RESULTS

Two hundred seven patients (134 females, 73 males), mean age 52.7 ± 12.5 years (range: 18–79 years) were included. Sixty-two patients had a past history of sclerotherapy of varicose veins including 43 patients who had sclerotherapy by the same physician (67%). Risk factors for HCV infection are shown in Table II.

HCV serostatus of the physician who performed sclerotherapy sessions was done and was found to be negative.

Among the 43 patients who had sclerotherapy by the same physician, 4 patients were considered to have been infected by transfusion (because transfusion was before 1992) and 39 patients were considered to have been *infected by sclerotherapy on the basis of epidemiological* data. No statistical difference was observed regarding risk factors for HCV infection between the two groups except for transfusion ($P < 0.0001$) (Table II).

Patients who had sclerotherapy by the same physician had *many sessions carried out in the 1980s (from 1 to* more than 400) for many years (from 1 to more than 15 years). Five of these 43 patients developed jaundice a few weeks after a sclerotherapy session.

Nucleotide sequence analysis of E1 in 17 of the 43 patients who had sclerotherapy by the same physician revealed that they were all infected with the same HCV subtype (genotype 2c). The aligned sequences of 258 nt, encompassing the E1 and E2 regions, obtained from the 17 patients, were bootstrapped and a phylogenetic tree was obtained, as shown in Figure 1. The most evident feature of the tree is the clustering of all patients involved in the outbreak (denoted by PT). The bootstrap value of 98 of the node leading to the PT cluster lends statistical robustness to the interpretation that all of the patients involved in the outbreak were infected by a common source. Prototype sequences of genotypes 2a and 2b also form separate clusters. The unrelated local controls (LCs) LC2, LC3, LC7, attributed to genotype 2a/2c on the basis of their sequences in the 5′ NC region, clustered with the 2a prototypes; LC16, LC8, LC13, LC4, and LC5 clustered with the 2b prototypes.

The characteristics of the 43 patients who had sclerotherapy by the same physician are shown in Table III. No patient had HBV or HIV infection. Patients with a past history of sclerotherapy were significantly more frequently females ($P = 0.0004$), older ($P = 0.01$), and with alcohol consumption <40 g/day ($P = 0.001$) compared to patients with no past history of sclerotherapy by this physician. Mild hepatitis (normal ALT and/or METAVIR score <A2F2) was observed in 53.5% of cases. Neither cirrhosis nor hepatocellular carcinoma were observed.

DISCUSSION

This study shows that sclerotherapy of varicose veins could be a risk factor for HCV infection and careful documentation of a history is needed. To our knowledge, this is the first documented report of a transmission of HCV infection during sclerotherapy for varicose veins, and the phylogenetic analysis of the HCV hypervariable region 1 (HVR1) provides strong evidence for transmission of HCV from a common source of infection.

Nucleotide sequencing and phylogenetic analysis of different genomic regions of the virus provide more convincing evidence of patient-to-patient transmission of HCV. These techniques allow for accurate tracing of viral spread and constitute a powerful tool in epidemiological research. The study of highly conserved regions, such as the 5′ UTR, is not suitable for the exact characterization of HCV strains. Our molecular investigations were based on sequence analyses of HCV HVR1, which is used commonly to distinguish between related

TABLE II. Risk Factors Associated With Hepatitis C Virus Infection in Patients With or Without Past History of Sclerotherapy by the Same Physician

Risk factors (N)	Patients with a past history of sclerotherapy by the same physician N (%)	Patients with no past history of sclerotherapy by the same physician N (%)	Odds ratio	95% Confidence interval	P
Sclerotherapy (207)	43 (100)				
Blood transfusion (201)	6 (13.9)	68 (43.0)	0.21	0.09–0.54	<0.0001
Intravenous drug or cocaine use (199)	0	6 (3.8)	0.78	0.72–0.84	0.23
Acupuncture therapy (200)	16 (37.2)	36 (22.9)	1.99	0.97–4.1	0.059
Mesotherapy (199)	4 (9.3)	14 (8.9)	1.07	0.33–3.45	0.55
Previous surgery (200)	20 (46.5)	65 (41.4)	1.23	0.62–2.42	0.55
Previous coelioscopy (198)	5 (11.6)	10 (6.4)	2.04	0.68–6.34	0.21
Previous endoscopy (200)	8 (18.6)	32 (20.4)	0.89	0.38–2.11	0.80
Cardiovascular explorations (200)	1 (2.3)	6 (3.9)	0.6	0.07–5.12	0.64
Previous voluntary termination of pregnancy (199)	3 (7)	12 (7.7)	0.9	0.24–3.44	0.87
Previous hospitalization >15 days (200)	2 (4.6)	18 (11.5)	0.38	0.08–1.69	0.20

No statistical difference was observed concerning previous immunoglobulin injection, transplantation, hemodialysis, history of incarceration, institutional living, tattoo or body piercing, health profession, and infection of the spouse
Results are >100% since one patient could have more than one risk factor

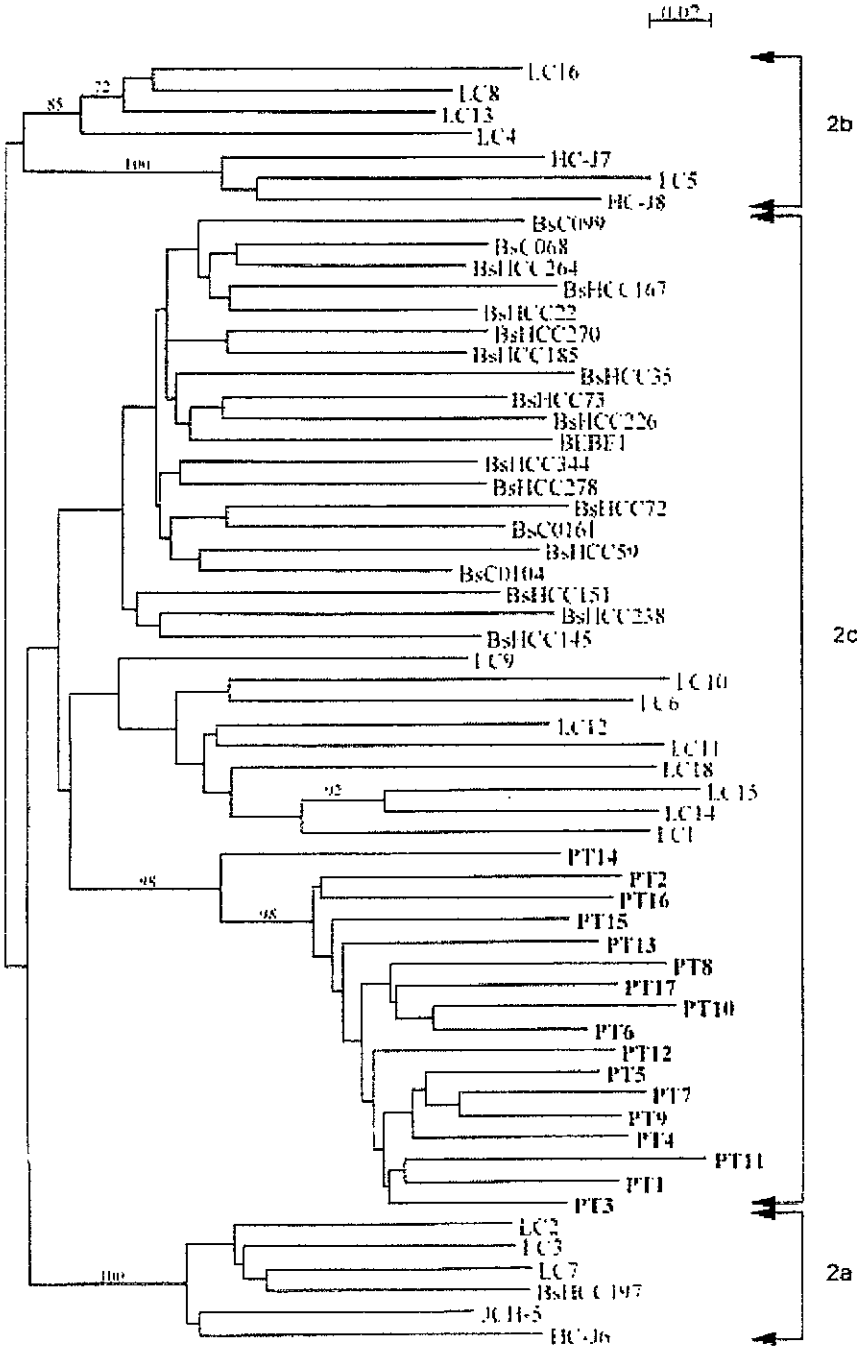

Fig. 1. Phylogenetic tree analysis comparing coding sequences in the HCV regions for the envelope glycoproteins E1 and E2 from 59 isolates. For phylogenetic analysis, 17 sequences from 17 randomly selected HCV RNA positive patients with a past history of sclerotherapy by the same physician (PT) were compared with 17 sequences (3 of genotype 2a, 5 of genotype 2b, and 9 of genotype 2c) from patients without a past history of sclerotherapy and followed-up in our laboratory taken as unrelated local controls (LCs), with 20 sequences (19 of genotype 2c, and 1 of genotype 2a) derived from a previous study (Larghi et al., 2002) (BsC and BsHCC), and with 5 prototype sequences sampled from GenBank (D00944: HC-J6 and D10075: HC-J5 for genotype 2a, D10077: HC-J7 and D10988HC-J8 for genotype 2b, D50409: BEBE1 for genotype 2c). Bootstrap values greater than 70/100 are reported at the nodes.

and unrelated isolates of the same subtypes, because of its variability [Major and Feinstone, 1997]. However, when this sequence is used, phylogenetic relationships can sometimes be obscured, especially if transmission occurred many years previously. In this study, it was confirmed that the HVR1 genomic sequences could provide relevant information for making close comparison of viral strains [Allander et al., 1994]. The demonstration of a high degree of homology among the sequences of the viral region encompassing E1 and E2 in

TABLE III. Demographic and Clinical Characteristics of the Patients With or Without Past History of Sclerotherapy by the Same Physician

	Patients with a past history of sclerotherapy by the same physician N (%)	*Patients with no past history of sclerotherapy by the same physician* N (%)	*P*
Gender (F/M)	38/5	96/68	*<0.0001*
Mean age (years)	57 ± 9.2	52 ± 13.0	0.01
Tobacco consumption (%)	5.9	31.2	NS
Alcohol consumption			
<40 g/day (%)	100	76.5	0.002
ALT <N (%)	*15 (34.9)*	*48 (29.3)*	*NS*
Mean viral load (IU/ml)	507,147 ± 811,846	941,489 ± 1,619,012	NS
Liver biopsy	35 (81.4)	134 (81.7)	NS
Activity grade			NS
A0	0	3 (2.2)	
A1	9 (25.7)	35 (36.1)	
A2	21 (60)	77 (57.5)	
A3	5 (14.3)	19 (14.2)	
Fibrosis stage			NS
F0	0	5 (3.7)	
F1	13 (37.1)	53 (39.5)	
F2	17 (48.6)	45 (33.6)	
F3	5 (14.3)	13 (9.7)	
F4	0	18 (13.4)	

NS, not significant

all of the subjects studied strengthens the probability of a common source of infection. Moreover, the rate of sequence change shown in the virus from the 17 patients with a past history of sclerotherapy of varicose veins by the same physician has been slow enough to preserve evidence of relatedness over a considerable period of time.

Transmission from an infected patient to another patient being treated simultaneously in the same room has emerged as the main mechanism of HCV transmission among patients, treated by hemodialysis [Katsoulidou et al., 1999; Kokubo et al., 2002]. The frequent percutaneous procedures provide many opportunities for contamination of surfaces and instruments with small amounts of HCV-infected blood. Moreover, a history of hospitalization in the distant past is a risk factor associated significantly with HCV infection [Chen et al., 1995; Chiaramonte et al., 1996; Comandini et al., 1998]. Several reports indicate that medical treatment could be the cause of HCV transmission in some patients with acute hepatitis and inadequate procedures were identified in most cases of suspected or proven nosocomial transmission of HCV [Sata et al., 1997; Schvarcz et al., 1997].

It has been suggested that the vehicle of transmission could be a nurse who did not change gloves regularly when moving from patient-to-patient [Katsoulidou et al., 1999]. Retrospective surveys of patients with chronic HCV infection have shown that therapeutic injections with non-disposable syringes and needles are risk factors for HCV infection. It has been reported, in an arthroscopy episode, that the anesthetist re-used the drawing-up needle left in the ampoule and syringe to withdraw additional medication [Tallis et al., 2003]. It has also been reported that the use of multidose vials was associated with nosocomial HCV transmission [Widell et al., 1999; Krause et al., 2003].

In our study, a patient with chronic hepatitis C could be the putative source patient. Indeed, all patients had many sessions for many weeks. Therefore, this putative patient, returning many times, could have allowed infection of many vials. The physician used the same bottle for many patients and did not change the vial after each patient. A common feature of these cases is the routine use of intravenous sclerotherapy agent ampoules on more than one patient, which may have allowed the transmission of HCV. Experimental investigations suggested HCV could have survived in either drugs: Propofol or Fentanyl [Druce et al., 2001]. This result could be applied to the sclerotherapy drug. In our study, the syringe used to administer the drug to the source patient was also used to draw the drug from the vial and administer it to the following patient. Therefore, blood contamination of the syringe is likely to have resulted and to have caused the spread of HCV infection. Experimentally, detachment of a needle from a syringe results in a transient negative pressure, which may lead to backflow of the needle contents into the end of the fluid in the syringe [Evans and Spooner, 1950]. Finally, the source of the initial infection could be a patient since HCV serostatus of the physician who performed sclerotherapy sessions was negative.

A case-control study was not carried out since we were unable to determine the number of patients who received sclerotherapy during the same period and who did not have HCV infection. Indeed, this outbreak occurred more than 15 years ago and we were unable to find all patients this physician treated between 1970

and 1990. Similarly, we were unable to evaluate the median number of sessions received by patients since they did not remember such information.

The findings emphasize the risk for nosocomial spread of HCV during intravenous therapy. There have been previous cautions about the inappropriate use of medication ampoules to provide doses for more than one patient and the re-use of syringes. Ampoules of injectable drugs should only be used on single patients. Strict adherence to universal precaution measures is an important issue, not only for HCV but also for other bloodborne virus infections, particularly in developing countries where these infections are more common.

REFERENCES

Allander T, Medin C, Jacobson SH, Grillner L, Persson MAA. 1994. Hepatitis C transmission in haemodialysis unit: Molecular evidence for spread of virus among patients not sharing equipment. J Med Virol 43:415–419.

Bedossa P, Poynard T, the METAVIR cooperative study group. 1996. An algorythm for the grading of activity in chronic hepatitis C. Hepatology 24:289–293.

Bronowicki JP, Venard V, Botté C, Monhoven N, Gastin I, Choné L, Hudziak H, Rihn B, Delanne C, LeFaou A, Bigard MA, Gaucher P, Rhin B. 1997. Patient-to-patient transmission of hepatitis C virus during colonoscopy. N Engl J Med 337:237–240.

Chen TZ, Wu JC, Yen FS, Sheng WY, Hwang SJ, Huo TI, Lee SD. 1995. Injection with non disposable needles as an important route for transmission of acute community acquired hepatitis C virus infection in Taiwan. J Med Virol 46:247–251.

Chiaramonte M, Stroffolini T, Lorenzoni U, Minniti F, Conti S, Floreani A, Ntakirutimana E, Vian A, Ngatchu T, Nuccarato R. 1996. Risk factors in community acquired chronic hepatitis C virus infection: A case-control study in Italy. J Hepatol 24:129–134.

Comandini UV, Tossini G, Longo M, Ferri F, Cruzzi G, Noto P, Zaccarelli M, Visco G. 1998. Sporadic hepatitis C virus infection: A case-control study of transmission routes in a selected hospital sample of the general population in Italy. Scand J Infect Dis 30:11–15.

Druce JD, Catton MG, Ryan G, Birch CJ. 2001. Survival of hepatitis C surrogate in anaesthetic and analgesic drugs. Aust Infect Control 6:89–90.

Esteban JI, Gomez J, Martell M, Cabot B, Quer J, Camp J, Gonzalez A, Otero T, Moya A, Esteban R, Guardia J. 1996. Transmission of hepatitis C virus by a cardiac surgeon. N Engl J Med 334:555–560.

Evans RJ, Spooner ETC. 1950. A possible mode of transfer of infection by syringes used for mass inoculation. BMJ 2:462–466.

Katsoulidou A, Paraskevis D, Kalapothaki V, Arvanitis D, Karayiannis P, Hadjiconstantinou V, Hatzakis A. 1999. Molecular epidemiology of a hepatitis C virus outbreak in a haemodialysis unit. Nephrol Dial Transplant 14:1188–1194.

Kokubo S, Horii T, Yonekawa O, Ozawa N, Mukaide M. 2002. A phylogenetic-tree analysis elucidating nosocomial transmission of hepatitis C virus in a haemodialysis unit. J Viral Hepatitis 9:450–454.

Krause G, Trepka MJ, Whisenhunt RS, Katz D, Nainan O, Wiersma ST, Hpkins RS. 2003. Nosocomial transmission of hepatitis C virus associated with the use of multidose saline vials. Infect Control *Hosp Epidemiol* 24:122–127.

Lagging LM, Aneman C, Nenonen N, Brandberg A, Grip L, Norkrans G, Lindh M. 2002. Nosocomial transmission of HCV in a cardiology ward during the window phase of infection: An epidemiological and molecular investigation. Scand J Infect Dis 34:580–582.

Larghi A, Zuin M, Crosignani A, Ribero ML, Pipia C, Battezzati PM, Binelli G, Donato F, Zanetti AR, Podda M, Tagger A. 2002. Outcome of an outbreak of acute hepatitis C among healthy volunteers participating in pharmacokinetics studies. Hepatology 36:993–1000.

Major ME, Feinstone SM. 1997. The molecular virology of hepatitis C. Hepatology 25:1527–1538.

Mondelli MU, Silini E. 1999. Clinical significance of hepatitis C virus genotypes. J Hepatol 31:65–70.

Power JP, Lawlor E, Davidson F, Holmes EC, Yap PL, Simmonds P. 1995. Molecular epidemiology of an outbreak of infection with hepatitis C virus in recipients of anti-D immunoglobulin. Lancet 345:1211–1213.

Ross RS, Viazov S, Gross T, Hofmann F, Scipp HM, Roggendorf M. 2000. Transmission of hepatitis C virus from a patient to an anesthesiology assistant to five patients. N Engl J Med 343:1851–1854.

Sanchez-Tapias JM. 1999. Nosocomial transmission of hepatitis C virus. J Hepatol 31:107–112.

Sata M, Hashimoto O, Noguchi S, Uchimura Y, Akiyoshi F, Matsukuma MB, Fukushima H, Suzuki H, Kage M, Kojiro M, Tanikawa K. 1997. Transmission routes and clinical course in sporadic acute hepatitis C. J Viral Hepatitis 4:273–278.

Schvarcz R, Johansson B, Nystrom B, Sonnerborg A. 1997. Nosocomial transmission of hepatitis C virus infection. Infection 25:74–77.

Tullis GF, Ryan GM, Lambert SB, Bowden DS, McCaw R, Birch CJ, Moloney M, Carnie JA, Locarnini SA, Rouch GJ, Catton MG. 2003. Evidence of patient-to-patient transmission of hepatitis C virus through contaminated intravenous anaesthetic ampoules. J Viral Hepatitis 10:234–239.

Thompson JD, Higgins DG, Gibson TJ. 1994. CLUSTAL W: Improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. Nucl Acids Res 22:4673–4680.

Widell A, Christensson B, Wiebe T, Schalen C, Bertil Hansson H, Allander T, Persson MA. 1999. Epidemiologic and molecular investigation of outbreaks of hepatitis C virus infection on a pediatric oncology service. Ann Intern Med 130:130–134.

Young KKY, Resnick RM, Myers TW. 1993. Detection of hepatitis C virus RNA by a combined reverse transcription-polymerase chain reaction assay. J Clin Microbiol 31:882–886.

医薬品
医薬部外品　研究報告　調査報告書
化粧品

別紙様式第2-1
No. 36

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2005. 5. 25	該当なし	

一般的名称	（製造承認書に記載なし）	研究報告の公表状況	Tawk HM, Vickery K, Bisset L, Lo SK, Cossart YE; Infection in Endoscopy Study Group. Transfusion. 2005 May;45(5):807-13.	公表国 オーストラリア
販売名（企業名）	合成血「日赤」（日本赤十字社） 照射合成血「日赤」（日本赤十字社）			

研究報告の概要

○現在発症しているB型肝炎及びC型肝炎感染のリスクとしての過去の輸血の意義：内視鏡検査患者における研究
【背景】この研究の目的は、内視鏡検査のために大病院に通院している患者において、現在発症しているB型またはC型肝炎感染のリスクに対する過去の輸血の関与を判断することであった。
【実験デザイン及び方法】通常の方法を用いて、各肝炎マーカーの検査を行った。患者が記入した包括的なリスク因子に関する質問表の結果を解析した。
【結果】2120名の参加者のうち、27%が過去に輸血を受けていた。輸血を受けた患者において、B型肝炎有病率の増加は認められなかった。輸血を受けていない患者と比較して、1990年のC型肝炎（HCV）スクリーニング実施前に輸血を受けた患者は、HCV感染のリスクが4.6倍高く、スクリーニング後の輸血を受けた患者では3倍高かった。スクリーニング前後の患者のオッズ比における差は、有意ではなかった。
【結論】HCVはスクリーニングによりほぼ完全に血液製剤から除去されているにもかかわらず、HCV感染と輸血の関連が引き続き認められたことは予想外だった。このことから、患者が輸血を受けるような状況においては、C型肝炎感染に対するその他の重要な院内リスクがあることが示唆される。これに関し積極的な調査が必要である。

報告企業の意見	今後の対応
輸血を受けていない患者と比較して、輸血を受けた患者のB型肝炎有病率の増加は認められなかった。HCVはスクリーニングによりほぼ完全に血液製剤から除去されているにもかかわらず、HCV感染と輸血の関連が引き続き認められ、輸血に伴う他の院内リスクがあることが示唆されるとの報告である。輸血後肝炎感染の調査には、院内感染など輸血以外の伝播ルートについて考慮する必要がある。	HBV、HCV感染の新たな伝播ルート等について、今後も情報の収集に努める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

The significance of transfusion in the past as a risk for current hepatitis B and hepatitis C infection: a study in endoscopy patients

Hani M. Tawk, Karen Vickery, Linda Bisset, Sing Kai Lo, Yvonne E. Cossart, and the Infection in Endoscopy Study Group

BACKGROUND: The objective was to determine the contribution of transfusion in the past to the risk of current infection with hepatitis B or C among patients attending a large hospital for endoscopic procedures.

STUDY DESIGN AND METHODS: Blood samples had been tested for hepatitis markers by routine methods. Patients completed a comprehensive risk factor questionnaire and results were analyzed using computer software.

RESULTS: Twenty-seven percent of the 2120 participants in the study received transfusions in the past. There was no increase in prevalence of hepatitis B among those transfused. Compared with nontransfused participants, recipients of blood before the implementation of hepatitis C virus (HCV) screening in 1990 had a 4.6-fold increased risk of HCV infection, whereas those transfused with screened blood had a 3-fold increased risk. The difference between the odds ratios for patients before and after screening was not significant.

CONCLUSIONS: Because screening has almost completely eliminated HCV from the blood supply, our finding of a continuing association of HCV infection with transfusion was unexpected. It implies that there are significant other nosocomial risks for hepatitis C transmission associated with the clinical situations where patients received blood. These should be actively investigated.

Both hepatitis B and C were discovered as complications of blood transfusion and preventing transmission of these blood-borne viruses remains a major preoccupation for transfusion services worldwide. A screening test which detects hepatitis B surface antigen (HBsAg) in currently infected individuals became available in the late 1960s and was widely implemented by the middle of the 1970s. Hepatitis C virus antibody (anti-HCV) tests, which are positive in people with current or past hepatitis C infection were devised in 1989 to 1990 and were then rapidly introduced. Exclusion of donations that are reactive in these tests has reduced the number of new transmissions of hepatitis B and C to such a low level that they cannot be detected by conventional prospective studies.[1]

It is difficult to estimate how many recipients were infected before these measures were introduced or to assess the significance of transfusion in the past in the overall pattern of current hepatitis-related liver disease in

From the Department of Infectious Diseases and Immunology, University of Sydney and the Australian Center for Hepatitis Virology, The George Institute for International Health, University of Sydney, and the Royal Prince Alfred Hospital, Sydney, Australia.

Address reprint requests to: Yvonne Cossart, Department of Infectious Diseases and Immunology, University of Sydney, D06, Sydney, New South Wales 2006, Australia; e-mail: ycossart@infdis.usyd.edu.au.

This study was supported in part by a National Health and Medical Research Council Project Grant 9937934. K.V. was in receipt of an Australian Clinical Research Fellowship No. 967008. The sponsors had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the report for publication. H.T. is in receipt of an NH and MRC Primary Health Care Postgraduate Research Scholarship, and K.V. is an NH and MRC Clinical Research Fellow.

Received for publication August 3, 2004; revision received October 21, 2004, and accepted October 29, 2004.

doi: 10.1111/j.1537-2995.2005.04317.x

TRANSFUSION 2005;45:807-813.

the community. After 25 years of follow-up in a US study, there was little statistical difference in overall mortality of patients who develop posttransfusion non-A, non-B hepatitis compared with transfusion recipients who did not develop hepatitis, although there was a small increase in the risk of death related to liver disease.[2] A similar situation is reported for hepatitis B positive donors.[3]

Almost a million blood donations are collected each year in Australia and there is good information about the prevalence and risk factors for blood-borne viruses among donors. In contrast, there are no published data about the proportion of the 20 million Australians who have ever received blood and may possibly have been exposed to blood-borne infections by this route. In a prospective study of nosocomial infection in endoscopy we collected information about past transfusion from more than 2000 participants, and in this article, we report the relation between these transfusion histories and serologic evidence of past and current hepatitis B and C.

MATERIALS AND METHODS

As part of a study of the risk of transmission of blood-borne viruses by endoscopy conducted at Royal Prince Alfred Hospital (RPAH), a large teaching hospital in central Sydney from 1999 to 2001, we collected histories of risk factors for these infections using a standardized questionnaire and tested before endoscopy blood samples for hepatitis B and C and human immunodeficiency virus (HIV). All patients scheduled for endoscopy were invited to participate in the study, unless they were obviously too ill for interview, could not communicate in English and lacked an interpreter, or were suffering from severe memory loss or dementia. Of the 2599 patients approached, 82 percent (2120/2599) agreed to participate in the study. Patient recall was relied on for details of past and current illness and exposure to potential risk factors. The study was approved by the Human Ethics Committees of the Central Sydney Area Health Service and the University of Sydney.

Patient serum samples were initially tested for HBsAg, anti-HBc, anti-HBs, and anti-HCV with an automatic analysis system (Cobas Core II, Boehringer Mannheim/Hoffmann La Roche, Nutley, NJ) and for anti-HIV-1 and -2 by an immunoassay analyzer (Abbott IMX, Abbott Diagnostics, Abbott Park, IL). Reactive anti-HCV and anti-HIV samples were retested by Western blot and/or testing by the Abbott IMX system. Tests for HBV DNA and HCV RNA were performed by in-house assays with a sensitivity of 10^5 and 10^4 geq per mL, respectively.

The date (year) of first transfusion reported by participants was recorded for recipients of blood and used to compare the risk of transfusion prior to the introduction of screening for HBV (1975) and HCV (1990). The outcome variables were current or past hepatitis B infection, shown by the patients' positive results for HBsAg, and/or anti-HBc antigens testing, and current or past hepatitis C infection, shown by the patients' positive results for anti-HCV.

Statistical analysis

Data were entered into a study database and analyzed using computer software (SAS statistical package, SAS Institute, Cary, NC). All variables with a natural order (i.e., age . . .) were grouped into categorical variables for analysis after testing for trend using the Mantel-Haenszel trend test and calculating the departure from the trend. The association between hepatitis B or C infection and receiving blood before or after routine screening was analyzed in two separate models. Factors that were related to hepatitis B infection or hepatitis C infection in univariate analysis ($p < 0.25$) and are known to be risk factors for infection were entered into a logistic regression model. Stepwise modeling was used, in which the nonsignificant factors were dropped out, one at the time, of the initially fitted logistic model to determine the significant ($p < 0.05$) independent risk factors for hepatitis B infection or hepatitis C infection and the confounder effects of these risk factors on blood transfusion.

Finally, the interaction term between blood transfusion and significant risk factors in the final model for hepatitis B and hepatitis C were tested. The adjusted odds ratios (ORs) and their 95 percent confidence intervals (CI) were then calculated.

In the final multivariate analysis model, the effect of receiving blood before or after the introduction of screening on hepatitis B or C infection was adjusted by the plausible and significant confounders. For hepatitis B these were having ever been diagnosed with hepatitis, having ever injected nonmedicinal drugs, sex, age group, place of birth, having ever been diagnosed with HIV, and having been vaccinated for hepatitis B. For hepatitis C they were having ever been diagnosed with hepatitis, having ever injected nonmedicinal drugs, ever having lived with someone with HIV, and ever having received any blood product other than red cells (RBCs). None of the interactions between blood transfusion and significant risk factors in either model was significant.

RESULTS

General demographics of the study group

Two-thousand one-hundred twenty patients participated in the study. Their median age was 52.3 years, with 33 percent more than 60 years, 43 percent between 40 and 60 years, and 24 percent less than 40 years. Fifty-one percent were men.

Fifty-seven percent of the patients were born in Australia; 11 percent in Asia or the Pacific Islands; 16 percent in North Africa, the Middle East, or Mediterranean countries; and 16 percent in the rest of the world. Australian

residency had been acquired before 1970 by 42 percent of the patients who were born overseas, 22 percent between 1970 and 1980, an additional 18 percent between 1980 and 1990, and 14 percent after 1990.

Hepatitis B prevalence

Hepatitis B serologic data were available for 2119 patients. Forty-five (2.1%) of the patients were HBsAg-positive; of these 14 were HBV DNA-positive. There were 626 anti-HBs-positive patients and of these 204 (33%) were also anti-HBc-positive. Of these 204 patients, 5 patients were simultaneously positive for the presence of HBsAg, indicating current infection. The other 422 patients (67%) had negative anti-HBc and they were categorized as vaccinees.

Overall, 244 (11.5%) of the total cohort had been infected with hepatitis B at some time in their life (40 patients were HBsAg-positive; 5 patients were HBsAg-, anti-HBs-, and anti-HBc-positive; and 199 patients anti-HBs- and anti-HBc-positive). In addition, 422 patients (20%) were classified as "vaccinated" for hepatitis B and the remaining 70.5 percent (1493/2119) of the patients were negative for all hepatitis B tests and were regarded as susceptible.

Hepatitis C prevalence

Hepatitis C results were available for 2108 participants. Ninety-nine (4.7%) of the patients were anti-HCV-positive and of these 92 were tested by PCR and 48 were positive for HCV RNA.

Twenty-five of the 244 (10%) of the patients with markers of HBV infection were also positive for hepatitis C antibody. Two of these were HBsAg-positive but were HBV DNA-negative whereas 12 were viremic for HCV.

HIV prevalence

Seventeen (1%) patients were anti-HIV-positive. Ten of these positive patients had evidence of current or past HBV infection and one was anti-HCV-positive. No further analysis was done on these HIV-positive patients because of the very low number involved.

Transfusion histories

Ten patients reported that they had been diagnosed with hepatitis B or C before they received any blood transfusion and were excluded from further analysis as were 33 patients who failed to answer the blood transfusion section of the questionnaire. Therefore, in subsequent analysis the sample size for hepatitis B became 2076 patients and for hepatitis C 2065 patients. More than one-fourth of the patients, 26.6 percent (553), had been transfused, 106 (19.2%) before the introduction of specific donor screening for hepatitis B (in 1975) and 242 (43.8%) before introduction of screening for anti-HCV (1990).

Ninety-two percent (509/553) of the transfusions had been performed in Australia or New Zealand, 4.5 percent (25) in another industrialized country in Europe or North America, and 1.1 percent (6) elsewhere in nonindustrialized countries. Thirteen patients did not state whether they had been transfused in Australia or abroad. The age at transfusion ranged from 2.9 to 86.1 years with the median at 43.7 years.

In those transfused, 48.5 percent (268/553) were men and 51.5 percent (285/553) were women. There was a small difference in the median age of transfusion in men (47.0 years) compared with women (41.6 years). The indications for transfusion were categorized as the result of acute blood loss due to trauma 28.6 percent, surgery 29 percent, hemorrhage 11.6 percent, hematologic disorders 13.4 percent, or anemia 8.1 percent. Fifty-one patients did not recall the indication for transfusion. There was little variation in the indications of transfusion in men compared with women.

Seventy-eight patients were unsure whether they had received blood product other than RBCs. Fifty-six of the 2042 (2.7%) stated that they had received blood product in the past; clotting factors in 27, and plasma, platelets (PLTs), or other types in 29. Sixteen of the patients who had received clotting factors (59.3%) and 15 of those who had received other blood products (51.7%) had also received blood. Data about date of administration of blood products were not collected so the impact of the screening test could not be evaluated. When compared with patients who had never received blood products, patients who had received clotting factors had a 4.7-fold increased risk of HCV infection. The prevalence of hepatitis B was not significantly affected by a history of receipt of blood products (Tables 1 and 2).

In Figs. 1 and 2, the prevalence of hepatitis B and C in blood recipients is shown according to the year of transfusion. For both infections, there was a peak in the period 1975 to 1979. For hepatitis B, this peak prevalence is about twice the background in untransfused patients, but for hepatitis C the difference is over sevenfold. In transfused patients, the increased risk subsequently fell to the background level for hepatitis B but remains significant (over twofold) for hepatitis C.

Transfusion as a risk for infection

Only 35 patients had transfusion as their only identified risk factors for hepatitis. Two of them had serologic evidence of hepatitis B infection and none for hepatitis C.

On univariate analysis the prevalence of HBV in patients transfused before the implementation of routine screening of donations in 1975 was lower (10.4%) than

TABLE 1. Univariate analysis of the association of receiving blood transfusion before and after screening with HBV and HCV prevalence in patients requiring endoscopy

Ever received blood transfusion	Hepatitis B infection* (n = 2076)				Hepatitis C infection† (n = 2065)			
	No‡	Yes‡	OR (95% CI)	Total	No‡	Yes‡	OR (95% CI)	Total
Before screening	95 (89.6)	11 (10.4)	0.97 (0.51-1.86)	106	221 (91.3)	21 (8.7)	2.97 (1.74-5.06)	242
After screening	387 (86.8)	59 (13.2)	1.28 (0.93-1.76)	446	283 (91.9)	25 (8.1)	2.77 (1.68-4.58)	308
Never	1362 (89.4)	162 (10.6)	1	1524	1469 (96.9)	47 (3.1)	1	1516
	$\chi^2 = 2.42$ with 2 degrees of freedom, p = 0.30				$\chi^2 = 26.20$ with 2 degrees of freedom, p < 0.0001			

* On univariate analysis, hepatitis B infection was significantly associated with sex (p = 0.0001), older age group (p = 0.01), place of birth (p = 0.0001), ever had any operation in the past (p = 0.05), ever had any operation overseas (p = 0.002), dentist visit (p = 0.005), ever injected drugs (p = 0.0006), ever had ear pierced (p = 0.0001), ever lived with someone with HIV (p = 0.002), ever lived in an institution for 3 months (p = 0.046), ever been vaccinated for hepatitis B (p = 0.0001), ever been diagnosed with hepatitis (p = 0.0001), ever been diagnosed with HIV (p = 0.0001), ever been diagnosed with a chronic disease (p = 0.003), and ever been immune suppressed (p = 0.04).

† On univariate analysis, hepatitis C infection was significantly associated with: ever received any blood products in the past (Fisher's Exact test, p = 0.0009), ever received any blood products-the type (p = 0.0001), ever injected drugs (Fisher's Exact test, p < 0.0001), ever been tattooed (p = 0.0001), ever had your body pierced (p = 0.02), ever lived with someone with hepatitis (p = 0.0001), ever lived with someone with HIV (Fisher's Exact test, p = 0.007), ever lived in an institution for 3 months (p = 0.0001), ever worked as a health-care worker (p = 0.05), ever been diagnosed with hepatitis (p = 0.0001), ever been diagnosed with a chronic disease (p = 0.001), and ever been immune suppressed (p = 0.02).

‡ Data are reported as number (%).

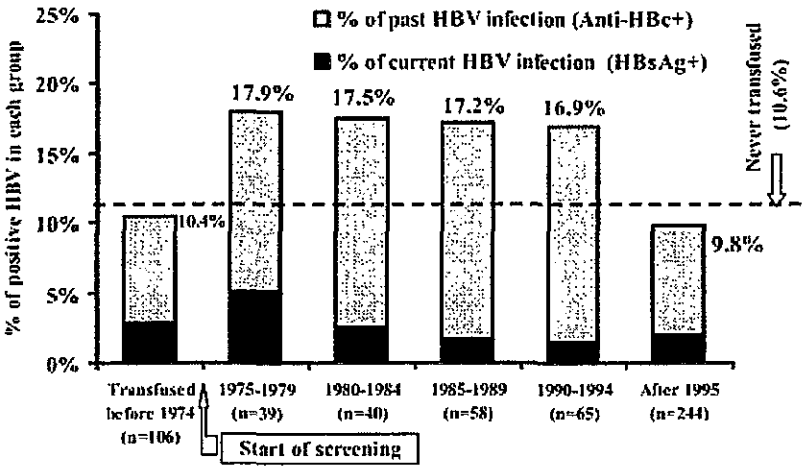

Fig. 1. The prevalence of current and/or past hepatitis B infection in patients transfused during different 5-year time intervals since 1975.

that in recipients of screened blood (13.2%) and not significantly different from that in untransfused (10.6%) patients (Table 1). In contrast, the hepatitis C prevalence, in patients transfused before screening in 1990 (8.7%), was slightly higher than that in recipients of screened blood (8.1%) and almost three times higher than that in nontransfused patients (3.1%) (Table 1).

After adjustment, in multivariate analysis, for the influence of the other significant risk factors for infection with hepatitis B and C, respectively (Table 2), the changes in OR for hepatitis B infection in the earlier "unscreened" transfusions was not significantly different from the unadjusted OR. It increased from 0.97 before (unadjusted 95% CI, 0.51-1.86) to 1.17 after controlling for other risk factors (adjusted 95% CI, 0.57-2.39). Similarly, the OR for hepatitis B infection in the recipients of screened blood remained almost the same (unadjusted OR, 1.28; 95% CI, 0.93-1.76; adjusted OR, 1.32; 95% CI, 0.92-1.89). The adjusted OR, however, for hepatitis B infection in either transfused group was not significantly different from that in *nontransfused patients* (Table 2).

In contrast, for hepatitis C infection, multivariate analysis showed that blood transfusion both before and after screening had an additional risk to lifestyle and nosocomial risks for infection ($\chi^2 = 20.66$ with 2 degrees of freedom, p < 0.0001; Table 2). The OR for infection in the earlier unscreened transfusions increased from 3.0 before (unadjusted 95% CI, 1.74-5.06) to 4.6 after controlling for other risk factors (adjusted 95% CI, 2.26-9.34) and the OR for hepatitis C infection for the recipients of screened blood remained almost the same before (OR, 2.77; 95% CI, 1.68-4.58) and after adjustment (OR, 2.99; 95% CI, 1.44-6.22). The adjusted OR for hepatitis C infection in recipients of the earlier unscreened transfusions was significantly 4.6-fold (95% CI, 2.26- to 9.34-fold) higher compared to nontransfused patients and 2.99-fold (95% CI, 1.44- to 6.22-fold) higher for recipients of screened blood. The difference in OR for recipients of screened and prescreened blood was not significant, and there was a considerable overlap in the CIs for the two ORs (Table 2).

The risk of hepatitis C was halved after the introduction of screening in 1990 and further reduced after successive improvements in screening tests had been introduced in 1995, but transfused patients still had more than twice