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ORIGINAL ARTICLE

A Cross-Sectional Study on Burden of Hepatitis C, Hepatitis B, HIV and Syphilis in Multi-Transfused Thalassemia Major Patients Reporting to a Government Hospital of Central India

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Abstract Need for frequent blood transfusions exposes thalassemia major patients to risk of transfusion-transmitted infections (TTIs). Screening of donor blood through national protocols for possible infections like hepatitis B and C, HIV, syphilis and malaria is considered the optimal preventive method. There is constant need to explore the effect of currently used protocols of blood-donor screening by determining the burden of TTIs in multi-transfused patients. The current study was conducted to determine the burden of TTIs among multi-transfused Thalassemia patients registered at a Government hospital of central India. Sixty-six multi-transfused Thalassemia patients reporting during a period of eight months were screened for hepatitis B and C, HIV as well as syphilis by using standard diagnostic tests. Selected clinical, socio-demographic and other characteristics were also recorded to understand the determinants of risks of these infections. The sero-prevalence of hepatitis B, hepatitis C, HIV and syphilis was 3.0, 18.2, 1.5 and 0 % respectively amongst the patients. Vaccination against hepatitis B was found to be protective. Majority of the infected patients had history of transfusion from non government blood banks. There is a considerable burden of Hepatitis C among multi-transfused Thalassemia patients. The currently used screening tests need to be re-validated or replaced to prevent false-negative diagnoses. All sectors need to optimally implement and control both, the quality of blood donors and the mandatory screening of blood and blood products against the TTIs along with prospective longitudinal data and follow up of patients.

Keywords Blood-transfusion · Burden · Thalassemia · Seroprevalence · Screening tests

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Introduction

Risk of transfusion-transmitted infections (TTIs) (e.g. viral hepatitis, cytomegalovirus, HIV infection, malaria, parvovirus B-19 etc.) is a serious problem in patients receiving chronic transfusions and undergoing invasive procedures with exposure of circulatory system [1–3]. The risk is higher among the subgroup of haemoglobinopathy subjects such as patients suffering from thalassemia and haemophilia [4]. Emergence of human immunodeficiency virus (HIV), Hepatitis B virus (HBV) and Hepatitis C virus (HCV) in the 1980s has brought forth on-going transformation in blood and blood product management protocols world-over. Based upon prevalence data for the particular donor population and surveillance data for other potentially transmissible agents, as well as the pathogenic potential of the agent, together with any political, social or ethical considerations, laws have

been formulated for mandatory testing of blood and blood-products against certain blood-borne microbial infections such HBV, HCV, HIV, syphilis and malaria. The screening of donated blood and blood-products for a minimum set of markers of blood-borne infectious agents is mandatory by law in most of the countries world-over including India. In India, the Drug and Cosmetics (1st amendment) Rules 1992 (3) Act, mandates the testing of each unit of donated blood for the presence of markers of HIV, HBV, malaria and syphilis [5, 6]. Since year 1997, professional blood-donation has been banned in India [7]. Blood units are screened with assays of steadily increasing sensitivity for Hepatitis B surface antigen (HBsAg) since 1971, against HIV since 1989 and against HCV since 2001 [8, 9]. A survey of blood transfusion practices noted that testing for transfusion-transmitted infections is unsatisfactory and poorly regulated in most blood banks, both private and government, throughout India [10]. Patients with thalassemia major are at high risk of hepatitis C due to the blood transfusion from donors infected by HCV. Number of transfusion units, years of transfusion history (6 or more), and number of treatment facilities (2 or more) have been reported to be associated with HCV infection. Although, improvement in screening of blood products from 1980 to 1990 decreased the risk of transmission of blood-borne diseases, however, Hepatitis C is still an important problem in patients with thalassemia patients. The chronicity and potentially fatal nature of these conditions pose a considerable burden on the management of the thalassemia patients. There are not many studies reporting the burden of blood-borne infections following multi-transfusion of blood in thalassemia patients from Central India. The need to explore the burden of transfusion-mediated infections in these patients cannot be overemphasized.

The current study was done to determine the burden of Hepatitis B, Hepatitis C and HIV infection in multi-transfused thalassemia patients of Bhopal and surrounding area. The effect of hepatitis B vaccination on its sero-prevalence in this group was also studied. We also have attempted to understand correlation of the serum ferritin level with transfusion index.

Materials and Methods

The current study was a hospital based cross-sectional study and was done at a 350-bedded multi-specialty tertiary healthcare centre of central India. The study enrolled multi-transfused thalassemia patients reporting for blood transfusion in the paediatrics out-patient department (OPD) spanning a period of 1 year and 7 months. We included all the patients of Thalassemia with a history of multiple-transfusion who reported to the OPD for another transfusion in the study. Informed consent was obtained after explanation to parents about the nature of the study. Previous studies have reported 10–20 % prevalence of Hepatitis C among multi-transfused thalassemia patients. Considering anticipated prevalence of Hepatitis C as 20 % and absolute sampling error of 10 %, we needed to recruit 64 patients to have 80 % chance of being within 95 % of population prevalence.

A semi-closed questionnaire was designed to obtain the medical history and selected socio-demographic information from the patients. Modified Kuppuswamy scale for assessment of socioeconomic status of the patients was used [11]. Vaccination history for Hepatitis B was obtained. The questionnaire had sections for recording the results of blood-tests for diagnosis of Hepatitis B, Hepatitis C, HIV and syphilis as well as serum levels of ferritin and transferrin. After taking informed consent and checking inclusion criteria, 5 ml venous blood sample was collected using aseptic precautions. After allowing complete retraction of the blood clot, serum was separated by centrifugation at 2,800 rpm for 15 min in aliquots. Proper labelling was done and the sample was preserved at minus 40 °C. The samples were tested for hepatitis B antigen (Eliscan HBsAg 3rd Generation ELISA), Anti HCV antibodies (HCV Microlisa 3rd Generation) and HIV-1 & HIV-2 antibodies (Eliscan HIV advanced) by qualitative enzyme linked immunosorbent assay (ELISA).

All the obtained information was coded and data was entered in Microsoft Excel. Data analysis was performed using statistical package for social sciences (SPSS) version 20 (IBM SPSS, Armonk, NY, USA). Proportions were obtained for categorical variables and confidence intervals were calculated. For continuous variables means and their standard deviations were calculated. Standard statistical tests for hypothesis testing like *t* test, Pearson's Chi square test etc. were performed to explore association with the dependent variables. To obtain a composite relationship between the dependent and independent variables, regression analyses were done as appropriate. We obtained odds ratios to quantify the risk of association.

Results

A total of 66 patients including 42 (63.6 %) males and 24 (36.4 %) females, multi-transfused thalassemia major patients were recruited during the study period having mean age of 8.1 years (0.75–25 years). In this study most patients (54, 81.8 %) were Hindu, 11 (16.7 %) patients were Muslim and 1 (1.5 %) patient was Christian. Majority of the patients (63, 97 %) were residents of Madhya Pradesh mostly residing (41, 63.1 %) within 50 kms of the health facility with mean distance of 80.6 km from

Table 1 Medical history of the study participants

	Male (%)	Female (%)	Total
Mean haemoglobin level (SD)	6.1 (0.3)	5.7 (0.4)	6 (0.2)
Mean weight in kilograms (SD)	19.9 (1.4)	18.2 (1.5)	19.3 (1)
Mean height in cm (SD)	113.6 (3.3)	107.7 (4.5)	111.4 (2.7)
Mean BMI in kg/cm^2(SD)	14.7 (0.3)	15 (0.5)	14.8 (0.3)
Blood groups			
A	7 (16.7)	1 (4.2)	8 (12.1)
B	14 (33.3)	11 (45.8)	25 (37.9)
AB	2 (4.8)	2 (8.3)	4 (6)
O	19 (45.2)	10 (41.7)	29 (44)
Rh status			
Positive	41 (97.6)	24 (100)	65 (98.5)
Negative	1 (2.4)	0	1 (1.5)
History of hepatitis B vaccination			
Complete	9 (21.4)	9 (37.5)	18 (27.3)
Incomplete	6 (14.3)	1 (4.2)	7 (10.6)
None	27 (64.3)	14 (58.3)	41 (62.1)
Mean age of diagnosis of thalassemia Major (SD)	1.4 (0.2)	2.1 (0.5)	1.6 (0.2)
Mean duration of blood transfusion (SD)	7 (0.7)	5.5 (0.7)	6.5 (0.5)
History of thalassemia major in family	3 (7.1)	1 (4.2)	4 (6.1)
History of consanguineous marriage in family	5 (11.9)	4 (16.7)	9 (13.6)
Main source of blood for transfusion (n = 65)			
Government blood bank	42 (100)	22 (95.7)	64 (98.5)
Private blood bank	0	1 (4.4)	1 (1.5)
Use of other source of blood for transfusion	24 (57.1)	13 (54.2)	37 (56.1)
Mean frequency of blood transfusion in days (SD)	24.9 (2)	28 (2)	26 (1.5)
History of chelation therapy (n = 43)			
Not indicated	3 (11.1)	2 (12.5)	5 (11.6)
Not given	17 (63)	9 (56.3)	26 (60.5)
Irregular	4 (14.8)	1 (6.2)	5 (11.6)
Regular	3 (11.1)	4 (25)	7 (16.3)
Transfusion index (High)	14 (53.9)	5 (31.3)	19 (45.2)
Thalassemia trait status of father (HPLC) (n = 35)			
No trait	0	1 (7.7)	1 (2.9)
Beta-thal trait	20 (90.9)	11 (84.6)	31 (88.6)
HbE trait	1 (4.6)	1 (7.7)	2 (5.7)
Soluble	1 (4.5)	0	1 (2.9)
Beta thalassemia/sickle cell trait (n = 29)			
No trait	2 (12.5)	1 (7.7)	3 (10.3)
Beta thalassemia trait	13 (81.2)	11 (84.6)	24 (82.8)
Beta thal& sickle cell trait	1 (6.3)	1 (7.7)	2 (6.9)
Mean serum ferritin level (SD)	3,457.2 (522.7)	2,933.4 (480.6)	3,262.3 (372.1)
Mean SGOT (SD)	71.1 (17.3)	54.6 (6.5)	65.1 (11.3)
Mean SGPT (SD)	64.1 (14.7)	46.2 (6)	57.6 (9.6)
Mean serum alkaline phosphatase (SD)	221.6 (11.2)	187.9 (10.1)	209.3 (8.2)

residence to health facility centre. The range of the distance from health facility was 10–790 Kms. Most patients (78 %) belonged to socioeconomic status of class II to IV. Table 1 depicts the details of the patients with history of Hepatitis B vaccination and HPLC studies for thalassaemia trait.

Nine patients (13.6 %) gave history of second-degree consanguineous marriage and majority belonged to Muslim community. The mean age of diagnosis of thalassemia major was 1.6 years with a range of 1 month to 7 years. A total of 37 (56.1 %) patients reported history of receiving blood from other sources in addition to the blood bank of the study hospital. Blood group analysis showed that 29 (43.9 %), 25 (37.9 %), 8 (12.1 %) and 4 (6.1 %) subjects were of blood groups O, B, A and AB respectively and all Rh positive except one patient. Pre-transfusion mean haemoglobin at hospital visit was 6 g/dl with a range of 2–11 g/dl. Transfusion index was high in 19 (45.2 %) patients. Mean duration of blood transfusions given was 6.5 years. Majority of participants (55, 83.3 %) had history of blood transfusion of less than 10 years. The range of total number of transfusion was 10–90. Mean of number of transfusions was 26 with a standard deviation of 11.6. 60 % of the patients did not receive any chelation therapy. Only 18 (27.3 %) patients reported history of complete vaccination against Hepatitis B, and 7 (10.6 %) patients had incomplete vaccination. Out of the 66 patients, 12 (18.2 %) were reactive for anti HCV antibodies (Table 2). The prevalence of Hepatitis B surface antigen (HBsAg) was 3.0 % and that of HIV was 1.5 %. Raised mean SGPT, SGOT and normal ALP levels were found in HBsAg positive patients. Increasing values of serum ferritin and liver enzymes with increasing duration of blood transfusion were reported in <5 to >10 years duration of blood transfusion respectively. The risk of Hepatitis C was highest in patients having history of transfusion between 5 and 10 years (30.8 %) and with a history of blood transfusion outside government health system (58.4 %). The frequency of transfusion, and duration of blood transfusion were not found to be statistically associated with risk of HCV infection or all TTI combined. Similarly, risk of HCV infection or TTIs was not found to be significantly associated with age, gender, religion or socio-economic status, ABO/Rh blood group status, weight or height of the patient, current SGPT/SGOT/SAP value, or family history of thalassemia or consanguineous marriage too. Relationship of TTIs with selected factors among multi-transfused thalassaemia major subjects studied has been presented in details in Table 3.

Table 2 Burden of transfusion transmitted infections (TTIs)

	Male (%)	Female (%)	Total
Prevalence of hepatitis C	8 (19.1)	4 (16.7)	12 (18.2)
Prevalence of hepatitis B	1 (2.4)	0	1 (1.5)
HBV indeterminate	0	1 (4.2)	1 (1.5)
Prevalence of HIV	1 (2.4)	0	1 (1.5)
Prevalence of syphilis (VDRL +ve)	0	0	0
Any TTI	10 (23.8)	5 (20.8)	15 (22.7)
History of adverse reactions during blood transfusion at the study facility (n = 65)			
None	17 (41.4)	12 (50)	29 (44.6)
One	13 (31.7)	10 (41.7)	23 (35.4)
Multiple	11 (26.8)	2 (8.3)	13 (20)

Similarly all the HBsAg positive patients reported receipt of transfusion from other sources in addition to government blood bank and history of blood transfusion of more than 10 years duration. The lone HIV positive patient during study period had a history of blood transfusion of more than 10 years duration and received blood from government blood banks only.

Discussion

We have reported the burden of Hepatitis C and B, HIV and syphilis among the multi-transfused thalassemia

Table 3 Various studies with seroprevalenceof TTIs amongst multi transfused thalassaemia patients

Authors	Year	Country	Seroprevalence (%), HBsAg, antiHCV and antiHIV respectively	Reference
Wonke et al.	1990	United Kingdom	23.2*	[11]
Amrapurkar et al.	1992	India	45, 17.5, 2.5	[12]
Karimi et al.	2001	Iran	0.53,15.7,0	[13]
Mollah et al.	2003	Bangladesh	13.8,12.5,0	[14]
Miromen et al.	2006	Iran	1.5, 19.3, 0	[15]
Samimi et al.	2007	Iran	5.1*	[16]
Shah et al.	2010	India	2, 2, 45	[17]
Vidj et al.	2011	India	3, 2, 2	[18]
Ataei et al.	2012	Iran	8*	[19]

* Only HCV studied

Table 4 Relationship of TTI(s) with selected factors among multi-transfused thalassemia major subjects studied

	TTI present	TTI absent	*P* value
Mean age (SD)	11.2 (1.2)	7.2 (0.6)	0.0019
Socio-economic status			
Class I	4 (30.8)	9 (69.2)	0.258
Class II	7 (35)	13 (65)	
Class III	1 (5.9)	16 (94.1)	
Class IV	3 (20)	12 (80)	
Class V	0	1 (100)	
Religion			
Hindu	13 (24.1)	41 (75.9)	0.787
Muslim	2 (18.2)	9 (81.8)	
Christian	0	1 (100)	
Mean distance from health facility(SD)	78.3 (39.8)	81.3 (18.9)	0.9417
Mean haemoglobin level (SD)	6.9 (0.3)	5.7 (0.24)	0.0206
Mean weight in kilograms (SD)	78.3 (39.8)	81.3 (18.9)	0.94
Mean height in cm (SD)	124.9 (3.9)	107.5 (3.1)	0.0052
Mean BMI in kg/cm^2(SD)	15.9 (0.6)	14.5 (0.3)	0.0202
Blood groups			
A	2 (25)	6 (75)	0.394
B	4 (16)	21 (84)	
AB	0	4 (100)	
O	9 (31)	20 (69)	
Rh status			
Positive	15 (23.1)	55 (76.9)	0.585
Negative	0	1 (100)	
History of hepatitis B vaccination			
Complete	2 (28.6)	5 (71.4)	0.361
Incomplete	6 (33.3)	12 (66.7)	
None	7 (17.1)	34 (82.9)	
Mean age of diagnosis of thalassemia major (SD)	1.4 (0.5)	1.7 (0.3)	0.627
Mean duration of blood transfusion(SD)	9.9 (1.3)	5.5 (0.5)	0.0004
Duration of blood transfusion			
<5 years	2 (6.9)	27 (93.1)	0.016
5–10 years	8 (30.8)	18 (69.2)	
>10 years	5 (45.5)	6 (54.5)	
History of thalassemia major in family	1 (6.7)	14 (93.3)	0.911
History of consanguineous marriage in family	2 (13.3)	13 (86.7)	0.969
Main source of blood for transfusion (n = 65)			
Government blood bank	15 (23.4)	49 (76.6)	0.581
Private blood bank	0	1 (100)	
Use of other source of blood for transfusion	9 (60)	6 (40)	0.727
Mean frequency of blood transfusion in days (SD)	21 (1.7)	27.6 (1.8)	0.0545
History of chelation therapy (n = 43)			
Not Indicated	0	5 (100)	0.019
Not Given	4 (15.4)	22 (84.6)	
Irregular	3 (60)	2 (40)	
Regular	4 (57.1)	3 (42.9)	
Transfusion index (High) (n = 11)	8 (72.7)	3 (27.3)	0.033

Table 4 continued

	TTI present	TTI absent	*P* value
Thalassemia trait status of father (HPLC) (n = 35)			
No trait	0	1 (100)	0.582
Beta-thal trait	5 (16.1)	26 (83.9)	
HbE trait	1 (50)	1 (50)	
Soluble	0	1 (100)	
Beta thalassemia/sickle cell trait (n = 29)			
No trait	0	3 (100)	0.455
Beta thalassemia trait	6 (25)	18 (75)	
Beta thal& sickle cell trait	0	2 (100)	
Mean serum ferritin level (SD)	4,799 (948)	2,734 (342)	0.0136
Mean SGOT (SD)	73 (10.9)	62.7 (14.2)	0.7038
Mean SGPT (SD)	66 (10.4)	55.1 (12.1)	0.6385
Mean serum alkaline phosphatase (SD)	227.3 (15.9)	204.1 (9.5)	0.239

patients reporting to the outpatient clinic of a Government medical college hospital of central India. There are not many studies reported on these parameters from this part of the country. The overall prevalence rate of TTI in our study population is 22.7 %. The sero-prevalence of Hepatitis C at 18.2 % is considerable among these subjects. The high prevalence of HCV in our study population is in concordance with many other studies around the world. The prevalence of TTI in multitranfused thalassemia patients has also varied as per the region, methods of donor screening and screening of blood units and quality systems adopted evident from Table 4 [12–20]. Previous studies in Iran have reported the prevalence of HCV in beta-thalassemia patient at a wide range of 7–64 %. In the study reported from Iran, anti-HCV positivity in thalassemiacs were related to the number of blood transfusion units, splenectomy and duration of thalassemia [16]. Our study reported similar findings. A Peruvian study identified a positive hemodialysis history as a common risk factor associated with HBV, HCV and HTLV-I infection among multi-transfused subjects. Similar to our finding, risk factor for HIV infection was identified as total number of transfusion units received in a multisite study from Peru [2].

The vaccination status against Hepatitis B was low in the current study as against 93.3 % reported in certain studies [14]. Hepatitis B has been recently introduced in the national immunization schedule in India and it is hoped that this measure would reduce the burden of Hepatitis B in multi-transfused patients further although studies have challenged the notion of protection offered by vaccination [21]. The HBsAg reactive case in our study was not vaccinated, however the indeterminate patient had had complete vaccination. Quality of donor-screening programmes is reflected in the burden of infected blood entering the transfusion process. In developed countries, stringent monitoring of the donor programme has resulted in negligible risk of infected blood entering the transfusion pool, let alone transfused to subjects [22]. NAT testing for improving blood safety was introduced in the developed countries in the late 1990s and early 2000s and presently around 33 countries in the world have implemented NAT for HIV [23]. The fact that the health benefit of prevention of TTIs indirectly by implementing NAT outweighs the direct costs of testing and thus increase in per unit cost of blood has led to introduction of NAT in a few blood centres in India. In a multi-centric study Makroo et al. [24] detected 8 NAT positive cases in 12,224 samples and their serological results collected from eight blood banks in India. These were individually tested by procleix ultrio assay for HIV 1, HCV and HBV. Another study from Jaipur reported a combined NAT yield (NAT reactive/seronegative) for HIV, HCV and HBV of 0.034 % in 23,779 donors [25] which is high compared to that reported from other developed countries. In another study conducted in north India, 18,354 donors were tested by both ID-NAT and fourth generation enzyme-linked immunosorbent assay (ELISA), 7 were found to be NAT-positive but ELISA-negative (NAT yield) for HBV and HCV. The prevalence of NAT yield cases among routine donors was 1 in 2,622 donations tested (0.038 %) [26]. High yield of NAT suggests higher prevalence of TTIs in India, highlighting the need for NAT in our country. Two pilot studies from our region revealed prevalence as high as 2.2 % for HBV and 0.3 % for HCV by NAT in seronegative blood donors gain highlighting existence of occult infection [27, 28]. Though this study is a not a prospective study co relating risk associations between donor sero prevalence and TTI in patients, a prospective multicentric study following up patients from a health facility and comparison of various prevalence rates with occurrence of TTIs in patients receiving transfusions would be interesting.

A repeat voluntary blood donor will be one who follows safe lifestyle behaviours; will be tested for infections like HIV, Hepatitis B, Hepatitis C, syphilis and malaria regularly and the chances of falling in the window period will be very low and thus will be the safest choice for being a blood donor. Burden of TTIs needs to be frequently assessed both in the setting of health facility and general population to understand the functioning of blood safety programmes of India. High prevalence of HCV necessitates better methods of screening like NAT in the transfusion facilities. Periodic monitoring of multi-transfused subjects through heamovigilance should be made a part of the blood safety programmes.

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