Incidence of Hepatitis E Virus Infection in Recipients of Blood or Blood Products Transfusion

Maj Gen AC Anand, ^{vsm*}, Surg Cdr KJ Singh⁺, Maj P Sharma[#], Lt Col S Kumar^{**}, Col RM Gupta⁺⁺

Abstract

Background: Hepatitis E, generally known to be transmitted faeco-orally, has been shown to have significant transmission by blood borne route. Paucity of data on asymptomatic viremia in blood donors and higher incidence of Hepatitis E in haemodialysis patients and thalassemics mandate a prospective study of blood recipients to elucidate the exact incidence and natural history of post transfusion Hepatitis E.

Methods: A total of 2000 recipients of blood or blood products transfusion were followed up for two months to detect development of post transfusion Hepatitis E, by clinical examination, transaminases and immunoglobulin M anti hepatitis E virus (IgM anti HEV). Estimation of hepatitis E virus ribonucleic acid (HEV RNA) was done in patients with elevated levels of transaminases.

Result: Out of 2000 patients, 5(0.25%) were positive for IgM anti HEV at the time of transfusion and were excluded from the study. Rest of 1995 patients were followed up for two months post transfusion. A total of 1303 (65.3%) patients were followed up for two months and 1636 (82.0%) patients at least once in two visits. None of the followed up patients reported development of jaundice or had clinically evident hepatitis, although 62 patients had raised transaminases detected at either one or both the visits.

Conclusion: All followed up patients were tested for IgM anti HEV at both the visits and none were found to be positive. Patients with raised transaminases were subjected to HEV RNA and all were found to be negative.

MJAFI 2010; 66 : 204-207

Key Words : Hepatitis E; Post transfusion; Parenteral transmission

Introduction

Hepatitis E virus (HEV) is a common infection in India. Currently 40% of acute viral hepatitis infection in India results from HEV infection [1]. It has worldwide distribution, but predominating factors include tropical climates, inadequate sanitation and poor personal hygiene. It is found most often in developing countries near the equator, in both the Eastern and Western hemispheres. Outbreaks are associated with rainy seasons, floods and overcrowding. The first outbreak in India was reported in Delhi between 1955 and 1956 with 29,000 cases [2].

Although the overall mortality due to hepatitis E is low, the case fatality rate among pregnant women is reported as high as 20% [3], which increases during the second and third trimesters. Reported causes of death include encephalopathy and disseminated intravascular coagulation. The rate of fulminant hepatic failure in infected pregnant women is high [3].

Transmission occurs mainly by faeco-oral route; however recent reports indicate a significant transmission by blood borne route [4-7]. In a study carried out in India 1.5% of voluntary blood donors

screened for HEV were positive for HEV RNA. However, a highly significant proportion (76%) of paid plasma donors were positive for immunoglobulin G (IgG) antibodies to HEV indicating a possible role of blood derived HEV in transmission of virus among plasma donors [4]. In a retrospective analysis of blood transfusion recipients approximately 5% individuals acquired fresh HEV infection following transfusion [5]. Blood borne transfusion is more common in patients who have received multiple transfusions and there are reports to indicate that these patients are more likely to have icteric disease and higher serum alanine amino transferase levels, however exact natural history of post transfusion Hepatitis E is still not fully elucidated [7,8]. Higher incidence of HEV infection has been reported in hemodialysis patients further corroborating evidence towards blood borne spread of [9]. There is a need to find out the exact incidence of transfusion associated HEV infection and natural history of such an infection.

Material and Methods

It was a prospective study conducted at a tertiary care center. A total of 2000 patients receiving blood or blood

*MG (Med), HQ (SC), Pune-40. ⁺Reader, [#]Clinical Tutor (Dept of Internal Medicine); ^{**}Associate Professor (Dept of Transfusion Medicine); ⁺⁺Associate Professor (Dept of Microbiology); AFMC, Pune-40.

Received : 23.03.09; Accepted : 10.04.10 E-mail : kjsaltosax@hotmail.com

products between Mar 2007 to Jun 2007 were included in the study and studied for a period of 60 days.

- Inclusion criteria: All consecutive patients receiving blood or blood products transfusion.
- Exclusion criteria: Individuals who test positive for IgM anti HEV prior to transfusion.

Detailed information and important events in the history and investigations of the patients was obtained from the patients and recorded. Thorough follow up and medical examination was carried out to detect and diagnose Hepatitis E clinically and serologically. At each follow up visit at monthly intervals patients were clinically assessed for development of hepatitis as well as tested for rise in aspartate and alanine transaminases (AST/ALT) levels. Clinical evaluation for Hepatitis E infections was supplemented by basic investigations (ALT, AST and IgM anti HEV) and high yield investigations (HEV-RNA) when indicated and feasible. All followed up patients were tested for IgM anti HEV at both the visits. Presence of IgM anti HEV was considered an evidence of recent HEV Infection.

Results

A total of 2000 consecutive patients, receiving blood or blood products from blood transfusion department of Armed Forces Medical College (AFMC) were enrolled in this study. The study population represented a diverse group of patients from general medical and most surgical specialties who had received a transfusion during this period. The patients included represent a fair cross section of general population and comprised of local population as well as patients referred to this centre from central, western and south India. There were 1239 males and 761 females. The mean age of males was 44.9 (SD±22.4) years and females 39.9 (SD±19.4) years. The age and sex distribution of the patients is shown as Table 1.

All patients were subjected to IgM anti HEV at the time of transfusion using commercially available enzyme immunoassay kits. Five patients were found to be positive for IgM anti HEV and hence were excluded from the study. Rest of 1995 patients who had tested negative for IgM anti HEV were followed up monthly for next two months post transfusion.

At each follow up visit patients were clinically assessed for development of hepatitis as well as tested for rise in

transaminases (AST/ALT levels). A total of 1303 (65.3%) patients were followed up for two months and 1636 (82%) patients at least once in two visits, out of the 1995 patients recruited for the study.

None of the followed up patients reported development of jaundice or had clinically evident hepatitis, although 62 patients had raised transaminases detected at either one or on both the visits (Table 2). All followed up patients were tested for IgM anti HEV at both the visits and none were found to be positive. All 62 (3.1%) patients who had raised transaminases were tested for HEV RNA and were found to be negative for the same (Table 3).

Subsequently, IgM anti HEV tests were also done on the stored aliquots of blood of the 2000 consecutive voluntary donors who donated blood at the time of the study and all were found to be negative.

Discussion

Transfusion associated hepatitis is the most common serious consequence of blood transfusion therapy. Although transfusion associated acquired immunodeficiency syndrome (AIDS) has captured the world's attention because of its devastating clinical syndrome and universal fatality, the number of cases of transfusion associated AIDS have been miniscule as

Table 2
Variation of Transaminases in followed up patients

HEV RNA	AST 30	ALT 30	AST 60	ALT 60
Not Applicable				
Mean	34.4	35.2	33.6	34.2
n	1470	1472	1372	1353
Std. Deviation	16.2	18.4	14.6	14.8
Negative				
Mean	119.8	125.9	100.9	105.6
n	60	60	53	53
Std. Deviation	207.5	227.9	91.5	103.6
Total				
Mean	37.8	38.8	36.1	36.9
n	1531	1533	1425	1406
Std. Deviation	46.8	51.4	25.9	28.1

AST 30 (AST levels at 30 days follow up)

AST 60 (AST levels at 60 days follow up)

ALT 30 (ALT levels at 30 days follow up)

ALT 60 (ALT levels at 60 days follow up)

Not applicable: HEV RNA not done in those cases in which transaminases were within normal range

Units of AST/ALT- IU/l

Table 1
Age and sex distribution

Age (years)	Sex		Total
	Females (%)	Males (%)	
≤ 5	23 (3)	66 (5.3)	89 (4.5)
6 - 15	47 (6.2)	127 (10.3)	174 (8.7)
16 - 25	132 (17.3)	92 (7.4)	224 (11.2)
26 - 35	175 (23)	124 (10)	299 (15)
36 - 45	118 (15.5)	190 (15.3)	308 (15.4)
46 - 55	74 (9.7)	154 (12.4)	228 (11.4)
≥ 56	192 (25.2)	486 (39.2)	678 (33.9)
Total	761 (100)	1239 (100)	2000 (100)

Table 3
PCR for HEV RNA

HEV RNA	Frequency	Percent
Not Applicable	1933	96.9
Negative	62	3.1
Total	1995	100.0

Not applicable: HEV RNA not done in those cases in which transaminases were within normal range

compared with transfusion associated hepatitis. Once a screening test for human immunodeficiency virus (HIV-1) was developed and implemented in 1985, the risk of transfusion associated AIDS fell to approximately one case per 100,000 transfusion recipients (0.001%), whereas the simultaneous rate for transfusion associated hepatitis was 4-8 cases per 100 recipients (4-8%) [10].

A continuous decline in transfusion associated hepatitis prevalence has been seen, from rates that exceeded 30% in the 1960s to rates below 1% in 1990s and even lower in recent prospective studies [10]. As rates of transfusion associated hepatitis B and C are declining, focus is shifting to either new viral agents like transfusion transmitted virus (TTV), SEN virus, etc., or to viruses generally not known to be transmitted parenterally like HEV whose predominant mode of transmission is faeco-oral. HEV infection can theoretically be transmitted parenterally during the initial viraemic phase and has been conclusively demonstrated to be transmitted by blood transfusion but in isolated case reports only [11-16]. There have been no prospective studies till date to elucidate the risk of transfusion associated HEV infection.

In our study none of the transfused patients were found to develop IgM anti HEV positivity, taken as the evidence of recent HEV infection on follow up, indicating a very low risk for transmission of HEV even in a hyperendemic country like India. Among patients who had elevation of transaminases, none were found to be positive for HEV RNA thus substantiating the low risk of transmission by blood transfusion.

Subsequently, in our study we screened 2000 consecutive donor samples for the presence of IgM anti HEV, and none were detected to be positive. HEV RNA or transaminases levels were not done. This difference can probably be explained by strict selection criteria for voluntary blood donation, being followed by blood transfusion departments in the armed forces setting. There is also a role for donor initiated self exclusion as made evident by some studies.

Every effort is made to minimise the risk of transfusion transmitted infections, but a theoretical possibility of transmission remains. Previously estimates of the frequency of transfusion transmitted have relied on reported cases of infection but these are often underreported. No large scale prospective studies have been reported till date which can guide whether the screening of donated blood for HEV is warranted in HEV-endemic areas to protect blood recipients from infection.

Blood transfusion provides a unique opportunity to define precisely the date and source of exposure and

hence provides an ideal setting in which to study viral epidemiology and serology and to define the sequential events that follow hepatitis virus exposure.

This prospective study directly estimated the incidence of transfusion transmitted HEV infection, for which blood is currently not being tested. Despite ample but indirect evidence being available in literature of possibility of transfusion transmitted HEV infection in the form of isolated case reports, we did not find any patient among those followed up, to develop post transfusion Hepatitis E. If such a risk exists, it is extremely small, probably because of the short viremic period and the lack of chronic carriers of HEV.

Conflicts of interest

This study has been funded by research grants from the O/o DGAFMS.

Intellectual Contribution of Authors

Study Concept : Maj Gen AC Anand, VSM

Drafting & Manuscript Revision : Surg Cdr KJ Singh, Maj P Sharma

Statistical Analysis : Surg Cdr KJ Singh, Maj P Sharma

Study Supervision : Col RM Gupta, Lt Col S Kumar

References

1. Bartnof HS. Hepatitis E emerges as a significant cause of liver inflammation worldwide. 10th International symposium on viral hepatitis and liver diseases. CDC, April 9-14, 2000. Atlanta, Georgia. Accessed from www.pkids.org/pdf/phr/05-00hev.pdf
2. Vishwanathan R. Infectious hepatitis in Delhi (1955-56): a critical study. *Indian J Med Res* 1957; 451-529.
3. Balayan MS. Epidemiology of hepatitis E virus infection. *J Viral Hepat* 1997; 4:155-65.
4. Arankalle VA, Chobe LP. Hepatitis E virus: can it be transmitted parenterally? *J Viral Hepat* 1999; 6: 161-4.
5. Arankalle VA, Chobe LP. Retrospective analysis of blood transfusion recipients evidence for post-transfusion hepatitis E. *Vox Sang* 2000; 79: 72-4.
6. Aggarwal R. Hepatitis E: Is it a blood borne pathogen? *J Gastroenterol Hepatol* 2004; 19: 778-84.
7. Lee CK, Chau TN, Lim W, Tsoi WC, Lai ST, Lin CK. Prevention of transfusion-transmitted hepatitis E by donor-initiated self exclusion. *Transfus Med* 2005; 15: 133-5.
8. Khuroo MS, Kamili S, Yatoo GN. Hepatitis E virus infection may be transmitted through blood transfusion in an endemic area. *J Gastroenterol Hepatol* 2004; 19: 729-31.
9. Mahnaj T, Manouchehr K, Latif G, Mohammad J, Ehsani A. Hepatitis E virus infection in hemodialysis patients. A seroepidemiological survey in Iran. *BMC Infectious Diseases* 2005; 5: 36.
10. Leslie H, Tobler Michael, Busch P. History of post transfusion hepatitis. *Clinical Chemistry* 2005; 43:1487-93.
11. Xia NS, Zhang J, Zheng YJ, Ge SX, Ye XZ. Transfusion of plasma from a blood donor induced hepatitis E in Rhesus monkey. *Vox Sang* 2004; 86: 45-7.
12. Matsubayashi K, Nagaoka Y, Sakata H, Sato S, Fukai K, Kato T. Transfusion-transmitted hepatitis E caused by apparently

- indigenous hepatitis E virus strain in Hokkaido, Japan. *Transfusion* 2004; 44: 934-40.
13. Mitsui T, Tsukamoto Y, Yamazaki C, Masuko K, Tsuda F, Takahashi M. Prevalence of hepatitis E virus infection among hemodialysis patients in Japan: evidence for infection with a genotype 3 HEV by blood transfusion. *J Med Virol* 2004; 74: 563-72.
 14. Boxall E, Herborn A, Kochethu G, Pratt G, Adams D, Ijaz S. Transfusion-transmitted hepatitis E in a 'nonhyperendemic' country. *Transfus Med* 2006; 16: 79-83.
 15. Tamura A, Shimizu YK, Tanaka T, Kuroda K, Arakawa Y, Takahashi K. Persistent infection of hepatitis E virus transmitted by blood transfusion in a patient with T-cell lymphoma. *Hepatology* 2007; 37: 113-20.
 16. Matsubayashi K, Nagaoka Y, Sakata H, Sato S, Fukai K, Kato T, et al. A case of transfusion-transmitted hepatitis E caused by blood from a donor infected with hepatitis E virus via zoonotic food-borne route. *Transfusion* 2008; 48: 1368-75.

CIRCULAR FROM THE OFFICE OF DGAFMS/DG-3B SCIENTIFIC ARTICLES FOR AWARDS

1. Scientific articles are invited from serving Medical/Dental officers of the Army, Navy & Air Force for the following awards:
 - (a) Chief of Army Staff Award for best published article in the field of Pathology, Microbiology, Hematology and Biochemistry.
 - (b) Chief of Naval Staff Award for best published article in the field of Medicine and allied specialties including Marine Medicine and Aviation Medicine.
 - (c) Chief of Air Staff Award for best published article in the field of Surgery and allied specialties including dental surgery.
 - (d) DGAFMS and Sr Col Comdt Award for best published article in the field of Preventive and Social Medicine including Epidemiology, Biostatistics, Health and Hospital Administration.
 - (e) Late Lt Gen RS Hoon, PVSM, AVSM Award (Cardiac Sciences) for work carried out in Cardiology in the field of medicine and surgery and allied specialties.
2. Article should be submitted through proper channels as per the instructions to the authors printed in Jan 2010 issue of MJAFI. Ten copies each of the article should reach this office by 31 Aug 2010. Article received after due date and not through proper channel will not be considered for award.
3. The awards will be presented in the 59th Armed Forces Medical Conference at AFMC, Pune in Feb 2011.
4. Officers will be entitled to submit only one article for consideration of each award. A board of officers at the office of the DGAFMS will evaluate the articles for selection of the best paper (s). The recipient (s) of the award will be given an opportunity, subject to exigencies of service to present his/her work at the AFMRC at the time of presentation of the award.
5. Officers working in office of the DGAFMS are not eligible to compete for the awards. Articles submitted by the officers other than those working in office of the DGAFMS but having co-authors working in the office of the DGAFMS will, however, be eligible for consideration of the award. However, the officers will not be eligible for any award/certificate or share of the prize money.