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ADVERSE EVENTS OF BLOOD TRANSFUSION AND BLOOD SAFETY IN CLINICAL PRACTICE

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Abstract:

Blood transfusions can be lifesaving. The majority are completed without incident. However, every transfusion recipient runs the risk of developing a transfusion reaction or adverse event. These reactions can be acute, occurring during or soon after transfusion, or delayed, occurring days to weeks later. Hemovigilance is defined as a set of surveillance procedures covering whole transfusion chain from the collection of blood and its components to the follow up of its recipients, intended to collect and access information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence and recurrence. Haemovigilance will also have a major impact on optimal blood usage. It is expected that existing haemovigilance systems in hospitals will contribute in the near future also to the surveillance of optimal blood use. A functional haemovigilance system can act as a backbone to monitor the transfusion practices and be accountable to appropriate documentation, reporting and investigation of transfusion reaction. In this review, we will review about the haemovigilance process and the different transfusion reactions associated with blood transfusion in clinical practice.

Keywords: *transfusion reactions, haemovigilance, blood components.*

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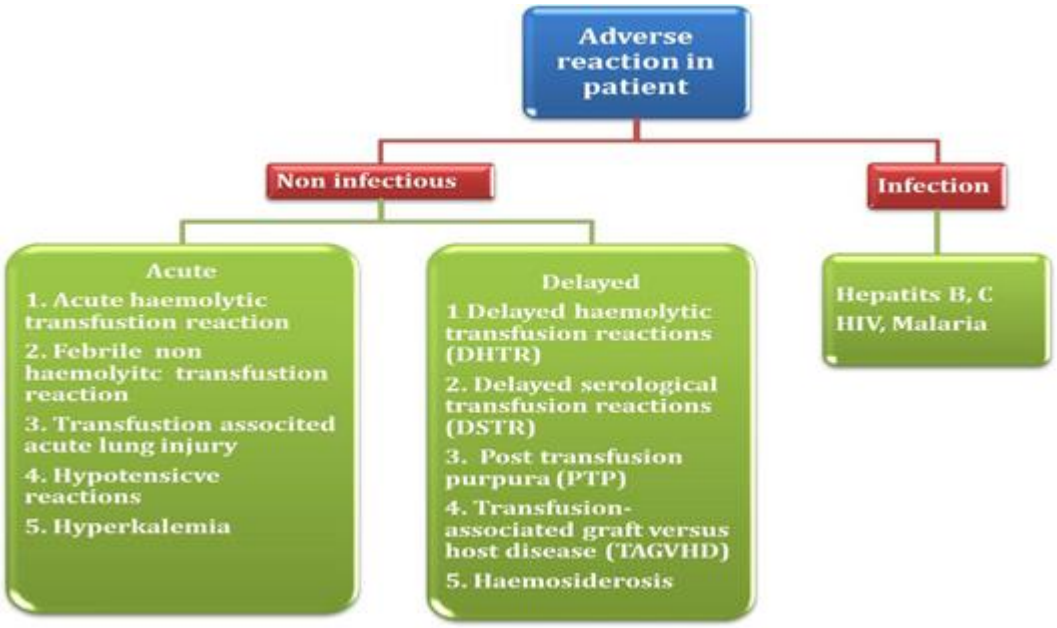
INTRODUCTION:

Blood transfusions can be lifesaving. The majority are completed without incident. However, every transfusion recipient runs the risk of developing a transfusion reaction or adverse event. These reactions can be acute, occurring during or soon after transfusion, or delayed, occurring days to weeks later [1]. Although the substantial level of awareness on transfusion transmitted diseases has already attracted considerable attention from transfusion medicine professionals, no significant advances have been made to minimize preventable transfusion errors in developing countries. There is a lack of awareness and proper training about the management of transfusion related to adverse reactions among health workers and this leads to under-reporting of transfusion errors. Many African countries do not have an effective haemovigilance system and very few data regarding transfusion incidents in Africa are available [2]. In India, there is a lack of standardized and effective haemovigilance system as the reporting of adverse transfusion event is not mandatory [3]

The term hemovigilance is derived from the Greek word 'hema' = blood and the Latin word 'vigilans' = watchful. Hemovigilance is defined as a set of surveillance procedures covering whole transfusion chain from the collection of blood and its components to the follow up of its recipients, intended to collect and access information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence and recurrence[4]. Haemovigilance is a key area of focus and is defined by the International Haemovigilance Network (IHN) as:'… A set of surveillance procedures covering the whole transfusion chain (from the collection of blood and its components to the follow-up of recipients), intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence or recurrence …'[5,7]. Haemovigilance is an important and integral part of transfusion medicine. International programs, such as the UK's Serious Hazards of Transfusion (SHOT) provide valuable data on the occurrence of transfusion-related adverse events and as a result drive the introduction of initiatives which enhance the safety of the transfusion process. Haemovigilance also has a significant role to play in optimal blood usage and patient blood management initiatives, key areas for the Blood Service [6]. Hemovigilance plays an essential role in ensuring patient safety with regard to blood transfusions. The data generated through the hemovigilance system helps in framing important changes in the whole blood transfusion process which are useful for better patient safety [8]. Haemovigilance is an organised scheme of monitoring, identifying, reporting, investigating and analysing adverse events and reactions pertinent to transfusion and manufacturing blood products. This system is also an elemental part of quality control in a blood system, bringing about corrective and preventive measures, and for the perpetual advancement of the quality and safety of blood products and the transfusion process [9].

The term haemovigilance is derived from the term pharmacovigilance which relates to activities and systems to collect information useful in supervising medicinal products , with particular reference to adverse drug reactions in human beings and to evaluate such information scientifically. Adverse reactions are defined as reactions that are harmful and unintended and that occur at doses normally used in man for the prophylaxis , diagnosis or treatment or the modification of physiological function . Haemovigilance deals with blood components ; whole blood, erythrocyte-concentrates, thrombocyte-concentrates and fresh frozen plasma. Pharmacovigilance in transfusion medicine deals with plasma derivatives: clotting factor concentrates, immunoglobulins, albumin and other fractionated products [10]. The spectrum of adverse reactions arising from the receipt or donation of blood is quite protean. Recent data from the Food and Drug Administration in seven different reports have shown that mortality from blood transfusion ranged from 20 to 75%, majority of these were reported to be due to patient misidentification [11]. In another report, the predominant cause of death among transfusion recipients was transfusion-related acute lung injury (30%), followed by haemolytic transfusion reactions (16%) and bacterial contamination of blood donor units (16%) [12]. Donor-adverse reactions to blood donation are increasingly encountered; prevalence rates of 1.6 and 0.7% have previously been reported among Nigerian and Indian blood donors . The predominant donor-adverse reactions in these series were vasovagal reactions and anxiety [13,14]. Addressing donor-adverse events is vital to blood transfusion safety since its occurrence has been shown to constitute a significant deterrent to repeat blood donations and subsequent attainment of self-sufficiency in blood procurement [15].

Classification of blood transfusion reaction [16] :



History of haemovigilance

Hemovigilance was first introduced in France in 1993 with mandatory reporting and in United Kingdom (UK) with first voluntary reporting system in 1996. Most of the developed countries like Canada, Ireland, Netherlands, and Denmark have a voluntary reporting requirement. Hemovigilance program in these countries is linked to International Hemovigilance Network, which presently has 28 members [17] .Hemovigilance systems, depending upon the country, are governed either by regulators (e.g., France, Germany, Switzerland), blood manufacturers (e.g., Japan, Singapore, South Africa), medical societies (e.g., Netherlands, UK), or public health authorities including regulators (e.g., Canada) [18]. Member states of the European Union have to implement hemovigilance program with reporting to a Central Office as per the commission directive [19-21].Among the Asian countries, a well-established hemovigilance system is lacking and there is paucity of data on hemovigilance data except for Japan, which has published a report on adverse reactions [22]. Around 107 million units of blood donation are collected globally every year. Blood donation rate in high-income countries is 39.2 donations per 1000 population, 12.6 donations in middle income and 4 donations in low income countries. Around 65% of blood transfusion are required in children <5 year of age in low income countries whereas in high income countries majority of blood transfusion takes place in patients >65 years of age. Thus to address global concerns on the availability, safety and accessibility of blood transfusion, a hemovigilance system is required in the country to have a comprehensive approach to address the issues of adverse reaction following blood transfusion and blood product administration.

Haemovigilance program of India

A Hemovigilance program as an integral part of pharmacovigilance program of India at a national level has been launched on December 10, 2012 with a road map of 5 years, i.e., year 2012–17, with four phases, i.e., initiation phase, expansion and consolidation phase, expansion and maintenance phase, and optimization phase. A core group to coordinate theactivities of hemovigilance between the medical colleges and National Coordinating Centre at IPC has been constituted [17].

Furthermore, an advisory committee has also been constituted to a) finalize hemovigilance—Transfusion ReactionReporting Form (TRRF) to be introduced in the country, b) give expert opinion for collection, collation, and analysis ofhemovigilance data and development of the software for the same, c) monitor the functioning and quality of the datacollected by the Adverse Transfusion Reaction Reporting Centres, i.e., ADR Monitoring Centres of PvPI, d) developtraining modules and guidelines for

implementation of hemovigilance program under PvPI, and e) develop a roadmap forlinking hemovigilance program under PvPI with International Haemovigilance Network[17].

Initially, 60 medical colleges that are already enrolled under pharmacovigilance program of India have been broughtunder the ambit of this program. This number will be increased to a total of 90 medical colleges by March 2013.

Hemovigilance program has been launched with the following objectives:

a) To monitor transfusion reactions
b) To create awareness among health care professionals
c) Generate evidence-based recommendations
d) Communicate findings to all key stakeholders
e) Create national and international linkages
f) Advise Central drugs standard control organization (CDSCO) for safety related regulatory decisions

The Medical Colleges enrolled under hemovigilance program will collect data in respect of adverse reactions associated with blood transfusion and blood product administration in TRRF from their respective Department of Transfusion Medicine or the blood bank. The information collected in TRRF will be forwarded to the coordinating Centre NIB through software developed in-house by NIB Information technology division. This data will be collated and analyzed to identify trends and recommend best practices and interventions required to improve patient care and safety. These recommendations will be forwarded to national coordinating Centre IPC, PvPI for onward transmission to Drugs Controller General (India), and Central Drugs Standard Control Organization. These recommendations will be used to formulate safety related regulatory decisions on blood and blood products transfusion that will be communicated to various stake holders [17].

Reporting of Severe Transfusion Reactions [23]

Table 1. Summary of Diagnostic Findings and Management Strategy for Severe Transfusion Reactions

Diagnosis	Symptoms	Timing	Lab Findings	Management
TRALI	Dyspnea/tachypnea, Fever, Hypotension	During or post-transfusion (within 4-6hrs)	CXR = Diffuse lung infiltrate (Non-cardiogenic) BNP/proBNP = Normal Donor Anti-leukocyte Ab+ Abnormal leukocyte crossmatch	Stop transfusion if ongoing Supportive = Oxygen (O_2) Intubation, if necessary
HTR	Fever/chills, Chest pain, Hypotension, Severe *Back or Abdominal pain *Dyspnea *Vomiting/diarrhea	Immediate up to several hours post transfusion Delayed–3 to 10 days post transfusion	DAT+, Ab screen on repeat + ↑LDH, ↑Bilirubin ↓Haptoglobin Severe *↑PT/PTT *↑BUN/Cr	Stop transfusion, Recheck crossmatch, Recheck documentation, Supportive care, Oxygen support, Urine output >100mL/hr, Monitor hematocrit
TACO	Dyspnea/tachypnea, Cough, ↓O_2 saturation, Hypertension/Tachycardia, Jugular vein distension	4-6 hours post Tx	↑BNP/proBNP, CXR = pulmonary edema ↑central venous pressure	Stop transfusion if ongoing Get patient upright, Diuretics, Slow infusion or split units for future
Septic	Fever/chills (>1-2°C rise), Hypotension/shock, Oliguria, Dyspnea	During transfusion or shortly after	Gram stain + Bag culture + Blood cultures + ↑D-dimer/↑ PT (if DIC)	Stop transfusion, Empirical antibiotics Hemodynamic stability Respiratory support (O_2)
Anaphylactic	Rash/erythema, Pruritus/ angioedema, Dyspnea/ chest pain, Hypotension, Vomiting/diarrhea	Seconds or minutes into transfusion	Normal CXR, Gram stain/ Blood cultures NEG Anti-IgA + IgA < 0.05 mg/dL on pre-transfusion sample	Stop transfusion, Supportive care (epinephrine, saline, diphenhydramine, airway patency)
PTP	Purpura, PLT-type bleeding (mucosal)	3-12 days post transfusion (5-10 days usual)	PLT count <15k/μL PLT Ab +	IVIg (+ random PLTs if needed) HLA-matched PLTs
TA-GVHD	Erythematous rash, Fever, Diarrhea	3-30 days post Tx (8-10 days usual) Delayed in newborns	Skin biopsy with mononuclear cell infiltrate ↑LDH, ↑ALT/AST, ↑Bili (Hepatitis)	Supportive but poor prognosis Irradiation for prevention

Ab, antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Bili, total bilirubin; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; CXR, chest x-ray; DAT, direct antiglobulin test; DIC, disseminated intravascular coagulation; HTR, hemolytic transfusion reaction; IVIg, intravenous immunoglobulin; LDH, lactate dehydrogenase; PT, prothrombin time; PTP, post-transfusion purpura; PTT, partial thromboplastin time; TACO, transfusion-associated circulatory overload; TA-GVHD, transfusion-associated graft-versus-host disease; TRALI, transfusion-related acute lung injury; TX, transfusion.

An overview of important non-infectious adverse transfusion reactions [24]

Type	Pathophysiology	Clinical presentation	Management*
Acute (occurring<24 h after transfusion)			
Immune mediated			
Acute haemolytic transfusion reaction	Red blood cells mismatch between donor and recipient	Fever, chills/rigors, back pain, hypotension, haemoglobinuria, pain along IV line, bleeding diathesis	Stop transfusion and keep IV line open; maintain urine output>1 ml/kg/h and IV diuretic; analgesics; low-dose dopamine for hypotension; blood components for bleeding
Febrile nonhaemolytic transfusion reaction	Cytokines in blood unit	Rise in temperature>1°C, chills and/or rigors, discomfort, vomiting, flushing	Antipyretics (acetaminophen but not aspirin); meperidine for rigors; use of leukofiltered blood components
Urticarial	Recipient's IgE react with donor plasma protein leading to release of mast cell mediators	Pruritus, urticaria, or flushing	Antihistamine treatment or premedication; restart unit slowly after antihistamine if symptoms have resolved
Anaphylactic	Antibodies to donor plasma proteins including IgA, haptoglobin, complement, ethylene oxide	Hypotension, urticaria, bronchospasm, stridor, local oedema	Adrenaline 0.5 ml of 1:1000 solution (500 µg) SC or IM in adults; in severe cases, 1:10,000 IV, initial rate 1 µg/min; antihistamines (10 mg of chlorphenamine IM or IV), corticosteroids (200 mg of hydrocortisone IM or IV); washed or IgA-deficient blood components
Transfusion related acute lung injury	Leukocyte antibodies in donor or recipient	Hypoxemia, noncardiogenic pulmonary oedema, respiratory failure, hypotension, fever, cyanosis	Treatment may range from oxygen to ventilator support
Non immune mediated			
Transfusion related sepsis	Blood products contaminated with bacteria	Fever≥102°F, chills, hypotension within 90 min of transfusion	Antibiotics and management of shock; bacterial culture; pathogen inactivation of blood components
Non immune haemolysis	Physical/mechanical/ chemical destruction of blood (*in vitro* haemolysis)	Features of intravascular haemolysis of red cells, namely, haemoglobinuria, haemoglobinemia	Symptomatic treatment
Transfusion associated circulatory overload	Volume overload in susceptible patients	Signs of congestive heart failure, shortness of breath, wheezing, hypertension	Diuretics; oxygen; phlebotomy; careful monitoring of transfusion flow rates
Air embolism	Air infusion via IV line (open system)	Sudden dyspnoea, acute cyanosis, shoulder or back pain, cough, hypotension	Left trendelenberg position; aspiration of air; possibly priming of all lines before connection
Delayed (occurring>24 h after transfusion)			
Immune mediated			
Delayed haemolytic transfusion reaction	Anamnestic immune response to red cell antigens	Fever, decreasing haematocrit, mild icterus with other features of haemolysis	Crossmatch compatible unit to be transfused after identifying red cell antibody
Alloimmunization to red cell antigens, platelets and leukocytes (HLA)	Immune response to red cells, platelets, leukocytes antigens	Haemolytic disease of fetus and newborn, delayed serologic reaction, platelet refractoriness	Rational use of blood components; leukofiltered blood
Transfusion associated immunomodulation	Allogeneic leukocytes or their soluble products	Increased chances of postoperative infections, cancer recurrence, multiple organ dysfunction	Leukofiltered blood, autologous blood
Transfusion associated graft versus host disease	Engraftment and multiplication of donor lymphocytes in the recipient leading to host tissue destruction	Rash, watery diarrhoea, fever, anorexia, vomiting, abnormal liver function tests, bone marrow failure	Corticosteroids; cytotoxic agents; irradiation of cellular blood components
Posttransfusion purpura	Antibodies against platelet specific antigens	Thrombocytopenia, purpura, bleeding	Steroids; IVIG; plasmapheresis; avoid platelets
Non immune mediated			
Iron overload	Iron deposition in a multi-transfused patient	Diabetes, cardiomyopathy, cirrhosis	Iron chelating agents

IV – Intravenous; IM – Intramuscular; SC – Subcutaneous; HLA – Human leukocyte antigen; IVIG –Intravenous immune globulin

CONCLUSION:

In order to have a well organized hemovigilance system in developing countries like India, a comprehensive approach is required. A streamlined mechanism for data collection using standardized tools at hospital level and good coordination at the national level can bring up effective hemovigilance system in a country. A functional hospital transfusion committee can act as backbone for this by developing policies for transfusion practices, appropriate documentation, reporting and investigation of transfusion reaction. Ideally, the hemovigilance system should cover processes throughout the entire transfusion chain, from blood donation, processing, and transfusion to patients for the monitoring, reporting, and investigation of adverse events and reactions and near misses related to blood transfusion. It should be well coordinated between the blood transfusion service, hospital clinical staff and transfusion laboratories, hospital transfusion committees, regulatory agency, and national health authorities. Haemovigilance will also have a major impact on optimal blood usage. It is expected that existing haemovigilance systems in hospitals will contribute in the near future also to the surveillance of optimal blood use. A functional haemovigilance system can act as a backbone to monitor the transfusion practices and be accountable to

appropriate documentation, reporting and investigation of transfusion reaction.

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