Transfusion Medicine, 1991, 1, 103–108

Post-transfusion hepatitis after open-heart surgery in Finland—a prospective study

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Received 5 November 1990; accepted for publication 6 November 1990

SUMMARY. A countrywide prospective study on open-heart surgery patients was performed between 1987 and 1989 to determine the prevalence and nature of post-transfusion hepatitis in Finland. Altogether 685 coronary by-pass operation patients, who received on average 12·3 units of blood products, were postoperatively followed for 6 months. Ten blood samples were drawn from each patient. Hepatitis was diagnosed when the alanine aminotransferase values exceeded the upper normal value 2·5 times in one sample and twice in another, and non-viral causes could reasonably be excluded. Eleven hepatitis cases (1·6%) were recorded with a mean incubation period of 8·4 weeks; all represented the non-A, non-B type. The majority had mild symptoms or were asymptomatic but two became icteric. Six patients (55%) had abnormal alanine aminotransferase values for at least 6 months, which indicates possible chronicity. These 685 open-heart surgery patients received a total of 8,436 units of blood products; thus the rate of NANBH cases per 1000 units was as low as 1·3. This is less than recently reported in six other prospective studies.

Key words: blood transfusion, hepatitis, non-A, non-B, post-transfusion, viral.

The incidence of non-A, non-B hepatitis (NANBH) varies and tends to be higher in southern Europe and the U.S.A., and lower in mid- and northern Europe (Reesink & van der Poel, 1989). It is typically mild or even asymptomatic in its acute phase, but about half the patients are known to develop chronic hepatitis, which in some cases leads to cirrhosis (Koretz *et al.*, 1985).

Attempts to prevent development need data from prospective studies about the existing situation in the country; both about the hepatitis rate and the blood donors. In Finland, the number of reported transfusion hepatitis cases has been very low; the order of 10 per year (Helske, 1974) in a population of 4·9 million and from approximately 250,000 annual transfusions. The incidence of NANBH after cardiac surgery was estimated to be 4·6% in a previous smaller study (Lagerstedt *et al.*, 1982). The purpose of the present study was to determine the current incidence and types of post-transfusion hepatitis among open-heart surgery patients from all parts of Finland. The second objective was to obtain donor samples for future evaluation of possible preventive strategies.

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PATIENTS AND METHODS

Patients

Coronary artery bypass patients from 1 December 1987 to 30 November 1988 were invited to a 6-month follow-up with 10 blood samples: preoperatively, then bi-weekly during the first 3 months, and monthly for the next 3 months. If more than one sample was missing (excluding the first postoperative one) the follow-up was considered to be interrupted. Alanine aminotransferase (ALT), γ-glutamyl transferase (GGT) and hepatitis-B surface antigen (HBsAg) were tested on all samples; antibodies to the hepatitis-B surface (anti-HBs) and core (anti-HBc) antigens pre-transfusion and at 3 and 6 months post-transfusion. The inclusion criteria are listed in Table 1. One patient was excluded because he received additional transfusions (before ALT-elevations of > 100 U/l) during a later hospital period, donor samples of which were unavailable. Patients were recruited in all five univer-

PEN.017.1778

Table 1. The inclusion criteria for patients in the study

The patient's written consent
Normal preoperative ALT value ($\leq$40 U/l)
HBsAg negative
No clotting factor concentrates
No transfusion-requiring reoperations later than 7 days postoperatively during the same hospitalization period
A donor blood sample available for every transfused unit the patient received in connection with the operation

Table 2. The coronary artery bypass patients in the study

Recruited patients	Patients (*n*)	Units transfused (average)
The primary patient population	765	13·1
Follow-up interrupted	80	13·9
Postoperative complications, cardiac symptoms	31	
Death	19	
Practical obstacles	18	
Reason unknown	12	
The final study population	685	12·3

sity central hospitals in Finland (Helsinki, Kuopio, Oulu, Tampere and Turku). An age- and sex-matched control group was also recruited in Helsinki. They were the subject of a surgical procedure (prostatic electroresection, hernioplasty, cholecystectomy, thyroid resection, etc.) without transfusion.

Seven hundred and sixty-five patients met the inclusion criteria. The follow-up was completed by 685 patients, who received a total of 8,436 units of blood products (red blood cell concentrates, platelet concentrates, whole blood, fresh frozen plasma) from 8,346 donations; the average per patient was 12·3 units (range 1–72, SD 7·5) (Table 2). The mean age of the patients was 55·7 years (31–74 years, SD 7·2), and 84·7% were male. The control group of 89 patients was followed similarly. Their mean age was 55·9 years (35–74 years, SD 8·5), 83·2% were male.

Definition of possible hepatitis

Hepatitis was defined as an elevation of ALT to at least 2·5 times the upper limit of normal (100 U/l) plus in one other sample to at least twice the limit (80 U/l). This definition is in accordance with several other prospective studies (Koziol *et al.*, 1986; Reesink *et al.*, 1988).

Differential diagnosis of the possible hepatitis cases

Other factors such as medication, congestion, alcohol, etc., were evaluated by one of us (FE) who interviewed the patient and examined the hospital records. The following tests were also used: serum ALT, aspartate aminotransferase (AST), GGT, alkaline phosphatase, total and conjugated bilirubin, triglycerides, Hb, MCV, WBC, platelet count, serum protein level, albumin, IgM, protein electrophoresis, antimitochondrial and smooth muscle antibodies, HBsAg, anti-HBs, anti-HBc, IgM antibodies to the hepatitis A virus (anti-HAV-IgM) and paired sera for antibodies to the cytomegalo, Epstein-Barr and herpes simplex viruses (anti-CMV, anti-EB, anti-HSV). An independent expert panel drew the final diagnostic conclusions for all the patients who met the ALT criteria.

Laboratory methods

The ALT, AST, GGT and alkaline phosphatase activity determinations were performed at 37°C (The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology 1974 and 1976). The HBsAg and anti-HBs were tested with a radioimmunoassay method, FRC-RIA (Koistinen,

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1978), anti-HBs during the latter part of the study with EIA (Enzygnost Anti-HBs, Behring). The anti-HBc testing was performed with EIA (Corzyme, Abbott). The anti-CMV testing was performed with EIA (Microstrips, Labsystems), anti-EBV by immunofluorescence, anti-HAV-IgM by EIA and anti-HSV by complement fixation.

RESULTS

ALT, hepatitis B serology

In total, 37 coronary bypass patients developed an ALT-elevation to 100 U/l or more during the 6 postoperative months. Fifteen of them had an elevation to at least 80 U/l in one other sample.

No appearance of HBsAg was detected during this follow-up. In four coronary bypass patients, a primarily negative anti-HBs was positive in the 3-month sample. This was interpreted to be passive transfer of antibody and not a sign of infection, as in all cases the antibodies were found to be already present in the first postoperative sample (the 2-week sample), and because no anti-HBc was detected during the follow-up. The anti-HBs antibodies declined gradually but were still detectable in the 6-month sample in two cases. Furthermore, all four patients were found to have an anti-HBs-positive donor. In one patient, the anti-HBc turned positive in the 3-month sample despite having been negative 4 weeks earlier. The anti-HBc-IgM, however, was negative in the 3-month sample. The reason for the appearance of anti-HBc antibodies in this patient remains unclear.

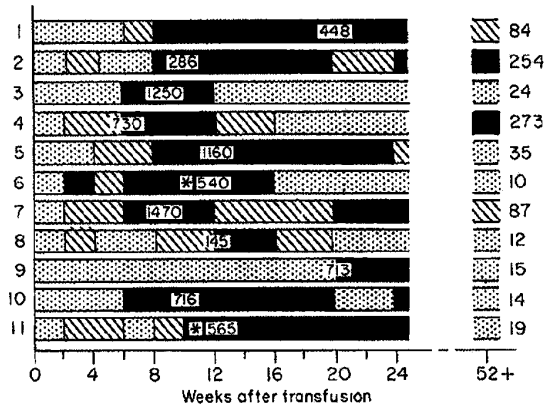

Fig. 1. Course of hepatitis in the 11 non-A, non-B post-transfusion hepatitis cases in the study. Each horizontal bar represents the transaminase development in one patient. Both the maximum and the 1-year ALT values of each patient are shown. (The upper limit of normal: ALT 40 U/l.) (▨) ALT ≤ 40 U/l, (▩) ALT 41–99 U/l, (■) ALT ≥ 100 U/l. * = appearance of icterus.

Possible hepatitis cases

Of the 15 cases who met the ALT criteria, the expert panel regarded four mild elevations (max. 145 U/l) as probable non-viral (one as amiodarone toxicity, one as nicotinic acid and alcohol effect, one as an early postoperative elevation and one as a consequence of various antiarrhytmic drugs and congestion). The remaining 11 patients were all considered to have an acute NANBH by a diagnosis of exclusion. No evidence for other viral causes was found. Two patients, however, were considered to have a simultaneous reactivation of old CMV infection because of a considerable rise in pre-existing anti-CMV titres, but both with an equivocal (±) anti-CMV-IgM result during the hepatitis. Later, both patients developed chronic ALT-elevations. The clinical picture for these two patients was unlike that described for post-transfusion CMV hepatitis (Alter *et al.*, 1982). Thus, the incidence of NANB post-transfusion hepatitis among these coronary bypass patients was 1·6% (11/685).

Non-A, non-B hepatitis cases (Fig. 1)

The 11 NANBH patients generally had mild symptoms (diffuse fatigue, decreased appetite, nausea) or were asymptomatic. Two (18·2%) developed icterus (patients 6 and 11), one of whom also had moderat pain in his upper abdomen. The mean incubation time from transfusion to onset of hepatitis (defined as first elevation of ALT ≥ 100 U/l) was 8·4 weeks (range 2–20 weeks). The ALT development was variable; the maximum value for a patient ranged from 145 U/l to 1470 U/l (mean 729 U/l), and six (cases 2, 4, 6, 7, 9 and 10) had two distinct peaks. Seven still had abnormal ALT 6 months postoperatively. The average number of transfused units to the NANBH patients was 12·4. The corresponding mean in the total coronary bypass operation group was 12·3 units per patients (Table 3).

The clinical courses were followed later from hospital records (the patients with persistent ALT elevations were sent for follow-up in their own hospitals after the study period) and with an additional sample 1 year postoperatively. Of the above mentioned seven patients, only three still had raised ALT in the 1-year sample. A fourth patient, however, had a novel ALT-elevation up to 273 U/l after normal values at 4, 5 and 6 months. Six patients (55%) had persistently or intermittently abnormal ALT for at least 6 months, and still

Table 3. The coronary artery bypass patients, their transfusions and the non-A, non-B hepatitis cases in the five centres studied

	Operated patients (*n*)	Average amount of units per patient	Non-A, non-B cases (*n*)
Site 1	275	9·2	6
Site 2	45	22·3	1
Site 3	152	16·4	1
Site 4	100	15·4	2
Site 5	113	7·9	1
All	685	12·3	11

at 23–36 months postoperatively; but none have since had recorded signs of liver insufficiency. Patient 4 underwent liver biopsies 17, 21 and 24 months after the onset of hepatitis; the latest two showed a predominantly lymphocytic inflammation, and the ALT levels continue to fluctuate between 200 and 600 U/l.

Control patients

None of the 89 non-transfused control patients had ALT-elevations of 80 U/l or more. No HBsAg was found. One patient first became anti-HBs-positive in the 6-month sample without the appearance of anti-HBc.

DISCUSSION

The overall incidence of post-transfusion hepatitis has declined in the 1980s (Mattsson *et al.*, 1988; Alter, 1989). This is partly due to changes in transfusion practice towards fewer units per patient, and also to a reduced infection risk per unit (Mattsson *et al.*, 1988). In Finland, the incidence was higher (4·6%) in a previous small scale report (Lagerstedt *et al.*, 1982) than in the present study, however, the incidence of NANBH among cardiac surgery patients has been 2·3–10·7% in six recent reports (Reesink *et al.*, 1988; Koziol *et al.*, 1986; Mattsson *et al.*, 1988; Sugg *et al.*, 1988; Aymard *et al.*, 1986; Hoyos *et al.*, 1989). In these prospective studies (from The Netherlands, U.S.A., Sweden, Germany, France and Spain) the mean number of transfusions per patient was 5·4–13·5 units. The rate of NANBH cases per 1000 transfused units varied from 1·7 (Reesink *et al.*, 1988) to 9·6 (Hoyos *et al.*, 1989).

We found a 1·6% incidence of NANBH among 685 open-heart surgery patients (about 40% of the coronary bypass operations in Finnish university hospitals during the study period). Their mean number of transfusions was 12·3 units per patient, which gives a rate of 1·3 NANB cases per 1000 transfused units (11/8436). This incidence is even lower than previously reported from northern Europe (Mattsson *et al.*, 1988; Widell *et al.*, 1987) and much less than elsewhere in Europe and North America.

There are many contributing factors. In Finland, blood donation has always been voluntary and unpaid, and the country is self-sufficient. (The routine screening during the study period included HBsAg, anti-HIV and cardiolipin, but no surrogate tests such as ALT or anti-HBc.) The apparent prevalence of the NANB carrier-state and post-transfusion hepatitis risk seem to parallel the HBsAg carrier-prevalence in other parts of Europe. In Finland, only 0·05% of new blood donors were HBsAg positive in 1985–1988.

The clinical picture of post-transfusion NANBH in this study corresponds to that previously described (Dienstag, 1983): the incubation period of about 8 weeks, the high proportion of mild, subclinical and anicteric cases, and a tendency towards prolonged transaminase pathology in about half the cases.

The ALT elevation follows different patterns (Tateda *et al.*, 1979). The monophasic pattern has been associated with complete recovery in contrast to an ALT development with several peaks (Pastore *et al.*, 1985). Patient 4, however, shows that even after a rapidly subsiding hepatitis episode the transaminase pathology can recur after several months of normal values, as described before (Dienstag, 1983). Thus, the length of follow-up is essential to determine the real proportion of chronic cases, and if it extends for only some months after the acute episode, later recurrences may be undetected.

Our NANBH cases appeared during three distinct periods: in late winter–early spring 1988, at the end of 1988 and in late winter 1989. A somewhat similar seasonal clustering of post-transfusion NANBH was described by Cossart in Australia (Cossart *et al.*, 1982). As stated by Cossart, it might mean that the transfusion-associated cases represent a small visible part of the common asymptomatic infection in the general population.

Although a rare phenomenon in our country, NANBH is still the most common infectious complication of blood transfusion and deserves further preventive measures; especially because of the often protracted course of the disease. The newly developed test to detect antibodies to the hepatitis C virus (Kuo *et al.*, 1989) offers major advantages in this respect (Ebeling *et al.*, 1991).

PEN.017.1781

ACKNOWLEDGEMENTS

The authors thank the staff of the thoracic surgery wards of the five university central hospitals for help in patient recruitment and follow-up information. The follow-up sampling was made possible by the co-operation of local health centres and hospitals all over Finland. The authors would like to thank Dr Pentti Ukkonen from the Department of Virology, University of Helsinki, for serological consultations; and Drs Eero Ikkala, Mikko Salaspuro, Ville Valtonen and Kalle Varis from the Helsinki University Central Hospital, who formed the hepatitis expert panel.

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