

Blood Transfusion Associated Diseases and Complications in Thalassaemia Patients

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ABSTRACT

Background: Transfusion Transmitted Infections (TTIs) are going to hit as a major risk factor in overpopulated regions of the world comprising thalassaemia as a main concern. The variety of infectious diseases that transfer from blood donors to thalassaemia patients leading complications which result in delay hemolytic transfusion reactions and different types of infections whose causative agents may be HBV, HCV, HIV and Syphilis etc.

Epidemiology: The thalassaemia affects almost 4.4 of every 10000 births worldwide although its rate in Pakistan is 5000 to 10000 births per year with 5-7 % estimated carrier rate. The blood transfusion and transmissible infections ratio in low income countries is as, HIV presence is from 0.33% to 1.66%, HBV presence is from 2.00% to 4.50%, HCV presence is from 0.50% to 2.23% and Syphilis presence is from 0.60% to 1.81%.

Diagnostics: The Immuno-chromatographic tests are affordable and can be valid to be used for blood screening throughout world. Blood samples should be processed for a counter check via ELISA/ CLIA and NAT technique to eliminate risk of HBV, HCV, HIV and syphilis deadly infections.

Treatment: Patients must be provided regular blood transfusion to keep average hemoglobin level at 10-12 g/dl. Other treatments include Iron Chelation therapy which is mandatory for better life expectancy as well as splenectomy, stem cell transplant and gene therapy.

Conclusion: The blood transfusion infections based on ICT (Immuno-chromatographic technique) prove unreliable while CLIA (Chemiluminescence Immunoassay) is reliable comparatively due to capturing weak positive and low titer infectious agents. In order to avoid the delayed hemolytic transfusion reactions it is enforced to detect the subgroups of blood like A (A1 and A2) and AB (A1B and A2B).

Key Words: Blood Transfusion, Complications, Infections, Thalassaemia

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INTRODUCTION

Patients suffering from thalassemia represent abnormal hemoglobin production.¹ It was identified in the early hours as a molecular disease which is a genetic disorder that transfers from parents to offspring throughout the pedigree. Thalassaemia is considered to be a major health problem for children in third world countries and developed nations reported by World Health Organization.² In Pakistan there are children suffering from thalassaemia which are dependent on blood transfusion therapy associated with factors including cousin marriages, increase in birth rate and over population.³ The treatment of thalassaemia associated with infectious diseases like HBV, HCV, and HIV which are most likely to affect severely under treatment patients.⁴ The Government of Pakistan had passed the law in which thalassaemia test was made compulsory before marriage but unfortunately, it was not successfully implemented due to the high cost of thalassaemia diagnostic tests and improper management system in Pakistan.⁵ In Pakistan, this Molecular disease is most prevalent as minor disease, carrier of disease and the major thalassaemia. Estimation of 100,000 patients suffering from thalassaemia, these numbers are increasing day by day.⁶ Patients are entirely dependent on blood transfusion therapy to maintain a healthy life as compared to expensive chelation therapy, this type of expensive treatment poses a lot of financial and psychological stress on the patient and associated families.⁷ The blood transfusion infections are the major dilemma that occurs in thalassaemia patients in underdeveloped and developing countries.⁸ In Pakistan viruses which are more likely to get invasion of HCV following HBV and HIV spreading due to poor screening of blood transfusion in thalassaemia patients.^{9,10} HIV is recently reported in thalassaemia patients and this is all occurring because of low standards of blood safety which is neglected till now. Therefore, efficient screening of blood must be made possible.¹¹

Acute hemolytic transfusion reaction occurs during the process of transfusion, soon after or more delayed up to 24 hours. The delayed hemolytic transfusion reaction and complications of blood or blood component occur within the time span of 48 to 96 hours.¹² The chances of hemolytic reactions happening are out of 70,000 units applied so far. Delayed HTRs are occurring due to secondary immune response against an antigen on the RBCs of donor. The ABO mistake or error with the induction

of alloantibodies by former blood transfusion as well as the gravidity which is directed towards antigens other than ABO on the donor's RBCs.¹³ The delayed hemolytic transfusion reactions occurring in thalassaemia as well as other patients according to the blood group complications while its major reason is neglecting or inappropriately checking at the time of cross match and transfusion.¹⁴

The objectives of this review study are to identify and elaborate the transfusion associated infections and to perform the A as well as AB sub grouping to get rid of from delayed hemolytic transfusion reactions spread continuously in the patients of thalassaemia.

Guidelines for Blood Transfusion:

Blood transfusion in β - thalassaemia patients can be life-saving as it may be helpful for patients suffering chronic anemia, it also prevents bone deformities and prove a source for promoting normal body growth.¹⁵ Blood transfusion provides fresh red blood cells which are effective in suppressing anemia and helpful in preventing major disorders like hepatosplenomegaly and involved in reduction of bone marrow hyperplasia. Life span of β - thalassaemia has been increased since immune-chromatographic test have developed and introduced in the market for blood screening.¹⁶ Patients with β -thalassaemia must be given RBCs having total content of hemoglobin of at least 40g.¹⁷ The blood collected must be tested, processed and stored under optimum sterilized conditions. The volume and frequency of blood transfusion is based upon the age and weight of the patient.¹⁸ Patients having biliary tract infections may be given blood transfusion at regular intervals i.e. at times of illness for example pregnant women. This strategy is adopted to ensure that patient would not subject to iron overload. To ensure it, the level of hemoglobin (Hb) in pre-transfusion mostly ranges from 7 to 9 g/dl while post-transfusion it should be from 11 to 13 g/dl.¹⁹

Blood Group Discrepancy and Delayed Hemolytic Reactions of Blood Transfusion:

Karl Landsteiner ABO blood groups comprised A, B, AB, and O blood groups. Landsteiner's ABO blood groups system is most significant in transfusion medicines while blood groups A and AB have subgroups which are categorized on the behalf of antigen A1, Antigen A2, Antigen A1B and Antigen A2B respectively. From the given individuals about 20% belong to Antigen A2 while rest comprising

80% are related to A1. Anti-A1 Lectin which is a reagent used for the recognition of A1 subgroup in agglutination test and work as a cold agglutinin which destroy A1 cells is clinically significant when it reacts at 37°C results in transfusion reactions.²⁰ The blood group A has two phenotypes which are A1 and A2 and AB blood group also has two phenotypes like A1B and A2B as shown in Tables 1 and 2.²¹

Table 1: Showing A and AB subgroup phenotypes

Phenotypes	Whites European	African American	Asian
A1	45 %	21 %	31 %
A2	12 %	8 %	8 %
A1B	5 %	6 %	10 %
A2B	2 %	2 %	4 %

The Subgroups of A and AB blood groups have great significance for blood transfusion which is ignored always and responsible for delay hemolytic transfusion reactions.

Table 2: Antibodies present in the serum of blood groups with antigen A1 and antigen A2

Group	Antibody found in serum
A1	Contains Anti B
A2	Contains Anti B and anti A, is up to the level of 20 %
A1B	Contains None
A2B	Contains Anti A1 is up to level of 25 %

Quality of Thalassaemia Patient's Life:

Thalassaemia patients have influence on their quality of life due to number of factors such as their appearance, treatment burden as visiting hospitals very often and having iron-chelating therapy.²² There are uncertainties regarding future life there is risk of early death due to complications caused by disease severity.²³ The social life of disease suffered people is highly affected by thalassaemia. Patients get disturbed because of continuous treatments and illness suffers from depression, anxiety, stress, anger and loneliness.²⁴ Most of patients are concerned with their future due to

fear of complications that can possibly occur at any time which make their lives stressful.²⁵ Parents of under-treatment patients also face financial burden due to their kid's life-long illness. They have to deal with costly treatments to their young ones for thalassaemia disease.²⁶ This problem is associated with psychological trauma in children life having thalassaemia that is creating hindrance in living normal life without depression. Hence, there should be proper support for thalassaemia patients including psychiatric sessions so that they can live their life without taking too much stress and have near to a healthier mind and body.²⁷

Practices of Blood Transfusion:

Globally, more than 22,500 deaths occur each year because thalassaemia patients receive inadequate transfusions due to number of factors.²⁸ Most probable shortage in blood supply, costly treatments as thalassaemia patients in developing countries got insufficient transfusions and receives hemoglobin below the recommended level.²⁹ In blood transfusion process there are many requirements that should be fulfilled while completing this task and making sure that patient is getting appropriate treatment. These requirements include a well-maintained infrastructure, continuous supply of electricity, professionals, availability of supplies, reagents and resources during blood transfusion, patient might be subjected to some deadly diseases and infections.³⁰

Transfusion Associated Infections:

Transfusion transmitted infections may be viral, bacterial or parasitic, it is recommended to screen out blood before transfusion ,if the blood is not screened, the patient may be subjected to HBV, HCV, HIV and syphilis.³¹ The risk of such infections is most prevalent in underdeveloped countries where there are no means of blood screening.³² Pakistan is being a developing country also facing problem of proper blood screening before transfusion as there is use of immune chromatographic test kits for blood screening at optimum level. Blood samples are not perfectly screened as molecular kits are not available due to economy crisis of the country. Emerging disease such as Cruetzfeldt-Jacob disease, Zikavirus and hepatitis E has some special recommendations in some areas. In low-income countries, it is deduced that almost 0.33% to 1.66% of all blood donations are infected with HIV.^{31,33}

Viral Infections:

a. Hepadnaviridae virus:

Hepatitis B virus is one of the most common infections found to be occurring in patients during blood transfusion.³⁴ Hepatitis B (Surface Antigen) HBsAg virus is a DNA virus belongs to hepadnaviridae family and its incubation period is average 60 to 90 days.³⁵ The research studies have shown that about 4.6% of blood donor community is HBV infected and out of 1440 blood donors, 44 were positive with HBV in Pakistan. According to another study, approximately 7 to 9 million populations is hepatitis B positive and about 3 to 5% are carrier for this disease.³⁶ Seroprevalence studies have been conducted on populations carrying out blood transfusions from Peshawar, Rawalpindi, Abbottabad, Multan, Bahawalpur, Quetta, and Karachi, which depicted HBV prevalence rates are 2.51%, 1.9%, 3.3%, 1.55%, 4.93%, 2.69%, and 4.90%, respectively.³⁷ There are eight different genotypes of hepatitis B virus and their prevalence of each type region to region.^{36,38} The research studies have shown that the genotype which is most prevalent in Pakistan is genotype D.³⁹ This serotype has a special viral pattern that may predict a long term response to lamivudine treatment.⁴⁰

b. Flaviviridae Virus:

Hepatitis C, commonly known as a silent killer and it is able to exhibit no more symptoms for a considerable time span. Upto the time when any symptom is being seen when liver of an individual works improperly or may be victims of cancer.⁴¹ It is taken as abrupt cause of death due to its fatality. Hepatitis C virus belongs to Flaviviridae family first identified in 1989, major agent of acute and chronic conditions. Its incubation period is 3 to 26 weeks.⁴² The causative virus (HCV) has a diameter of 80 nm with a lipid coat & a single strand of linear RNA.⁴³ The transmission of HCV is

from transplant or the transfusion of un-screened blood or even blood products like acupuncture, tattooing and body piercing in healthy individuals. In the current research aim was to uncover the prevalence of HCV in apparently healthy voluntary blood donors by using ELISA to inhibit or minimize the immunochromatography test.⁴⁴ The numbers of samples were compared with CLIA and NAT technology, Immunochromatographic test kits where best results were found out through CLIA and NAT techniques.⁴⁵ The difference in HCV prevalence was higher in males as compared to females on the base of gender.⁴⁶

c. Retroviruses:

Retroviruses are a group of RNA viruses that insert its DNA copy into their host cell in order to replicate for example HIV is a retrovirus and its window period may range from 3 to 12 weeks.⁴⁷ In 1986, the screening test for anti-HTLV-1 and anti-HIV-1 antibodies became essential before blood transfusion.⁴⁸ The screening test for anti-HIV-2 antibody was added in 1994 for the purpose of blood transfusion.⁴⁹ In western Japan, the proportion of Human T lymphotropic virus-1 (HTLV-1) carriers were large as 1(%) percent of the population. The rate of infection due to blood transfusion was very high around 10 (%) percent in the world population. However, the horizontally infected individuals through blood transfusion rarely develop viral diseases such as leukemia, lymphoma, or neurological diseases, suggesting that the introduction of antibody detection made assured level of safety at almost satisfactory.⁵⁰ The HIV infections have a great impact on society because of the poor prognoses for the infected persons, as stated above, multiple reports of HIV infection through blood donation during the window period led to the introduction of Nucleic Acid Testing (NAT) for HIV along with two types of viruses. However, it should be noted that the

Table 3: Screening results of viral markers and bacterial infections in Thalassaemia patients on the base of ICT technique and CLIA technique

ICT Technique	Frequency	%	CLIA Technique	Frequency	%
HCV Reactive	840	76.37	HCV Reactive	1080	73.17
HBs Ag Reactive	120	10.90	HBs Ag Reactive	168	11.38
HIV Reactive	60	5.45	HIV Reactive	88	5.96
TP/VDRL Reactive	80	7.28	TP/VDRL Reactive	140	9.49
Total	1100	100	Total	1476	100

window period exists even with Nucleic Acid testing (NAT).⁵¹

The data shown here was taken on July 2016, 2018 and December 2019 by ICT method and out of 4000 screened samples 1100 (27.5%) were reactive for infectious diseases and sample screened through CLIA technique out of 4000 samples 1476 (36.9%) samples were reactive for infectious diseases as shown in table 3.^{52,53,54}

New-variant-creutzfeldt-jakob Disease (nvCJD):

The first case of New-variant-Creutzfeldt-Jakob Disease (nvCJD) was found in Britain in 1994, more than 100 cases in Britain, 3 in France, and 1 in Ireland have been observed. This disease carries striking clinical and pathological resemblance to Bovine spongiform encephalopathy (BSE) a mad cow disease that occurred explosively in Britain before nvCJD and characteristically develops within the young generation; this was named nvCJD so as to differentiate it from the first isolated CJD.⁵⁵ Like scrapie in sheep or kuru stemming from the cannibalism of the aboriginal people of latest Guinea, the body of infection of nvCJD is abnormal prion agents.⁵⁶ An epidemiological study has harshly recommended that patients had been infected with this disease across the species barrier by ingesting tissues of Bovine spongiform encephalopathy (BSE), infected cows.⁵⁷ This Infection is completed in the lymphatic tissue of the intestinal tract. The possibility has been shown that prion agents maybe accumulated in lymphocytes, particularly the dendritic cells of lymph follicles and travel all over the body.⁵⁸ By year 2000, the British government took measures to remove white blood cells from all donation of blood before reserve while importing all plasma derivatives, for which removal and inactivation of prion agents are difficult, from other countries.⁵⁹ Whether nvCJD is transmitted by blood remains unclear because the incubation period for this disease lasts long, it is possible that many people in the incubation period during blood donation then immeasurable damage to the state by blood transfusions is anticipated, therefore, other European and American countries employed similar policies on the handling of blood. When sheep arise transfused with blood from other sheep that had ingested brain tissues of BSE-infected cows, one sheep arise encephalopathy almost like mad cow infection.⁶⁰ These results strongly suggest the likelihood of infection of this disease

through transfusion and accumulation of stronger evidence is predicted. In Japan there would be blood donors are interviewed to exclude people that have spent a particular period of your time in European countries, like Britain or France, where nvCJD and BSE are occurring. However, if BSE goes widespread, Japan can also need to consider adopting those measures that European countries were adapted quickly.⁶¹

Bacterial Infections:

The safety and security of blood arrangements, now looks almost appropriate against known pathogens which would be detected only by screening. At Current, the leading distressing kind of infection is the disease with bacteria mixed by any mean into the blood preparations. Yet, this problem is ignored or overlooked in Japan.⁶² Actually, only 0.05 % or 1 out of 2,000 units of platelet preparations which are formally stored at room temperature is unconsciously contaminated with bacteria and it is probable that almost more than 150 deaths are resulted annually from those applied preparations which are contaminated prior through any source, in the United States of America.⁶³ The preparations made for red blood corpuscle (RBC) which is stored at cold temperature; the species of psychrophilic bacteria like *Yersinia enterocolitica* and *Serratia* cause a risk. The platelet preparations, next to that, are stored at room temperature, indigenous bacteria formally present on the skin like *Staphylococcus epidermidis* are a drag in this regard. The extreme life-threatening bacterial contamination caused by the species *Yersinia enterocolitica* is outcome by blood donated by donors affected with short- term bacteremia. It is considered that the time duration of at least three weeks or more of storage is necessary for the bacterium to achieve the noxious level. In reflection of the danger, storage of red blood cells preparations (RBC) is limited up to 3 weeks, though in Japan, it might be stored for 5 weeks.⁶⁴ The cases of post-transfusion sepsis occurring from the platelet preparations are erratic according to the reports shown by Japan while assessment of the conditions are imperative and depends on the results obtained so manufacturers may also be asked to perform screening for conformity as is done by the number of their European and American counterparts now.⁶⁵

Problems Associated with Blood Transfusion:

a. In Hospital Allogenic Blood Collection:As stated prior, blood preparations extracted from donated blood of donors is collected and

processed by the Japanese Red Cross Blood Center for general purposes are satisfactorily safe because of their outstanding work done. However, numerous medically facilitating centers are still using Allogeneic blood which is collected at the locality of centers. Such blood should not be used in ordinary conditions except during facing disaster, emergency or at the time when the available stock of blood has shortened because the blood collected in the hospital can never be assured. The security compatibility for the protection of blood donated by donors appreciates to the expressed potential shown for the performance of screening tests like NAT. There is no doubt about the relative benefits entertained by using donated blood to the recipients.⁶⁶ It should not be allowed if consent for the transfusion is taken without informing the tolerant individual. Recently, Japanese Society of transfusion has submitted "Guidelines on Collection, Processing and Usage of Blood as well as its Components Intended for Treatment at Medical Facilitating centers" to the Ministry of Health, Welfare and Labor. Guidelines mapped on the handling and management of blood and its components at medical facilities are going to published soon.⁶⁷

b. Autologous Blood and Nosocomial Infections:

The consent form for the blood transfusion has been made compulsory and use of autologous blood during processes like elective surgery has become general. The duration of storage for preoperative blood sometimes is extended to 5 weeks and there exist concern about contamination due to bacterial species like *Yersinia enterocolitica* due to that special caution should be exercised to prevent from nosocomial infections.⁶⁸ These conditions should keep continue to be reviewed regularly and autologous blood should always be collected and stored at a dedicated administrative sections which are following the procedures prescribed in the Guidelines on Autologous Transfusions. The autologous transfusion should be far safer than the allogeneic transfusion and must be re-evaluated gradually as well as time suitably. The medical professionals should definitely take lot of care in handling autologous blood taken unconsciously from the patients with communicable diseases to protect themselves.⁶⁹

The ultraviolet blood irradiation therapy is taken as the edge due to its positive effects on more than 70 different types of viral as well as bacterial infections including respiratory disorders, circulatory, cardiovascular and the general

inflammation.⁷⁰ Ultraviolet radiations (UV) are basically the type of electromagnetic radiations with the range of its wavelength which is comparatively lesser than visible light but longer than x rays. It has been divided into four phases like UV, UVA, UVB, and UVC. From the time of 1940, it has been used as a reliable source for the eradication of the infectious agents especially bacteria.⁷¹

CONCLUSION

Our study findings are of view that blood transfusion infections (HCV, HBV, HIV and some bacterial infections) are high and always being suffered by thalassaemia patients. Immuno-chromatographic technique (ICT) is not reliable for blood screening prior to blood transfusion especially in thalassaemia patients while generally for all types of transfusions. The Chemiluminescence Immunoassay (CLIA) technique is most appropriate and trust worthy one for blood screening purpose to capture weak positive and low titer infectious agents which do not expose during their window period with Immuno-chromatographic (ICT). In order to prevent delayed hemolytic transfusion reactions, it is suggested that the subgroups of blood group A (A1 and A2) and AB (A1B and A2B) must be performed at the time of cross-match following procedure. Therefore, it is suggested that radiation therapy should always be performed before all types of blood transfusions hence there will be least chance of blood contaminations i.e. bacterial infections etc.

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