Review Article

Transfusion transmitted diseases in perioperative and intensive care settings

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ABSTRACT

Patients in the perioperative period and intensive care unit are commonly exposed to blood transfusion (BT). They are at increased risk of transfusion transmitted bacterial, viral and protozoal diseases. The risk of viral transmission has decreased steadily, but the risk of bacterial transmission remains same. Bacterial contamination is more in platelet concentrates than in red cells and least in plasma. The chances of sepsis, morbidity and mortality depend on the number of transfusions and underlying condition of the patient. Challenges to safe BT continue due to new emerging pathogens and various management problems. Strategies to restrict BT, optimal surgical and anaesthetic techniques to reduce blood loss and efforts to develop transfusion alternatives should be made. Literature search was performed using search words/phrases blood transfusion, transfusion, transfusion transmitted diseases, transfusion transmitted bacterial diseases, transfusion transmitted viral diseases, transfusion transmitted protozoal diseases or combinations, on PubMed and Google Scholar from 1990 to 2014.

Key words: Blood transfusion, transfusion, transfusion transmitted bacterial diseases, transfusion transmitted diseases, transfusion transmitted viral diseases

INTRODUCTION

One of the adverse effects of allogenic blood transfusion (BT) is the transmission of infectious agents. Although Transfusion transmitted diseases (TTDs) have reduced significantly over the past decade the risk still exists. Perioperative BT is mandatory in situations where patient's haemoglobin has to be built up to an optimum level prior to Surgery and the surgical procedure entails significant blood loss. The patients requiring BT in intensive care unit (ICU) are those with coagulation abnormalities, haematologic disorders, severe sepsis and on-going blood loss. In a multicentric observational study, it was found that anaemia is commonly present in critically ill patients and require a large amount of BT.[1] Various studies have shown that, there is frequent use of transfusion of blood and its components in post-operative period.[2] The organisms responsible for TTD can be bacteria, virus and protozoa. The manifestations of infection can be immediate or delayed. It may lead to a chronic carrier state or asymptomatic infection; all of these invariably contribute to patient's morbidity or mortality.

To be transmitted by BT, the infective agent:[3]

- must be present in the blood stream of donors
- must be able to withstand the processing in the production of blood components
- must retain viability during storage
- must retain infectivity and the receiver should be sero-negative, to generate infection in the blood receiver.

TRANSFUSION TRANSMITTED BACTERIAL INFECTIONS

The incidence of transfusion transmitted bacterial infection (TTBI) has been found to be 24.7/million platelet concentrates (PCs) and 0.39/million red cells transfusion. The incidence of fatal TTBI is 5.14/million in PCs transfusion.[4] Bacterial contamination is more common in PCs as these are stored at 20-24°C, the temperature that favours the growth of bacteria.[5]

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The rate of contamination of PCs is 0.02-1.2% and for packed red blood cells (PRBCs) is 0.1-0.2%.[6] Sources of bacteria are donors, environment of blood bank or hospitals, contaminated bag and tubing, skin of the donor or recipient (insufficient skin preparation of venipuncture site). The bacteria are mainly skin contaminants like coagulase negative staphylococcus although both staphylococcus and streptococcus are transmitted through stored platelets.

Next to platelets, the red cells are more likely to be contaminated. The longer the red cells are stored, more is the chance of infection. Bacthem study shows that organisms that mostly grow are Gram-negative bacteria like *Yersinia*, *Serratia*, *Escherichia*, *Pseudomonas*, *Proteus*, *Klebsiella*, and *Acinetobacter*.[7] These bacteria are capable of growth at 1-6°C the temperatures at which red cells are stored. Bacterial contamination of plasma is uncommon for the temperature at which it is stored. Only few cases of contamination were reported in Canada and Germany.[8,9] Organisms identified are *staphylococcus*, *Klebsiella*, *Propionobacterium* and *Pseudomonas*. Water baths that are used to thaw plasma are the potential source.[10]

Transfusion transmitted bacterial infection can manifest as high fever, chills, rigor, tachycardia, hypotension, nausea, vomiting, dyspnoea, backache and abdominal pain[7] which may be confused with febrile non-haemolytic transfusion reaction. Gram-negative endotoxaemia can cause abrupt symptoms with temperature as much as 109°F, progressing to fulminant sepsis, shock, disseminated intravascular coagulation and even death. A high mortality rate of 60% has been reported.[11]

A systematic review by Guinet *et al*. reported that transfusion recipients who were already anaesthetised or in sepsis before transfusion was initiated had blurring of clinical symptoms of *Yersinia enterocolitica* post-transfusion sepsis and these patients also had higher mortality rate.[12] On suspicion of TTBI, transfusion should be stopped immediately, followed by administration of broad spectrum antibiotics and symptomatic management of the patient. The blood bank should be informed. Gram-staining, bacterial culture of both donor and recipient, should be done. Coombs test of recipient blood is necessary to rule out haemolytic transfusion reaction. Transmission of syphilis has become very rare after implementation of serological test for antibodies to *Treponema pallidum*.

TRANSFUSION TRANSMITTED VIRAL DISEASES

Transfusion-transmitted viral infection may not pose an immediate threat in the perioperative period or in ICU, but definitely is a matter of great concern due to its potential transmission in the window period. Transfusion-transmitted viruses are human immunodeficiency virus 1 and 2 (HIV-1 and 2), hepatitis B virus (HBV), hepatitis C virus (HCV), other hepatitis viruses, *Cytomegalovirus* (CMV), Dengue virus, Chikungunya virus, human T-cell leukaemia virus, parvovirus, Epstein–Barr virus, human herpes virus and West Nile virus. Most developing countries practice the serological test for HIV as a routine practice, but it is a low sensitivity test. The HIV-1 p24 antigen test is considered superior because it reduces the window period by 6 days. It has been replaced by Mini Pool and individual donation nucleic acid amplification test (MP- and ID-NAT) because it reduces the residual risk of infectious window period by 11 days. However, this current technology cannot detect HIV ribonucleic acid in the first 1-2 weeks.[13]

Commonly HBV surface antigen (HBsAg) and less commonly antibody for HBV core antigen (anti-HBcAg) detection test are done in most countries. NAT is not practical because of slow viral replication and very low level of viraemia and hence may be implemented along with serological testing to provide safe blood. The routine donor screening of anti-HCV antibodies has grossly reduced the risk of post-transfusion acute HCV infection. The HCV NAT reduces the window period to 15 days. Rare cases of transmission of HAV and HEV through transfusion have been reported.[14,15]

The clinical features and detection methods of transfusion transmitted viral and protozoal diseases that have been reported are shown in Tables 1 and 2. Around 68 infectious agents have been identified and described in detail in an analysis done on TTD and published in detail.[16] It is beyond the scope of this article to describe all of these.

EFFECT OF BLOOD TRANSFUSION IN PERIOPERATIVE AND INTENSIVE CARE UNIT SETTING

In an analysis, it was found that there was increased morbidity and mortality after BT in ICU, trauma and surgical patients.[17] Red cells are transfused in critically ill patients with the aim to improve tissue

Table 1: Transfusion transmitted viral diseases

Viral diseases/causative agent	Clinical features	Incubation period	Detection methods
AIDS (HIV-1 and 2)	Fever, headache, fatigue, swollen lymph glands, rash	2 weeks-6 months	Serological test for HIV-1 and 2 (ELISA), p24 antigen test, NAT
Hepatitis (hepatitis A, B, C, D and E)	Fatigue, flu-like symptoms, dark urine, light coloured stools, fever, jaundice, fulminant hepatic failure	HAV: 2-6 weeks HBV: 4-26 weeks HCV: 2-23 weeks HDV: 6-26 weeks HEV: 2-9 weeks	Immunoassays for antibodies and antigen,nucleic acid-based tests, PCR and TMA, genotyping tests
CMV	Fever, swollen glands, tiredness to serious illness, fever, pneumonia	3 and 12 weeks	Antigen assays, PCR and culture
Dengue	Fever, as high as 106° F, headaches, muscle, bone and joint pain, pain behind eyes, widespread rash, nausea and vomiting, bleeding gums or nose	4-10 days	Virus isolation, serological tests, or molecular assays, RT-PCR
Chikungunya	Fever, rash, arthritis, headache and muscle pain	3-7 days	Virus isolation, serology and PCR
Parvovirus B 19	Sore throat, low grade fever, GI disturbance, headache, fatigue, itching, facial rash	4-14 days	Serology, PCR and dot-blot hybridization
West Nile virus	Fever, headache, body aches, fatigue, back pain, skin rash, swollen lymph glands, eye pain, encephalitis, meningitis and acute flaccid paralysis	3-14 days	Immunoassays, viral cultures, RT-PCR
Epstein–Barr virus	Extreme fatigue, fever, sore throat, head and body aches, cervical and axillary lymphadenopathy, hepatosplenomegaly, rash, respiratory complications and neurological complications	4-6 weeks	Viral capsid antigen, early antigen and antibody
Variant Creutzfeldt-Jakob disease	Atypical clinical features, psychiatric or sensory symptoms, ataxia, involuntary movement, dementia and myoclonus	Variable (mean duration of 16 years)	Immunoassay, prion protein gene analysis
HTLV	Asymptomatic in the beginning, including adult T-cell leukaemia/lymphoma, HTLV-associated myelopathy/tropical spastic paraparesis, uveitis, rheumatic syndromes	15-20 years	ELISA, western blot, immunofluorescence assay or radioimmunoprecipitation assay and PCR

ELISA – Enzyme linked immunosorbent assay; NAT – Nucleic acid amplification testing; PCR – Polymerase chain reaction; RT-PCR – Reverse transcription polymerase chain reaction; TMA – Transcription-mediated amplification; CMV – *Cytomegalovirus*; HTLV – Human T– cell lymphotrophic virus; GI – Gastrointestinal; HEV – Hepatitis E virus; HBV – Hepatitis B virus; HCV – Hepatitis C virus; HDV – Hepatitis D virus

oxygenation, but in reality they rather lead to worse clinical outcome.[18] In a recent study, Mahdi *et al*. found that perioperative BT was one of the risk factors for surgical site infection (SSI).[19] In a prospective study, SSI and reduced graft survival had been found in kidney transplanted patients who received intraoperative BT.[20] The risk of post-operative infection was present both in leukocyte-depleted and non-leukocyte-depleted transfusion.[21] Although leukocyte-depleted red cells have not been proven to be superior over non-leukocyte-depleted, nonetheless, they increase the microcirculatory flow in septic patients.[22] Transfusion of more than 5 PRBCs in both operating room and during the first post-operative day in ICU was found to be an independent predictor of nosocomial infection in cardiac surgery. The majority of nosocomial infections were respiratory tract infection and central venous catheter related infections.[23] In comparison to homologous BT, there was decreased incidence of complications, early extubation and shorter ICU stay after autologous transfusion in cardiac surgery.[24] BT was one of the independent risk factors for post-operative infectious complications in hepatectomy patients.[25] Moderate degree of trauma patients with injury severity score of <25 had ventilator-associated pneumonia, acute respiratory distress syndrome and death after delayed BT beyond 48 h.[26] In major burn injury, there was increased risk of infection and mortality which depends on the number of transfusions.[27] There was increased risk of sepsis in patients with severe burns (>60% total body surface area with inhalational injury) paediatric patients who received higher (PRBCs >20/fresh frozen plasma >5) amount of blood products.[28]

Rosland *et al*., found in their prospective multicentre cohort study that patients with sepsis who received PRBC transfusion had higher simplified acute physiology score II, sepsis related organ failure assessment score, more length of stay in ICU and higher 90 days mortality.[29] There was a two-fold increase in blood stream infection after PRBC

Table 2: Transfusion transmitted protozoal diseases

Disease (causative agent)	Clinical feature	Incubation period	Detection
Malaria (*Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae*)	Fever with chills and rigor, headache, hepatic and renal dysfunction, disorientation or decreased sensorium	9-40 days	Antigen test, peripheral blood smear
Babesiosis (*Babesia microti*)	Malaria like illness, haemolytic anaemia and renal failure	1-6 weeks	Peripheral blood smear, indirect fluorescent antibody tests, polymerase chain reaction, inoculation of animals
Trypanosomiasis (*Trypanosoma cruzi*)	Fever, lymphadenopathy and hepatosplenomegaly, myocarditis and encephalitis	1-2 weeks	ELISA
Leishmaniasis (*Leishmania donovani*)		2-4 months	Microscopy, serology, culture and nucleic acid detection
Microfilariasis	Allergic reaction of varying degree depending upon quantum of microfilaria	8-16 months	Peripheral smear, ELISA, PCR

ELISA – Enzyme linked immunosorbent assay; PCR – Polymerase chain reaction

transfusion and it was dose dependent.[30] Critically ill patients on ventilatory support and in severe sepsis who receive BT are more prone to CMV activation leading to increase in morbidity and mortality.[31] There was increased incidence of opportunistic infection in immunocompromised patients like HIV after BT. Sloand *et al*. found in their retrospective study an increased incidence of CMV and bacterial infections who received BT. Also there was significant bacterial infection that occurred in patients with CMV infection and increased death rate after BT.[32] The risk of transmission of diseases and occurrence of sepsis is enhanced due to immunosuppressive effect of BT. In fact this immunomodulatory effect of allogenic BT is due to associated pro-inflammatory burden in the recipient which is found to be proportional to the stored age of blood. This effect is also linked with recurrence in cancer surgery.[33]

THREAT TO SAFE BLOOD TRANSFUSION

A challenge to safe BT is lack of preventive measure for new emerging pathogens. Current screening methods based on culture like BacT/ALERT system sometimes do not detect bacterial contamination.[34] Many countries still do not implement either ID or MP-NAT and continue to use rapid test or enzyme-linked immunosorbent assay for anti-HIV 1 and 2, HBsAg and anti-HCV. BT service is highly decentralized and lacks vital resources like skilled manpower, adequate infrastructure and financial support in India. Lack of 100% blood donation from voluntary non-remunerated donors and a significant percentage of replacement donors result in high prevalence of TTD.

PREVENTION OF TRANSFUSION TRANSMITTED DISEASES

Restrictive BT strategy should aim at transfusing blood components based on individual needs rather than transfusing on the basis of transfusion trigger. Autologous blood donation, using recombinant human erythropoietin and optimal surgical and anaesthetic technique to reduce blood loss should be adopted. TTD can be largely prevented by ensuring safety steps like deferring the donors with recent dental treatments, minor surgery or fever at presentation, proper donor screening and testing, optimal blood product handling, processing and storage, carrying out proper skin disinfection of donor arm and ensuring diversion of first 30-40 ml of whole blood from collection bag. Bacterial detection methods should be applied to stored blood closer to the transfusion time. Gram-staining, screening for markers of contamination and culture of stored blood before transfusion should be done. Blood should yield a negative culture at least 24-48 h before it is released for transfusion. Application of pathogen reduction technology like use of synthetic psoralen, riboflavin, prestorage leukocyte reduction and apheresis derived platelet to reduce transmissible pathogens should be carried out.[35] Efforts should be taken to improve on patient blood management modalities and multicomponent apheresis, a patient centre paradigm in transfusion medicine that attempts to reduce the transfusion risk to a level of as low as reasonably achievable risk.[36] Mass vaccination of the population will offer protection against some TTD. 'Look Back' programmes may be adopted in developing countries. Efforts should be made to develop artificial oxygen carrier and recombinant clotting factors.

SUMMARY

There is a potential risk of transmission of diseases and immunosuppression after BT. Patients in perioperative period and ICU are more vulnerable to TTD due to increased number of transfusions, low immune status and comorbidities. The transfused patients carry high risk of morbidity and mortality due to bacterial infection and sepsis. Early diagnosis of TTD by sound, vigilant clinical acumen and detection methods followed by prompt management will reduce the morbidity and mortality. Applying the principle of restricted BT, use of transfusion alternatives, improving BT service and implementing newer technologies are the methods to prevent TTD.

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Announcement

CALENDAR OF EVENTS OF ISA - 2014

Certain important dates are given here for the members. All the applications should be sent by registered post (with Acknowledgement Due)

Date	Name of the Award/Post	Application has to be sent to
30th June 2014	Bhopal Award for Academic Excellence	Hony. Secretary, ISA
15th August 2014	Prof. A. P. Singhal Life Time Achievement Award	Hony. Secretary, ISA
31st October 2014	Dr. (Mrs.) Rukmini Pandit Award - Publication format along with Conference Presentation Certificate	Hony. Secretary, ISA
31st October 2014	Y. G. Bhoj Raj Award - Best Review Article in IJA	Hony. Secretary, ISA
31st October 2014	Dr. Kop's Award	Chairman Scientific committee of ISACON with a copy to Hony Secretary ISA
27th November 2014	Dr. TN Jha Memorial & Dr. KP Chansoriya Travel grant	Hony. Secretary, ISA
27th November 2014	Late Dr. Venkata Rao Memorial Oration	Hony. Secretary, ISA
27th November 2014	Ish Narani Best Poster Award	Chairman Scientific Committee ISACON
28th November 2014	ISA GOLDCON QUIZ Competition	Chairman Scientific Committee ISACON
28th November 2014	Awards for 1. Best City Branch 2. Best State Branch 3. Best Metro Branch 4. Public Awarness Individual 5. Public Awarness City 6. Public Awarness State 7. Ether Day State 8. Ether Day City 9. Membership Drive % (State) 10. Membership Drive No.s (State) 11. Individual Drive	Hony. Secretary, ISA

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