Indian Journal of Gastroenterology (March–April 2020) 39(2):161–164
https://doi.org/10.1007/s12664-020-01033-y

ORIGINAL ARTICLE

Blood transfusion is unlikely to be a source for hepatitis E virus transmission in India

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Received: 14 November 2019 / Accepted: 25 March 2020 / Published online: 5 May 2020
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Abstract

Introduction Transmission of hepatitis E virus (HEV) through transfusion has been reported from countries where genotype 3 virus is predominant. Data from countries with predominantly genotype 1 HEV, such as India, are limited. We studied the risk of HEV transmission following transfusion of blood or blood components in India.

Methods Adult patients undergoing cardiac surgery who received transfusion of blood or blood products in the peri-operative period and who lacked history of any transfusion or surgery in the preceding 1 year were studied. A pre-transfusion blood specimen was collected for IgG anti-HEV antibody test. For the participants who were seronegative for anti-HEV, follow up specimens were collected at every 2–3-month intervals for up to 6 months after surgery and were tested for IgM and IgG anti-HEV antibodies.

Results Of the 335 participants originally enrolled, 191 (57%) could be followed up. Of them, 103 (53.9%) were seropositive for HEV IgG at baseline and were excluded. Of the remaining 88 participants (age 42 ± 14.1 years; 55 [63%] male), none reported hepatitis-like illness during the follow up period of 81 ± 23 days. Also, none of these 88 participants was found to have seroconversion to anti-HEV IgM or IgG positivity in the follow up specimens.

Conclusion Transfusion-mediated transmission of HEV was not observed in our cohort and may be infrequent in the Indian population, where genotype 1 is the predominant HEV type.

Keywords Epidemiology · Hepatitis E virus · Transfusion-transmitted infections · Viremia

Introduction

Infection with hepatitis E virus (HEV) is the commonest cause of acute viral hepatitis in developing countries of Asia and Africa. HEV consists of virions which measure 27–34 nm in diameter and contain a single- and positive-stranded RNA genome. At least some types of HEV are also known to cause infection in several mammalian species, including pigs, deer, boars, rabbits, camels, and mongooses [1]. The virus is hepatotropic and is extruded from the liver cells into the bile. It is thus excreted in the feces of infected humans and animals, and is transmitted to naïve hosts via fecal-oral route.

Based on phylogenetic analysis of their genomic sequences, HEV isolates from human and animal sources around the world have been grouped into at least 8 different genotypes. The human isolates have mostly belonged to four genotypes, named as 1 to 4. Of these, HEV isolates belonging to genotypes 1 and 2 appear to be capable of infecting only humans but not other mammals, and have primarily human-to-human transmission, through ingestion of contaminated drinking water and possibly food [2, 3]. These genotypes are prevalent primarily in countries in Asia and Africa, i.e. areas where human HEV disease is frequent and where opportunities for contamination of water and food with human fecal material are frequently present. By contrast, genotypes 3 and 4 HEV have a widespread natural circulation in several animal species with occasional zoonotic transmission to humans; this is believed to be mediated by consumption of undercooked meat from or close contact with HEV-infected animals, in particular pigs [4]. These genotypes appear to cause human

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Bullet points of the study highlights

What is already known?

- Hepatitis E virus (HEV) can be transmitted through blood/component transfusion.
- Transfusion related transmission is primarily limited to HEV genotype 3 and 4.
- HEV infection in India is exclusively caused by genotype 1.

What is new in this study?

- Transfusion related transmission of HEV is not detected in our cohort.
- HEV genotype 1 may not be transmitted by transfusion.

What are the future clinical and research implications of the study findings?

- Larger and multicentric studies are needed to determine the risk of transfusion related HEV transmission in India.

disease mainly in developed countries of Europe, North America, and some developed countries in Asia, where sewage disposal and quality of water supplies are better.

In recent years, transmission of HEV in humans through transfusion of infected blood or blood products has also been reported [5, 6]. The strongest evidence for such transmission came from a study in the UK [7], where 1 in every 2848 blood units was found to contain HEV RNA, and some of the recipients of such blood were shown to develop HEV infection. HEV viremia among healthy blood donors has also been reported from other developed countries [8]. This demonstration of transfusion-related HEV infection has led to the introduction of screening of blood and blood products for HEV RNA in some European countries.

The information on transfusion-associated HEV infection is primarily from countries where genotype 3 HEV is predominant. Similar data from developing countries such as India, where genotype 1 HEV is highly endemic, are lacking [9]. It is clearly important to have such data because the propensity of various HEV genotypes for transmission by transfusion can be expected to differ—since genotypes 3 and 4 HEV are known to cause persistent infection, but genotype 1 HEV is not. Hence, in this study, we assessed the risk of HEV transmission following transfusion of blood or blood component in an Indian tertiary-care healthcare institution.

Methods

This prospective observational study was conducted between May 2016 and December 2018. During this period, adult patients admitted to our institution for cardiac surgery, who were expected to receive transfusion of blood or blood products during surgery, were prospectively enrolled. Those patients who had received any blood or blood component transfusion or had undergone surgery in the preceding 1 year were excluded. The subjects received blood and blood components in the peri-operative period as per the usual practice and decision of the surgical team. For each subject, a specimen of peripheral venous blood was collected on the day prior to surgery (before transfusion of blood or any blood product), and serum was stored at − 80 °C in aliquots. In addition, for each subject, the relevant clinical and laboratory data, including the number of units of each blood component transfused during surgery and immediate postoperative period, was recorded.

After discharge, those participants who received transfusion of a blood product during surgery were followed at 2–3-month intervals for up to 6 months. At each follow up visit, the participants were asked about symptoms and/or signs of hepatitis, and a blood specimen was collected for measuring serum bilirubin, alanine aminotransferase (ALT) activity, and anti-HEV antibody testing.

All the pre-transfusion specimens were tested for IgG anti-HEV antibody. For the group of participants, whose pre-transfusion specimen tested negative, the last collected follow up specimens were tested for the presence of IgM and IgG anti-HEV antibodies followed by HEV RNA in those with positive IgG or IgM results; furthermore, we had also planned to test other intermediate follow up specimens for anti-HEV antibody and HEV RNA for these participants.

Table 1 Clinical characteristics and transfusion details of the study participants ($n = 88$)

Characteristics	Value
Gender	
Male	55 (62.5%)
Female	33 (37.5%)
Age, completed years	42 (14.1)
Average number of blood or blood component units transfused in each participant	
Packed red blood cells	1 (1.1)
Fresh frozen plasma	3 (1.6)
Random donor platelets	1 (1.1)
Cryoprecipitate	0.4 (0.7)
Total	5 (3.8)
Interval between transfusion and follow up specimen collection, days	81 (23.1)
Laboratory parameters in follow up specimen	
Total serum bilirubin, mg/dL	1.0 (0.4)
Alanine aminotransferase, IU/L	48 (29.6)

Data are expressed as numbers (%) or mean (standard deviation)

IgG and IgM anti-HEV antibodies were detected using a commercial enzyme-linked immunoassay (Wantai, Beijing, China). Detection of IgM anti-HEV in the follow up specimen, in the absence of this antibody in the baseline specimen, was taken as evidence of transfusion-related recent HEV infection.

The study was approved by our institution's Ethics Committee, and each participant provided a written informed consent. Categorical and numerical variables were expressed as proportions and mean (standard deviation, SD), respectively.

Results

A total of 335 participants fulfilling the entry criteria were enrolled in the study and provided pre-operative (baseline) blood specimens. Of them, only 191 (57%) could be followed up and provided subsequent specimens; the remaining patients were excluded either because they did not receive any transfusion ($n = 34$), were not available for follow up ($n = 100$), or declined to provide a further blood specimen ($n = 10$). The pre-transfusion specimens of the participants ($n = 144$), for whom no follow up specimens were collected, were not tested for HEV IgG. One hundred and three among 191 (53.9%) tested positive for HEV IgG in their baseline specimens and were excluded from the analysis. Data from the remaining 88 participants were analyzed further.

The relevant clinical and transfusion details of these 88 subjects are summarized in Table 1. None of these 88 patients reported a hepatitis-like illness or jaundice in the follow up period after the peri-operative transfusions. Furthermore, none of the 88 participants were found to have detectable anti-HEV IgM antibodies or seroconversion to anti-HEV IgG positivity in the follow up specimens.

Discussion

In the present study, we followed a cohort of 88 persons undergoing cardiac surgery who lacked IgG anti-HEV antibody and had received blood or blood components transfusions around the time of cardiac surgery. During follow up, none of these persons had clinical or serological evidence of exposure to HEV during follow up for an average duration of 80 days post-transfusion.

Majority of the global burden of clinical HEV disease is in Asia [10]. This is related to insufficient access to safe drinking water, food hygiene, sanitation facilities in this region, and environmental factors leading to waterborne transmission of HEV. Such transmission is expected to be unlikely in Europe and North America. Hence, recognition of the occurrence of sporadic cases of HEV-related illness in developed world prompted a search for alternative routes of HEV transmission. Thus, studies in Europe led to the recognition of transfusion-mediated transmission of HEV. The strongest evidence for such transmission came from the study by Hewitt et al. [7] in the UK, in which 225,000 donated blood units were screened for HEV RNA and 79 of these were found to have HEV viremia. Furthermore, follow up of recipients of blood products prepared from these HEV-viremic units showed evidence of HEV infection in 43% of recipients. Similar data on HEV viremia in healthy blood donors have since been reported from other countries [11]. However, in a large majority of such viremic donors, the infection was with genotype 3 HEV.

The fact that human-to-human fecal-oral transmission of HEV occurs in countries with high HEV disease prevalence and preponderance of genotypes 1 and 2 HEV does not mean that transfusion-related transmission cannot occur. If such nosocomial transmission of HEV does exist in these regions, it is important to identify it since it can be prevented through specific strategies aimed at rendering blood supplies safe. For instance, in India, nearly 9 million units of blood are collected and transfused as such or as blood components annually [12]. If even a small proportion of these transfusions carry a risk of transmission of HEV, the burden of transfusion-related hepatitis E could be substantial. In fact, given that HEV disease is more common in such areas, the prevalence of viremia and

the risk of such transmission here may be even higher, further accentuating the risk.

A difference in the risk of transmission of HEV through blood transfusion between areas where genotype 1 or 2 and genotype 3 or 4 circulate may not be unexpected. The virus belonging to latter genotypes is known to cause persistent infection in some of those infected [13], whereas this appears to either not happen or be extremely infrequent with genotypes 1 and 2 HEV. Persistence of HEV in a person's body for a longer duration would be expected to increase the risk of transfusion-related transmission.

Risk of transfusion-related transmission of a pathogen can be examined in two ways—by testing the donor units for the presence of a pathogen, e.g. of HEV RNA, or by studying the transfusion recipients for evidence of infection, e.g. for clinical disease or serological evidence of recent infection. Some data are available for either from India. In studies done several years ago, HEV viremia was identified in 3 of 200 (1.5%) blood donors in a study from western India [14] and in 4 of 107 (4%) donors in Kashmir [15]. Furthermore, in the latter study, transmission of HEV was shown to occur in three of 22 recipients of blood or blood products [15]. These data were obtained when tests for the detection of HEV RNA were not well developed. A recent study from India looked for the presence of HEV viremia in 1799 blood donors and failed to find it in any of them [16]. Hence, we decided to look at the issue from the other end, i.e. in transfusion recipients. Our failure to find HEV seroconversion in the current study too suggests that transmission of HEV through transfusion may not be very common.

However, our data are limited by a relatively small sample size. We did start with a large number of transfusion recipients. However, more than half of them turned out to have anti-HEV antibodies at baseline, reducing the effective sample size. It may be argued that such persons may be protected from HEV infection by pre-existing antibodies, and hence, we have used a more conservative denominator of only those who were seronegative.

Overall, we believe that our data indicate that transmission of HEV through blood transfusion is unlikely to be a major problem in India and in other countries with similar epidemiologic pattern of this infection. It would however be useful to undertake further larger, multicentric studies to answer this question with greater clarity in the context of areas where HEV disease is highly endemic.

Funding information This work was supported by an intramural research grant from the Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, to AG. HK was supported by a grant from the Department of Biotechnology, Government of India.

Compliance with ethical standards

Conflict of interest VJH, AG, HK, SKA, SP, and RA declare that they have no conflict of interest.

Ethics statement The study was performed conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com. The study was approved by our institution's Ethics Committee, and each participant provided a written informed consent.

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