International Journal of Science and Healthcare Research
Vol.5; Issue: 2; April-June 2020
Website: ijshr.com
Review Article *ISSN: 2455-7587*

Blood Transfusion in Auto-Immune Haemolytic Anaemia

Eswara Prasad Chennamsetty[1], Daljit Kaur[1], Gita Negi[1], Ranjan Mukherjee[1], Anju R Kurup[1], Sudheer Tale[2]

[1]Department of Transfusion Medicine, All India Institute of Medical Sciences, Rishikesh
[2]Department of Pulmonary Medicine, All India Institute of Medical Sciences, Rishikesh

Corresponding Author: Eswara Prasad Chennamsetty

ABSTRACT

Auto-immune haemolytic anaemia (AIHA) is an immune disease associated with red cell destruction. Transfusion support may be needed to support the anaemia as a result of haemolysis while steroids and other therapies become effective. Autoantibody which reacts with normal red cells pose challenge to identify a compatible unit for transfusion. Prophylactically phenotype matched units are safe for transfusion, but phenotype of the patient is seldom available. It is essential to evaluate for presence of allo-antibody before transfusion and the masking nature of autoantibody makes it more challenging in its identification. Auto- and allo-adsorption can be used if there is enough time available before the patient needs transfusion. Dilution technique can be handy to provide a red cell unit if there is little or no time available for transfusion. Although, transfusion in a case of AIHA comes with risk of reduced survival of red cells post transfusion, often it can be life-saving.

Key Words: Auto-immune haemolytic anaemia, Transfusion, Auto-adsorption, Allo-adsorption, Dilution Technique

INTRODUCTION

Auto-immune haemolytic anaemia (AIHA) is an acquired disease of immune system, where auto-antibodies attack self-red cells of individual & remove them from circulation either by complement mediated intravascular destruction or phagocytosis by splenic macrophages. [1] Gabriel Andral (1843) described AIHA as "Spontaneous anaemia without prior blood loss", which was further expanded to "destruction of what is present in blood" by Vogel (1853), linking AIHA to red colour urine. [2] Classification, incidence and age distribution of AIHA is described in Table 1. [3]

Laboratory Evaluation of AIHA:

Anaemia without blood loss, with raised reticulocyte count, serum bilirubin, serum lactate dehydrogenase is suggestive of haemolysis as a cause for decreased oxygen carrying capacity. [1] Haemolytic picture associated with positive direct anti-globulin test (DAT) is diagnostic of AIHA, with 83% positive predictive value. [4]

Transfusion Triggers In AIHA:

Transfusion requirement inAIHA varies with severity of presentation. Chronic anaemia due to low grade haemolysis may not require transfusion unless the patient is symptomatic. Fever, malaise and pain in abdomen, back and legs associated with haemoglobinemia and haemoglobinuria are suggestive of severe haemolysis that would require an urgent transfusion. [5] A pre-transfusion haemoglobin of less than 5g/dl is considered a trigger for transfusion with red cells. [6]

Transfusion although is life-saving in a case of AIHA, it is associated with risks due to immunological incompatibility with patient's auto- or allo-antibody. This is because auto-antibodies usually react with all normal red cells, making it impossible to obtain a packed red cells unit that is clearly

compatible with patient's serum. Survival of such incompatible red cells post-transfusion is comparable to autologous red cells and may cause only a temporary benefit. [7] Also, transfusion with such incompatible red cells may rarely result in acute renal failure, disseminated intravascular coagulation or post transfusion haemoglobinuria. [8]

A case of chronic AIHA who previously had blood transfusion or a previously pregnant woman may be at a risk of allo-antibody. In about 12-40% of cases of AIHA a clinically significant allo-antibody is identified. It is crucial to identify the presence of such allo-antibodies as they can be clinically significant. Such allo-antibodies may result in acute haemolytic transfusion reaction if transfused with antigen positive red cells. [9,10]

Finding a compatible red cell unit for transfusion in a patient with warm AIHA (WAIHA) is one of the most difficult tasks faced in a blood transfusion laboratory. This is because the autoantibody tends to react with all normal red cells.

Table 1: Classification, incidence and age distribution of AIHA

1. Warm auto-immune haemolytic anaemia (WAIHA) Most common; 80% of all AIHA Incidence: 1-3 cases/one lakh population/year Females are most commonly affected with median age of 49 years i. Primary: idiopathic ii. Secondary: a. Malignancies- leukaemia, lymphoma, ovarian tumours b. Auto-immune or connective tissue disorders (SLE) c. Immunodeficiency states d. Infections- HIV
2. Cold AIHA i. Cold agglutinin disease i. Primary: Idiopathic 15-25% of all AIHA Females in 70s are most common affected ii. Secondary: B-Cell Neoplasms Mycoplasma Pneumonia Infectious Mononucleosis ii. Paroxysmal cold haemoglobinuria i. Primary: Idiopathic Incidence: 1-10 cases/one million population Median age is 30 years with female preponderance ii. Secondary: Tertiary syphilis Upper respiratory infection of viral origin
3. Drug Induced AIHA I. Drug adsorption mechanism: Penicillin II. Immune complex mechanism: Quinidine III. Auto-immune induction mechanism:α-Methyldopa

Phenotype Matching:

Prophylactically antigen matched (PAM) red cells are phenotype matched units that provide significant immunological safety for transfusion. [11] So, it is essential to obtain any document that mentions the extended phenotype of the patient before beginning for cross-match testing. This is because, phenotyping is impossible after the patient had any recent transfusions (within last 3 months) and difficulties in phenotyping as some antisera require testing at anti-human globulin phase, which is not possible on red cells that are already DAT positive. Micro-haematocrit method and age-fractionation are techniques that can be used to separate autologous reticulocyte red cells from transfused cells. [12,13] Cells that are separated can be used to obtain the phenotype of patient and for transfusing red cells that are phenotype matched.

Allo-Antibodies:

It is prudent to identify the allo-antibody if any, before giving transfusion of red cells that are either cross-match compatible or phenotype matched. This prevents acute and delayed haemolytic transfusion reactions. It begins with performing an indirect anti-globulin test (IAT). A positive IAT in a case of AIHA does not indicate the presence of allo-antibody as it can be due to spill-over of autoantibody after saturation of all available red cells antigens. Grades of reaction between DAT and IAT can be compared to predict the presence of allo-antibody. If the grade of IAT is more than that of DAT, the presence of allo-antibody along with autoantibody is strongly suspected. [14]

Although serum of AIHA patient reacts positively with all cells in a cell panel due to autoantibody, if a varying grade of reaction due to weakly reacting autoantibody and strongly reacting allo-antibody is forming a pattern, identification of specificity is still possible. Identifying an allo-antibody is not always possible in the presence of an autoantibody. Adsorption to remove autoantibody that is interfering with identification of allo-antibody is done either

by using either autologous cells (auto-adsorption) or allogenic cells (allo-adsorption). Auto-adsorption is optimal method for detection of allo-antibodies as it adsorbs autoantibody and leaves allo-antibody with an advantage of adsorption with only one sample of red cells requiring only less amount of serum. [14] Incubating autoantibody coated autologous cells may not be efficient during auto-adsorption for obtaining autoantibody free serum. Dissociating IgG antibodies coated on the red cells may increase the uptake of free autoantibody in the serum during incubation process. For this purpose, ZZAP reagent treated red cells can be used. ZZAP consists of 0.1M dithiothreitol (DTT) and 0.1% cysteine activated papain or 0.1% ficin. [10] Adsorbed serum (either auto- or allo-adsorbed) is used for antibody identification.

Once the specificity of the antibody is identified, it is essential to determine the corresponding antigen negative status for the patient. Unless the patient is not transfused in last three months and phenotyping does not require testing at anti-human globulin phase, antigen typing does not require additional testing except for using specific antisera. For those with history of transfusion in last three months, separating reticulocytes by micro-haematocrit method is helpful. For those antigens that require phenotyping at anti-human globulin phase, a gentle heat elution or elution by chloroquine di-phosphate that remove autoantibodies to leave red cells uncoated may be helpful. [15] Antigen negative status for the corresponding antibody specificity would confirm it as an allo-antibody.

Often the specificity of autoantibody may mimic that of allo-antibody and even the phenotyping of autologous may corroborate for same as there would temporary suppression in antigen expression for the period of acute phase of disease. [16] The only way to determine such occurrence is comparing the current phenotype with historical phenotype of the patient or preserving the current red cells and comparing their phenotype with cells obtained once the disease is resolved. Most common specificities identified were of Rh, particularly towards 'e'. [17]

Once the specificity of allo-antibody is determined, a red cell unit that is antigen negative for identified specificity is selected and cross-matched. Cross-match may be incompatible due to autoantibody reactivity and this still can be used for transfusion.

Transfusion in Emergency:

In a case of severe or fulminant AIHA there is often little or no time available for elaborate serological workup to evaluate allo-antibody before providing red cells for transfusion. In such cases selection of "least incompatible unit" is practiced in some centres. It is based on the assumption that presence of allo-antibody gives a more positive reaction when compared with presence of only autoantibody. [1]

Dilution technique proposed by Petz & Garratty can be used instead of using a least incompatible unit, as this technique is less time consuming and had been reliable in predicting the presence of allo-antibody. It is based on the assumption that allo-antibody in the presence of an autoantibody will have higher titres. Selecting a highest dilution of serum that reacts with 1+ reaction in IAT and using to identify on cell panel may help in detecting potential clinically significant allo-antibodies. [14,18]

In-Vivo Compatibility:

This can be an additional investigation of compatibility or it can be used when elaborate testing for compatible red cell identification could not be performed due to time or resource constraints. Small amount of red cells, about 10-20 ml are injected intravascular to the patient. A sample is withdrawn after about 10 minutes to check for red discoloration of supernatant or quantitatively measure plasma free haemoglobin for determination of kinetics of haemolysis. [1,19]

Volume of Transfusion:

It is vital to understand that transfusion is not the primary treatment for AIHA and it is used to support the patient for hypoxiaduring recovery. Patient may be elderly or having a chronic anaemia with cardio-pulmonary decompensation which may not tolerate high volume of transfusion. So the volume to be transfused depends on the amount that would alleviate symptoms of anaemia and hypoxemia. It is advised to transfuse as little as 100ml per transfusion episode, if requires two episodes of such transfusions per day. [20]

Monitoring of Transfusion:

Either PAM or red cell unit that is antigen matched for allo-antibody, transfusion should be at slower rate due to the possibility of haemolytic reaction as all normal red cells would react against autoantibody. Based on the patient specific kinetics of haemolysis, a rapid transfusion may result in severe side effects such as renal failure due to haemoglobinuria and disseminated intravascular coagulation. [20,21]

If not previously started, either corticosteroids or intravenous immunoglobulin therapy should be given along with transfusion to prevent adverse events if any due to autoantibody. [22]

Follow-up for Transfusion:

By calculating reticulocyte production index, life span of red cells can be determined and this will predict the possibility for next transfusion and if required, estimate of when and what volume of transfusion that may be required. [23]

CONCLUSION

Transfusion support in AIHA is life-saving, if not bridging therapy for those who are waiting for response from steroids or other immunosuppressant therapy. Providing a compatible unit is often a huge task owing to complexities in battery of tests that are required. So it is essential to determine the urgency of transfusion such that, what and how to proceed is determined to provide transfusion in stipulated time.

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How to cite this article: Chennamsetty EP, Kaur D, Negi G et.al. Blood transfusion in auto-immune haemolytic anaemia. International Journal of Science & Healthcare Research. 2020; 5(2): 258-262.

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