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## **REVIEW ARTICLE**

# Hemovigilance and Blood Safety: A Review

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## ABSTRACT

Blood transfusion has certain risks, and any unfavorable event occurring in a patient during or after transfusion, for which no other reason can be found, is called a transfusion reaction. These untoward effects vary from being relatively mild to severe and require rapid recognition and management. Transfusion services rely on transfusion reaction reporting to provide patient care and protect the blood supply. Unnecessary discontinuation of blood is a major wastage of scarce blood, as well as man, hours, and funds. Although strict procedures are applied during blood donations preparations and transfusions, errors in transfusion and infection complications still serve a problem in clinical practice. Hemovigilance is intended for the detection and analyzing all untoward effects of blood transfusion to correct their cause and prevent recurrence. In this review, we will discuss hemovigilance and transfusion-related adverse events.

Keywords: Adverse events, blood transfusion, hemovigilance

## **INTRODUCTION**

Blood transfusion is an indispensable component of clinical medicine.<sup>[1]</sup> Transfusion of blood and blood components is often required with the objective of improving the blood counts and clinical condition of the patient.<sup>[2]</sup> It is an event which carries potential advantages as well as risks to the recipient. Any adverse event that results in a patient during or after transfusion of blood and blood products and for which no other cause can be found is called as a transfusion reaction.<sup>[3]</sup> These adverse events may be infectious or noninfectious in nature. With the improvements in donor screening and infectious diseases testing, the risk of infectious complications has declined in the past few decades. However, the risks of non-infectious complications have become more apparent. These non-infectious complications can occur rapidly after transfusion (acute) or many days or weeks after transfusion (delayed).<sup>[2]</sup> Acute transfusion reactions (ATRs) occur within 24 h of administration of transfusion, and most of them

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occurs within the first 4 h. Acute hemolytic reaction, febrile non-hemolytic reaction, allergic reaction, volume overload, bacterial contamination, and isolated hypotension are the most common experienced ATRs.<sup>[4]</sup>

Hemovigilance encompasses a set of surveillance procedures covering the whole transfusion chain, aimed at collection and assessing information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products and to prevent their occurrence or recurrence.<sup>[5]</sup> Hemovigilance consists of reporting all complications related to transfusion. The aim is to have a system of surveillance so that the risks associated with the transfusion can be identified along with causes and these can be avoided in future.<sup>[6]</sup>

## **Background of hemovigilance**

Hemovigilance as safety concept appeared in the beginning of the 1990s. It was initially developed by the French Blood Agency as a national system of surveillance and alert, from blood collection to the follow-up of the recipients.<sup>[7]</sup> Since then, such systems have identified issues requiring attention and helped improve blood product safety and transfusion processes. It has been implemented in many countries with numerous significant differences in field of blood transfusion, different definitions, goals, organizational schemes, and report systems. As a result, there is no simple and universal concept for hemovigilance.<sup>[8,9]</sup>

Most of the advanced countries such as Denmark, Ireland, Netherland, and Canada have a voluntary reporting necessity. Hemovigilance programs in these countries are connected to International Haemovigilance Network (IHN) which presently has 28 members.<sup>[10]</sup> The European Union state members ought to implement hemovigilance program with reporting to a central office as per the commission directive.<sup>[11,12]</sup> Within the Asian countries, a well-established hemovigilance system is missing, except for Japan, which has published a report on adverse reactions.<sup>[13]</sup>

In 1990s to address global concerns about the availability, safety, and accessibility of blood transfusion, the WHO global database on blood safety was established. The aim of these activities was to collect and analyze data from all countries on blood and blood product safety on the basis for effective action to improve blood transfusion services globally. To achieve this, a hemovigilance system is required in every country to have a well-rounded approach to tackle the issue of transfusion reaction following administration of blood and blood products.<sup>[14]</sup>

# National Haemovigilance Programme of India (HvPI)

HvPI was launched on 10<sup>th</sup> December 2012 by Indian Pharmacopoeia Commission in association with National Institute of Biologicals, Noida, Uttar Pradesh, across the country under its Pharmacovigilance Programme of India. Hemovigilance program has been launched with the following aims:

- To monitor transfusion reaction
- To create awareness among health-care professionals
- To generate evidence-based recommendation
- To communicate findings to all key stakeholders
- To create national and international linkages
- Advising Central Drugs Standard Control Organization for safety-related regulatory decisions.

To collect and collate the data pertaining to all over the country, a software "hemovigil" has been developed. Program has already enrolled 117 medical colleges and hospitals in India. The coordinating center for HvPI is National Institute of Biologicals and it collates and analyzes data with respect to biological and hemovigilance. A core group and advisory committee in this regard have already been constituted, and the first meeting of advisory committee was held on 29 November 2012 to finalize Haemovigilance Transfusion Reaction Reporting Form and Guidance Document. The ultimate goal of this HvPI is to be a part of the IHN, which presently has 28 countries as its members and provide a global forum for sharing best practices and benchmark of hemovigilance data.<sup>[15]</sup>

# **Reports on transfusion reactions**

Study has shown that only 0.13% transfusion reactions were reported, points to the lack of regular reporting of transfusion reactions. In a study carried out at the Department of Clinical Transfusion of the Service for Blood Transfusion of Vojvodina in Novi Sad., of 180 reported hospital reactions, 98 (54.4%) were febrile non-hemolytic transfusion reactions, 69 (38.3%) allergic reactions, and 2 (1.11%) hemolytic reactions. Blood components that caused most of the transfusion reactions were erythrocytes (62.4%), fresh frozen plasma (11.2%), and platelets (14.4%). The estimates of the incidence of adverse event in blood donors based on other reported informational studies range considerably from 5% to 33%.<sup>[16,17]</sup>

However, there have been very few published studies addressing ATRs in resource-limited settings, in general, and in sub-Saharan Africa in particular and those that are available report extremely different results. In retrospective studies from Uganda and Ghana, transfusion reactions were recorded for 0.6% and 0.8% of patients who received transfusions, respectively, while the investigators of prospective studies performed in Nigeria and Cameroon reported that ATRs occurred in, respectively, 8.7 and more than 50% of transfusions.<sup>[18-21]</sup>

Various studies have been carried out in India also, such as, in Punjab, where the incidence of ATRs was found to be 1.09%.<sup>[22]</sup> Two larger studies done in New Delhi and Chandigarh, however, showed a relatively lower frequency of transfusion reactions (0.05% and 0.18%, respectively).<sup>[23,24]</sup>

#### Possible risks of blood transfusion

With the improvements in donor screening and infectious disease testing, the risk of infectious complications has declined in the last few decades. However, the risks of non-infectious complications have become more apparent.<sup>[2]</sup>

#### Acute hemolytic transfusion reactions (AHTRs)

AHTRs is one in which symptoms and clinical or laboratory signs of increased red cell destruction are produced by transfusion. In AHTRs symptoms appear within minutes after starting the transfusion, common laboratory features are hemoglobinemia, hemoglobinuria, decreased serum haptoglobin, unconjugated hyperbilirubinemia, increased lactate dehydrogenase and serum glutamic-oxaloacetic transaminase levels, and decreased hemoglobin. interaction of recipient's performed The antibodies with donor's red cell antigens resulting in immediate destruction of the transfused red cells is the immunologic basis for AHTRs. Rarely transfusion of ABO-incompatible plasma (e.g., ABO mismatch platelet transfusion) can cause hemolysis of the patient's red cells, especially if donors have high titer of ABO antibodies. AHTRs and related mortality have been reported to occur at approximately 1 in 76,000 and 1 in 1.8 million units transfused, respectively.<sup>[3]</sup>

# Febrile non-hemolytic transfusion reactions (FNHTRs)

FNHTRs are characterized by an otherwise unexplained rise in temperature of at least 1°C during or shortly after transfusion. Antipyretic pre-medications may mask a fever, but they do not usually prevent chills and rigors, which are due to cytokine-mediated systemic inflammatory response. Other causes of fever should be excluded before making a diagnosis of FNHTR. FNHTRs are seen more often after transfusion of platelets (up to 30% of platelet transfusions) than red blood cells (RBCs) because platelets are stored at room temperature, which promotes leukocyte activation and cytokine accumulation.<sup>[25]</sup> Patients who have had febrile reactions or who are at risk for them are usually given blood products

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that are leukoreduced. This means that the white blood cells have been removed by filters or other means.<sup>[26]</sup>

### Allergic reactions

Symptoms may either occur within seconds or minutes of the start of transfusion or may take several hours to develop. This is the most common reaction. It happens during the transfusion when the body reacts to plasma proteins or other substances in the donated blood. Usually, the only symptoms are hives and itching, which can be treated with antihistamines such as diphenhydramine.<sup>[26]</sup>

#### Urticaria

Urticaria is the mildest form of an allergic reaction that appears suddenly, usually causes itching, and can last for hours or up to several days before fading. More extensive cases may be accompanied by angioedema. The incidence of uticaria is 1-3%.<sup>[3,25,27,28]</sup> Once the symptoms subside, the transfusion may be resumed. Severe reactions may be managed with methylprednisolone (125 mg intravenously) or prednisone (50 mg orally).<sup>[26]</sup>

#### Anaphylaxis

Anaphylaxis is a more severe form of an allergic reaction with an incidence of 1:20,000–1:50,000 transfusions,<sup>[29]</sup> in which severe hypotension, shock, and loss of consciousness may occur.<sup>[30]</sup> Anaphylaxis is commonly seen in IgA deficient recipients where it is caused by antibodies against donor IgA. Patient antibodies against haptoglobin penicillin, the C4 determinant of complement, and ethylene oxide have all been implicated in the causation.<sup>[31]</sup> The term "anaphylactoid" is used for reactions with symptoms similar to anaphylaxis but which are not mediated by IgE. If the patient is unconscious or in shock, injection adrenaline may be given intravenously with cardiac monitoring.<sup>[32]</sup>

## Transfusion-related acute lung injury (TRALI)

TRALI is very serious transfusion reaction but very rare. It can occur with any type of transfusion, but those which contain more plasma, such as fresh frozen plasma or platelets, seem more likely to cause it. It usually begins within 1–2 h of starting the transfusion but can occur anytime up to 6 h after a transfusion. There is also a delayed TRALI syndrome, which can start up to 72 h after the transfusion is given. Mostly trouble breathing is symptom of TRALI, which can lead to lifethreatening condition. If TRALI is suspected during the transfusion, the transfusion should be stopped at once. Physicians now believe that several factors are involved in this illness, and medicines do not seem to help. Many of the patients who suffer from TRALI have had recent surgery, trauma, cancer treatment, transfusions, or have an active infection. In most cases, TRALI goes away within 2 or 3 days if breathing and blood pressure are supported, but even with support, it is dangerous in 5-10% of cases. TRALI is more likely to be deadly if the patient was already very ill before the transfusion. Most often a patient will require oxygen, fluids, and sometimes support with a breathing machine. If a patient who has had TRALI needs RBCs, doctors may try to prevent future problems by removing most of the plasma from the RBCs using a diluted salt water solution. Researchers are working on other ways to lessen the risk with careful donor selection and testing.<sup>[33,34]</sup> The lung injury in TRALI is most often transient, and approximately 80% of affected patients will improve within 48-96 h.[3]

## Transfusion-related sepsis

Although uncommon, transfusion-related sepsis can be fatal. The diagnosis is based on the presence of at least one of the clinical features: (1) Fever, (2) tachycardia, (3) shaking chills, and (4) change in systolic blood pressure within 90 min of transfusion.<sup>[35]</sup> Isolation of the same organism from both the patient and the remainder of the bag are useful in diagnosing the transfusion-related sepsis and differentiating it from AHTRs and FNHTRs.<sup>[36]</sup> As platelets are stored at room temperature, they are more susceptible than RBCs to bacterial contamination with a greater risk. The transfusionrelated sepsis chances were more with randomdonor platelet than with an apheresis unit. Broadspectrum antibiotics should be used for management of transfusion-related sepsis with other standard care for sepsis. Screening of platelet units for bacterial contamination and adopting "diversion technique" during blood collection can decrease the risk.[37]

#### Non-immune hemolytic reactions

Red cell hemolysis due to transfusion can also occur from several non-immune-mediated causes

(also termed as pseudohemolysis) which may be temperature-related or mechanical, for example, improper storage temperature, improper use of blood warmer, use of hot water bath and microwave oven, using a needle with an inappropriately small bore size or employing a rapid pressure infuser, infusion of RBCs through same tubing with hypotonic solution, or some pharmacologic agent. The management is same as in the AHTRs.<sup>[26]</sup>

*Transfusion-associated circulatory overload (TACO)* Major morbidity and mortality are associated with transfusion-associated circulatory overload.<sup>[38]</sup> Elderly patients, infants, patients with renal failure having hypoalbuminemia, anemia, CHF or fluid overload or history of plasma transfusion are at increased risk of TACO. Symptoms and signs include dyspnea, orthopnea, cyanosis, tachycardia, jugular venous distension, and pedal edema.<sup>[39]</sup> Management is an optimization of the primary cause and mechanical ventilation, fluid restriction, and diuretics.<sup>[40]</sup>

### Transfusion-associated dyspnea

It is designated by respiratory distress within 24 h of transfusion that does not meet the criteria of TRALI, TACO, or hypersensitive reaction or other known causes.<sup>[41]</sup>

#### Acute hypotensive transfusion reaction

It is defined as abrupt and early drop in BP with lack of other causes of hypotension. Thus, it may occur as an isolated finding; however, it responds quickly to cessation of the transfusion and supportive treatment.<sup>[42]</sup> Patients with otherwise unexplained hypotensive transfusion reactions should be given a trial of washed blood products. Bedside leukoreduction filters have been implicated more often in acute hypotensive transfusion reaction although it has also occurred with pre-storage leukofilters.<sup>[43]</sup>

# Transfusion-associated graft-versus-host disease (TG-GvHD)

TG-GvHD is a clinical syndrome characterized by fever, maculopapularrashprogressing to hemorrhagic bullae, enterocolitis with watery diarrhea, elevated liver function tests, pancytopenia, and findings of characteristic histological appearances on biopsy that typically begin 8–10 days after transfusion.<sup>[44]</sup> Although rare in occurrence, it has a mortality of 90%. Therefore, emphasis is placed on prevention of TA-GvHD by irradiation of all cellular blood components, especially in patients at risk of TA-GvHD.<sup>[45]</sup>

#### Delayed hemolytic transfusion reactions (DHTRs)

The incidence of DHTRs is estimated at approximately 1 in 6000 units transfused.<sup>[46]</sup> DHTRs are seen due to reactivation of pre-existing antibodies against antigens on the transfused red cells. Symptoms may occur days to weeks after transfusion of apparently cross-matched compatible RBCs. Patients with DHTR may have unexplained anemia or show no increment in hemoglobin following transfusion. The majority of DHTRs require no treatment because red cell destruction occurs gradually as antibody synthesis increases. However, antigen-negative blood may be required for a bleeding patient with low hemoglobin.<sup>[39]</sup>

#### Other reactions

Along with the above-mentioned reactions, the various blood transfusion reactions may be as: Metabolic and hemostatic derangement, citrate toxicity, hyperkalemia, hypokalemia, coagulopathy, hypothermia, air embolism, alloimmunization, transfusion-associated immunomodulation, and post-transfusion purpura.<sup>[26]</sup>

## CONCLUSION

Transfusion safety has improved because of clinical and basic science research, effective adverse event monitoring, and development in blood product manufacturing. Awareness about various clinical features of ATRs with an ability to assess the serious reactions on time can lead to a better prognosis. An encouraging environment for reporting of adverse reactions and near misses in a supportive, non-blaming learning culture is required to have an effective hemovigilance system. Vigilance in hospital transfusion practice and procedure and analysis of this data is of paramount importance to improve transfusion safety. Establishing a hemovigilance system with proper education of the health-care team and active participation of all can be a better choice to gain

understanding and minimizing the transfusion-related events.

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