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Original Research Article

DETECTION OF HEPATITIS C VIRUS INFECTION AND ITS GENOTYPIC CHARACTERISATION AMONG HEMODIALYSIS PATIENTS BY HCV CORE ANTIGEN ELISA AND RTPCR- A HOSPITAL-BASED PROSPECTIVE STUDY IN A TERTIARY CARE HOSPITAL IN SOUTH INDIA

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Abstract

Background: Identification of HCV infection in hemodialysis patients and its genotypic characterisation from a tertiary care hospital. The aim is to identify the HCV infection and the genotypic characterization of the HCV among the patients undergoing hemodialysis at a tertiary care hospital. The present prospective study was conducted in a tertiary care hospital. A total of 60 patients undergoing hemodialysis were selected for the study. **Materials and Methods:** The blood samples collected were subjected for HCV core Ag ELISA & RT-PCR to detect HCV. Genotypic characterization of HCV positive samples was done by Gen-C 2.0 - in-vitro line probe assay. The statistical analysis was carried out using SPSS software. **Result:** Out of the 60 samples, 11 were tested positive by HCV Core Ag ELISA & 25 by RT-PCR. The genotyping revealed that the HCV belonged to the genotype 1. **Conclusion:** The incidence of HCV infection in hemodialysis patients increases with the number of blood transfusions (more than 2-3) and the duration of hemodialysis (4-6 years). The core antigen ELISA may not be sensitive enough to detect low levels of antigens in early viraemic pre-sero conversion phases, single HCV core antigen assay coupled with RT-PCR might be useful for a definite diagnosis of early HCV infection.

INTRODUCTION

Hepatitis C is the most important blood borne virus infection transmitted via parenteral routes in the chronic kidney disease (CKD) patients undergoing hemodialysis.[1-3] CKD patients require hemodialysis, peritoneal dialysis or renal transplantation in its terminal stage.[4-6] In hemodialysis blood is removed from the patients and pumped across the dialysis membrane. Poisons and toxins in the blood are discarded after entering the dialysate and blood is returned to the patient.[7] Vascular exposure for prolonged periods and frequent blood transfusions increases the risk of acquiring blood-borne infections. Contaminated equipment, environmental surfaces and health care workers play a crucial role in the nosocomial transmission of these infections.[8,9] It is estimated that approximately 71 million people have infected with HCV infection worldwide and in the year 2016 alone, approximately 3,99,000 people died from hepatitis C.[10] There are wide variations in the prevalence of HCV infection in different dialysis units and countries, according to Dialysis Outcomes and Practice Patterns Study (DOPPS). Mean HCV prevalence was found to be13.5% with variations ranging from 2.6% to 22.9% among different countries (DOPPS).[11] According to various recent studies, the prevalence of HCV in hemodialysis patients ranges from 8 to 19.23% in India.[12,13] Number of blood transfusions, duration of CKD, Hepatitis B/HIV coinfection, prior transplant are the main risk factors that have been identified.[14-20] There is a strong association between HCV infection and renal diseases of glomerular origin like membranous nephropathy, mixed cryoglobinemia, polyarteritis nodosa and membranoproliferative glomerulonephritis.[21-23] The risk of CKD and ESRD associated with HCV is 1.3 and 2.14-fold respectively.[24-27] Treating these patients with conventional therapy is a big challenge because of differences in response rates compared to the normal individuals. Virological diagnosis and monitoring of HCV infection is based on two categories of laboratory tests, namely serologic assays detecting

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specific antibodies to HCV (anti-HCV) and assays that can detect, quantify or characterize the components of HCV viral particles such as HCV RNA.[28] Early stages of the infection are missed because the antibodies develop only after one and half months of infection and the tests for anti HCV antibody may be negative in the initial period before the seroconversion phase.[29] This window phase can be longer in hemodialysis patients as these patients are severely immunocompromised.[30] In such situations, the HCV RNA detection by polymerase chain reaction (RT-PCR) is highly sensitive and is a reliable test in the early diagnosis of HCV infection.[31] However, since the test is expensive and needs certain amount of expertise, it is not used routinely in the diagnostic laboratories, especially in developing countries. The latest break- through in diagnosing early HCV infection is by detecting HCV core antigen (HCV cAg) that is present during the early stage or before seroconversion.[32,33]

High rate of genotype diversity, chronicity of infection and lack of an effective vaccine is a challenge for the clinicians to treat HCV infected patients successfully. Moreover, in recent trend, selection of new antiviral agent, duration of treatment and prognosis of patients are decided on the basis of HCV genotype and its subtypes. All these factors have led to the necessity of the study of HCV prevalence with its genotypic variation in the CKD patient so as to make the treatment effective. Hence the present study is aimed to know the prevalence of HCV in patients undergoing hemodialysis by detection of HCV core Ag by ELISA, HCV RNA by RT PCR and genotyping of the HCV strains to know the probable prevalent genotypes.

MATERIALS AND METHODS

Study Design

This prospective study was conducted over a period of 2 years (2017 to 2019) at a tertiary care hospital. Chronic renal failure patients undergoing treatment for maintenance hemodialysis, who have given informed consent, of both sexes and all age groups were included in the present study, excluding patients not willing to give informed consent, acute renal failure patients undergoing hemodialysis and HIV seropositive patients prior to the study. Based on the formula $N=4PQ/D^2$ sample size was calculated as 60. 5 ml of blood was collected from the patients under strict aseptic conditions and used for the serological and molecular testing.

ELISA

Serum and plasma were separated by centrifugation at 3000 rpm for 5 min. Samples were labeled and stored at -20 degree & -80 degree respectively, for HCV core Ag and HCV RNA. Serum samples were subjected for HCV core Ag detection by Quick TITERTM ELISA KIT supplied by CELL BIOLABS which is a Quantitative ELISA. ELISA performed as per the manufacturer's instructions. The results were interpreted using standard curve.

Genotyping of HCV

Nucleic acid from HCV samples was extracted using Spin Star Viral™ Nucleic Acid Extraction Kit 1.0 (BioServUK Ltd. UK). Viral nucleic acid extraction procedure comprised 4 steps (lyse, bind, wash, elute) and is carried out using SpinStar columns in a standard microcentrifuge. The detection and quantification of HCV specific RNA were carried out by RT-PCR using Real Star HCV RT-PCR kit from Altona Diagnostics (Hamburg, Germany). Genotyping of the samples tested positive by RTPCR were subjected for genotyping by Gen-C 2.0 - in-vitro line probe assay. Nuclear laser medicine HCV RNA REALTIME 2.0 kit was used to distinguish genotypes 1, 2, 3, 4, 5, 6, and 7 and major subtypes 1a, 1b, 2a/2c, 2b, 3a, 3b, 3c, 3k, 4a, 4b, 4c/4d, 4e, 4f, 4h, 5a, 6a/6b, 6g, 6f/q, 6m and 7a.

RESULTS

The present study was a prospective study done from 2017 to 2019 at a tertiary care hospital. Total 60 serum and plasma samples were collected from chronic kidney disease patients undergoing maintenance hemodialysis in Nephrology Department of the General Hospital. Out of 60 patients, 42 were males and 18 were females. All serum samples were tested for HCV Core Antigen by ELISA and plasma samples tested for HCV RNA by RT PCR. Out of 60 samples tested for HCV Core Ag,11(18%) was positive of which7 were males and 4 were females. Twenty-five (41.6%) patients were positive by HCV RT-PCR. More male patients were predominantly undergone hemodialysis compared to females. High prevalence of HCV was observed in the age group of 41-60 years by RT-PCR. Clinicopathological details of patients who were tested by HCV RTPCR is shown in [Table 1].

Table 1: Clinicopathological details of the patients included in Real Star HCVRT-PCR assay

Category		Total (%)	Real Star HCV RT-PCR DET* (%)	RealStar HCV RT-PCR NDE** (%)	p Value
Gender	Male	48(80%)	20(41.6)	28 (58.3)	1
	Female	12(20%)	5(41.6)	7(58.3)	
Age	≤20 Years	1(1.66)	NIL (0)	1 (100)	0.896
	>20 ≤40 Years	24 (40)	11 (45.83)	13 (54.16)	
	>40 ≤60 Years	30(50)	12 (40)	18 (60)	
	>60 ≤80 Years	5(8.33)	2 (40)	3(60)	
Hemodialysis Duration	>1 ≤ 3 Years	36 (60)	9(25)	27(75)	0.001
	>3 ≤6 Years	24 (40)	16(66.66)	8(33.33)	

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No. of blood transfusion	0	5(8.33)	2(40)	3(60)	0.743
	1≤2	23 (38.33)	11(47.82)	12(52.17)	
	>2≤3	32 (53.33)	12(37.5)	20 (62.5)	
Alanine Transamina se (ALT)	Normal	28(46.6)	12(42.15)	16(57.14)	0.210
	Elevated	2(3.3)	2(100)	Nil	
	Depressed	30(50)	11(36.66)	19 (63.33)	
ESRD	Contrast induced nephropathy	6(10)	2 (33.33)	4 (66.66)	0.922
	Glomerulonephritis	11 (18.33)	5 (45.45)	6 (54.54)	
	HTN	18 (30)	8 (44.44)	10 (55.55)	
	DM	20 (33.33)	10(50)	10 (50)	
	Obstructive uropathy	5 (8.33)	3 (60)	2 (40)	
Hemodialysis in ESRD patients/ week	Twice	35 (58.3)	11 (31.42)	24 (68.57)	0.057
	Thrice	25 (41.6)	14 (56)	11(44)	

*DET - Detected, **NDE – Not Detected

The HCV positive percentage was increased with the duration of hemodialysis. The patients undergoing hemodialysis more than 4-6 years were showing a high percentage of HCV positivity. The aetiology of ESRD in HCV positive patients revealed that 2 patients were diagnosed with contrast induced nephropathy (CIN), 5 were diagnosed with glomerulonephritis (GN), 8 were hypertensive (HTN), 10 were diabetic (DM) and 3 were having obstructive uropathy (OU) [Figure 1].

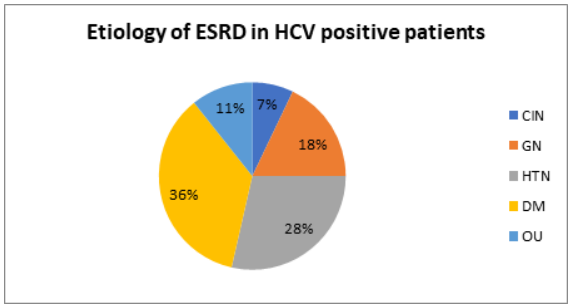

Figure 1: The HCV positive patients in comparison with etiology of ESRD. CIN- contrast induced nephropathy; GN- glomerulonephritis; HTN- hypertension; DM- diabetic mellitus; OU- obstructive uropathy.

Percentage of positivity was more when number of blood transfusions were more than 2 [Table 1]. ALT levels were elevated in 2 patients and depressed in 11 patients. The genotyping by LINE PROBE ASSAY revealed that of the 25 RT-PCR positive samples subjected for Genotyping, all 25 belonged to Genotype-1 in which 24 were subtype 1a and 1 could not be subtyped.

DISCUSSION

Viral infections in hemodialysis patients are a major problem in developing countries. HCV and HBV are the major viruses that are transmitted in hemodialysis patients apart from HIV and less commonly CMV. Transmission occurs mainly through blood transfusions, contaminated devices, sharing of equipment, improper cleaning of dialysis machines and through medical personnel. The present study was carried out for a period of 2 years from 2017 to 2019 to know the prevalence of hepatitis C viruses in patients on maintenance hemodialysis. In the present study, high HCV positivity was observed in the age group of 41-60 yrs (48%) by HCV RT PCR. This is correlated with the study done by Roy et al where the high positivity rate (60%) was observed in the age group of 41-60 years. Several studies indicated that the high positivity in this age group is because of the high incidence of CKD.[34-36] Male predominance was seen in the present study with 80% of HCV positive patients being males which can be associated with higher incidence of CKD per se and in males owing to higher incidence of Diabetes and Hypertension. The low incidence (20%) of HCV in the female patients of the present study could be because of the high HCV clearance rate in females compared to males. The HCV positivity by RT- PCR observed in the present study was 41.6%, which is correlated with the studies carried out by various scientific groups showing the positivity percentage ranging from 67.4-79.16.[34,37-40]

In the present study prevalence of HCV positivity by RT PCR was 56% for duration of 3-6years of blood transfusion. The mean duration observed for HCV positivity was 17 months to 6 years.[37,41] In the present study 12 out of 25 (48%) HCV RT PCR infected patients had a history of 2-3 blood transfusions, showing as a significant risk factor for HCV positivity. The HCV prevalence was higher in patients with long duration of dialysis and high number of blood transfusions.[34] The most common cause of CKD was diabetes (54%) followed by HTN (41%), Glomerulonephritis (4%) and the rest was 1% for which cause is not specified. Primary diseases causing ESRD in a study done by Reddy et al,[37] were chronic nephritis (33.33%), DM (24.7%), HTN (22.58%), cystic renal diseases (3.23%), SLE (0.54%) and unknown etiology (11.29%). In the

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present study, three patients were positive for HCV RNA and negative for core antigen indicating that core antigen may not be sensitive enough to detect low levels of antigens in early viraemic pre-seroconversion phases. A significant correlation of RNA positivity and elevated liver enzymes was reported by Reddy et al,[37] and Jasuja et al.[41] Jasuja et al,[41] showed HCV prevalence by RT PCR as 27.7 %. Peterson et al,[42] observed that 87% of HCV RNA positive specimens were positive for core antigen. In another study, core antigen was present in 88 % of HCV RNA positive pre-seroconversion specimens and in 83% of HCV RNA positive but antibody negative blood donors. Hence, HCV core antigen assay solely may not be useful in early HCV infection diagnosis.[43-46]

The distribution of HCV genotypes and sub-genotypes varies according to geographic variation in different parts of the world. Nowadays, it is very crucial to know the genotypes and its subtypes to determine clinical status, to decide effective therapy and prognosis of the patient. Our study showed genotype1 and subtype 1a as the most prevalent genotype. Yabaji et al,[47] reported that Genotypes 1 and 3 have a major worldwide distribution, accounting for 60-70% of infections. The most prevalent genotype in the Middle East and North Africa (MENA) region is genotype 1.[48,49] Genotype 1a is most prevalent in the United States and Northern Europe,[50,51] in our study genotype 1a is the most commonly found subtype. One Indian study of showed genotype 3 predominates in the north, east and west India, whereas genotype 1 is commoner in south India.[52-54]

CONCLUSION

The present study was conducted to determine the prevalence of HCV in patients on maintenance hemodialysis. The results showed that the prevalence of HCV by RT-PCR was 41.6%. The most common age group for HCV positivity was 41-60 years, and the most common cause of CKD was diabetes. The prevalence of HCV was also higher in patients with a history of blood transfusions and a longer duration of dialysis. The most common genotype found in the study was genotype 1, with subtype 1a being the most common subtype. The high prevalence of HCV in patients on maintenance hemodialysis is a serious public health concern, as it can lead to serious liver disease and other complications. Hence, the patients on maintenance hemodialysis should be screened for HCV infection. The patients who are positive for HCV should be offered treatment. Infection control measures should be implemented to prevent the spread of HCV in hemodialysis units. Further research is needed to better understand the risk factors for HCV infection in patients on maintenance hemodialysis and to develop more effective treatments for HCV.

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