Epidemiol. Infect. (1994). **112**. 595–601

Risk factors for hepatitis C virus infection. A case-control study of blood donors in the Trent Region (UK)*

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(*Accepted 22 December 1993*)

SUMMARY

The introduction of screening for hepatitis C virus (HCV) by the National Blood Transfusion Service identified donors who had acquired HCV infection. We undertook a case-control study amongst blood donors in the Trent Region to determine risks for HCV infection. A total of 74 blood donors confirmed positive for hepatitis C infection and 150 age, sex and donor venue matched controls were included in the study. Fifty-three percent of hepatitis C infected blood donors reported previous use of injected drugs compared to no controls; relative risk (RR) not estimatable (lower limit 95% CI = 20). Other risk factors were a history of: receipt of a blood transfusion or blood products RR = 3·6 (95% CI 1·5–8·3), having been a 'health care worker' RR = 2·8 (95% CI 1·1–7·6), tattooing RR = 3·3 (95% CI 1·2–8·7), and an association with having been born abroad RR = 3·2 (95% CI 1·1–9·5). No risk was shown for a history of multiple sexual partners, ear piercing or acupuncture. Injecting drug use explains more than 50% of hepatitis C infections in blood donors, a group who are less likely to have injected drugs than the general population.

INTRODUCTION

Hepatitis C virus (HCV) was the commonest cause of post transfusion hepatitis [1–3] before the screening of all blood donations for HCV. Previous studies of clinical cases have identified injecting drug use [3, 4] and transfusion of blood products [3,4] as major factors in the transmission of hepatitis C infection. The importance of sexual transmission is less clear [5]. The introduction of routine screening of all blood donations in the UK, together with confirmation of the screening test by a more specific second-generation RIBA-2 test [6] has identified a group of apparently healthy people with hepatitis C infection. Previous studies on blood donors have used first-generation Recombinant Immunoblot Assay (RIBA) tests [7, 8]. To evaluate risk factors for HCV in blood donors we undertook a case-control study of blood donors in the Trent region.

* On behalf of the Trent Hepatitis C Study Group.

MATERIALS AND METHODS

Case ascertainment

Cases were recruited from the routine screening of all blood donors in the Trent region in the first year of screening from 1 September 1991 to 31 August 1992. Donors who were initially identified by the routine screening ELISA test (United Biomedical Inc.) as HCV reactive then had a confirmatory test using the RIBA-2 test (Ortho). All those positive in the RIBA-2 test were eligible for inclusion in the study. Seventy-eight cases met this case definition and were invited for interview, of whom 74 (95%) attended and were included.

Selection of controls

One hundred and fifty controls, two for each case, were selected using age (± 2 years), sex and venue of donation as matching criteria. All donors requested to be controls agreed to participate. The second control was unobtainable for six cases.

Interview

Cases and controls were interviewed using a structured questionnaire concerned with personal, past medical, family, occupational and travel histories, along with specific questions on potential risk factors; misuse of injected drugs, receipt of blood or blood products, tattoos, ear-piercing, acupuncture, number of sexual partners, and sexual orientation. Health care work was defined as paid employment with exposure to patients or their body fluids. Interviews were conducted from December 1991 to January 1993 with the cases and matched controls interviewed at similar times.

Statistical analysis

Relative risks (RR), as approximated by odds ratios, were derived by two methods. Epi Info [9] was used for the calculation of univariate relative risks and as the database. Unconditional logistic regression analyses were conducted with HCV positivity as the dependent variable and the other factors in the questionnaire as independent variables using the EGRET package [10]. Confidence intervals for 2×2 tables with a zero term were estimated using the approximation recommended by Breslow and Day [11]. Multiple regression analyses were not possible with the inclusion of cases with a history of injecting drug use because no controls had injected drugs; these cases were removed from further analyses. Adjustments were made for all variables associated with HCV infection.

RESULTS

Of the 74 cases, 46 were male (mean age 34·6 years) and 28 female (mean age 37·6) and of the 150 controls 92 were male (mean age 34·2) and 58 female (mean age 36·6). The prevalence figures for Trent blood donors were 0·58/1000 (40 in 69473) for all donors in the first 4 months of screening, a time period which avoids repeat donations and 0·63/1000 (16 in 25346) for new donors in the first year of screening. Seven donors were reported positive with 5-1-1 and c100 as the two positive bands.

Table 1. *Univariate relative risks for hepatitis C infection: all cases and controls*

Exposure	Cases ($n = 74$)	Controls ($n = 150$)	Relative risk (95% CI)	P value
Parenteral				
Injecting drug use	39	0	N.E. (lower limit 20)*	$< 10^{-8}$†
Tattoos	29	11	8·3 (3·6–19·6)	$< 10^{-8}$
Blood transfusion	15	10	3·5 (1·4–9·1)	0·003
Ear piercing	57	71	3·7 (1·9–7·4)	0·00002
Acupuncture	2	4	1·0 (0·1–6·7)	n.s.
Health care worker	8	6	2·9 (0·9–10·0)	0·05
Sexual				
6 or more lifetime partners‡	25	43	2·9 (1·1–8·0)	0·02
2–5 lifetime partners‡	18	66	1·4 (0·5–3·8)	n.s.
Homosexual partners§	5	0	N.E. (lower limit 1·3)*	0·001†
Sex with drug user	11	2	13·1 (2·6–90)	0·0001†
Hepatitis or jaundice				
Personal history	17	8	5·2 (2·0–14·2)	0·0001
Family history	10	12	2·0 (0·7–5·3)	n.s.
Travel				
Foreign travel	66	131	1·2 (0·5–3·2)	n.s.
Born abroad	4	4	2·1 (0·4–10·4)	n.s.

* N.E. not estimatable as no controls with risk factor probabilities χ^2 test unless † = 2-tailed Fisher exact test.

‡ Relative to 0 or 1 sexual partner.

§ Males only.

Table 2. *Adjusted relative risks of selected exposures for HCV infection after exclusion of all donors giving a history of injecting of injecting drug use**

Exposure	Cases ($n = 35$)	Controls ($n = 150$)	Relative risk (95% CI)	P value
Parenteral				
Blood transfusion	8	10	3·6 (1·5–8·3)	0·003
Tattoo	6	11	3·3 (1·2–8·7)	0·019
Health care worker	5	6	2·8 (1·1–7·6)	0·038
Ear piercing	23	71	1·4 (0·7–2·9)	n.s.
Sexual				
Sex with homosexual man	2	0	7·0 (0·9–5·5)	n.s.
6 or more sexual partners	6	43	0·4 (0·2–1·1)	n.s.
Travel				
Born abroad	4	4	3·1 (1·1–9·5)	0·033
Foreign travel	30	131	0·8 (0·3–2·3)	n.s.

*Risks adjusted for all significant associations.

Table 1 shows the univariate relative risks for exposure variables. Table 2 shows the multivariate relative risks for significant exposure variables after the exclusion of all donors giving a history of injecting drugs. No independent risk was shown for ear piercing, acupuncture, foreign travel, a personal or family history of either jaundice or hepatitis, or multiple sexual partners, after adjusting for other risk factors.

There were insufficient numbers of different health care workers to analyse risks

https://doi.org/10.1017/S0950268800051293 Published online by Cambridge University Press

Table 3. *Estimated attributable causes of HCV infection in blood donors*

Exposure	Attributable risk	Attributable cases ($n = 74$) (%)
Injecting drug misuse	N.E.*	39 (53)
Tattoo	2·3	6 (8)
Blood transfusion	2·6	4 (5)
Health care work	1·8	3 (5)
Born abroad	2·2	3 (4)
Total cases explained		55 (74)

* N.E. not estimatable as no controls with risk factor.

for subgroups but nurses predominated in both cases and controls. Of the 15 cases who had received blood, 7 had also injected drugs. Of the 8 non-drug-users, 6 gave no personal history of hepatitis or jaundice, an asymptomatic infection rate of 75% (95% confidence intervals 35 to 97%). Table 3 shows the estimated attributable number of HCV infections for the significant associations in the 74 blood donors identified during the first year of screening in Trent region. Sixteen cases did not give a history of any behaviour shown to be associated with HCV infection.

DISCUSSION

Our study demonstrates that injecting drug use is the likely route of transmission in over 50% of hepatitis C infected blood donors in the Trent Region. As the assessment procedures for potential blood donors are designed to exclude people who have injected drugs, it is likely that injecting drug use is responsible for a higher percentage of cases in the general population. A similar frequency of injecting drug misuse has been shown amongst HCV positive blood donors in London [12] but our study also shows that the prevalence of this behaviour is very low in the HCV negative blood donor population. There are no reasons to believe that injecting drug use is not a major factor in HCV infection in the rest of the UK. Little publicity was given to hepatitis C testing so it was unlikely that these donors gave blood to obtain a hepatitis C test and most cases were on the regular donor panel. The contrast between Tables 1 and 2 shows that many cases who had multiple sexual partners, homosexual partners and ear piercing had also injected drugs which explains the associations seen in the unadjusted relative risks, but not seen when the results were adjusted for injecting drug use and other risk factors.

Fifteen cases were associated with the administration of blood or blood products of whom seven had also injected drugs. All received blood before the screening of donations for HCV. This study confirms post transfusion hepatitis C is commonly asymptomatic although people who have had clinical post transfusion hepatitis may be less likely to donate blood than people with previous non-clinical infection.

Our study suggests the possibility of an increased risk for health care workers. This finding has been shown by some workers [13, 14] whilst others have failed to find an association [15]. More work is required to assess the risk to health care workers. The independent association with tattooing was only seen in males as all women who gave a history of tattoos had also injected drugs. Associations with

tattooing have been shown [7] and direct evidence to support transmission by tattooing is documented [16]. Descriptions of groups of people tattooing themselves with unclean needles, given by some of the cases, support tattooing as a route of transmission. The association with being born abroad requires more work to identify the nature of the risk, if any.

The relative risk for more than six lifetime sexual partners is below one after controlling for other factors. Although multiple sexual partners cannot be protective against HCV infection, this finding is evidence against significant heterosexual transmission of hepatitis C. This agrees with some studies [17, 18] whilst being contrary to others [19, 20]. The risk for partners of men who have sex with men was based on small numbers, as would be expected in a blood donor population. The majority (4 out of 5) of homosexual men infected with HCV had also injected drugs, a finding similar to that of Osmond and colleagues [21]. The overall role of sexual transmission in HCV infection remains unclear.

No independent association was seen with ear-piercing or acupuncture. Hepatitis B transmission has been associated with acupuncture [22]. In Japan, where HCV prevalence is higher, acupuncturists have no increased risk of HCV infection [15]. An association with being born abroad (Italy 2, Hungary 1 and Poland 1 for the cases) was noted, but not with foreign travel. The significance is unclear although this may reflect acquisition in early life. Italy has a higher prevalence of HCV infection than the United Kingdom [23].

There are few other case-control studies in blood donors [7, 8], none from the UK, and this is the first study to use the more specific RIBA-2 test [6]. All three studies found associations with injecting drugs, tattoos and blood transfusion. It is difficult to make comparisons on other associations between the three studies due to different donor recruitment policies, the choice of inappropriate controls [7], the effects of the less specific RIBA-1 test and lower participation rates [7, 8].

Whatever donor selection policy is used, it is of concern that people who have engaged in high-risk patterns of behaviour still donate blood. An explanation for this failure of donors with a history of high-risk behaviour to exclude themselves was that the self-exclusion criteria were in the information aimed at preventing HIV transmission. Firstly, some donors did not identify with HIV-oriented literature, and secondly some donors have injected drugs before 1977, the date specified in the leaflet after which drugs should not have been injected. This failure of communication has now been addressed by the UK National Blood Transfusion Service.

The main source of bias in this study is response bias. Cases were interviewed after they had tested positive for HCV infection, whilst the controls had no such information so it is possible that the cases responded more truthfully. The potential response bias would probably be greatest for a history of injecting drugs and for sexual histories. The strength of the association seen with injecting drug use in this study suggests that this would not affect the overall results unless the effect was very large. The number of lifetime sexual partners may lead to incorrect answers [24] but the use of only three categories should minimize misclassification. Questions on sexual history have recently become more acceptable [24]. Recall bias should be low when the donors are given time to answer the questions and it is also unlikely that people forget that they have injected drugs, have been

tattooed or worked as a health care worker. The high participation rate improves the validity of the study. Any misclassification owing to the inclusion of the seven cases who would now be defined as indeterminate could result in weaker associations being shown than might actually exist, but this is preferable to redefining the case definition during a case-control study which can lead to unsuspected and unrecognized errors [25].

Our results show that injecting drug use is the likely route of infection in over 50% of hepatitis C infected blood donors in the Trent region. We have also shown associations with receiving a blood transfusion or blood products, tattooing, being a health care worker, and evidence against significant sexual transmission. The main associations seen in this study are recent developments and do not explain the natural mode of transmission that has previously maintained infection in the population. The addition of new opportunities for transmission such as injecting drug misuse and within the health care setting may lead to an epidemic of hepatitis C infection.

ACKNOWLEDGEMENTS

The work was done in co-operation between the Department of Public Health Medicine and Epidemiology, University of Nottingham, Trent Region Blood Transfusion Service and the Trent Hepatitis C Study Group.

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