Injections in Health Care Settings: a risk factor for Acute Hepatitis B Virus Infection in Karachi, Pakistan

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Summary

A case control study was conducted to identify the association of therapeutic injections with acute hepatitis B virus (HBV) infection in Karachi, Pakistan. We enrolled 67 cases of acute HBV infection (1gM anti-HBc positive) and 247 controls (anti-HBc negative) from four hospitals of Karachi during July 2000-June 2001. Exposure to various risk factors during the period relevant to the incubation period of HBV was recorded both from cases and controls using a structured questionnaire. Multivariate logistic regression analysis of the data showed that cases were more likely to have received one injection (OR=4.O; 95% Cl 1.4, 11.1), or more than one injection (OR=6.3; 95% Cl 3.2, 12.4) compared to controls. The estimated population attributable risk (PAR) for therapeutic injections was 53%. Also the cases compared to controls were more likely to have household size of seven or more (OR=1 .9; 95% Cl 0.95, 3.9).This study showed that unsafe therapeutic injections appear to be the major risk factor for acute HBV infection and needs immediate focus from public health standpoint.

Introduction

An estimated two billion people have been exposed to hepatitis B virus (HBV) worldwide. Of these, more than 350 million are chronically infected with this virus as determined by the presence of HBV surface antigen (HBsAg).[1] Case-control studies in various settings have demonstrated strong association of HBV with hepatocellular carcinoma (HCC).[2-5] HBsAg has also been frequently identified among the patients with liver cirrhosis[2], which along with HCC kill about one million persons each year around the world.[1]

Pakistan has been categorized as having intermediate endemicity with 2-7 %HBsAg prevalence.[1] Hospital-based serological testing has revealed that 48% of patients with chronic liver disease (CLD)[6] and up to 66%4 to 78%[6] of patients with HCC were positive for HBsAg in Pakistan. Variable HBsAg prevalence has been documented among army recruits (10.7%)[8], health care personnel (7%)[9] and healthy blood donors (2.3%)[10] in Pakistan. Cross sectional studies in selected parts of the country have also shown 4-10% HBsAg prevalence in the general population.[11,12]

Both community[11] and hospital-based studies[13] in Pakistan have implicated therapeutic injections given in health care settings as a major risk factor for hepatitis C virus (HCV) infection. Although these case-control studies of HCV positive cases may have suffered imperfect recall with regard to history of therapeutic injections, the results of these studies suggest a potential role of therapeutic injections in transmission of HCV and other blood-borne pathogens including HBV. Notwithstanding the fact that HCV and HBV are blood-borne pathogens that share common transmission routes, though with varying efficiency, a parallel evaluation of the role of therapeutic injections as a risk factor for HBV infection in

Pakistan is still awaited. Furthermore, recently Pakistan has included universal childhood HBV vaccination in the expanded programme on immunization (EPI). Public health benefits of this initiative will take some time to accrue, primarily because the vaccination programme is only for neonates and secondarily a similar low HBV immunization coverage is expected as with other EPI administered neonatal vaccines. Therefore, a simultaneous option for the control of HBV infection may be an intervention targeted at the risk factors for HBV infection. However, there is a paucity of empirical data on the role of various risk factors including therapeutic injections in the transmission of HBV infection in Pakistan and other developing countries in the region. This case- control study therefore evaluated therapeutic injections given in health-care settings as an independent risk factor for acute HBV infection in Karachi, Pakistan.

Methods

Setting

The study was conducted in Karachi, the capital of Sindh province. It is situated on the eastern coast of the Arabian Sea and to the north west of the Indus River. Karachi is Pakistan's largest city with a population of 9:8 million comprised of different ethnic groups. Several public and private sector hospitals cater for the medical needs of the population along with private practitioners. Study subjects were enrolled from four hospitals of the city. The hospitals included were Jinnah Postgraduate Medical Center and Civil Hospital, both providing health facilities to general population, and two social security hospitals which provide health care to the factory workers and their families in Karachi. All these hospitals had internal medicine specialists supported by laboratory facilities. Generally, people from lower and middle socio-economic classes seek treatment from these hospitals.

Definitions

Acute viral hepatitis (AVH). An acute illness of not more than 6 weeks duration with discrete onset of symptoms including anorexia, vague abdominal pain, nausea, and vomiting and elevated serum alanine amino transferase (ALT) levels (>100u/l).

Case: A patient with AVH and positive for 1gM antibody to hepatitis B core antigen (1gM anti-HBc) who lived in Karachi for at least 6 months prior to the onset of illness. Cases were excluded if unconscious or unable to respond to questions.

Control: A patient with any condition other than AVH who was anti-HBc negative and who lived in Karachi for at least 6 months prior to the interview.

Recruitment of Cases and Controls

Consecutive patients of AVH (potential cases) were enrolled from the laboratories of selected hospitals when they came to collect their liver function tests (LFTs) reports between July 2000 and June 2001. Research assistants interviewed 229 potential cases in the hospitals using a structured questionnaire after obtaining informed consent to participate in the study. A lOmi blood sample was also collected at the end of the interview. Serum was separated by centrifugation and stored in cryovials at -70°C within 8 h of collection at The Aga Khan University Research Laboratory.

Patients coming to the laboratories of the same hospitals for ailments other than AVH were asked to participate in the study as potential controls. We planned to enroll two potential controls of same gender and within 5 years of age for each patient with AVH. Subsequent to obtaining informed consent, 373 sub-jects were recruited as potential controls. They were interviewed and a 5m1 blood sample was collected, and serum was stored as described earlier.

Data Collection

As mentioned earlier, trained research assistants interviewed the study subjects using a pre-tested structured questionnaire translated in Urdu at the time of blood sample collection. Data were collected on age, gender, language spoken at home, marital status, duration of marriage, years of formal

schooling, occupation, number of household members, and monthly household income. History of exposure to potential risk factors from 6 weeks to 6 months prior to the onset of illness for the cases and from the time of interview for the controls was also recorded. Exposures included therapeutic injections (number, provider, and syringe source), intravenous drips (number and provider), hospitalization, blood transfusion, dental treatment, professional blood/syringe contact (for adults only), facial and armpit shave from barber (for male adults only), tattooing and ear piercing, intravenous drug use, and presence of liver disease patient in the household.

Laboratory tests

The serum samples from 229 patients of AVH were tested for 1gM anti-HBc to identify subjects who fulfilled our case definition. To identify final control subjects, the sera from 373 potential controls were tested for total antiHBc. Third generation enzyme capture immunoassay was used to test 1gM anti-HBc and total anti-HBc, essentially following the instructions of the manufacturer (International Immuno-Diagnostics,USA).

Data management and analysis

Data were entered in Epi-Info (version 6.04. Atlanta, GA; Centers for Disease Control and Prevention; 1995) and analysed using SPSS (version 8.0. Chicago, IL: SPSS mc; 1996). Descriptive statistics were computed for sociodemographic variables among cases and controls. For each potential risk factor, an unadjusted OR and its 95% confidence interval (CI) were computed by univariate logistic regression model. Multivariate logistic regression analysis was performed to study the association of potential risk factors with acute HBV infection while adjusting for the confounding effect of other variables. Variables significantly (P_0.2) related to the outcome variable in univariate analysis or of known biological significance were considered for inclusion in final multivariate logistic regression model. Age, gender, and hospital were kept in the final model to adjust for any potential selection bias. After developing the final model, plausible interactions between the independent variables were evaluated. The HosmerLemeshow test statistic was used to evaluate goodness-offit of the final model. Population attributable risk (PAR) for therapeutic injections was estimated using adjusted OR obtained from the final model.[14]

Results

This case-control analysis included 67 cases of acute HBV infection (1gM anti-HBc positive) and 247 controls from 4 different hospitals in Karachi. The mean (±S.D.) age (years) was 29±13 and 27±14 for cases and controls respectively. Among cases, 67% (45/67) were males compared to 58% (143/247) among the controls. Pashto was the most frequently (45%) spoken dialect among cases followed by Urdu (18%), Sindhi (12%), Punjabi (10%), Hindko (8%), and others (8%). Among controls, Urdu was the most frequently (38%) spoken dialect followed by Pashto (27%), Punjabi (16%), Sindhi (5%), Hindko (5%) and others (9%). Thirty-seven percent of the cases were never married compared to 48% of the controls. Thirty-six percent of both cases and controls did not have formal school education, while 45% of cases and 31% of controls had 1-8 years of formal schooling. The proportion of non-earning individuals among the cases and controls were 45% and 55% respectively. Also, being a factory worker was a common occupation both among the cases (28%) and the controls (20%).Cases more frequently (76%) tended to reside in household size of seven or more compared to controls (62%) (Table 1).

Table 1. Distribution of sociodemographic variables among acute hepatitis B virus cases and controls Karachi, 2000-2001).

Variable	Cases = 67 n (%)	Controls = 247 n (%)
Enrollment hospital		
SSHL*	27 (40.3)	85 (34.4)
K V SITEΦ	16 (23.9)	64 (25.9)
JPMC‡	12 (17.9)	63 (25.5)
Civil HospitalΣ	12 (17.9)	35 (14.2)
Age in years by category		
1-18	12 (17.9)	65 (26.3)
19-25	27 (40.3)	60 (24.3)
26-35	12 (17.9)	70 (2.3)
36-72	16 (23.9)	52 (21.1)
Gender		
Male	45 (67.2)	143 (57.9)
Female	22 (32.8)	104 (42.1)
Ethnicity		
Urdu	12 (17.9)	93 (37.7)
Sindhi	8 (11.9)	13(5.3)
Punjabi	7 (10.4)	39 (15.8)
Pashto	30 (44.8)	67 (27.1)
Hindko	5 (7.5)	12 (4.9)
Others	5 (7.5)	23 (9.3)
Marital status		
Never married	25 (37.3)	118 (47.8)
Ever married	42)62.7)	129 (52.2)
Duration of marriage in years# $	15.8 (13.0)	15.3 (12.7)
Years of formal schooling		
Nil	24 (35.8)	90 (36.4)
1-8	30 (44.8)	76 (30.8)
9-12	13 (19.4)	71(28.7)
Above 12	9 (0.0)	10 (4.0)
Occupation		
Non-earning	30 (44.8)	136 (55.1)
Business	6 (9.0)	23 (9.3)
Govt. service	5 (7.5)	12 (4.9)
Factory worker	19 (28.4)	50 (20.2)
Service providers	7 (10.4)	20 (8.1)
Professionals	9 (0.0)	6 (2.4)
Number of household members		
1-6	16 (23.9)	94 (38.1)
7 or more	51 (76.1)	153 (61.9)
Monthly household income**		
<Rs. 2500	12 (17.9)	20 (8.1)
Rs. 2500-5000	39 (58.2)	163 (66.0)
> Rs. 5000	16 (23.9)	64 (25.9)

* Social Security Hospital, Landhi, Karachi.
Φ Kulsoom Bai Valika Hospital, SITE, Karachi.
‡ Jinnah Postgraduate Medical Centre, Karachi.
Σ Civil Hospital, Karachi.
Mean with standard deviation.
$ Presently married subjects (41 cases, 129 controls).
** Rs. 63 = 1 US Dollar

Univariate analysis showed that the cases were more likely than controls to have received one injection (P=0.02) or more than one injection (P<0.001) during the time window considered for exposures. Also, the univariate relationship of type of health-care provider with acute HBV infection status was

significant (P<0.001). This relationship was much stronger for non-physician providers (crude OR = 11.7; 95% CI 3.8, 35.7) than for physician providers (crude OR = 4.9; 95% CI 2.7, 9.0). Furthermore, cases were more likely to have received injections with syringes from open source (crude OR=18.2; 95%CI 4.4, 75.1), or closed packets (crude OR = 4.6; 95% CI 2.5, 8.5) when compared to controls. Other exposures considered including IV drips, hospitalization, blood transfusion, dental treatment and injury causing bleeding; these were not statistically significantly related to acute HBV infection status. Also, for men in this study, having had a facial shave or armpits have from the barber was not significantly related to outcome variable (Table 2).

Table 2. Univariate analysis showing the association of variouspotential risk factors* with acute hepatitis B virus infections by theirodds rati (ORs) and 95% CI (Karachi, 2000-2001).

Exposures	Cases = 67 n (%)	Controls = 247 n (%)	OR	95% CI	
Number of injections					
Nil	24 (35.8)	187 (75.7)	1		
One	7 (10.4)	18 (7.3)	3	1.2	8.0
More than one	36 (53.7)	42 (17.0)	6.7	3.6	12.4
Injections received from					
Physician	34 (50.7)	54 (21.9)	4.9	2.7	9.0
Non-physician	9 (13.4)	6 (2.4)	11.7	3.8	35.7
No injection	24 (35.8)	187 (75.7)	1		
Syringe source					
Closed packet	32 (47.8)	54 (21.9)	4.6	2.5	8.5
Open	7 (10.4)	3 (1.2)	18.2	4.4	75.1
Don't know	4 (6.0)	3 (1.2)	10.4	4.4	75.1
No injection	24 (35.8)	187 75.7)	1		
IV drip					
No	58 (86.6)	229 (92.7)	1		
Yes	9 (13.4)	18 7.3)	2	0.84	4.6
IV drip received from					
Physician	8 (11.9)	17 (6.9)	1.9	0.76	4.5
Non-physician	1 (1.5)	1 (0.4)	3.9	0.24	64.1
No IV drip	58 (86.6)	229 (92.7)	1		
Hospitalization					
No	63 (94.0)	239 (96.8)	1		
Yes	4 (6.0)	8 (3.2)	1.9	0.55	6.5
Blood transfusion					
No	65 (97.0)	246 (99.6)	1		
Yes	2 (3.0)	1 (0.4)	7.6	0.67	84.8
Dental treatment					
No	63 (94.0)	238 (99.6)	1		
Yes	4 (6.0)	9 (3.6)	1.7	0.5	5.6
Injury causing bleeding					
No	61 (91.0)	237 (96.0)	1		
Yes	6 (9.0)	10 (4.0)	2.3	0.82	6.7
Professional blood/syring contactΦ					
No	59 (100.0)	204 (100.0)	-	-	-
Yes	9 (0.0)	0 (0.0)	-	-	-
Facial shave from barberψ					
No	22 (52.4)	76 (62.3)	1	-	-
Yes	20 (47.6)	46 (37.7)	1.5	0.74	3.1
Armpit shave from barberψ					
No	28 (66.7)	99 (81.1)	1		
Yes	14 (33.3)	23 (18.9)	2.2	0.98	4.7
Tattooing					
No	67 (100.0)	246 (99.6)	-	-	-
Yes	0 (0.0)	1 (0.4)	-	-	-
Ear piercing					
No	66 (98.5)	242 (98.0)	1		
Yes	1 (1.5)	5 (2.0)	0.73	0.08	6.4
IV drug use					
No	65 (97.0)	247 (100.0)	-	-	-
Yes	2 (3.0)	0 (0.0)	-	-	-
Liver disease patient in household					
No	62 (92.5)	229 (92.7)	1		
Yes	5 (7.5)	18 (7.3)	1.02	0.36	2.9

* History of potential risk factors was recorded for the period of 6 weeks to 6 month prior to the onset of illness for cases and to the time of interview for controls.

Φ 59 cases and 204 controls (adults only).

ψ 42 cases and 122 controls (male adults only).

The final multivariate logistic regression model revealed that after adjusting for the effects of age, gender and ethnicity, the cases compared to controls were more likely to have received one injection (adjusted OR=4.O; 95% CI 1.4, 11.1), or more than one injection (adjusted QR=6.3; 95% CI 3.2, 12.4). Also the cases tended to live in household size of seven or more (adjusted OR=1.9; 95% CI 0.95, 3.9)

(Table 3).

Table 3. the final multivariate logistic regression model of risk factors associated with acute hepatitis B virus infection (Karachi, 2000-2001)

Variable*	Adjusted OR	95% CI	
Number of injectionsΦ			
Nil	1		
One	4.0	1.4	11.1
More than one	6.3	3.2	12.4
Number of household members			
1-6	1		
7 or more	1.9	0.95	3.9
Ethnicity			
Urdu	1		
Sindhi	5.4	1.7	18.0
Punjabi	1.3	0.44	4.1
Pashto	2.5	1.1	5.8
Hindko	3.7	0.97	14.0
Others	1.4	0.41	4.9

* variables of age, gender and enrollment hospitals were included in the model to adjust for any selection bias introduced while selecting controls.

Φ During the period of 6 weeks to 6 monthsprior to the onset of illness for cases and to the time of intervew for controls.

The estimated population attributable risk (%) for therapeutic injections was 53% (95% CI 40%, 58%). The Hosmer-Lemeshow goodness-of-fit test for the final model showed a good fit (X2 =13.14, P=0. 11).

Discussion

Of 67 cases of acute HBV infection in the present study, 43 (64.2%) received one or more therapeutic injection from health-care providers including physicians and non-physicians during the 6 weeks to 6 months previous to the onset of illness. Of 247 controls, 60 (24.3%) subjects received therapeutic injections from these two types of health-care providers. There was also a dose-response relationship between the number of injections received and strength of association with acute HBV infection status. These findings corroborate the findings of earlier studies reported from developing countries on the role of therapeutic injections as a risk factor for HBV infection.[15-19] HBV is efficiently transmitted through contaminated needles and its transmission probability is nearly 10 times higher than that of HCV and 20 times more than that of HIV.[20] Furthermore, the study identified significant association between HBV infection and receiving an injection from syringe in closed packet. This may suggest repackaging of used syringes, a finding for which there is dearth of information in published literature and needs further attention.

Overuse of therapeutic injections is common in Pakistan[21,22] and in other developing countries in the region. Common use of injections stems from patients' demand coupled with providers' preference to give injections. Patients believe this method of drug administration to be more efficacious and symbolizes more advanced technology. Pain associated with injection is also considered a sign of potency. The providers also consider this mode as more efficacious with better compliance, and it is often associated with a financial benefit for them.[23]

The estimated population PAR% for therapeutic injections in our study was 53%, which is not substantially different from those reported from Moldova (52%)[15] and India (57%).[16] Our study hospitals are operating in low socio-economic neighbourhoods and had the controls developed similar illness, they would have gone to the same hospitals-a requirement of representation of cases and controls in the same source population to calculate the PAR%. Furthermore, we enrolled acute cases of acute HBV infection rather than HBV carriers to evaluate the therapeutic injections as a risk factor, which gives a better estimation of relative risk and population attributable risk. The result of this study may provide a baseline estimate of PAR% for therapeutic injections before the implementation of envisaged safe injection interventions in Karachi. Repetition of this study subsequent to implementation of safe injection interventions may help evaluate the effectiveness of these interventions in this and similar settings.

In our study, cases were more likely to have lived in a household size of seven or more compared to controls. The cases might have additional REV positive members and have had acquired infection through horizontal transmission. The association between household size and HBV infection has been documented in several previous studies.[25-28] However, evaluation of such risk behaviours that might have been associated with HBV transmission was beyond the scope of this study.

As noted earlier, being a Pathan, Hindko and Sindhi was associated with acute HBV infection. They are socially and culturally distinct ethnic groups with specific lifestyle characteristics, the assessment of which in relation to HBV infection was beyond the scope of this study. These ethnic groups need to be further explored with respect to HBV infection and its association with their living and sexual behaviours.

History of multiple sex partners has been identified as a risk factor for HBV infection among adults.[29,31] However, we could not evaluate this risk behaviour in our study. People in Pakistan are socially and culturally constrained in talking about their sexual behaviours. Thus, we could not collect information on the sexual behaviours of our study subjects and sexually acquired infection can not be excluded as a source of acute HBV infection in the cases.

Recall bias is an inherent limitation of case control study design. We attempted to minimize this

problem by enrolling hospital controls suffering from ailments other than acute viral hepatitis to have comparable recall and asking exposure history for only the last 6 months.

In conclusion, educational interventions based on identified risk factors both for health care providers and the general population may help to reduce the burden of HBV infection in Pakistan. Elsewhere[32] intervention based on guidelines and education of health care personnel has successfully decreased the use of injections and improved knowledge regarding sterilization. It is likely to bring similar changes in Pakistan and other developing countries, there by reducing the frequency of HBV and other blood-borne infections. Further research is indicated to implement and evaluate any such educational programme.

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