Screening Transfusions for Hepatitis E Virus: Is it needed in India?

Hepatitis E, a disease caused by infection with hepatitis E virus (HEV), is linked intimately to the Indian subcontinent. Its existence as a distinct disease was first suspected during an outbreak in the Kashmir valley in 1978. It was also shown to be responsible for a large epidemic of hepatitis in Delhi in 1955–56 through retrospective analysis of stored sera.

Hepatitis E is the most common cause of sporadic acute viral hepatitis, and of most of the outbreaks of hepatitis in India. Though initially it was believed to be a disease of developing countries, in recent years, indigenous cases of hepatitis E have been reported from developed countries of Europe and North America. Some cases of this infection in these areas have been shown to be transmitted by blood transfusion, leading to calls for screening of blood and blood products for HEV before transfusion. Considering its highly endemic presence in India, should we too screen blood transfusions for HEV infection?

Human HEV infection can be caused by four distinct genotypes, named 1 to 4. Of these, genotypes 1 and 2 infect only humans, are highly prevalent in Asia including the Indian subcontinent, the Mediterranean region, the Middle East and Africa, are transmitted primarily through contamination of drinking water supplies, and cause acute hepatitis. The disease due to these genotypes is more common among young adults, and is more likely to lead to liver failure and have a fatal outcome when it affects pregnant women. Chronic infection with these genotypes has not been reported. By contrast, genotypes 3 and 4 HEV circulate widely in several mammalian animal species, in particular pigs, wild boars and deer, and only occasionally cause disease in humans, primarily in geographical regions where infection with genotypes 1 and 2 HEV is infrequent. The disease due to these genotypes is more common among the elderly and in immunosuppressed persons; in the latter group, persistent or chronic HEV infection is known to occur, which may progress to cirrhosis of the liver.

The recent discovery of locally acquired HEV infection in Europe and North America has revived the interest in this infection and its routes of transmission, because contamination of water and food (the previously known main routes of HEV spread) are less relevant there. Studies have shown that a majority of cases with locally-acquired hepatitis E in Europe are related to zoonotic transmission, primarily through ingestion of meat, especially undercooked liver, from infected animals, particularly pigs. However, the disease has also been traced in some persons to transfusion of HEV-infected blood or blood products.

A UK study, which screened nearly 225,000 individual blood donations for HEV RNA, provided the strongest evidence for the role of transfusion in transmission of HEV. The study used a sensitive, real-time amplification assay in mini-pools of up to 24 donations each, followed by testing of individual specimens in positive pools. Seventy-nine donations (0.04%; one per 2848 donations) tested positive, a majority (56/79; 71%) of which were negative for both IgM and IgG anti-HEV antibodies; 54 isolates could be genotyped and all had genotype 3 HEV. These viraemic blood units had been used to prepare 129 blood components, 62 of which had been transfused to 60 patients by the time HEV RNA results became available and the remaining 67 were discarded. Of the 43 recipients who could be followed up (already dead 9, terminally ill 5, lost to follow-up 2, declined 1), 18 (42%) had laboratory findings suggestive of HEV infection. Though the data were unable to determine whether the risk of HEV infection was increased among immunosuppressed recipients and by how much, 10 of the 18 patients deemed to have...
post-transfusion HEV infection had moderate or severe immunosuppression. Of these 18, only one developed clinical hepatitis with mild jaundice, and 4 had asymptomatic transaminase elevation. In 3 additional patients, all of whom had moderate-to-severe immunosuppression, the treating physicians elected to either reduce immunosuppression or administer ribavirin, as pre-emptive measures to prevent chronic hepatitis E.

Similar data on the presence of HEV viraemia among healthy blood donors have been reported from other developed countries. In these studies, the positivity rates for HEV RNA have been: 1 per 658 to 2436 donated blood units in the Netherlands, 1 per 3333 units in Spain, 1 per 1240 to 4525 units in Germany and 1 per 2218 units in France.9 Interestingly, the rates have been somewhat lower in North America with 1 per ~9500 units testing positive in the USA and none of 14 000 units testing positive in Canada.9 Even within the UK, the positivity rate of HEV RNA was only 1 in 14 520 donations in Scotland.10

The presence of viraemia in these studies has lent support to the suggestion for screening of blood and blood products for HEV. However, this evidence can be viewed from another angle. In the UK study discussed above, 225 000 blood units were screened, and nearly half of the blood components prepared from HEV-infected blood were actually transfused, leading to one clinical case of mild hepatitis E. Extrapolating this to a situation where the remaining blood components too had been transfused (assuming that none of these would have expired through ageing, and that HEV does not become inactive with ageing of components), one would have expected two cases of clinical disease. Thus, to prevent each clinical case, one would need to screen 112 500 blood units, an enormous number. Not surprisingly, even developed countries have been ambivalent on this issue.11 Could transmission of HEV through blood transfusion happen in India? Yes. In 1999, Arankalle and Chobe reported detectable HEV viraemia in 3 (1.5%) persons in a small sample of 200 Indian blood donors.12 In 2000, the same authors also reported HEV seroconversion in 2 of 37 HEV-seronegative transfusion recipients.13 In 2004, Khuroo et al. found an even higher rate of viraemia among blood donors (4/107; 4%), and of HEV infection among recipients of blood transfusions (3 of 22 seronegative recipients).14 These rates are much higher than those from Europe, suggesting that such transmission may be commoner in India.

However, these studies used rather unreliable techniques. Assays for anti-HEV antibodies15 as well as for HEV RNA,16 in particular the in-house assays, are known to perform suboptimally. Moreover, the sample size of these studies was small. To make a case for screening for HEV in our setting, we need larger studies across India using more reliable assays.

The Indian situation may have other differences from that in Europe and North America. First, the HEV genotype prevalent in Europe is almost exclusively genotype 3, whereas that in India is genotype 1. These genotypes differ markedly in their propensity to cause chronic infection and of causing infection among immunosuppressed persons.17 Thus, transfusion-related HEV infection in Europe has the potential to lead to persistent HEV infection—a more serious outcome, but not in the Indian population. Second, a larger proportion of transfusion recipients in India would be expected to have prior exposure to HEV and hence partial protection; thus, a low-level exposure to HEV may be less likely to induce clinical disease in them.

Finally, screening of blood for HEV in India would pose major logistic and economic challenges. Since a majority of blood donors with HEV viraemia lack anti-HEV antibodies, any screening strategy would have to use molecular testing for HEV RNA, rather than an antibody-based test. Besides the non-availability of validated commercial tests for such screening anywhere in the world, most blood banks in India do not have facilities for molecular testing. The few blood banks that do undertake molecular screening for other transfusion-transmitted infections too will need additional equipment and manpower for testing HEV RNA. Such a test will make blood transfusion more expensive, and worsen the blood supply in India.

Hence, we need to focus on gathering more data on the frequency and consequences of HEV viraemia among blood donors in India. Once these data are in hand and commercial tests for detecting HEV RNA in multi-donation blood pools become available, we can do studies in a few selected blood banks as well as mathematical modelling studies to determine the cost–benefit ratio of screening for HEV RNA. Any intervention before that would be premature.
REFERENCES


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