Hepatitis C virus infection and haemodialysis: experience of a district general hospital in Brunei Darussalam

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ABSTRACT

Introduction: Hepatitis C virus (HCV) infection is prevalent among patients undergoing haemodialysis (HD). This study assessed the characteristics and outcomes of HCV infections among patients undergoing regular HD in a small dialysis centre.

Methods: All patients (total 71, male 52 percent) who had HD were identified from the dialysis register and retrospectively reviewed.

Results: The mean age was 48.0 (+/– 14.7) years at the start of HD and the overall incidence of HCV IgG seropositivity (+) was 31 percent (22 patients). Ten patients were documented to have acquired HCV infection after starting HD, and nine cases before the institution of control measures. HCV RNA was detected in 14 of 17 (82.4 percent) patients who had RNA testing. Genotyping was done for seven patients; genotype 1a (two), genotype 1a/b (one) genotype 2b (one) and genotype 3a (three). HCV IgG (+) patients were younger, had longer duration of HD and had more transaminitis (all p-values less than 0.05) compared to HCV IgG (–) patients. Five patients had interferon treatment and three had sustained viral response (HCV RNA undetected at six months post-completion). At a mean HD duration of 54.8 (+/– 40.3) months, 25 patients (35.2 percent) died, with similar proportion from those HCV IgG (+) (31.8 percent) and those HCV IgG (–) (36.7 percent), respectively (p-value equal to 0.688). There were no difference in age (p-value equal to 0.444) and duration of HD (p-value equal to 0.534) between these two groups. None of the deaths were due to liver disease.

Conclusion: HCV infection is common among patients attending HD and sharing of dialysis machines is an important factor. HCV infection was not a significant factor on the mortality in this study but longer follow-up is required.

Keywords: end-stage renal failure, genotypes, haemodialysis, hepatitis C

Singapore Med J 2008; 49(11): 916-920

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INTRODUCTION

Hepatitis C virus (HCV) infection commonly leads to chronic liver disease and eventually leads to liver cirrhosis, complications of portal hypertension and hepatocellular carcinoma.[1] This usually occurs after a long natural history of over two to three decades. The incidence of HCV infection among patients undergoing haemodialysis (HD) is high, and this has been attributed to cross infections from sharing of dialysis machines and possibly through the increased requirement of blood transfusions before the routine use of erythropoietin.[2-5] There is data to suggest that progression of HCV infection is faster in end-stage renal failure (ESRF) patients.[6,7] In Brunei Darussalam, there are four dialysis centres; three located in the capital city (Raja Isteri Pengiran Anak Saleha [RIPAS] Hospital Renal Unit, Rimba Dialysis Centre and Kampong Kiarong Dialysis Centre) and one located in Suri Seri Begawan Hospital (SSBH), a district general hospital. This study assessed the incidence of HCV infections and looked at the characteristics and outcomes among patients undergoing HD at the dialysis centre in SSBH.

METHODS

The dialysis centre at SSBH started operation in 1990. This dialysis centre catered to all patients requiring regular maintenance HD in that district. The population catchment of this centre was approximately 67,000. The dialysis centre initially had four dialysis points and was located near the medical intensive care unit. Later, the dialysis centre moved to the current location which had eight dialysis points. Two of these dialysis points are

Table I. Demographics and aetiologies of end-stage renal diseases of patients.

Demographics and aetiologies	No. (%) of patients
Age at HD# (years)	48 ± 14.7 (17–72)
Gender (male : female)	37 (52.1) : 34 (47.9)
Race	
Malay	49 (69.0)
Chinese	12 (16.9)
Indigenous	9 (12.7)
Others	1 (1.4)
Aetiology of ESRF*	
Diabetes mellitus	22 (31.0)
Hypertension	25 (35.2)
Glomerulonephritis	12 (17.0)
Polycystic kidney disease	5 (7.0)
Stone diseases	4 (5.6)
Hepatorenal syndrome	1 (1.4)
Renal tubular acidosis	1 (1.4)
Benign nephrosclerosis	1 (1.4)
Unknown	6 (8.5)
Presence of comorbid conditions	65 (91.5)
Medications**	
No.#	8.9 ± 2.1 (6–16)
Hepatotoxic medications§	22 (47.8)

ESRF: end-stage renal failure
expressed as mean and standard deviation (range)
§ include statin, ticlopidine and allopurinol
* six cases had an overlap of diabetes mellitus and hypertension as a cause of ESRF
** based on prevalent patients (n = 46)

designated and specially used for HCV IgG seropositive (+) patients as part of infectious control measure to reduce cross infections. This was implemented in February 2000 after a notable increase in the number of HCV IgG (+) cases. Patients who were positive for hepatitis B serology did not have their HD in this centre, and were referred to another centre located in the capital city for their HD. Three 4–6 hours sessions were carried out daily, except for Sunday. Emergency dialysis may be carried out in this centre, or patients were referred to the main hospital located in the capital for further management until the patients' conditions were stable.

Patients routinely had their liver function tests checked four-monthly and viral serologies (HCV IgG by ELISA method, HBsAg, anti-HBs antibody and HIV antibody) checked at six-monthly intervals. Patients whose anti-HBs antibodies titres fell below 20 IU/L were routinely given booster doses. Any abnormalities were followed-up closely. HCV IgG and HBsAg were repeated, if alanine aminotransferase (ALT) level remained elevated and if infection was suspected. HCV RNA (PCR method done in overseas centres) was done for patients who were HCV IgG (+) with persistently abnormal ALT. Patients who were positive for HCV RNA were referred to the gastroenterology unit for further evaluation and consideration for treatment. Genotype testing was done in an overseas centre using the direct sequencing of PCR products.

Demographical data (age, gender and race), causes of ESRF, duration of HD, viral serologies (HCV IgG, HBsAg, anti-HBs and HIV antibodies), biochemical data (liver function test, serum urea and creatinine levels), medications, treatment regimes and outcome data were retrieved from the case notes, dialysis registers and computerised laboratory results. Causes of deaths for patients where information was not available from the case notes, were obtained from the Birth and Death Registry. The data were coded and entered into the Statistical Package for Social Sciences version 10.0 (SPSS Inc, Chicago, IL, USA) programme for analysis. Comparisons were made between those with HCV infection to those without infection using Mann-Whitney, χ^2 or Fisher's exact test, where appropriate. Significant results were taken when $p < 0.05$.

RESULTS

At the time of review, 71 patients (male 52%) with a mean age of 48.0 ± 14.7 years at the start of HD were identified from the dialysis register. The demographical data and the aetiologies of ESRF are shown in Table I. The overall incidence of HCV IgG (+) among patients undergoing HD was 31% (n = 22/71). No patient was positive for HIV. 60 patients (85%) were positive for anti-HBs at some point of follow-up. Of these, 37% had intermittently lost their anti-HBs titres to undetectable levels. Among HCV IgG (+) patients, ten patients were documented to be HCV

Table II. Comparison between HCV IgG (+) and IgG (−) patients

	HCV IgG (+) (n = 22)	HCV IgG (–) (n = 49)	p-value
Age at start of HD (years) †	38.8 ±14.7	52.2 ± 12.7	0.001
Gender (male)	15 (68.2)	24 (49.0)	0.133
Duration of HD (years) †	89.9 ± 43.7	38.9 ± 26.2	< 0.001
Comorbid conditions present	17 (77.3)	48 (98.0)	0.004
No. of medications† *	7.8 ± 1.9	9.4 ± 2.0	0.012
Hepatotoxic medications *	6 (40)	16 (51.6)	0.460
Liver function test			
Transaminitis	19 (86.3%)	9 (18.4)	< 0.001
Latest biochemical†			
ALT (IU/L)	22.3 ± 14.5	14.1 ± 9.4	0.121
Bilirubin (mmol/L)	17.1 ± 21.4	13.3 ± 9.9	0.453
Albumin (g/L)	39.3 ± 4.3	37.5 ± 6.1	0.243
No. of deaths	7 (31.8)	18 (36.7)	0.688

ALT: alanine Aminotransferase, HD: haemodialysis
† data is presented as mean and standard deviation; all other data is expressed as no. (%)
* based on prevalent patients (n = 46)

IgG (–) at the start of HD, suggesting acquisition of HCV infection after initiation of HD. The median time for HCV IgG to become positive after starting HD was 45 (range 20–70) months. Only one new case was detected after the implementation of infectious control measures. Among patients who had HCV RNA testing, this was positive in 82.4% (n = 14/17) at some point of follow-up.

Genotyping was done for seven patients: genotype 1a (two), genotype 1a/b (one) genotype 2b (one) and genotype 3a (three). Five patients had undergone therapy (median 12 months, range 4–12 months) with standard interferon given three times a week administered subcutaneously. All had biochemical responses during treatment. Three patients who had treatment had sustained viral response (SVR, defined as HCV RNA undetected at six months post-completion). Two of these SVR patients died during follow-up.

At a median follow-up of 57 (range 9–83) months, none of the HCV IgG (+) patients had any evidence of significant liver disease. The latest serum albumin and bilirubin levels among HCV IgG (+) patients were within normal limits. Apart from the case of living donor liver transplant (LDLT) where the patient developed renal failure requiring HD after transplant, there was no case of advanced liver disease. 61% of these patients had undergone upper gastrointestinal endoscopy and none had evidence of varices or portal hypertensive gastropathy. Nine (29%) patients who were HCV IgG (–) also had transient elevation of serum ALT, with a median of one elevation (range 1–3). These normalised on follow-up.

Comparing the two groups, HCV IgG (+) patients were significantly younger, had significantly longer duration of HD but significantly less comorbidities. They also had more episodes of transaminitis (Table II). At a mean HD duration of 54.8 ± 40.3 months, a total of 25 patients (35.2%) died. One patient had renal transplant after undergoing HD for approximately one year. He died the following year. Causes of deaths are listed in Table III. Equal proportion of HCV IgG (+) and HCV IgG (–) patients have died at review (31.8%, n = 7/22 vs. 36.7%, n = 18/49) (p = 0.688). There were no significant differences in the age at the start of HD (51 ± 10.9 vs. 54.6 ± 11.3 years, p = 0.444) and duration of HD (40.7 ± 9.7 vs. 46.2 ± 28.3 months, p = 0.534) between the HCV IgG (+) and HCV IgG (–) groups. None of the deaths were due to liver disease.

Table III. Place and cause of death (n = 25).

Place of death	Cause of death	No. (%)
Hospital	Sepsis	12 (48.0)
	Cardiovascular/cerebrovascular	6 (24.0)
	End-stage renal failure	1 (4.0)
	Disseminated gastric carcinoma	1 (4.0)
Home	Unknown	5 (20.0)

DISCUSSION

Our study showed that HCV infection is common among our patients undergoing HD, with up to a third of the overall cohort testing positive for HCV IgG serology at some point of their follow-up. We previously showed that HD accounted for up to 13.6% of the aetiologies among our overall HCV-infected patients.[8] It is important to note that a large number of patients who were HCV IgG (–) at the start of HD, later became HCV IgG (+). This indicated that these patients acquired the infection after starting HD. It is likely that the majority acquired their

infection through the sharing of HD machines, rather than through transfusion or operation exposure, such as fistula operations.[9,10] This mode of transmission has been well documented. After the introduction of infectious control measures where HCV IgG (+) patients were segregated using designated HD machines and dialysis points, there was only one new case detected. This showed that sharing of HD machines is an important risk factor in our patients. Blood transfusion has not been shown to an important factor,[11] and this mode of acquisition has become an extremely rare event especially with the introduction of blood screening with HCV IgG serology.[12] Studies have shown that nosocomial transmissions via healthcare workers looking after these patients are also important risk factors.[13,14]

The genotypes found in our study are consistent with the genotypes breakdown in our local setting. We previously showed that genotypes 3 and 1 accounted for 60% and 34.7%, respectively, in our local setting.[15] Consistent with published data on chronic HCV infection, viraemia was present in 80% of our patients who had HCV RNA testing. In our study, HCV IgG (+) patients were significantly younger and had significantly longer duration of HD. These patients were exposed to the risk factor for a longer duration and this has been shown to be an important factor.[16] HCV IgG (–) patients had significantly more comorbidities. There were no significant differences observed in the latest liver function parameters among patients who were HCV IgG (+) and HCV IgG (–). Apart from one patient who had LDLT, there was no documented case of chronic liver disease during a mean follow-up. However, considering the long natural history of HCV infection, a longer duration of follow-up will be required to assess the impact of HCV IgG (+) among patients undergoing HD.

Five patients had treatment with standard interferon monotherapy and three had SVR. Two of these patients subsequently died on follow-up. Despite our data showing a 60% response rate, we are not able to draw any conclusion as the sample size of patients was small. More importantly, the treatment is now better defined with better response rates based on a combination of ribavarin and pegylated interferon. Patients who are considering renal transplant should first undergo treatment to eradicate the virus before transplantation. HCV infections in transplanted patients have been shown to have liver disease progression at a faster rate.[17,18] Patients with ESRF have significant comorbidities, and as a result, life expectancies are shorter.[19-21] The mean age of our patients who have died was lower than the national average. In our study, HCV IgG (+) status did not have a significant impact on mortality. The majority of our patients died of infectious, cardiovascular or cerebrovascular complications.[22] However, larger and longer follow-up studies are required.

There are several limitations with our study. First, the retrospective nature of the study is inherently associated with many limitations. Second, the sample size was small. Third, the follow-up duration was short considering the long natural history of chronic HCV infections. However, the results are consistent with published findings.

In conclusion, our study showed that HCV infection is common among our ESRF patients who attended a district general hospital for HD; however, the prevalence is decreasing. Sharing of dialysis machines represented an important factor, and implementation of strict infectious control measures, such as designated dialysis machines for infected cases, was effective in reducing the number of new cases. HCV infection was not a significant factor on the mortality in this study, but a longer follow-up is required.

ACKNOWLEDGEMENTS

We would like to acknowledge the assistance provided by Assistant Senior Nurse Hjh Normadiah Hj Ibrahim and the staff from the dialysis unit, Suri Seri Begawan Hospital, as well as the assistance provided by Ainah from ward 19 for her help in tracing the missing data.

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