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Prevalence of Hepatits C infection among haemodialysis patients from Central Kerala, India - A cross sectional study

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Abstract

Background: The high prevalence of Hepatitis C virus (HCV) infection contributes to morbidity and mortality among patients on maintenance hemodialysis. Nosocomial transmission can be prevented by strict infection control measures and early screening. Present study aims to determine the prevalence of HCV infection in a hemodialysis unit in Central Kerala, India using Real-time PCR and third-generation ELISA. **Methods**: The present descriptive cross-sectional study conducted from November 2017 to June 2018 included 117 patients with chronic renal failure who underwent maintenance hemodialysis. Sociodemographic data and detailed history regarding risk factors were taken by interview and from medical records. HCV RNA estimation using real-time PCR and antibody detection using third-generation ELISA were performed using blood samples collected from the patients. **Results:** Most of the patients were males with a mean age of 48years. Prevalence was 9.4% for HCV RNA and 10.3% for antibodies. The performance of the third-generation ELISA was comparable to the PCR method. Duration of hemodialysis, dialyzer reuse, history of blood transfusion, and positive antibody status was found to be significant risk factors for HCV viremia. **Interpretation & conclusions**: The prevalence of HCV infection is low in our setting. But there is a need to review infection control practices to identify lapses in dialyzer reuse and safe blood transfusion. A robust infection control program including isolation policy along with screening using high performance third generation ELISA kits can reduce the incidence of HCV infection in hemodialysis centers.

Key-words: *Haemodialysis, Hepatitis C, Real Time PCR, ELISA*

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Introduction

Chronic Kidney Disease (CKD) is an important public health problem with its prevalence ranging from <1% to 17% globally. [1] Renal replacement therapy by haemodialysis (HD) or transplantation remains the main stay of treatment for End Stage Renal disease (ESRD). Patients on chronic haemodialysis are highly susceptible to hepatitis B & C infections. Apart from the immunosuppression due to chronic kidney disease, this is mainly attributed to frequent and prolonged contact with blood through blood transfusions, surgical interventions, and vascular access.

Breach in infection control practices including contaminated machines is also a significant risk factor. High prevalence of HCV infection among haemodialysis patients compared to the general population is supported by different studies across the world [2,3].

There are many published reports of hepatitis C outbreaks in haemodialysis units.[4]

Hepatitis C infection can lead to chronic liver disease with complications such as cirrhosis and hepatocellular carcinoma. This along with worsening kidney functions can definitely add on to morbidity and mortality among haemodialysis patients.[5] Thus it is highly essential to prevent transmission and spread of hepatitis C infection in dialysis units with strict infection control practices and early detection by routine screening. Currently there is high cure rate of hepatitis

C infection using newer antiviral therapy.[6]

Indian studies show a prevalence ranging from 1 % to 45.2%.[7] Screening with third generation Enzyme Linked Immuno Sorbent Assay (ELISA) kits incorporating antigens of core, NS3 and NS5 regions alone may fail to identify the acute phase and active infection. Moreover antibody production can be affected due to underlying immunosuppression compromising the sensitivity of the test. [8] Hence HCV RNA measurement which can diagnose Hepatitis C infection even During serological window is considered as the gold standard. [9] The published data on prevalence using Real Time Polymerase Chain Reaction (RT-PCR) from India is scanty.

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The present study had been undertaken in a large haemodialysis unit of a government tertiary care centre in Central Kerala catering patients from three major districts. The study was conducted to determine the prevalence of HCV infection in the haemodialysis unit. The diagnosis of hepatitis C infection was performed using HCV RNA detection by RT-PCR complemented by HCV antibody detection by third generation ELISA. Association of HCV positivity with various risk factors was also studied. The outcome of this study will be helpful to measure the efficacy of infection control practices followed.

Materials And Methods

The present descriptive cross sectional study was performed in the Departments of Microbiology and Nephrology after obtaining approval from the Institutional Ethical Committee. A total of 117 patients with chronic kidney disease who underwent maintenance haemodialysis in the dialysis unit during the study period from July 2017 to July 2018 were enrolled in the study. Patients with acute renal failure undergoing dialysis and those receiving anti HCV treatment were excluded from the study. The sample size was calculated using the formula $4pq/d^2$ where p=prevalence, q=(100-p) and d=20% of P based on the reference study.[10]

Methodology

Patients were enrolled after getting written informed consent. Basic data were collected with the help of a proforma, interview, case sheets and medical records. This included sociodemographic data and detailed history regarding the disease leading to chronic kidney disease (CKD), duration of haemodialysis, frequency of dialysis, blood transfusions in last one year, number of dialysis centers visited, reuse of dialyzer, and risk factors.

The haemodialysis centre consisted of two routine areas consisting of 14 machines and one isolation area equipped with two dedicated machines each for hepatitis B and C positive patients. Patients were routinely screened using ELISA test for HCV antibodies and Hepatitis B Surface antigen (HBsag) before initiation of dialysis, following dialysis at an outside centre and also as follow up on monthly basis. Dialysers were reused except for known Hepatitis B and C positive patients.

Specimen collection

Two blood samples of 5ml each were collected from the patients in EDTA vials and plain vials to perform HCV RNA estimation and anti-HCV antibody detection respectively. All samples were stored in deep freezer at −20 degrees and processed within one week.

Real time Polymerase Chain reaction (PCR)

HCV RNA estimation was performed using IVD certified artus HCV RG Real time PCR test kit (QIAGEN) according to manufacturer's instructions.

Serology

Blood samples were allowed to clot and the clear serum was separated in sterile plastic vials. These were centrifuged to collect clear supernatant in vials and stored at 4^0 C. Anti HCV antibody detection was done using third generation ELISA kit, QUALISA (Tulip diagnostics) according to the manufacturer 's instructions.

Statistical analysis

Data were analyzed by descriptive analysis using IBM SPSS software version 25. Continuous variables were expressed as means ± standard deviation while qualitative variables were expressed as percentages. Quantitative variables were expressed as the median (interquartile range) and compared between HCV positive and negative patients using Mann–Whitney U-tests. Chi-square test was used to compare categorical data. Logistic regression analysis was performed to determine the independent risk factors for HCV RNA positivity. P value of less than 0.05 was considered as statistically significant. Receiver operating characteristics (ROC) curve was plotted to find out the cut off value of duration of dialysis with HCV RNA positivity.

Results

Among 117 patients enrolled during the study period, there were 82 (70.09%) males and 35 (29.91%) females. The age of the patients ranged from 13 to 84 years with a mean age of 48.03+/-standard deviation12.86. Majority of patients were within the age group of 41 to 50 years. Age and sex distribution of patients is given in Table. I.

Table I: Age and Sex distribution of patients on dialysis

Age	Sex		Total
	Male n(%)	Female n(%)	
10-20	1 (1.2)	1 (2.9)	2
21-30	4 (4.9)	4 (11.4)	8
31-40	19 (23.2)	6 (17.1)	25
41-50	21 (25.6)	10 (28.6)	31
51-60	22 (26.8)	7 (20.0)	29
61-70	13 (15.9)	7 (20.0)	20

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71-80	1 (1.2)	0 (0.0)	1
>80	1 (1.2)	0 (0.0)	1
Total	82 (100.0)	35 (100.0)	117

The duration of haemodialysis ranged from 2 months to 92 months with a mean of 28.34months. Most of the patients were on twice weekly dialysis (59, 50.4%). Analysis of causes of CKD showed that 46 (39.31%) patients had diabetic nephropathy and 30 (25.64%) patients had hypertensive nephropathy. Other identifiable causes were IgA nephropathy (15, 12.8%), pyelonephritis (5,4.3%), congenital anomalies and hereditary causes (8,6.8%). Baseline characteristics of study population is shown in Table. II

Table II: Baseline characteristics of study population (Total patients, N= 117)

Character	Number (Frequency)	Percentage
Sex		
Male	82	70.0
Female	35	29.9
Duration of Dialysis (Months)		
< 6	7	6.0
6-12	19	16.2
12-24	22	18.8
25-36	38	32.5
37-48	21	17.9
>48	10	8.5
Frequency of Weekly dialysis		
Thrice	53	45.3
Twice	59	50.4
Once	5	4.3
Etiology of CKD		
Diabetic Nephropathy	46	39.3
Hypertensive Nephropathy	30	25.6
IgA Nephropathy	15	12.8
Pyelonephritis	5	4.3
Congenital Anomalies	4	3.4
Hereditary	4	3.4
Interstitial Nephritis	3	2.6
Reflux Nephropathy	1	0.9
Obstructive Uropathy	1	0.9
Nephrotic Syndrome	1	0.9
Others	7	6.0
	117	100

Prevalence of HCV infection based on real time PCR was 9.4%. Out of the 117 patients, 11 (9.4%) patients were positive for both anti HCV antibody and RNA where as one male patient was positive only for antibody but negative for HCV RNA . Prevalence of HCV RNA and antibodies based on different criteria is shown in table no.III. Sensitivity and specificity of ELISA kit used was found to be 100% and 95.75 % respectively.

Table III: Prevalence of Hepatitis C Virus antibodies and RNA among study population

Criteria	No of Positives	Percentage
Both HCV Antibody and RNA positive	11	9.4
HCV Antibody Positive and RNA Negative	1	0.9
HCV Antibody Negative and RNA Positive	0	0.0
Both Negative	105	89.7
Total	117	100.0

Baseline characteristics of HCV RNA positive patients are shown in table no.IV. Most of the patients were males and the mean age of HCV positive patients were 47.36 ± 11.90 (Mean ± SD). All positive patients were on maintenance haemodialysis for more than a year and 82 % of them had history of blood transfusion and dialyzer reuse. Comparison and analysis of various clinical and risk factors are shown in table no.V. Duration of haemodialysis, dialyser reuse, history of blood transfusion and positive antibody status were found to be statistically associated with HCV viremia (p value less than 0.05).

Table IV: Baseline characteristics of HCV positive patients by PCR (Total patients, N= 11)

Character	Number (Frequency)	Percentage
Sex		

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Male	8	72.7
Female	3	27.3
Duration of Dialysis (Months)		
< 6	0	0.0
6-12	0	0.0
12-24	1	9.1
25-36	2	18.2
37-48	6	54.5
>48	2	18.2
Frequency of Weekly dialysis		
Thrice	3	27.3
Twice	8	72.7
Once	0	0.0
Etiology of CKD		
Diabetic Nephropathy	4	36.4
Hypertensive Nephropathy	3	27.3
IgA Nephropathy	3	27.3
Pyelonephritis	1	9.1
History of Blood Transfusion		
Yes	9	81.8
No	2	18.2
Dialyser Reuse	9	81.8
No of Dialysis centre visited		
One Centre – Our Centre	8	72.7
Two	2	18.2
Three or More	1	9.1
Comorbidities		
Diabetes	4	36.4
Hypertension	5	45.5
CVA/ Heart Disease	4	36.4
Smoking	3	27.3
Alcoholism	1	9.1

Table V: Comparison of Variables- HCV RNA positive patients and HCV RNA Negative Patients

Parameters	**HCV RNA Positive (n=)**		**HCV RNA Negative (n=)**		**Mann Whitney U Value**	**p Value**
	Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**		
Quantitative						
Age	47.36 ± 11.90	45 (38-60)	48.09 ± 13.01	48 (39.5-58.0)	564.5	0.863
Duration of dialysis (Months)	44.09 ± 18.82	37 (36-44)	26.71 ± 16.47	26 (13.5-36.0)	237.5	0.001
Frequency of Weekly dialysis	2.73 ± 0.47	3 (2-3)	2.38 ± 0.58	2 (2-3)	399.0	0.052
Qualitative						
Parameters	n=11	%	n=106	%	χ^2 Value	p Value
Sex						
Male	8	72.7	74	69.8	0.000	1.000
Female	3	27.3	32	30.2		
Diabetes	4	36.4	40	37.7	0.000	1.000
Hypertension	5	45.5	43	40.6	0.000	1.000
Heart disease / Stroke	4	36.4	21	19.8	0.789	0.374
Dialyzer Reuse	9	81.8	49	46.2	5.050	0.025
History of blood transfusion	9	81.8	46	43.4	5.906	0.015
Centre > 1	3	27.3	8	8.8	1.828	0.176
Anti HCV Antibody Positive	11	100.0	1	0.9	95.749	<0.001

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Logistic Regression analysis was done by taking HCV RNA positivity as a dependant variable and other variables such as duration of haemodialysis, frequency of dialysis, dialyser reuse and history of blood transfusions as independent variables as shown in table no.VI.Duration of dialysis had significant association with HCV RNA positivity.

Table VI: Logistic Regression

Variables	Beta Coefficient	p Value	Adjusted odds ratio	95% CI of odds ratio
History of Reuse of dialysis				
No	Reference			
Yes	0.761	0.450	2.141	0.297-15.423
Blood Transfusion				
No	Reference			
Yes	1.312	0.120	3.712	0.710-19.410
Duration of Dialysis	2.594	0.002	13.38	2.66-67.36
Frequency of dialysis	1.260	0.076	3.526	0.876-14.194

ROC curve was plotted to find out the cut off value of duration of dialysis with HCV RNA positivity. The cut off value was found to be more than 35.50 days for developing HCV RNA positive with Sensitivity of 81.8%, Specificity of 74.5%, PPV of 25.0% and NPV of 97.5%.

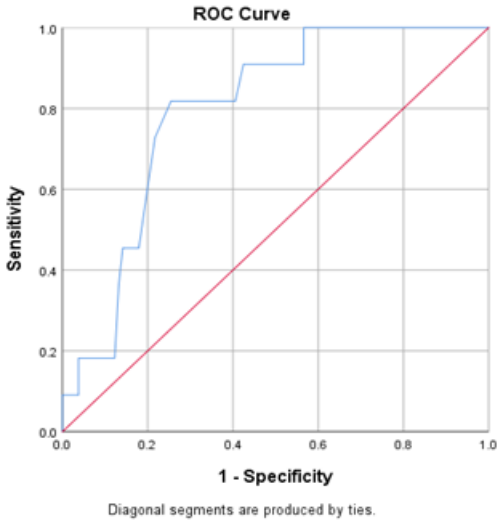

Figure 1

Discussion

HCV prevalence differs among haemodialysis units according to geographical location, prevalence in general population, type of health care facilities, socioeconomic factors, performance characteristics of the test and adherence to infection control practices. A large scale observational study called Dialysis Outcomes and Practice Patterns Study (DOPPS) conducted in 308 dialysis centres across 7 countries reported a mean seroprevalence of 13.5%, ranging from 2.6% to 22.9% during 1997-2001 .[11] The estimated prevalence of HCV infection was 8% in US haemodialysis centres (2002) whereas some centres in Romania reported HCV positivity as high as 50% .[12,13] Hinrichsen et al reported a prevalence of 4% HCV RNA positivity in a large scale multicenter study where as Mexican study by Nahum Me´ndez-Sa´nchez, showed prevalence of 5% by PCR and 6.7% antibodies .[14,15]

Our study showed a prevalence of 9.4% for HCV RNA positivity and 10.3% for antibodies. There were very few studies from India utilizing molecular methods such as PCR for measurement of prevalence. A study from Kerala by Anitha Madhavan et al during the same period showed 8% prevalence by conventional PCR which is comparable to our study. [7] Jasuja et al in Delhi reported a prevalence of 27.73% by PCR and 21.84% by ELISA which was higher than our data. [10] Our data was comparable to many South Indian studies using third generation ELISA. Report from Reddy et al showed a prevalence 13.23% from Hyderabad in 2005, Kumar et al reported 12.4% from Coimbatore 2011 and and study conducted in Calicut, Kerala by Razmin S et al showed 8.33% prevalence .[16,17,18] But Chigurupati, et al reported a moderately high prevalence of 23.5% from Andhra in 2014 based on ELISA [19] . Low prevalence of HCV infection in our haemodialysis unit can be due to strict implementation of infection control practices and isolation policy.

Centre for Disease Control (CDC) recommends screening for anti HCV antibodies and Alanine Amino Transferase (ALT) estimation on initiation of HD, therafter ALT monthly and anti HCV every 6 months.

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Confirmation of active infection by nucleic acid detection is done only for antibody positive patients and routine screening with molecular testing is not recommended .[20] With the introduction of third generation ELISA with excellent specificity and specificity, antibody detection is possible as early as 10 weeks. [21]

Many studies have proved comparable results between HCV RNA detection and third generation ELISA for detecting anti HCV antibodies[22,23,24,25]. Our study also proved this fact as third generation ELISA kit used with high sensitivity could detect all true positive cases. There was only one patient positive for antibody but without viremia, which may be indicative of spontaneously resolved infection. Though the importance of HCV RNA testing for detection of HCV infection was demonstrated by many studies, most of those studies were performed using second generation ELISA. A study conducted by Sheu et al. in Taiwan showed that among 47 HCV RNA-positive cases, only 83.0% were positive by a second-generation anti-HCV immunoassay[26]. Another study by Schroter et al. in a German population found that HCV infection could be detected in 5.0% of cases exclusively by PCR among 238 sero-negative patients [27]. But study by Anitha Madhavan et al showed high false negativity for third generation ELISA. This may be because of the variation in performance of the assay used. Considering the high cost and technical expertise required for PCR testing in low income centres, it is wise to follow CDC guidelines. The chance of missing an occasional positive patient may be compensated by monthly screening with ELISA which was practiced in our centre.

Epidemiological data were analysed to find out the potential risk factors for HCV infection. Most of the patients were males and mean age was 47 which was similar to the study by Prakash et al where the mean age was 45 [28] .But age and sex factors were not statistically associated with HCV positivity as per Jasuja et al and many other studies including us [29]. Many studies have proved that risk of HCV infection increases with duration of haemodialysis and it is an independent predictor which was concordant with the present study [28,29]. Studies from Kerala also showed HCV positive population had high duration of HD compared to the negative patients [7,18]. Mean duration of HD among positive patients in our study was 44 months compared to 27 months among HCV negative patients. Surendra Kumar et al found mean duration was 36.67 ± 31.68 months compared to 18 18.50 ± 21.29 months in HCV negative patients [17]. This point towards the nosocomial transmission of HCV in dialysis centres.

Previous history of blood transfusion is considered to be an important risk factor for acquiring HCV infection [30,31,32]. Moreover studies have shown that risk increases with number of blood transfusion [14,28].Though failed to prove as an independent risk factor, 81.8% of our HCV positive patients had history of blood transfusion multiple times, which was statistically significant similar to Prakash et al [28]. But Jasuj et al failed to demonstrate any significant association with blood transfusion. Screening of blood for transfusion in our hospital is done using third generation ELISA test, the sensitivity and specificity can vary depending on the performance of the assay used. Further studies are needed in this area to rule out the potential risk of transfusion transmitted hepatitis C in our setting. There has been considerable reduction in transfusion associated hepatitis worldwide with the introduction of screening of blood products and use of erythropoietin to correct anaemia.

CDC does not recommend dedicated machines, isolation or ban on reuse of dialyzer in dialysis setting for preventing HCV transmission. Strict adherence to standard precautions including proper disinfection of machines is mandatory and lapses in infection control can lead to outbreaks. Our study showed a significant association of HCV positivity with dialyzer reuse similar to studies by dos Santos JP et al [33]. Some Studies did not demonstrate impact of reuse in preventing HCV transmission in dialysis units [10,12,34]. A possible lapse in disinfection procedure of dialysers and tubings especially during manual washing has to be considered in our setting for possible nosocomial transmission.

Limitations

Genotyping and further phylogenetic analysis to find out genetic relatedness of the strains to demonstrate possible nosocmial transmission was not performed in the study due to lack of infrastructure and financial constraints. Laboratory parameters related to liver function like alanine amintransferase estimation were not recorded and analysed.

Conclusions

Prevalence of HCV infection is comparatively low in our dialysis unit. Our study demonstrated duration of haemodialysis, blood transfusion and reuse of dialyser as potential risk factors of HCV positivity. Though we have an infection control program implemented in our setting, routine audits and monitoring to check compliance related to procedures like reprocessing of dialyser has to be implemented strictly. Safety of blood transfusion has also to be ensured. Third generation ELISA can be used as a routine screening tool in our setting rather than RT PCR. We recommend isolation of HCV positive patients, dedicated equipments and machine, screening with ELISA monthly in dialysis units to prevent transmission

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