Revista da Sociedade Brasileira de Medicina Tropical 47(3):295-301, May-Jun, 2014
http://dx.doi.org/10.1590/0037-8682-0054-2014

Major Article

Risk factors for hepatitis C virus transmission in the municipality of Catanduva, State of São Paulo: a case-control study

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ABSTRACT

Introduction: Hepatitis C virus (HCV) is primarily transmitted via contact with the blood of infected patients, although the form of contact has not been identified for a significant percentage of carriers. The present study evaluated possible risk factors for HCV transmission in a medium-sized town located in the northwest region of the State of São Paulo. **Methods**: This was a case-control study, with the case group consisting of 190 chronic HCV carriers older than 18 years residing in the municipality of Catanduva. The control group also consisted of 190 individuals with HCV-negative serology. The groups were paired (1:1) for gender, age range (± five years), and place of residence. The same structured questionnaire was applied to all subjects, who gave written informed consent to participate in the study. The data were statistically analyzed using crude and adjusted logistic regression, and the results were expressed as odds ratios with a 95% confidence interval. **Results**: The demographic profiles of the groups indicated a predominance of males (68.9%) and mean ages of 47.1 years (case group) and 47.3 years (control group). After adjusting for conditional regression, the following factors were found to represent risks for HCV: history of sexually transmitted disease (STD) and blood transfusion; accidents with syringes and/or needles; tattoos; and the use of non-injectable drugs and injectable medications. **Conclusions**: The transmission of HCV via the blood route has been well characterized. Other forms of contact with human blood and/or secretions are likely to transmit the virus, although with a lower frequency of occurrence.

Keywords: Hepatitis C. Risk factors. Transmission.

INTRODUCTION

The hepatitis C virus (HCV) is widely disseminated, representing a global pandemic of huge proportions. It is currently estimated that there are approximately 170 million carriers in the world, which comprises approximately 3% of the world's population[1].

In Brazil, the actual prevalence of hepatitis C has yet to be adequately determined. A recent study evaluated the presence of anti-HCV antibodies among populations living in the capitals of five macro-regions of the country, and a similar distribution in anti-HCV prevalence was noted for these different regions (in approximately 1% of the 10-19 age group and 2% of the 20-69 age group), with a slight increase in the northern region for the latter age group[2].

HCV is predominantly transmitted via the parenteral route, primarily through contaminated blood, as well as with a lower proportion through other body fluids. Among blood borne pathogens, HCV is considered a major pathogen[3].

Although the incidence of HCV infection is apparently declining, healthcare services continue to record new cases of hepatitis C with considerable frequency but with undefined routes of transmission. Parenteral transmission (use of intravenous drugs, occupational exposure), hemodialysis, intradomiciliary transmission, and, with a lower proportion, sexual and vertical transmission, in general account for approximately 60-80% of infections. However, the cause of the infection cannot be determined in 20-40% of the patients, mainly in developing countries[4,5].

With regard to the *non-classical* route of transmission, any intervention involving penetration of the skin with contaminated perforating/cutting instruments may be related to HCV transmission.

The present study aimed to assess several risk factors among HCV carriers in a medium-sized town in the northwest region of the State of São Paulo.

METHODS

The municipality of Catanduva is located approximately 380km from the capital of the northwest region of the state. Currently, the town has a population of 112,820 (51.3% women),

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Received 10 March 2014
Accepted 19 June 2014

an urbanization rate of 98.91%, an economically active population comprising 41.53%, and an annual growth of 1.28%[6].

Measures to control hepatitis B and C were initiated in Catanduva in 2002 through a municipal law directing the town's sexually transmitted disease/acquired immunodeficiency syndrome (STD/AIDS) program, in place since 1987, to address hepatitis, resulting in the STD/AIDS/Viral Hepatitis Program.

A case-control approach was used for the present study. For the case groups, patients older than 18 years enrolled in the STD/AIDS/Viral Hepatitis Program between 2002 and 2007 were included; all lived in Catanduva and demonstrated hepatitis C virus-ribonucleic acid (HCV-RNA) detected by polymerase chain reaction (PCR) in the peripheral blood.

The control group consisted of subjects with negative serology for HCV infection, which was determined with a previous test for anti-hepatitis C virus (anti-HCV) and anti-human immunodeficiency virus (anti-HIV) antibodies. Subjects with positive serology were not included in the study and were referred for adequate follow-up in the STD/AIDS/Viral Hepatitis Program.

All participants (case and control groups) were administered the same structured questionnaire by the same researcher. The variables analyzed were related to previous sexual contact with HCV carriers or sporadic or frequent illicit drugs users, previous blood transfusions, contact with perforating/cutting objects, tattoos and previous use of illicit drugs and injectable medications.

With regard to the use of injectable medications with non-disposable syringes and/or needles, two different situations were considered in the present study: whether the participant had already used injectable medications in the past via non-disposable needles and/or syringes and whether the participant had previously used or was currently using injectable stimulants via the sharing of syringes or needles with other people.

Before answering the questionnaire (case and control groups) and permitting blood collection (control group), all the participants were told about the study and signed an informed consent form. The case group subjects were approached in STD/AIDS/Viral Hepatitis outpatient units, some during routine visits and others during specific interviews. Data collection for the control group mostly occurred in the participant's residence and, in sporadic cases, in his/her workplace. All necessary precautions for obtaining data confidentially were taken (the questionnaire was applied only in the presence of the interviewee and interviewer). However, these different environments may favor information biases in the control group, particularly with regard to questions related to lifestyle, such as the previous use of drugs and previous sexual risks. Those agreeing to take part in the study were asked to have their blood collected at the university hospital laboratory for further evaluation of anti-HCV and anti-HIV activity, always in the presence of the researcher. Control subjects were selected by gender, age group (approximately 5 years), and location of the case before being paired at a ratio of 1:1 (one control to one case). Based on the case address, the researcher sought to identify an individual who matched the gender profile and the previously determined age in nearby dwellings.

After examination, the negative results with an explanatory text were mailed to the respective participants. For cases with any biased results (reactive to anti-HCV or anti-HIV), the participants were asked to come to the Specialized Healthcare Service for adequate evaluation.

Anti-HCV detection was performed using a third-generation micro-particle enzyme immune-assay **(**Etistar - ET-AB-HCVK-4 - DiaSorin South Africa (Pty) Ltd. 22 Kyalami Boulevard, Kyalami Business Park, Kyalami, 1684) **-** for qualitative determination of anti-HCV in blood serum according to the protocol, and the assay results were interpreted according to the manufacturer's specifications.

Anti-HIV detection was performed using a third-generation micro-particle enzyme immune-assay **(**TetraELISA HIV1/HIV2 DiaSorin S.p.A.; UK Branch, Central Road, Dartford Kent, DA1 5LR UK**)** - to qualitatively determine the presence of anti-HIV antibodies in the blood serum according to the protocol, and the assay results were interpreted according to the manufacturer's specifications.

A conditional univariate logistic regression analysis was initially performed for statistical data evaluation, with the results given as an odds ratio (OR) at a confidence interval of 95%. Multivariate analysis was conducted using an adjusted conditional logistic regression model, with the results also given as an odds ratio at 95% confidence interval (95%CI). The model was adjusted using the Proc Logistic procedure found in the statistical analysis software (SAS), version 9.

Ethical considerations

The present study was approved by the Research Ethics Committee of the Padre Albino Integrated Faculties on the 21st of November, 2008 under protocol number 51/08.

RESULTS

Of 252 subjects carrying HCV residing in the municipality of Catanduva that were enrolled in the STD/AIDS/Viral Hepatitis Program between 2002 and 2007, 202 (80.1%) took part in the study. The non-participation of the other subjects was attributable to several reasons, such as refusal (n=13), change of address (n=11), change of town (n=15), hospitalization in another town (n=5), and imprisonment (n=6).

Once the subjects of the case group (n=202) were selected according to previously defined matching criteria (i.e., gender, age group, and residence), a questionnaire was administered to recruit 202 subjects to form the control group. Because 12 subjects in the control group refused to have their blood collected for examination, their matching case subjects were excluded from the study, resulting in 190 pairs for the final analysis (cases and controls). Among the 190 participants in the case group, 141 were monoinfected by HCV and 49 demonstrated coinfection with HIV; in this study, all participants were presented as a single group.

The demographic profiles of the groups indicated a predominance of males (68.9%) and mean ages of 47.1 (case group) and

47.3 years old (control group). In terms of marital status, 59.5% of the participants in the case group and 72.1% of the participants in the control group were married. The majority of the case subjects (65.2%) and control subjects (74.2%) were white.

Table 1 lists comparisons of sex-related variables as measured in terms of proportions. In the univariate analysis, sexual contact with HCV carriers, drug users, and individuals who had STDs was found to be associated with infection by HCV.

Table 2 compares previous contact with healthcare services as well as human blood and/or secretions between the groups. The univariate analysis indicated that the risk factors for acquisition of HCV infection were: history of blood transfusion,

TABLE 1 - Distribution of variables related to sexual contact for HCV carriers compared to their controls, according to frequency and crude logistic regression, in Catanduva, State of São Paulo, Brazil.

	Case (190)		Control (190)			
Variables	n	%	n	%	OR	95%CI
Sexual contact with HCV carrier						
yes	25	13.1	4	2.1	6.25	2.17 - 19.96
no	165	86.0	186	97.9		
Previous history of STD						
yes	73	38.4	17	8.9	7.22	3.59 - 14.50
no	117	61.6	173	91.1		
Sexual contact with illicit drug users						
yes	87	45.8	20	10.5	7.09	3.77 - 13.33
no	103	54.2	170	89.5		

HCV: hepatitis C virus; **OR:** odds ratio; **95%CI:** 95% confidence interval; **STD**: sexually transmitted disease.

TABLE 2 - Distribution of variables related to contact with healthcare services and blood and/or secretions among chronic HCV carriers compared to their controls, according to frequency and crude logistic regression, in Catanduva, State of São Paulo, Brazil.

	Case (190)		Control (190)			
Variables	n	%	n	%	OR	95%CI
Contact with blood and/or secretion in healthcare services						
yes	53	27.9	30	16.3	1.96	1.19 - 3.20
no	137	72.1	160	83.7		
Previous history of blood transfusion						
yes	55	28.9	20	10.5	3.92	2.07 - 7.38
no	135	71.1	170	89.5		
Accidents with syringes and/or needles						
yes	16	8.4	3	1.5	7.50	1.71 - 32.80
no	174	91.6	187	98.5		
Sharing of perforating/cutting objects						
yes	78	41.0	67	35.2	1.28	0.84 - 1.94
no	112	59.0	123	64.8		
Tattoos						
yes	59	31.0	14	7.4	8.50	3.64 - 19.81
no	131	6.9.0	176	92.6		

HCV: hepatitis C virus; **OR:** odds ratio; **95%CI**: 95% confidence interval.

contact with blood and/or secretions during healthcare services, accidents with syringes and/or needles, and tattoos. A history of sharing perforating/cutting objects such as razors, nail clippers, and so on was found to be more frequent among the case subjects, but there was no significant difference between the groups.

Table 3 compares previous contact with illicit drug users between the case and control groups. Here, the univariate analysis indicated that domiciliary contact with users of illicit drugs (injectable or not) was a risk for HCV infection.

With regard to the use of illicit drugs, the large proportion of HCV carriers exhibiting this behavior (53.7%) should be noted; the univariate analysis indicated that this was a risk factor for the acquisition of hepatitis C virus.

It was found that 33.2% of HCV carriers had a previous or current history of injectable drug use, with cocaine being used by the great majority. Among the control group, no subjects exhibiting this behavior were identified, which did not permit us to conduct comparative analyses.

The use of injectable stimulants occurred at a higher use frequency among HCV carriers compared to controls: 35.8% *versus* 2.1%. However, when the participants were paired, no control subject with a previous history of injectable stimulants was identified, which did not permit a comparative analysis. The univariate analysis indicated that the use of injectable medications with non-disposable syringes and/or needles in the past was a risk factor for HCV infection.

The multivariate analysis was performed using adjusted conditional logistic regression, which takes into account the pairing of subjects in the groups when case-control studies are performed. Some convergence problems were detected in the computational algorithm, specifically noting that some models were attributable to low or zeroed frequencies in the cells. When this occurs, the maximum likelihood estimation (parameter estimation method) may not exist. In this situation, the validity of the model adjustment is questionable, and therefore these models were not considered here.

As a result, ten variables showing association with HCV according to the univariate analysis were subjected to the adjusted conditional logistic regression.

Table 4 lists both the crude and adjusted results for the statistical analyses of these variables. An association with HCV infection was observed for the following variables: history of STD (OR = 6.90/95%CI = 1.56 - 30.37), blood transfusion (OR = 7.33/95%CI = 2.44 - 22.00), accidents with syringe and/or needle (OR = 11.04/95% CI = 1.30 - 93.72), tattoo (OR = 6.90/95%CI = 1.56 - 30.37), use of non-injectable illicit drugs (OR = 7.61/95%CI = 2.48 - 23.35), and past use of injectable medications with non-disposable syringes and/or needles (OR = 2.16/95%CI = 1.13 - 4.11).

DISCUSSION

In the great majority of studies that have assessed the possible routes of transmission of the hepatitis C virus, the results showed the clear predominance of the cutaneous route, either by blood transfusion or the use of contaminated syringes/needles, primarily injectable illicit drugs. However, the route of virus transmission cannot be clearly identified in a considerable percentage of cases[7,8].

Possible causes of transmission could be the following: sexual contact, sharing of toothbrushes and perforating/cutting objects (e.g., nail nippers, beard razors), repeated and frequent contact with secretions from small wounds, and vertical transmission (mother-child)[9].

Among the possible routes of hepatitis C virus transmission, sexual intercourse surely is the most controversial. In some

TABLE 3 - Distribution of variables related to use of illicit injectable or non-injectable drugs and use of injectable medications with non-disposable syringes and/or needles for chronic HCV carriers compared to their controls, according to frequency and crude logistic regression, in Catanduva, State of São Paulo, Brazil.

	Case (190)		Control (190)			
Variables	n	%	n	%	OR	95%CI
Domiciliary contact with illicit drug user						
yes	49	25.8	24	12.6	2.67	1.47 - 4.83
no	141	74.2	166	87.4		
Use of non-injectable illicit drugs						
yes	102	53.7	17	8.9	17.80	7.23 - 43.82
no	88	46.3	173	91.1		
Use of injectable medication in the past						
yes	77	40.5	52	27.4	1.83	1.17 - 2.86
no	113	59.5	138	72.6		

HCV: hepatitis C virus; **OR:** odds ratio; **95%CI**: 95% confidence interval.

TABLE 4 - Statistical analysis of chronic HCV carriers compared to their controls, according to crude (univariate) and adjusted (multivariate) conditional logistic regression, in Catanduva, State of São Paulo, Brazil.

	Crude logistic regression		Adjusted logistic regression	
Variables	OR	95%CI	OR	95%CI
Sexual contact with HCV subject	6.25	2.17 - 17.96	3.12	0.81 - 19.96
Previous history of STD	7.22	3.59 - 14.50	3.57	1.30 - 9.80
Contact with blood and/or secretions				
in the healthcare services	1.96	1.19 - 3.20	1.67	0.71 - 3.86
blood transfusion	3.92	2.07 - 7.38	7.33	2.44 - 22.00
accidents with syringes and/or needles	7.50	1.71 - 32.80	11.04	1.30 - 93.72
tattoos	8.50	3.64 - 19.81	6.90	1.56 - 30.37
Domiciliary contact with illicit drug user				
sexual contact with illicit drug user	7.09	3.77 - 13.33	1.16	0.43 - 3.09
use of non-injectable illicit drugs	17.80	7.23 - 43.82	7.61	2.48 - 23.35
use of injectable medications in the past	1.83	1.17 - 2.86	2.16	1.13 - 4.11

HCV: hepatitis C virus; **OR**: odds ratio; **95%CI**: 95% confidence interval; **STD:** sexually transmitted disease.

reports, transmission between heterosexual monogamous couples was markedly low when it was not null, while sometimes it was not possible to define whether transmission occurred via sexual relations or via other coexisting mechanisms, such as contact with perforating/cutting objects, syringes and needles. In other cases, the risk was larger when related to the presence of other factors, such as multiple sexual partnerships, the presence of sexually transmitted diseases and, primarily, concomitance with HIV infection[10,11]. Other studies reporting associations between HCV infection and STDs have produced varying results[12,13].

In the present study, univariate analysis indicated an association between HCV infection and sexual contact with HCV carriers, although this behavior was also less frequent, largely among subjects of the control group (2.1%). However, this association was not confirmed in the adjusted regression. Both frequency of sexual contact with drug users and a history of STDs were also shown to have an association with HCV infection in the univariate analysis, but this difference was only confirmed in the adjusted regression for the latter variable.

In Brazil, serological testing to identify HCV infection in blood banks has been mandatory since the 10th of November, 1993, according to law 1376[14].

In our study, we found that 28.9% of subjects had a history of transfusion of blood and/or derivatives, with 70.9% (39/55) occurring before 1993. No discrimination was observed regarding the number of transfusion episodes. The multivariate analysis indicated that transfusion of blood or derivatives had a strong association with HCV infection.

For healthcare practitioners, risk magnitude is dependent upon the biological characteristics of the pathogen involved, such as the nature of the secretion and the type of contact, among other things. With regard to hepatitis C, after percutaneous contact with contaminated blood, there is a risk rate ranging from 0% to 7%, with a mean of 1.8%[15]. Other forms of transmission involving HCV carriers have been described elsewhere, such as contact between contaminated blood and skin or the ocular mucosa[16,17], or even in the absence of direct contact, as experienced by cleaning personnel working in hospital environments[18].

In the present work, accidents with needles or syringes were reported by 19 subjects, with the majority (16/19) belonging to the case group. In the adjusted logistic regression, this variable was found to be a risk factor for HCV infection.

Another possible form of transmission is contact with perforating/cutting objects, such as nail clippers and beard razors, in either professional (e.g., beauty salons and barber shops)[19-21] or domiciliary environments[22,23].

The habit of sharing perforating/cutting objects was found to be highly frequent among the study subjects, with a rate of 41% among HCV carriers and 35.2% among controls. However, the present study demonstrated no association with HCV infection, even in the univariate analysis.

Other possible mechanisms of *non-conventional* transmission of HCV through the percutaneous route include the practices of acupuncture, piercing, and tattooing[24-27].

In our study, we did not discriminate based on the locality of a practice or the number of tattoos. Among the 380 participants, 73 (19.2%) reported a previous positive history, and the great majority (59/73) of these were in the case group. The adjusted logistic regression indicated that a history of tattooing was a risk factor for HCV infection, whereas a history of acupuncture and piercing was less frequent, demonstrating no comparative difference between the case and control groups.

Hepatitis C virus transmission among users of injectable drugs occurs in an efficient manner. It is estimated that the possibility of virus transmission via a contaminated syringe is five times higher than that of HIV[28].

In our study 63 (33.2%) of all 190 subjects carrying HCV reported a previous history of injectable drug use, with 61 using cocaine only, one using cocaine and heroin, and one using amphetamines. The habit of sharing syringes or needles was reported by almost all of these subjects (60/63), thus corroborating the high degree of vulnerability of this population to infection by pathogens through percutaneous transmission. We did not identify any control subjects with such behaviors, which permitted no comparative analysis.

Among users of non-injectable drugs, the sharing of equipment, such as a smoking pipe or drinking straw, may favor the transmission of HCV[29,30].

Of the 380 participants, 119 (31.3%) reported using non-injectable drugs currently or in the past, most predominantly in the case group (102/119). In the adjusted logistic regression, the use of non-injectable drugs was shown to have a strong association with HCV infection.

Another form of the parenteral route of pathogen transmission, including for HCV, occurs via the application of injectable medications with non-disposable and/or poorly sterilized syringes and/or needles[31,32]. The parenteral use of anabolics and energetics as stimulants for recreational purposes or improvement of professional performance (mainly among athletes) has been acknowledged to be associated with HCV transmission[33,34].

In the present study, we assessed patient history of injectable medications with non-disposable syringes and/or needles as a whole, without determining the route of administration (intravenous or intramuscular), for two distinct situations: use of drugs for medical purposes and use of energetics for recreational or professional purposes.

Among the 380 participants, 129 (33.9%) reported previous use of injectable medication, predominantly in the case group (77/129), with adjusted logistic regression indicating an association between this variable and HCV infection.

Seventy-two (18.9%) subjects reported using energetics by injection in the past, with almost all belonging to the case group (68/72). Because the number of control subjects with positive exposure was very small, it was not possible to map the groups, thus impeding any comparative analysis.

Case-control studies are more vulnerable to biases, such as memory bias, largely with regard to group formation. For the statistical analysis of this type of study, it is necessary to pair case and control group subjects, and any comparison based on proportions can be difficult when there is a small number of subjects. In the present work, this was a considerable limiting factor that compromised the evaluation of the actual influence of some variables as risk factors for the transmission of HCV.

Among the variables found to be associated with infection by the hepatitis C virus in the univariate analysis, ten were subjected to adjusted conditional logistic regression, resulting in the identification of six variables that were associated with HCV infection: history of STD, history of blood transfusion, previous accidents with syringes and/or needles, presence of tattoos, use of non-injectable illicit drugs, and use of injectable medications in the past. The transmission of HCV preferably occurs via the blood route. Other forms of contact with human blood and/or secretions may lead to HCV infection but likely with a lower frequency.

In summary, there remains considerable doubt regarding the form of virus acquisition for a significant proportion of HCV patients, a fact that can be minimized by carefully examining these patients' previous epidemiological history.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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