity was 212% (range: 50%-150%). Daily intravenous iron sucrose 100 mg was started on day 6 for 1 week. On day 8, the second dose of rituximab 375 mg/m² was given. On day 9, the patient received TPE with cryosupernatant. On day 10, another dose of Koate 2000 IU was given. Further doses of Koate were discontinued due to post-infusion FVIII activity of 364%. Her platelet count started to respond on day 11 and reached $141 \times 10^9/L$ on day 14. Unfortunately, platelet recovery was not sustained. Therapeutic plasma exchange with cryosupernatant was resumed daily from day 16 to day 22. Rituximab 100 mg was given on day 16 and 23.

On day 30, the patient was deemed stable for discharge with a hemoglobin of 11.4 g/dL, platelet count of $125 \times 10^9/L$, with normal haptoglobin and LDH levels. She returned back to her home state and followed up with a local hematologist.

Discussion

Using an individualized approach with joint decision-making, we report the successful utilization of cryosupernatant in the management of TTP in a Jehovah's Witness patient. Studies have demonstrated that there is significant heterogeneity that exists in Jehovah's Witnesses' attitude toward the receipt of other blood products (12). Hence, it

is important to understand whether the decision to refuse blood products is based on genuine knowledge of the medical situation as opposed to one based on misinformation or lack of knowledge. Our patient was familiar with albumin and IVIG, which she accepted, but unfamiliar with the different fractions of plasma available. Despite the urgency of the situation, we made a conscious effort via ongoing family discussion to ensure that the patient and family were educated thoroughly on the different types of fractionated plasma available. Patient education material from the advocates for Jehovah's Witness Reform on Blood (<http://ajwr.org/watchtower-approved-blood-transfusions>) and manufacturer's package insert on the different fractionated plasma products were provided to the family to ensure they were fully informed on how the plasma fractions were produced. Through our efforts, we were able to avoid coercion while maintaining patient autonomy in the medical decision-making.

Cryosupernatant is a fraction of plasma from which cryoprecipitate has been removed and is relatively depleted of high-molecular-weight von Willebrand factor multimers. It has been suggested that cryosupernatant may be more effective than fresh frozen plasma (FFP) during TPE in the management of TTP (13,14). However, this proposed superiority in efficacy was not demonstrated in a randomized trial of 27 patients conducted by the North American TTP group (15). Furthermore, as cryosupernatant is not readily available in most US institutions, including ours, our clinical experience is limited as compared to our Canadian colleagues who tend to favor cryosupernatant over FFP in the management of TTP (16,17).

One of the adjunct measures for the management of TTP we used was Koate, an intermediate-purity plasma-derived Factor VIII concentrate. Koate has the highest content of ADAMTS13 to factor VIII (FVIII), at 9.08 and 8.46 per 100 IU of FVIII for ADAMTS13: activity and ADAMTS13: antigen, respectively (18). In addition, Koate contains a low content of ultra large von Willebrand multimers (18). The successful use of Koate has been reported in both congenital and acquired TTP (19,20). Our patient received 2 doses of Koate at 25 IU/kg 4 days apart, similar to the dosing regimen used in patients with congenital TTP (20). Although no side effects were noted, further doses of Koate were withheld due to concern for thrombosis from elevated FVIII levels.

As there was a delay in starting TPE (on day 5, 9, and 16-22), it is unclear if the patient's successful recovery was due to TPE or the use of immunosuppressive therapy with high-dose corticosteroids and rituximab. It is possible that the patient could have improved on immunosuppressive therapy alone, similar to what has been reported in the literature (2-9). Regardless, given that TPE remains the standard of care in the initial management of TTP, our case highlights that cryosupernatant can be used as an alternative to FFP in Jehovah's Witness patients who are willing to accept fractions of plasma.

Conclusion

In summary, our case highlights the importance of an individualized approach with joint decision-making between patient and health-care provider, given the significant heterogeneity that exists in Jehovah's Witnesses' attitude toward the receipt of other blood products. In addition, as TPE remains the standard of care in the initial management of TTP, our case serves as a reminder to the general medical community who may be unfamiliar with cryosupernatant that it can be used as an alternative to FFP in Jehovah's Witness patients who are willing to accept fractions of plasma.

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