

Prevention of adverse reactions: Journey from blood safety to transfusion safety

Sadhana Mangwana

Transfusion therapy is the main treatment for patients with trauma, severe hemoglobinopathies and cancer patients. Transfusion of blood products has its own risks causing immediate and delayed adverse reactions. Complications such as transfusion transmitted infectious diseases (TTIDs), antibody formation to red and white cells, and preformed cytokines result in immediate and delayed adverse reactions and health consequences to transfusion recipients. Delayed adverse reactions develop days, months or years after administration of blood and blood products. There have been many advances in technologies and transfusion strategies to decrease the risk of transfusion reactions, yet transfusion services continue to pursue massive efforts to prevent infectious and non-infectious complications associated with blood transfusion. A large number of safety changes have been implemented to improve blood safety. Recently, a large attention has been focused by Transfusion Medicine community to decrease TTIDs for HIV/HBV/HCV through extensive donor questionnaires, infectious disease testing and introduction of Nucleic Acid testing (NAT) resulting in success in reducing risks of TTIDs.

BLOOD SAFETY IMPROVEMENTS

Bacterial contamination risk reduction

Transfusion-related microbial infections range from a mild, transient temperature increase to acute lung injury, fulminant septic shock and death. Blood collection centers have implemented a combination of techniques to reduce the risk of microbial contamination in the final

blood product, including improved disinfection methods for the venipuncture site, introduction of the diversion pouch during the blood collection procedure and automated bacterial culture of platelet products, as well as platelet additive solutions and PR systems. The leading sources of blood product contamination are skin bacteria from the venipuncture site during the blood collection procedure. Use of povidone iodine or isopropyl alcohol plus iodine tincture for disinfection has proved to reduce skin infections by 50%.

The diversion pouch is attached to the blood product collection set and collects initial few milliliters of whole blood, including any potential skin plug within the access needle, thus diverting the contaminating skin bacteria away from the final blood product container.

Storage of platelet products at room temperature up to five days make them more susceptible to bacterial growth. Combination of skin disinfection with iodine-containing solutions and use of diversion pouch effectively decreases the risk of bacterial contamination in platelet products. In 2004, American Association of Blood Banks (AABB) has recommended testing of 100% platelet products for bacterial contamination [1]. Combination of culture and rapid screening tests can be best risk reduction strategy for platelet transfusion-related septic reactions.

Prestorage leucoreduction

The immediate adverse reactions, most common but less severe, are Febrile Non Hemolytic Transfusion Reactions (FNHTRs) and allergic reactions. FNHTR is defined as an increase in temperature of $\geq 1^{\circ}\text{C}$ from the baseline value. The use of pre-storage leucoreduction, bedside use of filters for red blood cells to residual plasma proteins will add further to reduce incidence of reactions. Introduction of pre-storage leucoreduction in the transfusion medicine and immunohematology has helped further in reduction of FNHTRs.

Efforts to mitigate TRALI

Transfusion Related Acute Lung Injury (TRALI) is a severe transfusion reaction characterized by the acute onset of non-cardiogenic pulmonary edema occurring within six hours of transfusion which result from formation of antibodies between recipient human

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Received: 30 April 2019

Published: 13 June 2019

leukocyte antigens (HLA) on white blood cells and HLA antibodies in donor plasma. The prevalence of HLA antibodies in female donors is related to the number of prior pregnancies since females who have been pregnant and exposed to fetal white blood cells are most likely to develop HLA antibodies [2]. In 2014, AABB recommended that “plasma and whole blood for allogeneic transfusion shall be from males, females who have not been pregnant, or females who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies” [1]. Therefore, blood collection facilities have two options: either perform HLA antibody screening on all female donors whose plasma would be used for transfusion, irrespective of pregnancy history or target HLA antibody testing for any female who has had any number of pregnancies carried to term or delivered. Although there has been some evidence suggesting Human Neutrophil Antigen (HNA) antibodies play a role in the development of TRALI, and since HLA antibody co-occurs in the majority of HNA antibody-positive donors suggests HNA-positive blood products may already be reduced as a consequence of HLA antibody screening [3].

Pathogen reduction technologies

There have been risk of sepsis due to bacterial contamination and unknown pathogens which are being addressed through Pathogen Reduction (PR) techniques. The aim of pathogen reduction is zero risk from existing and emerging pathogens in blood products. These technologies use solvent and detergent, psoralen compound, amotosalen, methylene blue or riboflavin with ultraviolet (UV) light to make pathogens non-infectious. They are being used in European countries from last 10 years.

Potential benefits of PR include reducing risk of current transfusion transmitted infections to nearly zero. There is evidence that PR for platelets and plasma inactivates most pathogens with additional benefits of prevention of Transfusion Associated Graft-versus-host disease (TA-GVHD), prevention of cytomegalovirus (CMV) disease transmission and possible reduction of alloimmunization due to inactivation of white blood cells remaining in blood products [3]. At the same time, PR technology has some barriers also namely increased cost, toxicity, negative effects on platelet function and count, acute respiratory distress syndrome (ARDS) and increased risk of bleeding. Although current PR technologies are effective in preventing bleeding and adverse events in transfusion recipients, further studies are required to ensure PR blood products' efficacy and safety.

Platelet additive solutions (PAS)

Reducing the volume of plasma in platelets has been shown to decrease the incidence of some transfusion reactions [4]. Platelet additive solutions (PAS) are isotonic solutions commonly used as a substitute for

plasma to reduce the amount of plasma transfused with platelets, and thus reduced transfusion adverse events, to provide the possibility for pathogen inactivation using photochemical treatment and offers the possibility of adding certain components to improve platelet storage conditions. The use of PAS replaces 65% of plasma including plasma proteins and isohemagglutinins [5]. PAS is an available option to prevent transfusion adverse reactions specially TRALI in cases of platelet transfusion.

SAFE TRANSFUSION PRACTICES

Now focus is changing from blood safety to transfusion safety and new interventions are being studied by transfusion medicine experts to improve the safe delivery of blood to patients. There is need to ensure that patients get blood only when required, that they get the correct product of the correct blood group, at the right dose, at the appropriate infusion rate, to the correct patient, at the right time.

Accurate patient identification is one of the critical steps in the performance of these and other procedures. Transfusion of blood to the wrong patient is an important, avoidable, serious hazard of transfusion resulting from errors made at any step in the transfusion process, from blood sample collection, transportation, laboratory sample testing, blood retrieval from blood transfusion refrigerators and during the blood sample collection from bedside just prior to transfusion.

To improve hemovigilance procedures, measures are targeted to both recipients and blood components. The implementation of procedures aimed at unequivocal identification of patient and assigned blood components like active recognition of patient, identification wrist bands, and biometric parameters are fundamental to prevent ABO transfusion errors which are the most feared fatal complications [6, 7].

Radio frequency identification

Transition to bar-coding and Radio Frequency Identification (RFID) scanning will be the most important, first step of getting the right patient with the correct identification band. The implementation of RFID in transfusion medicine offers many benefits. RFID allows for accurate identification of blood products and recipient, eliminate transfusion error due to patient mis-identification to long-term savings and increased productivity. At the same time, RFID technology has specific concerns regarding security and patient confidentiality [8].

Irregular antibody screening and identification and extended phenotyping

Presence of antibodies, auto antibodies, allo antibodies or both complicates pre-transfusion and compatibility

testing and auto-antibodies poses difficulties in detection of alloantibodies by pan reactivity. The blood banks provide only ABO- and Rh (D) - antigens matched blood, which increases risk of alloimmunization to minor blood group antigens. Majority of these alloantibodies are of Rh blood group specificity, extended antigen matching (C, E, c, e, K) which can prevent RBC alloimmunization to great extent. Patients who have WAAs in their serum have a higher rate of alloimmunization. Monitoring of evidence of RBC destruction due to alloantibodies is difficult in patients, who already have AIHA [9]. It is vital to detect the appearance of new alloantibodies or disappearance of old alloantibodies to prevent hemolytic transfusion reaction during or after allogeneic transfusion. Regular screening for the development of allo-antibodies in multi-transfused patients and providing leucoreduced, Rh-phenotyped and antigen-matched blood would add towards the better management of patients. Prevention of RBC allo-antibody formation in multi transfused patients extends their life expectancy and reduces the need of blood transfusion.

Formulation and adherence to standard operating procedures and protocols

Another important aspect in successful completion of transfusion is the adherence to SOPs. Transfusion Medicine specialists should ensure that Standard Operating Procedures (SOPs) are regularly updated and validated by competent authority. Efforts should be made to ensure compliance to SOPs in maintaining turnaround time (TAT), maintaining component storage temperatures and maintaining transfusion times (start to finish) for respective blood components.

To improve the safety of transfusion, it is important to develop risk reduction protocol and set of corrective measures need to develop in close coordination with clinicians, transfusion medicine specialists and hospital administration. List of corrective measures are termed as “Plan, Do, Check, Act (PDCA)”. The “Plan” represents the identification and analysis of potential failures. The “Do” appears for developing potential solutions. The “Check” ensures testing the efficacy of each measure, and the “Act” appears for the timely and complete implementation of the corrective measures [10].

Audit and education

Predetermined transfusion guidelines and transfusion audits are useful tools in the education of all the stakeholders involved in transfusion practices. Clinical audit is a management tool for the appraisal and justification of appropriateness and efficiency of transfusion therapy. Audit is an important part of the quality assurance program, which provides patient’s information for improving transfusion medicine practice. Prospective auditing of case files, transfusion practices, protocols adherence and organizing Continued Medical Education programmes regarding the transfusion

services for all the stakeholders in the transfusion chain including doctors, nurses, phlebotomists, technicians and transporters have major role in improvement for the clinical transfusion practices in the hospitals.

Blood transfusion centers should have a proactive role in promoting good transfusion practice in hospitals as well as supplying blood components and specialist services. This role may be indirect in providing education and training, support for developing guidelines and auditing practice, and the means for sharing experience [11]. Transfusion service can thus reduce transfusion reactions and increase patient safety through a variety of means ranging from physician education, to implementation of best practice.

Transfusion medicine specialists have been successful in achieving great progress in blood safety and now it is time for improvements in transfusion safety by focusing on various processes and practices related to safe transfusions of blood and blood components.

Keywords: Blood, Transfusion, Transfusion risk reduction, Transfusion Adverse Reactions, Transfusion Safety, TRALI

How to cite this article

Mangwana S. Prevention of adverse reactions: Journey from blood safety to transfusion safety. Int J Blood Transfus Immunohematol 2019;9:100044Z02SM2019.

Article ID: 100044Z02SM2019

doi: 10.5348/100044Z02SM2019ED

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Author Contributions

Sadhana Mangwana – Conception of the work, Design of the work, Acquisition of data, Analysis of data,

Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Conflict of Interest

Author declares no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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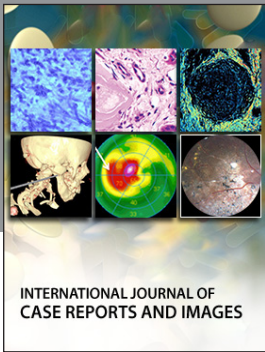
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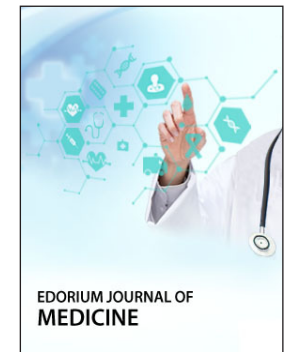
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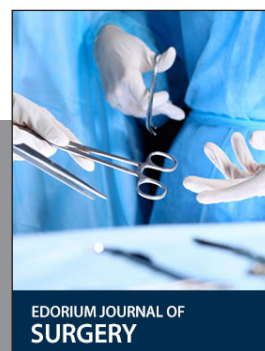
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