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

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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. 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. By 12th century, Hebrew physician Moses Maimonides recognized that these familial bleeding tendencies were transmitted through the mother. The term, haemophilia, originated with a German, Friedrich Hopff (1828), who coined the name “haemorrhaphilia” which was later abbreviated to hemophilia. 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. 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. 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. Further, widespread use of less sensitive “Rapid Kits” to screen blood units in Blood Banks leads to release of infectious units into the circulation. 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. Prevalence of anti-HIV, hepatitis B surface antigen (HBsAg), anti-HCV and syphilis positivity in Indian blood
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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 (± 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

<table>
<thead>
<tr>
<th>Type of replacement</th>
<th>Number of patients</th>
<th>Number of units transfused</th>
<th>Units of product/patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Blood</td>
<td>29</td>
<td>138</td>
<td>4.67</td>
</tr>
<tr>
<td>Fresh Frozen Plasma</td>
<td>52</td>
<td>1453</td>
<td>29.74</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>46</td>
<td>1694</td>
<td>36.61</td>
</tr>
<tr>
<td>Factor VIII conc.</td>
<td>11</td>
<td>165 vials</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 2
Comparison of prevalence of transfusion transmitted infections in hemophilia patients and voluntary blood donors.

<table>
<thead>
<tr>
<th>TTI</th>
<th>No. of patients</th>
<th>Prevalence &amp; 95% CI</th>
<th>No. of voluntary donors</th>
<th>Prevalence &amp; 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV positive</td>
<td>6</td>
<td>7.5% (1.73 to 13.27)</td>
<td>3</td>
<td>0.31 (0.3% to 9.92)</td>
<td>0.013</td>
</tr>
<tr>
<td>HBV positive</td>
<td>4</td>
<td>5% (0.22% to 9.78)</td>
<td>4</td>
<td>0.02 (0.3% to 9.22)</td>
<td>0.287</td>
</tr>
<tr>
<td>HIV positive</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Syphilis (RPR positive)</td>
<td>16</td>
<td>1.6% (0.23% to 2.97)</td>
<td>2</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10</td>
<td><strong>10</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 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**

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