Case Report

Red Blood Cell Transfusion for Pediatric Autoimmune Hemolytic Anemia in an Emergency Situation

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Abstrak

Autoimmune hemolytic anemia (AIHA) dapat menyebabkan penurunan nilai hemoglobin yang sangat rendah sehingga transfusi darah merah merupakan tata laksana yang harus segera diberikan. Pemberian transfusi pada pasien AIHA dengan nilai hemoglobin yang rendah kadang terkendala dengan tidak tersedianya darah cuci (PRC washed) di rumah sakit setempat. Laporan 2 kasus pasien AIHA dengan nilai hemoglobin 4,1 g/dL dan 5,3 g/dL. Kedua kasus tersebut terlambat diberikan transfusi darah selama beberapa hari di rumah sakit asal sehingga saat tiba di RSCM nilai hemoglobin sudah lebih rendah lagi. Keterlambatan pemberian transfusi darah ketika nilai hemoglobin sangat rendah tentu dapat mengakibatkan terjadinya gagal jantung dan dapat mengakibatkan kematian. Berdasarkan laporan kasus tersebut, dilakukan kajian literatur mengenai pemberian transfusi darah merah pada pasien AIHA. AIHA ditandai dengan produksi autoantibodi terhadap antigen di permukaan sel darah merah sehingga PRC washed tidak mutlak dberikan pada pasien AIHA terlebih pada kondisi gawat darurat ketika nilai hemoglobin sangat rendah. Selain itu PRC washed membutuhkan proses pembuatan yang lama dan tidak tersedia secara luas. Pada kasus darurat, sel darah merah yang cocok dengan ABO dan rhesus (Rh) dapat diberikan dengan aman jika aloantibodi dieksklusi berdasarkan riwayat transfusi sebelumnya. Transfusi PRC yang cocok dengan ABO dan Rh aman diberikan pada pasien AIHA dengan nilai hemoglobin yang rendah yang dapat mengancam nyawa jika tidak segera ditangani.
Kata kunci: *AIHA, transfusi darah, anemia, PRC washed*

Tranfusi Sel Darah Merah untuk Pasien Anak dengan Anemia Hemolitik Autoimun dalam Situasi Darurat

Abstract

Autoimmune hemolytic anemia (AIHA) often presented with decreased in hemoglobin values, so transfusion must be given immediately. Transfusion in AIHA patients with low hemoglobin values is sometimes constrained by the unavailability of washed blood (PRC) at the hospital. Reports of 2 cases of AIHA patients with hemoglobin values of 4.1 g/dL and 5.3 g/dL. Both cases were delayed for transfusion for for several days at the prior hospital, when they arrived at the RSCM the hemoglobin value was even lower. Delay in giving blood transfusions when the hemoglobin value is very low can certainly lead to heart failure and can result in death. Based on this case report, a literature review was conducted regarding the administration of red blood cell (RBC) transfusion in AIHA patients. AIHA is characterized by the production of autoantibodies against antigens on the surface of RBC, so washed PRC is not absolutely necessary for AIHA patients, especially in emergency conditions when hemoglobin values are very low. In addition, washed PRC requires a long process and is not widely available. In emergency cases, ABO and rhesus (Rh)-matched RBCs can be considered to safely administered if alloantibodies are excluded based on previous transfusion history. ABO and Rh-matched PRC transfusions are safe for AIHA patients with low hemoglobin values that can be life-threatening if not treated immediately.
Keywords*: AIHA, blood transfusion, anemia, washed PRC.*

Introduction

Autoimmune hemolytic anemia (AIHA) is a disease where patients' red blood cells (RBCs) were destructed because of autoantibodies against membrane antigens of RBCs. Anemia is commonly found in AIHA patients, sometimes presented with severe anemia.[1] Some centers and clinicians follow a standard operating procedure of using washed PRC only to transfuse to AIHA patients. However, washed PRC are not widely availablein all healthcare facilities in Indonesia and they are only found in big hospitals in central Indonesia. The process of washing PRC also takes several hours.[2] These issues can cause delays in treating AIHA patients presenting with severe anemia and clinical symptoms who urgently need blood transfusion. Delayed transfusion in severe anemia pediatric can increase patients' mortality, prolong respiratory distress and cardiac failure.[3] Moreover, washed PRCp are not merely the only option in AIHA transfusion management. Therefore, we wished to review whether washing transfused blood is important in treating emergency AIHA patients.

The Cases

Case 1

A 15-year-old girl was referred to Cipto Mangunkusumo Hospital (Rumah Sakit dr. Cipto Mangunkusumo/RSCM) from East Indonesia in May 2019 with a chief complaint of paleness and general weakness 1 week prior to hospital admission. The patient also suffered from fatigue; however, there were no signs of fever, bleeding, stomach pain, or blood in the urine. There were no palpitations or dyspnea. Laboratory results showed a hemoglobin (Hb) of 4.1 g/dL, white blood cell (WBC) 6,500/uL, and platelets 357,000/uL. The patient was diagnosed with autoimmune hemolytic anemia (AIHA) and scheduled to receive RBC transfusion. However, since there were incompatibilities with the donor's blood on the Coombs test, doctor did not give PRC transfusion. The patient was supposed to receive washed PRC; however, since it was not available, the patient was referred to RSCM. The transfusion was further delayed for 3 days for the referral.

In RSCM, five days after her first admission, laboratory examinations showed that the patient's Hb dropped to 3.5 g/dL, hematocrit 10%, WBC 8,800/uL, platelets 346,000/ uL, mean corpuscular volume 121.3 fL, mean corpuscular Hb 42.5 pg, mean corpuscular Hb concentration 35.1 g/dL, direct Coombs test +4, and indirect Coombs test +2. The patient was given two bags of washed PRC and corticosteroid Patient showed better outcome with increase of hemoglobin level after receiving transfusion.

Case 2

A 12-year-old girl was referred to RSCM in April 2019 with a chief complaint of general weakness 2 weeks prior to hospital admission. Five days before admission, the patient had a symptom of dark urine. There were no signs of bleeding elsewhere (hematemesis, epistaxis, or gum bleeding). The patient had normal food intake and showed no signs of fever. She was initially brought to hospital in Jakarta two days prior her referral; however, her transfusion was delayed because of the unavailability of washed PRC and doctor's reluctance to transfuse PRC.

On physical examination, blood pressure was 98/65mmHg,heartrate124beatspermin,respiratory rate 20 breaths per min, temperature 36.7°C, and oxygen saturation 98%. The patient had signs of anemia; however, other physical examination results were normal. Laboratory examination results showed a Hb level of 5.3 g/dL, Ht 12.6%, WBC 7,100/uL, and platelets 117,000/uL. RBCs were normocytic normochromic, anisopoikilocytosis, polychromic, and positive agglutination test with the impression of AIHA with thrombocytopenia. The patient was arranged to receive two bags of washed PRC and corticosteroid. Patient's hemoglobin level increased after transfusion and patient was discharged from hospital.

Discussion

From the two cases, we found that delayed transfusion in patients with severe anemia compromised their symptoms. As noticed, the hemoglobin level dropped after patients were referred. Currently, there is no standard transfusion management for AIHA patients, even some clinicians only using washed PRC to transfuse AIHA patients.

Autoimmune Hemolytic Anemia

AIHA is a disease characterized by the production of autoantibodies directed against antigens on the surface of RBCs and is often presented with severe and life-threatening anemia. Immune hemolytic anemia (IHA) occurs when antibodies of immunoglobulin G (IgG) and/or

immunoglobulin M (IgM) initiate an immune process via complement and reticuloendothelial systems to damage the RBCs. Based on the antigenic stimulus responsible for immune responses, IHA is classified as autoimmune, alloimmune, or drug induced. AIHA is characterized by the production of autoantibodies directed against antigens on the surface of RBCs.[4]

The classification of AIHA is based on the autoantibody isotype class and optimal temperature of reaction. From this characteristic, there are three main types of AIHA: warm AIHA (wAIHA), cold AIHA (cAIHA; cold agglutinin disease/CAD and paroxysmal cold hemoglobinuria/PCH), and mixed-type AIHA (mAIHA). Moreover, AIHA are classified in idiopathic (in which hemolysis occurs without any other coexisting disorder) and secondary forms (accompanying and complicating an underlying disease). AIHA can also be induced by drugs (drug induced AIHA), which occurs in an estimated 1:1,000,000.[5,6]

In wAIHA, the main type of antibody targeting the RBCs is polyclonal IgG, mainly IgG1 and less commonly IgG3.[5,7] This antibody has optimal reactivity with RBCs at a temperature of 37°C. These IgGs have an Fc portion that can activate macrophages and natural killer cells to induce hemolysis in RBCs (mainly extravascular in the spleen).[8] Intravascular hemolysis may also occur in IgM-mediated AIHA via the complement system. This can be detected by direct antibody testing (DAT) for C3. In this type of wAIHA, the symptom is usually severe and has a fatal outcome.[8] Complement system disorder found in systemic lupus erythematosus may also induce hemolysis of erythrocytes in wAIHA, which can also occur in other diseases that alter the functions of B and T cells such as in human immunodeficiency virus infection.[7]

There are two subtypes of cAIHA namely CAD and PCH.[5,8] In CAD, IgM and complement are the main immune system that induces hemolysis of RBCs. IgM in CAD is also called cold agglutinin antibody, which binds to erythrocytes at low temperature (0°C–4°C).[9] IgM binds with RBCs at low temperature and then attaches to the C3 protein to activate the complement cascade process intravascularly. Some of these RBCs also enter the reticuloendothelial system, where macrophages phagocyte some of these complement-coated RBCs and leave the rest of them to enter the bloodstream.[9,10] Another subtype of cAIHA is PCH, which is characterized by the presence of the Donath-Landsteiner antibody. This antibody attaches to RBCs, forms a complement complex at low temperature (around 4°C), and then actively completes the complement cascade at warm temperature (around 37°C).[11]

Another type of AIHA is mAIHA. In mAIHA, the DAT will be positive for both IgG and C3 like in wAIHA. However, the autoantibodies in mAIHA react to both warm (around 37°C) and cold (around 0°C–10°C) environments. Nevertheless, the temperature agglutination reactivity test needs to be measured to ensure the existence of both warm and cold temperature.[5,8]

The occurrence of underlying diseases, comorbidities, and the type and rate of hemolysis will determine the clinical features of AIHA.[12] The most common presenting complaint is anemia with occasional jaundice. Splenomegaly is also present in 20% of patients on physical examination.[5] The degree of anemia also varies; it can develop slowly with physiological compensation or have a fulminant onset with profound and life-threatening anemia.[5,12] In cases of patients with severe rapid onset, clinical symptoms may include fever, tachycardia, chest pain, and heart failure.[5]

Treatment of AIHA

Corticosteroids remain to be the first-line of treatment for wAIHA.[12,13] High initial doses are required; responses are often achieved slowly, and sustained remission following steroid weaning is only 15%–30%.13 For patients who are intolerant, unresponsive, and had multiple relapses with corticosteroids, second-line therapy should be considered. Splenectomy, combination of corticosteroid and rituximab are the most widely used second-line of treatment and have been shown to significantly increase response rate and duration.[12,14]

Cold AIHA is generally more insidious and mild and usually it only needs protection against exposure to cold temperature and occasional transfusion support during winter.[5,12] Treatment of patients with cAIHA should be reserved for patients with symptomatic anemia, transfusion dependance, or disabling circulatory symptoms. Rituximab is useful for acute symptomatic cases while chlorambucil and cyclophosphamide for more severe chronic cases.[5] Erythrocyte transfusions can be given safely in cAIHA, provided appropriate precautions are taken, such as keeping the infusion warm and avoiding blood products with high plasma content.[12]

Transfusing AIHA Patients

Transfusion in wAIHA is an important and complex issue because it can cause severe transfusion reactions.[13] All transfusions of AIHA patients should follow the standard protocol and perform the minimum tests required to infuse safe and least incompatible packed RBCs.[4] Compatible RBCs do not react with red cell antibodies in the patient's serum. However, in many AIHA patients, their autoantibodies react with all normal RBCs and might mask the presence of alloantibodies in a compatibility test, making it impossible to provide truly compatible blood.[15]

The minimum tests required for selecting an RBC donor are the DAT, antibody screen, and auto-control test.[4] The DAT is a standard procedure used to detect the presence of antibody (IgG) and or complement proteins (usually C3) bound to circulating RBCs in vivo. Usually, there is no specific autoantibody in the majority of wAIHA cases; therefore, another test besides DAT is needed to determine the specificity of autoantibody in these cases.[20]

The survival time of RBCs that are serologically incompatible because of autoantibody alone is similar to patient's autologous RBCs, except for cases with specific auto-antibody.[4,16] There has been a recommendation to ignore the specificity of antibody because it has not been proven that antigen-negative RBC transfusions will result in an increased RBC survival and has been demonstrated to be safe and effective in a number of transfusions.[12] However, transfusion of RBCs that possesses an antigen corresponding to alloantibodies that were obscured by autoantibodies may lead to increased hemolysis and worsening of the patient's clinical condition.[16]

Alloantibodies are developed because of previous transfusions or pregnancy and are capable of causing hemolytic transfusion reactions. Alloantibodies can be directed against antigens of a number of blood group systems, such as Rh, Kell, Kidd, and Duffy.[15] One of the major technical problems encountered in patients with wAIHA is related to the presence of RBC alloantibodies with autoantibodies. Undetected alloantibodies could be the cause of increased hemolysis following transfusion. A serological work-up to investigate the presence of RBC alloantibodies is needed.[17]

Several tests are available to detect alloantibodies in patients with warm autoantibodies. The most effective is the adsorption test that removes autoantibody from the patient's serum and allows for detection and identification of alloantibodies in the adsorbed serum.[15] However, weak alloantibodies may not be detected and incomplete adsorption and autoantibodies mimicking alloantibodies may cause interpretation problems.[16] Extensive RBC phenotyping of the patient and donor unit are not widely implemented in transfusion services. Extended phenotyping against numerous RBC antigens can determine which alloantibodies a patient could develop because of previous transfusion or pregnancy. Transfusions that are selected based on this test can provide a significant measure of safety. Another simple test is diluting the patient's serum before doing compatibility testing.[15]

Transfusion in wAIHA can often cause pan-agglutination of donor's RBCs so no true cross-matching is possible. However, transfusion can often be safely administered if alloantibodies are excluded.[18] In cases of urgent administration, ABO-matched and Rh-matched RBCs can be safely administered if alloantibodies are reasonably excluded based on the previous transfusion and pregnancy history.[12] The probability of developing alloantibodies in patients who have not been transfused or pregnant is very low, so in critical cases, transfusions should not be avoided or delayed because of uncertainty in matching.[12,15] Adequate testing for alloantibodies may take several hours (usually 4–6 h) to be completed, so in urgent cases and seriously ill patient, physicians must balance the risk of withholding transfusion and the possible benefit of correcting Hb level.[15,17]

Washing of RBCs is done for a variety of reasons, such as to remove excess electrolyte, allergens, and cytokines and or to prevent the effects of storage lesion. The washing process will remove 95%–99% of RBC supernatant, which contains plasma proteins, electrolytes, WBCs, platelets, cellular debris, etc. It is performed in an open or closed system using normal saline solution. Washed PRC are indicated for patients with IgA deficiency, prevention of allergic reactions not sensitive to antihistamine drugs, and post-transfusion febrile reactions that were present even when using leukodepleted RBCs are used. [19]

Universal leukoreduction has many benefits including reduced febrile nonhemolytic transfusion reactions, decreased platelet refractoriness caused by alloimmunization against leukocyte antigens, decreased transmission of cytomegalovirus, and decreased postoperative infections.[19] The primary cause of febrile nonhemolytic transfusion reactions is

cytokines produced by WBCs. Although the washing process can decrease WBCs, there are still some WBCs remaining in the blood products and WBC-derived cytokines increase as the blood product age.[19]

PRC washing is not widely available in many small-sized or medium-sized hospitals and blood banks. It is also not practical since it can take 1.5–2 h to complete the washing process. These disadvantages can cause delay of RBC availability in emergency cases and transfusion protocols.[2]

In cAIHA, the presence of the complement system in the exogenous donor plasma could induce hemolysis. Transfusion of washed PRC using a blood warmer or keeping the patients warm will reduce the risk of hemolysis during transfusion.[4] After transfusing one unit of washed PRC in an adult or 10 mL/kg in children, the symptoms should be assessed to ensure improvement in patient's condition.[20] Overtransfusion should be avoided for hemodynamic reasons. Transfusion also needs to be administered slowly and when possible, not exceeding 1 mL/kg/h.[12] Leukodepleted RBCs can be used to minimize the risk of febrile nonhemolytic reactions due to anti-leukocyte antibodies.[12]

A study conducted to evaluate the efficiency rate of RBC transfusion between washed and unwashed showed no significant differences. The efficiency rates for washed and unwashed PRC are 57.6% and 53.6%, respectively, without any significant difference.[20] RBC transfusion is not contraindicated in AIHA and is considered safe for the same ABO type. Blood transfusion in AIHA patients with severe anemia is needed to maintain their Hb at a clinically acceptable level.[17] There has been a lack of evidence for transfusion guidelines in AIHA patients; therefore, no specific Hb threshold can be recommended. Physicians should not feel obligated to transfuse based on the Hb value specified by any guideline. Instead, they should evaluate the patients' symptoms and risk factors. The decision for blood transfusion is mainly based on the severity of the hemolysis (presence of hemoglobinuria or hemoglobinemia), the progression of anemia, and the associated clinical findings and comorbidities (ischemic heart or severe pulmonary disease).[16,20]

Conclusion

From this case and review, we can conclude that RBC transfusion for AIHA patients, particularly in patients with severe anemia and threatening conditions, could be accepted as early treatment. Delayed transfusion may result in severe complications, compromise patient's prognosis, and even death.

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