

Transfusion Transmitted Infections In Patients With Hemophilia: A Study From A Tertiary Care Hospital In Western India.

M Mittal, S Zaman, N Bhatnagar, M Gajjar

Citation

M Mittal, S Zaman, N Bhatnagar, M Gajjar. *Transfusion Transmitted Infections In Patients With Hemophilia: A Study From A Tertiary Care Hospital In Western India.*. The Internet Journal of Infectious Diseases. 2013 Volume 12 Number 1.

Abstract

Transfusion transmitted infections (TTI) continue to endanger safe blood supply. The risk for acquiring TTI is even higher in multiply transfused patients. This study is aimed to estimate the prevalence of TTI in 80 multiply transfused patients of Hemophilia. 80 male patients of hemophilia and 320 normal voluntary blood donors were included in the study. Screening for anti-HIV, HBsAg and anti-HCV was carried out by enzyme linked immunosorbent assay (ELISA). Syphilis was tested using RPR card test. Out of 80 multiply transfused patients, 10 (12.5%) were infected with TTI. Seroreactivity for 7.5% for HCV and 5 % for HBV. No patient was found reactive for HIV and syphilis. In blood donors seroprevalence of viral markers was 0.31% for HCV and HIV, 0.94% for HBV whereas 1.25% donors showed reactive RPR test for syphilis. This study showed that HCV and HBV infection were more frequently identified than HIV in multitransfused hemophiliacs. Promoting voluntary blood donation, adopting sensitive screening methods and use of virally inactivated or recombinant factor concentrate will decrease the prevalence of TTI in people with hemophilia (PWH).

INTRODUCTION

The earliest written references to what appears to be hemophilia are found in Jewish texts from the second century AD in which Rabbinical rulings exempted male boys from circumcision if two previous brothers had died of bleeding after the procedure.¹ First medical professional to describe a bleeding disorder corresponding to hemophilia was Arab physician Abu al-Qasim Khalaf ibn al-Abbas Al-Zahrawi (936-1013 AD) who, in his book "Kitab al-Tasrif", or Methods in Medicine documented an illness localized to males of a particular village in which patients bleed profusely after minor trauma.² By 12th century, Hebrew physician Moses Maimonides recognized that these familial bleeding tendencies were transmitted through the mother.³ The term, haemophilia, originated with a German, Friedrich Hopff (1828), who coined the name "haemorrhaphilia" which was later abbreviated to hemophilia.⁴ Haemophilia is the commonest X-linked recessive hereditary bleeding disorder, arising due to absence of, decrease in, or deficient function of plasma coagulation factor VIII or factor IX.⁵ The disease affects 1 in 10,000 males worldwide, in all ethnic groups; hemophilia A represents 80% of all cases. Male subjects are clinically affected; women, who carry a single mutated gene, are generally asymptomatic.⁶

Primary modality of treatment in hemophilia is factor replacement therapy. Unlike developed nations, where factor concentrates are virally inactivated or are made by recombinant technology, patients in developing nations like India heavily depend upon "wet" blood products like Fresh Frozen plasma or cryoprecipitate for the prophylaxis and management of bleeding episodes. These products are usually not treated to eliminate blood-borne viruses. Therefore, Transfusion-transmitted infections (TTIs) such as Hepatitis B (HBV), and C (HCV) and HIV continue to thwart safe blood transfusion practices in healthcare facilities dealing with management of hemophilia patients. National blood supply heavily relies on replacement blood donors. Various studies done in India shows high incidence of HIV, HBV, HCV and syphilis in replacement blood donors as compared to voluntary non-remunerated blood donors.^{7, 8} Further, widespread use of less sensitive "Rapid Kits" to screen blood units in Blood Banks leads to release of infectious units into the circulation.⁹ A survey conducted by Kapoor et al. in 2000 involving 604 blood banks revealed that testing for transfusion-transmitted infections is unsatisfactory and poorly regulated in India.¹⁰ Prevalence of anti-HIV, hepatitis B surface antigen (HBsAg), anti-HCV and syphilis positivity in Indian blood

donors is 0.084-3.87%, 0.66-12%, 0.5-1.5% and 0.85-3% respectively.¹¹

Although government of India has made mandatory to screen donated blood for HBV (since 1971), HIV (since 1989), HCV (since 2001)^{12, 13}, risks of TTIs especially to multiply transfused patients who acquire infections due to blood donation by seronegative donors during the window period when the donors are undergoing seroconversion. The objective of this study was to compare the prevalence of TTIs in multiply transfused hemophilia patients and to compare the results with voluntary blood donors assuming that they represent the normal population.

METHODS

This study was conducted at BJ Medical College, Ahmedabad during May 2007 to May 2009. Informed consent was obtained from all adult participants, parents, or legal guardians as the case may be. A total of 80 cases of Hemophilia enrolled at our facility were included. Detailed clinical data was noted including age, family history, and interval of transfusion, Hemoglobin level and Hepatitis B immunization status.

Patients were tested for HBs Ag, anti-HIV and anti-HCV antibodies using 3rd generation ELISA kits manufactured by J. Mitra & Co. Syphilis serology was done using the rapid plasma reagin (RPR) card test (Tulip Diagnostics). Three hundred and twenty healthy blood donors served as normal controls. Donor selection was done by pre-donation structured questionnaire followed by brief physical examination and haemoglobin estimation as per the guidelines of Directorate General of Health Services guidelines, Ministry of Health and Family Welfare.¹⁴ Permission from Ethical Committee for this study was obtained before starting the study.

Statistical Analysis

Statistical values were determined by SPSS software version 15.0 (SPSS Inc. Chicago, Illinois). p-value less than 0.05 was considered as significant.

RESULTS

Eighty male haemophilia patients were evaluated. Most of the patients received liquid blood products as replacement therapy (Table 1). 77 (96.2%) patients were of hemophilia A and 3 (3.8%) of hemophilia B. Mean age of the patients was (\pm SD) was 23.31 ± 16.42 years (range 2–69 years). Total of 10 patients (12.5%) were tested positive for TTI (Table 2). Mean age for HBV positivity was 35.75 ± 17.59 years (range 16-58 years) whereas for HCV infection, mean

age was 44.67 ± 15.17 years (range 25-62 years). Voluntary blood donors were between 18-55 years of age (Mean 33 years). No coinfection was detected in any of the cases or controls.

Table 1

Replacement therapy given to patients

Type of replacement	Number of patients	Number of units transfused	Units of product/patient
Whole Blood	29	401	13.8
Fresh Frozen Plasma	52	1453	27.94
Cryoprecipitate	46	1684	36.61
Factor VIII concentrate	11	165 vials	15

Table 2

Comparison of prevalence of transfusion transmitted infections in hemophilia patients and voluntary blood donors.

TTI	No. of patients	prevalence and 95% CI	No. of voluntary donors)	Prevalence and 95% CI	p-value
HCV positive	6	7.5% (1.73% to 13.27%)	1	0.31 (-0.3% to 0.92%)	<0.001
HBV positive	4	5% (0.22% to 9.78%)	3	0.94 (-0.12% to 2%)	0.013
HIV positive	0	-	1	0.31 (-0.3% to 0.92%)	0.288
Syphilis (RPR positive)	0	-	5	1.6 (0.23% to 2.97%)	0.261
Total	10	-	10		

DISCUSSION

With population exceeding 1 billion, the expected number of patients with hemophilia in India would be approximately 60,000.¹⁵ Most of these patients are not able to afford expensive virally inactivated clotting factors and are dependent on 'wet' blood products i.e. Fresh Frozen plasma or cryoprecipitate for the prophylaxis and management of bleeding episodes. However, these products are usually not treated to eliminate blood-borne viruses. Therefore, TTIs such as Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and HIV continue to pose challenges to healthcare facilities dealing with management of hemophilia patients. Hepatitis C virus, discovered in 1989, is a member of the Flaviviridae family. It is a 30-60nm, enveloped, single-stranded RNA virus which is transmitted parenterally. HCV infection has gained importance particularly as one of the

major complications in multiply transfused patients during the last decade. This is especially true for countries like India where HCV prevalence is showing an increasing trend among blood donors.¹⁶ The high incidence of hepatitis after treatment with clotting factor concentrate from a large pool was first identified by Kasper and Kipnis in 1972.¹⁷ Various studies from India demonstrate 23-27% prevalence of anti-HCV in multiple-transfused patients of hemophilia.¹⁸⁻²⁰ The prevalence of HCV infection among hemophiliacs in our study is 7.5%. Reason for this relatively low prevalence could be small sample size of our study population and effective blood screening for TTIs by our blood bank. An significant observation of our study was mean age of anti-HCV reactive patients was 44.67 ± 15.17 years which may be because of the HCV untested blood transfusion before 2001.

Hepatitis B virus (HBV) is one of the major global public health problems. In India, HBsAg prevalence among general population ranges from 2% to 8%, placing India in intermediate HBV endemicity zone and the number of HBV carriers is estimated to be 50 million, forming the second largest global pool of chronic HBV infections.²¹ This, in the context of a large population and patchy coverage of hepatitis B vaccination in National immunization programme would translate in further increase in burden of hepatitis B in near future. HBsAg screening in blood units reduces but does not eliminate the risk of HBV transmission. HBsAg test may be negative in the window phase of HBV infection, in the convalescence phase and also in HBV chronic infection, with very low level of viremia.²² In addition to post-transfusion hepatitis, hemophiliacs are also at increased risk for hepatocellular carcinoma (HCC). In a questionnaire-based survey of 11,801 multitransfused hemophiliacs from 54 centres in the United States and Europe, 10 cases of HCC were reported that were invariably associated with cirrhosis due to either HBV or HCV infection.²³ Many prevalence studies have found that the HBV infections occurring in multiply transfused hemophiliacs patients range from 0.53% to 7.4, 20, 24-27. Results of these observations were in accordance of the present study, where reported prevalence of HBV was 5 %. The prevalence of HIV infection in haemophiliacs varies greatly worldwide, from 0% to more than 49, 20, 24, 25, 28-31. Our study showed zero prevalence of HIV in haemophiliacs. This again, could be due to small sample size of our study and also due to the fact that only 10% of the expected people are registered in the Haemophilia Federation of India.³²

Transfusion transmitted syphilis is not a major hazard of modern blood transfusion therapy. Treponemes are relatively fragile, in particular being heat-sensitive; storage below +20°C for more than 72 hours results in irreparable damage to the organism such that it is no longer infectious.³³ There are no studies suggesting prevalence of syphilis in Hemophilia patients.

CONCLUSION

As envisioned in National Blood Policy formulated by National AIDS Control Organisation, practice of replacement donors should be gradually phased out and blood centres should strive to achieve 100% voluntary non-remunerated blood donations.

Implementation of sensitive blood screening protocols like nucleic acid testing (NAT) and widespread use of viral inactivation methods would significantly decrease TTIs in hemophiliacs. Unfortunately, high cost involved in these procedures act as deterrent to both government and the patient. Government is reluctant to spend huge amount of money on this low volume-high cost disease. Hemophilia federation of India is the only organisation working for management of a people with Hemophilia (PWH) and that too, without any help from state or central governments. In absence of government sponsored scheme for management of hemophilia, recombinant factor concentrates remains unaffordable to most of the patients. Through this paper, Government of India is urged to immediately formulate national health programs for the betterment of hemophiliacs so that every person with this rare-disease can get recombinant or virally-inactivated factors whenever required and lead healthy life free from Transfusion transmitted Infections.

References

1. [No authors cited]. History of Hemophilia. [cited 2012 oct 23]; World Federation of hemophilia 2003. [Available at: http://www.wfh.org/2/1/1_1_8_History_Hemophilia.htm.
2. Kadan A, Angrini M. Who discovered hemophilia? . J Int Soc History Islamic Med 2009;8-9:46-50.
3. Rosner F. The medical legacy of Moses Maimonides. New Jersey: KTAV Publishing House 1998.
4. Nilsson IM. [Haemophilia--then and now]. Sydsvenska medicinhistoriska sällskapets årsskrift 1994;31:33-52.
5. [No authors cited]. Prevention and control of haemophilia: memorandum from a joint WHO/WFH meeting (World Federation of Haemophilia). Bull World Health Organ 1991;69:17-26.
6. Aruda V, High KA. Coagulation disorders. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine, 17th ed. New York: McGraw-Hill;2012. p. 974
7. Chandra T, Kumar A, Gupta A. Prevalence of transfusion transmitted infections in blood donors: an Indian experience.

Trop Doct 2009;39:152-4.

8. Fernandes H, D'souza PF, D'souza PM. Prevalence of transfusion transmitted infections in voluntary and replacement donors. *Indian J Hematol Blood Transfus* 2010;26:89-91.
9. Torane VP, Shastri JS. Comparison of ELISA and rapid screening tests for the diagnosis of HIV, Hepatitis B and Hepatitis C among healthy blood donors in a tertiary care hospital in Mumbai. *Indian J Med Microbiol* 2008;26:284-5
10. Kapoor D, Saxena R, Sood B, Sarin SK. Blood transfusion practices in India: results of a national survey. *Indian J Gastroenterol* 2000;19:64-7
11. Chatteraj A, Behl R, Kataria VK. Infectious disease markers in blood donors. *Medical Journal Armed Forces India* 2008;64:33-5.
12. Narayan S. Microbes and blood transfusion. *Indian J Med Microbiol* 2001;19:119-26.
13. Sen S, Mishra NM, Giri T, et al. Acquired immunodeficiency syndrome (AIDS) in multitransfused children with thalassemia. *Indian Pediatr* 1993;30:455-60.
14. Saran RK. *Transfusion Medicine, Technical Manual* 2nd ed. New Delhi, India: Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare, Government of India 2003.
15. Srivastava A, You SK, Ayob Y, et al. Hemophilia treatment in developing countries: products and protocols. *Semin Thromb Hemost* 2005;31:495-500.
16. Meena M, Jindal T, Hazarika A. Prevalence of hepatitis B virus and hepatitis C virus among blood donors at a tertiary care hospital in India: a five-year study. *Transfusion* 2011;51:198-202.
17. Kasper CK, Kipnis SA. Hepatitis and clotting-factor concentrates. *JAMA* 1972;221:510.
18. Sengupta B, De M, Lahiri P, Bhattacharya DK. Sero-surveillance of transmissible hepatitis B & C viruses in asymptomatic HIV infection in haemophilics. *Indian J Med Res* 1992;95:256-8.
19. Bhattacharya DK, Bhattacharjee S, De M, Lahiri P. Prevalence of hepatitis C in transfusion dependent thalassaemics & haemophilics. *Indian J Med Res* 1991;94:430-2
20. Ghosh K, Joshi SH, Shetty S, et al. Transfusion transmitted diseases in haemophilics from western India. *Indian J Med Res* 2000;112:61-4.
21. Datta S. An overview of molecular epidemiology of hepatitis B virus (HBV) in India. *Virol J* 2008;5:156.
22. Jain R, Perkins J, Johnson ST, et al. A prospective study for prevalence and/or development of transfusion-transmitted infections in multiply transfused thalassemia major patients. *Asian J Transfus Sci* 2012;6:151-4
23. Colombo M, Mannucci PM, Brettler DB, et al. Hepatocellular carcinoma in hemophilia. *Am J Hematol* 1991;37:243-6.
24. Karimi M, Ghavanini AA. Seroprevalence of HBsAg, anti-HCV, and anti-HIV among haemophilic patients in Shiraz, Iran. *Haematologia (Budap)* 2001;31:251-5.
25. Al-Sheyyab M, Batieha A, El-Khateeb M. The prevalence of hepatitis B, hepatitis C and human immune deficiency virus markers in multi-transfused patients. *J Trop Pediatr* 2001;47:239-42.
26. Islam MN, Banatvala JE. The prevalence of hepatitis-B antigen (HB S Ag) and its antibody (Anti-HB S) among London hemophiliacs and blood donors from London and two tropical areas. *Transfusion* 1976;16:237-41.
27. Kacperska E, Gloskowska-Moraczewska Z, Seyfried H, Kolasinska-Kramer M, Cetnarowicz H, Lopaciuk S. [Serological markers of hepatitis B virus and cytomegalovirus in patients with hemophilia]. *Acta Haematol Pol* 1990;21:52-9.
28. Bhushan V, Chandy M, Babu PG, et al. Transfusion associated HIV infection in patients with haematologic disorders in southern India. *Indian J Med Res* 1994;99:57-60.
29. Singh YN, Bhargava M, Malaviya AN, Tripathy SP, Kakkar A, Khare SD. HIV infection in Asian Indian patients with haemophilia & those who had multiple transfusions. *Indian J Med Res* 1991;93:12-4.
30. Daul CB, deShazo RD, Andes WA. Human immunodeficiency virus infection in hemophilic patients. A three-year prospective evaluation. *Am J Med* 1988;84:801-9.
31. Borhany M, Shamsi T, Boota S, et al. Transfusion transmitted infections in patients with hemophilia of Karachi, Pakistan. *Clin Appl Thromb Hemost* 2011;17:651-5.
32. Stonebraker JS, Bolton-Maggs PH, Soucie JM, Walker I, Brooker M. A study of variations in the reported haemophilia A prevalence around the world. *Haemophilia* 2010;16:20-32.
33. [No authors cited]. In *Screening donated blood for transfusion-transmitted infections recommendations*. World Health Organisation; 2010

Author Information

Mahima Mittal, Senior Resident

Department of Transfusion Medicine All India Institute of Medical Sciences
New Delhi, India

Shamsuz Zaman, Senior Resident

Department of Transfusion Medicine All India Institute of Medical Sciences
New Delhi, India
shams_amu@yahoo.com

Nidhi Bhatnagar, Associate Professor

Department of Immunohematology and Blood Transfusion B.J. Medical College
Ahmedabad, Gujarat. India

M.D. Gajjar, Professor and Head

Department of Immunohematology and Blood Transfusion B.J. Medical College
Ahmedabad, Gujarat. India
drmgajjar@hotmail.com