*Clinical & Investigative Medicine*, Vol. 6, No. 4, pp. 327-330, 1983
Printed in Canada.

0147-958X/83 $3.00 + 0.00


# ABNORMAL ALANINE AMINOTRANSFERASE LEVEL IN BLOOD UNITS FROM DONORS IN MONTREAL DOES NOT INDICATE HIGH RISK OF TRANSMITTING HEPATITIS

URS P. STEINBRECHER, THOMAS O. G. KOVACS, ANDRE GELLY and MARC TOURIGNY
Division of Gastroenterology and Department of Medicine, Royal Victoria Hospital and McGill University Clinic, Montreal, Canada

Abstract—We undertook a prospective study to estimate the risk in Montreal of developing hepatitis following transfusion of blood with an elevated alanine aminotransferase (ALT) level. Two thousand consecutive donor units were screened for ALT activity; 133 (6.7%) had values $\geq 51$ IU $l^{-1}$. Twenty-four patients received one or more units with elevated ALT levels and completed follow-up; two (8%) developed hepatitis (one of these was type B hepatitis). One of the 10 'control' patients who received only units with normal ALT levels also developed hepatitis.

In this study, the risk of transfusion-transmitted hepatitis was the same in recipients of blood units with abnormal ALT levels as in those who received only blood with normal ALT, and very similar to the risk reported in other studies for recipients of volunteer donor blood with normal ALT. These findings require confirmation by a larger study, but suggest that the hepatitis risk associated with transfusion of high-ALT blood may be lower in Montreal than has been reported in several centers in the U.S.

Résumé—Nous avons entrepris une étude prospective du risque d'hépatite posttransfusionnelle survenant à la suite de l'administration de sang présentant un taux d'alanine aminotransférase (ALT) élevé. L'activité ALT a été déterminée sur 2000 unités de sang consécutives prélevées à Montréal: 133 unités (6,7%) presentaient des valeurs $\geq 51$ IU $l^{-1}$. Vingt-quatre patients ayant reçu une unité ou plus de sang à niveau d'ALT élevé ont été inclus dans cette étude. Parmi eux, deux cas d'hépatite (8%) se sont manifestés dont l'un était de type B. Un des dix patients témoins ayant reçu une ou des unités à activité ALT normale a également développé une hépatite. Le risque d'hépatite post-transfusionelle est donc apparu identique après administration de sang ALT normal comme ALT anormal. Notre étude suggère également que le risque d'hépatite à la suite de l'administration de sang ALT anormal serait moindre que celui retrouvé dans certaines régions des États-Unis.

*Key words:* Viral hepatitis; post-transfusion hepatitis; non-A non-B hepatitis; alanine aminotransferase.

## INTRODUCTION

THE INTRODUCTION of routine screening of blood donors for HBsAg has greatly reduced the frequency of transfusion-transmitted type B hepatitis; however, transfusion-transmitted 'non-A non-B' hepatitis remains a significant public health problem. The results of a number of prospective studies indicate that the incidence of non-A non-B hepatitis in recipients of volunteer donor blood is between 6.7 and 7.7% [1–6]. Although most patients with transfusion-transmitted non-A non-B hepatitis are asymptomatic at the onset of the disease, there appears to be a high frequency of progression to chronic hepatitis [7].

Several approaches have been undertaken in attempts to reduce the frequency of transfusion-transmitted hepatitis. Hepatitis B still accounts for approx. 10% of cases, and testing of donors for anti-HBc might further decrease the risk of hepatitis B. Also, in some populations anti-HBc is associated with non-A non-B hepatitis [8, 9]. However, the expense of the test, the number of hepatitis cases which would be prevented, and the large number of units which would be discarded make it impractical at present. In the absence of a specific marker for the virus(es) of non-A non-B hepatitis, nonspecific screening tests such as serum transaminase measurement have been studied. In contrast to earlier results, two recent prospective studies found an impressive correlation between the risk of transmitting hepatitis and alanine aminotransferase (ALT) level in donor blood [10, 11]. Because the test is neither specific nor highly sensitive, further studies are needed to determine if the number of hepatitis cases that would be prevented justifies the expense in terms of discarded donor units, cost of testing and consequences to donors found to have abnormal ALT values. Since the incidence of transfusion-transmitted hepatitis may vary with geography and donor population, the local incidence should be estimated before a decision regarding routine ALT screening is made [12, 13].

We undertook this prospective study to estimate the risk in Montreal of developing hepatitis following administration of donor blood with an elevated ALT level.

Address reprint requests to: Dr U. P. Steinbrecher, Department of Medicine, Division of Metabolic Disease, M-013-D, University of California, San Diego, La Jolla, CA 92693, U.S.A.

## METHODS

Between 5 August 1981 and 13 October 1981, 2000 units of blood or packed cells were received by the Royal Victoria Hospital Transfusion Service. All units were obtained from volunteer donors by the Montreal branch of the Canadian Red Cross Blood Transfusion Service. All donors were negative for HBsAg by radioimmunoassay.

Two segments of crossmatch tubing (containing approx. 0.5 ml plasma) from each unit were reserved for ALT measurement. The samples were kept at 4°C until tested; the interval between blood collection from the donor and ALT measurement on the plasma sample was nearly always $<7$ days. The ALT determinations were done by the Royal Victoria Hospital Biochemistry Laboratory using a standard method (SMAC, Technicon, Tarrytown, NJ).

The anticoagulant used by the transfusion service was citrate-phosphate-dextrose; 63 ml of anticoagulant were added to 450 ml of blood. To correct for the dilution of plasma enzyme activity by the anticoagulant, the measured ALT levels were multiplied by a factor of 1.24 (a hematocrit of 42% was assumed in calculating plasma volume of donor blood units). To exclude interference with the ALT assay by the anticoagulant, ALT measurements were performed on a panel of five simultaneously obtained serum and plasma samples. To demonstrate stability of ALT activity on storage of plasma at 4°C, serial ALT determinations were done over a 2-week period on a second panel of five citrated blood samples.

All donor units with corrected ALT values of 51 IU $l^{-1}$ or greater were classified as abnormal. Two 'control' units were selected randomly for every 'abnormal' unit identified. Each weekday the transfusion service records were examined and recipients of abnormal or control units were identified. The medical records of all recipients were reviewed, and the following information recorded: diagnosis, reason for transfusion, date and identification number of all blood units transfused, other blood products given, medications prescribed, and baseline ALT level (obtained within 1 week of the transfusion).

Patients were excluded from the study if they had a history of chronic liver disease, active medical problems likely to be associated with abnormal liver enzyme values, were receiving known hepatotoxic drugs, or if their baseline ALT values were abnormal. Control patients were also excluded if they had received transfusions in the preceding 6 months, or if they received platelet concentrates or plasma (ALT measurements could not be made in these blood products). Each patient was asked to return for two serum ALT measurements, one in the 6th and one in the 9th week following the transfusion. If an abnormal ALT result was obtained, a repeat sample was obtained 7 days later. Standard criteria for the diagnosis of post-transfusion hepatitis were used [7]: two consecutive elevations of ALT level to at least two standard deviations above the normal mean done at least 5 days apart, in the absence of other possible causative factors.

Determinations of HBsAg, anti-HBs, and anti-HBc by radioimmunoassay as well as estimation of the anti-HA IgM titer were done on all recipient sera with abnormal ALT values. Seroconversion to cytomegalovirus and Epstein–Barr virus was sought in patients with hepatitis. Patients with abnormal ALT results were followed by members of the Gastroenterology Division or by their treating physicians who were informed of these results. The identification numbers of all blood units administered to patients who developed post-transfusion hepatitis were reported to the Canadian Red Cross. Donors with elevated ALT values who did not transmit hepatitis to the recipient were not identified or investigated. All subjects gave informed consent to participate in the study, which was approved by a McGill University Ethics Committee.

## RESULTS

Comparison of ALT values in simultaneously obtained samples of serum and plasma (after correction for dilution by anticoagulant) indicated a high degree of correlation ($r = 0.995$) between serum and plasma measurements over a range of ALT values from 23 to 65 IU $l^{-1}$. ALT values in a second panel of samples did not change on storage of blood for 2 weeks at 4°C.

The ALT values of 133 donor units (6.7% of the total screened) were $\geqslant 51$ IU $l^{-1}$. Nineteen units were not transfused prior to the expiry date of the blood. Eighty-five patients received one or more of the remaining 114 units; 34 of these patients were excluded. The commonest reasons for exclusion were: death prior to completing follow-up (no deaths from hepatitis), abnormal baseline ALT, and disseminated malignancy. One patient developed a hypersensitivity reaction to chlorpropamide, and one had abnormal transaminases attributable to long-term parenteral nutrition. In one patient, there was no record of the transfusions having been received. Three patients were excluded because the transfusions were given in other hospitals and records were not available for review.

Of the 51 patients who remained eligible for study, 24 completed follow-up. Two patients had post-transfusion hepatitis; one was asymptomatic and had abnormal ALT values with transient appearance of circulating HBsAg, while the second patient developed fever, anorexia, and malaise associated with an elevated ALT level but no viral markers in the blood. One patient received 2 units with elevated ALT values but did not develop hepatitis. There were no differences in the number of units transfused, diagnosis, reason for transfusion, or duration of hospital stay in patients who completed the study in comparison with those who did not.

In the control group, 266 randomly-selected units of blood were traced; only 26 control patients were eligible for the study and of these only 10 completed follow-up. The proportion of 'control' units excluded was much

higher than the proportion of units with elevated ALT level because control patients who received other blood products were excluded, and because numerous control units were given to patients who also received blood with an elevated ALT value. One control patient developed posttransfusion hepatitis; results of tests for viral markers were negative.

The median number of units given per patient was four in the high-ALT donor group and three in the control group.

## DISCUSSION

In this study, two of 24 patients (8%) who received at least one unit of blood with an abnormal ALT value (in addition to other units with normal ALT) developed transfusion-transmitted hepatitis, and one of these patients had type B hepatitis. Because of the small number of patients who completed follow-up it is not possible to state whether in this population there is a difference in the risk of hepatitis in recipients of high-ALT vs normal-ALT blood units. However, even in the high-ALT group, the incidence of hepatitis was similar to values of 6.8 and 9% respectively found in recipients of only *normal*-ALT volunteer donor blood in two recent American studies: the Transfusion-Transmitted Viruses (TTV) study [10], and the NIH study [11]. The risk of hepatitis in the high-ALT group of our study was much less than the incidence of 29–33% found in high-ALT groups of the NIH and TTV studies. The apparent difference in risk of hepatitis associated with elevated ALT values in donor blood might be due, in part, to underestimation of the frequency of hepatitis in our study since more frequent ALT determinations were made in the other studies. However, transaminase elevations in post-transfusion non-A non-B hepatitis usually occur 6–8 weeks after transfusion and persist for several weeks [7], hence it is unlikely that more than a minority of hepatitis cases would have been overlooked. A second possible reason for the difference in hepatitis risk might be that the average number of units transfused per patient in the NIH study was larger than in the TTV or in the present study. However, even when only patients who received similar volumes of blood are compared, the differences persist. Another possible explanation might be that the proportion of donor units classified as abnormal was greater in our study (6.7%) than in the TTV or NIH studies (3.1 and 1.6%). However, even if we had selected an ALT cut-off value that excluded only 3% of donor units, the apparent risk of hepatitis would not have increased. We believe that the most likely explanation for the difference in hepatitis risk associated with elevated donor blood ALT level in our study compared to the two American studies is that the donor populations differ with regard to the prevalence of hepatitis carrier states.

The number of cases of hepatitis that would be prevented by ALT screening may not justify the cost in terms of discarded donor units, expense of testing, and implications for follow-up of asymptomatic donors with abnormal ALT levels [12–15]. A rational decision regarding implementation of ALT screening of donor blood in a given region may be facilitated by an analysis of resource costs vs economic benefits associated with such a program [15]. Such an analysis requires knowledge of the number of cases of hepatitis that could be prevented by ALT screening as well as estimates of the costs associated with the screening program and of the economic benefit associated with prevention of hepatitis in a blood recipient. If the risk of hepatitis in recipients of high-ALT blood is of the order of 30% (as in the NIH and TTV studies) and the risk with normal-ALT blood $< 10\%$, ALT screening may be economically justifiable [15]. On the other hand, if the risk of hepatitis in recipients of high-ALT blood is comparatively low, costs of screening become prohibitive because, even if the program were highly efficacious in preventing hepatitis, the number of cases prevented would be few.

Because of the small number of patients in the present study, the results cannot be considered conclusive and require confirmation by a larger study. However, the findings are consistent with other reports indicating considerable geographic variability in hepatitis risk in recipients [16, 17] and in ALT levels in donors [18]. Until a sensitive and specific test for non-A non-B hepatitis is developed, any non-specific screening test, such as ALT measurement, must be carefully evaluated in the population where its introduction is being considered.

*Acknowledgements*—We are indebted to the following individuals for assistance during this study: Irene Ohashi, Anna Da Mutten and Suzie Kiraly. We thank the staff of the Biochemistry Laboratory and the Transfusion Service of the Royal Victoria Hospital for their cooperation. This study was supported in part by the Department of Medicine, Royal Victoria Hospital, and by the Canadian Red Cross Society Transfusion Service.

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