ORIGINAL ARTICLE

RISK FACTORS AND TREATMENT OUTCOME OF CHILDREN WITH HCV INFECTION

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Background: Combination of pegylated interferon α-2a or α-2b has been considered to be the standard for treating HCV infection among children. Many new agents inhibiting HCV during various steps while replicating is under study around the world. This study was aimed to note the efficacy of sofosbuvir and ribavirin among children having HCV infection. **Methods:** This was an open label experimental trail done at Department of Gastroenterology, Children Hospital and The Institute of Child Health, Multan. The study duration was from July to December 2019. A total of 89 HCV treatment naïve children aged 6–16 years of age, having HCV PCR as positive were enrolled. Sofosbuvir as 400 mg once a day along with ribavirin 10–15 mg per kg per day in the form of once or twice as divided doses were given in all the cases. After starting the treatment, along with side effects, rapid virological response (RVR) as PCR at 4 weeks, early virological response (EVR) at 12 weeks and post treatment 12 weeks HCV PCR as sustained virological response (SVR) was noted. **Results:** Out of a total of 89 children, there were 53 (59.6%) boys and 36 (40.4%) girls. Mean age was noted to be 12.42±2.57 years. Majority of the children, 72 (80.9%) had genotype 3 while genotype 1 was noted in 11 (12.4%) and un-typable in remaining 6 (6.7%). History of blood or blood products transfusion was seen to be the commonest mode of HCV transmission, found in 41 (46.1%) children, perinatal transmission in 20 (22.5%) and history of previous surgery in 9 (10.1%). Rapid virological response was noted in 73 (83.1%) children, all 89 (100%) children achieved EVR whereas SVR was noted in 86 (96.7%). Headache was the commonest side effect, reported by 24 (27.0%) followed by nausea in 15 (16.9%). **Conclusion:** Regardless of the genotype, sofosbuvir and ribavirin combination therapy was noted to have excellent efficacy amongst children with HCV infection. History of blood and blood product transfusion was the commonest risk factor found.

Keywords: Genotype 3; Sofosbuvir; Virological response

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INTRODUCTION

Hepatitis C virus (HCV) infection is considered an important health issue throughout the world. Overall, more than 180 million people are considered to be affected with HCV infection. HCV is characterized as a hepatotropic virus that induces persistent inflammation and tissue harm, causing long-term complications attributed to cirrhosis and hepatocellular carcinoma (HCC).[1,2]

Low / medium income countries have been noted to have a comparatively high prevalence of HCV infection (1–5%) while high income countries have much lower numbers (0.05–0.36%).[3] In the United States, HCV infection is estimated to be prevalent amongst children of 6–11 years of age as 0.17% while children between 12–19 years have a recorded prevalence of 0.39%.[4,5] Recorded prevalence of HCV infection amongst Bangladeshi children is 0.6%[6] whereas in Pakistan, 0.58%[7].

Following 1992, blood transfusion has been devoid of HCV around the globe and thought to be around 0.001–0.01% per transfusion.[8]Among children, majority of the new cases found having HCV infection are due to vertical transmission.[4] Maternal foetal transmission is recorded to be responsible for above 60% cases while around 5% infants have HCV RNA positive mothers.[9]

Combination of pegylated interferon α-2a or α-2b has been considered to be the standard for treating HCV infection among children with an efficacy seen around 60%.[10,11] This treatment regimen accompanies side effects and about 4% of the cases discontinue treatment because of serious side effects. Typical symptoms like fever, anorexia, headache, etc are associated with interferon therapy.[12] Bone marrow suppression because of interferon is noted in around 30% of the cases. Although less prevalent but depression and suicidal intentions are also seen in patients using interferon.[12] Thyroid abnormalities are also associated with interferon and ribavirin therapy.[13] Haemolytic anaemia is widely documented to be associated with ribavirin.[14] Other than the side effects described, interferon and ribavirin combination therapy requires weekly

injection while efficacy with regards to genotype 1 and genotype 4 has not been appreciable.

Many new agents inhibiting HCV during various steps while replicating is under study around the world. Sofosbuvir has shown promise inhibiting viral replication through binding to NS5B dependent RNA polymerase.[15] Sustained virological response (SVR) rates of sofosbuvir have been documented to be impressive. Sofosbuvir has been widely used around the globe right after its approval from FDA in 2013 while in Pakistan, it got license from National Drug Regulatory Authority in November 2014. Efficacy of sofosbuvir was seen to be 93.9% when used in all genotypes while its tolerability even in cirrhotic cases has been documented as well.[16] Recent guidelines from "American Association for the Study of Liver Disease and the Infectious Diseases Society of America" about testing, management and treatment of HCV recommends direct-acting antiviral (DAA) treatment adopting approved regimen for all children and adolescents with HCV infection aged ≥3 years regardless of the disease severity.[17] These days, interferon is rarely used in our institution for treating paediatric patients with HCV however, DAAs have almost become a standard treatment for children with HCV but no study documenting efficacy of sofosbuvir among children having HCV infection is conducted in the South Punjab, Pakistan. The aim of this study was to note the efficacy of sofosbuvir and ribavirin among children having HCV infection. Risk factor for HCV infection among studied children were also planned to be documented.

MATERIAL AND METHODS

This was an open label experimental trail done at Department of Gastroenterology, Children Hospital and The Institute of Child Health, Multan. The study duration was from July to December 2019. Approval from Institutional Ethical Committee was taken and informed consent was sought from parents or guardians of the all the study participants.

By considering confidence level of 95%, margin of error as 5% and efficacy of sofosbuvir as 93.9%,[16] a sample size of 89 was calculated using WHO sample size formula. All cases were from 6–16 years of age, had HCV PCR as positive and did not receive any treatment for HCV prior to this study. Consecutive non probability sampling technique was used for enrolment. All cases having glomerular filtration rate less than 30 mL/min/1.73 m^2 (severe renal impairment), or having end-stage renal disease, decompensated liver disease as aspartate aminotransferase to platelet ratio index score of more than 1.5 post-liver transplant, or having any kind of active malignancy or receiving chemotherapy were not enrolled whereas children in remission who had completed chemotherapy were enrolled.

A predesigned proforma was used for recording all the relevant study data. Detailed physical examination along with laboratory investigations like complete blood count (CBC), liver function test, HCV genotyping were done in all the cases. All investigations were done free of cost from the central institutional laboratory. Possible mode of HCV transmission was noted as per questionnaire designed specifically regarding probable modes of transmission. Questions were enquired from the parents/guardians about possible mode of HCV transmission in children participating in this study.

Sofosbuvir as 400 mg once a day along with ribavirin 10–15 mg per kg per day in the form of once or twice as divided doses were given in all the cases. Sofosbuvir and Ribavirin is available as free of cost through Social welfare Department in our hospital so all patients were provided free treatment of Sofosbuvir and Ribavirin. Patients were asked to come for follow ups on 4 weekly spans. Children were asked for any kind of adverse effects related to treatment. This study was not funded by any of the pharmaceutical company.

Laboratory investigations like CBC, serum bilirubin, ALT, PT and APTT were asked during every follow up. PCR was done after 4 weeks and if positive, was repeated after 12 weeks. Treatment was given for 24 weeks.[18] PCR was asked at 12 weeks post treatment as well. HCV PCR Quantitative analysis was done using Sacycler 96, automated PCR Analyzer. Children were followed up for 36 weeks and data was analysed when a total of 89 cases completed full follow up.

Efficacy was declared as clearance of HCV RNA found by real time qualitative PCR. Rapid Virological Response (RVR) was declared as negative PCR at 4 weeks after starting the treatment. PCR positive at 4 weeks but negative after 12 weeks following the start of treatment was labelled as early virological response (EVR). Post treatment 12 weeks HCV PCR as negative was declared as sustained virological response (SVR). Side effects of treatment as well as number of cases stopping treatment due to side effects were also noted.

SPSS version 21.0 was used for data entry and analysis. Qualitative variables like gender, HCV genotypes, CLD stigmata, virological responses as well as side effects were represented in terms of frequency and percentages. Quantitative data like age, haemoglobin and ALT levels were expressed in terms of mean and standard deviation. Paired sample t test was used to compare haemoglobin and ALT at prior and post treatment intervals. Treatment responses in terms of various genotypes studied were

compared using chi square test. *p* value less than or equal to 0.05 was taken as of statistical significance.

RESULTS

Out of a total of 89 children, there were 53 (59.6%) boys and 36 (40.4%) girls, representing a boy to girl ratio of 1.47:1. Mean age was noted to be 12.42 years with standard deviation of 2.57 years. Mean aspartate aminotransferase to platelet ratio index (APRI) score was found to be 0.55 with standard deviation of 0.27.

Majority of the children, 72 (80.9%) had genotype 3 while genotype 1 was noted in 11 (12.4%) and un-typable in remaining 6 (6.7%). (Figure-1)

History of blood or blood products transfusion was seen to be the commonest mode of HCV transmission, found in 41 (46.1%) children, perinatal transmission in 20 (22.5%) and history of previous surgery in 9 (10.1%). There were 15 (16.9%) children who did not report any of the risk factors.

In terms of virological responses, 73 (83.1%) children achieved RVR (undetectable viral RNA at 4 weeks of treatment), all 89 (100%) children achieved virological remission at 12 weeks of treatment (EVR) whereas SVR was noted in 86 (96.7%) children. No statistical difference was found in between virological responses and genotypes (*p* value >0.05). (Table-1)

When mean pre-treatment (11.78±1.81 g/dL) and post-treatment (11.33±1.78 mg/dL) haemoglobin levels of children were compared, no statistical difference was found (*p* value = 0.0962). Mean pre-treatment (60.46±51.5 U/L) and post treatment ALT (26.4±11.5 U/L) showed a statistically significant difference (*p* value <0.001).

None of the children were withdrawn from the treatment because of side effects. Headache was the commonest side effect, reported by 24 (27.0%) followed by nausea in 15 (16.9%). (Table-2)

Table-1: Virological responses with respect to genotypes

Virological Responses	Genotype 1 (n=11)	Genotype 3 (n=72)	Un-typable (n=6)	*p*-value
Rapid Virological Response	9 (81.8%)	58 (80.6%)	6 (100%)	0.492
Early Virological Response	11 (100%)	72 (100%)	6 (100%)	-
Sustained Virological Response	11 (100%)	69 (95.8%)	6 (100%)	0.693

Table No.2: Frequency of side effects among children treated

Side Effect	Number of Children
Headache	24 (27.0%)
Nausea	15 (16.9%)
Abdominal pain	8 (9.0%)
Constipation	2 (2.2%)
Diarrhoea	2 (2.2%)

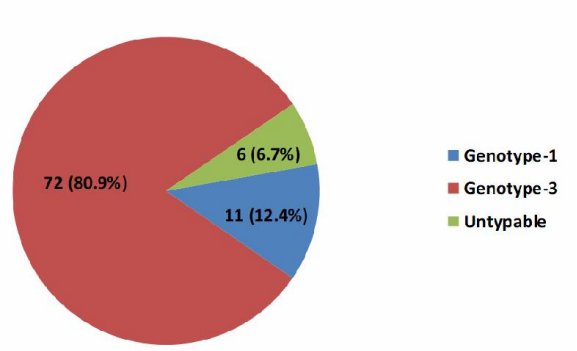

Figure-1: Distribution of HCV Genotypes amongst children

DISCUSSION

In paediatric population, Hepatitis C has emerged as an important health issue in the recent years. Newer treatment options are being experimented all around the globe but there is no certainty regarding the best approach for the treatment of chronic HCV infection amongst children. In 2018, Hepatology committee of "European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)" issued their position statement for management of chronic HCV infection among children. According to ESPGHAN guidelines, endpoint of therapy is undetectable HCV RNA in the blood by sensitivity essay 12 weeks (SVR) after the end of DAA treatment.[19]

In the current work, mean age was noted to be 12.42 years with standard deviation of 2.57 years. Another local study from Lahore found that the mean age among children treated for HCV infection was 10.24±2.80 years.[18] In the present study, we noted more boys as compared to girls, representing boys to girl's ratio of 1.47:1. Similar results were found in a meta-analysis where burden of HCV was found to be more on boys with predominant boy to girl ratio of 1.17:1.[20] Similar findings have been observed in another local study.[18]

In this study, blood products and transfusions and perinatal transmission of HCV were noted as the commonest risk factors. These results are very similar to what has been found earlier in a study conducted at Institute of Child Health, Lahore.[18] Our findings were also consistent with what has been found around the globe as well.[21] As in recent years, significant decrease in blood borne transmission of

HCV infection has been seen because of improved donor screening programs so perinatal transmission of HCV stands to be a very important etiological concern regarding transmission of HCV.[22]

Regimens involving interferon were the mainstay of HCV management but lots of dimensions have been added with the advent of DAAs. With the emergence of new data, both treatment naïve as well as treatment failure patients are reporting good success with the use of DAAs. Agents like Sofosbuvir, Ledipasvir, Daclatasavir and few others are fast replacing interferon-based regimens for the treatment of chronic HCV infection.[23] It is also a fact that data regarding above mentioned DAAs is mostly limited to adults so studies like this one will surely provide light to worldwide researchers for the efficacy and safety of the drugs selected for the current research.

In our study, only treatment naïve cases were included while majority of the children, 72 (80.9%) had genotype 3 while genotype 1 was noted in 11 (12.4%) and un-typable in remaining 6 (6.7%). HCV genotype 3 has been marked as the commonest genotype found amongst adults as well as paediatric population in Pakistan, our results were aligned to the published material.[18]

In terms of virological responses, 73 (83.1%) children achieved RVR (undetectable viral RNA at 4 weeks of treatment), all 89 (100%) children achieved virological remission at 12 weeks of treatment whereas SVR (12 weeks after completion of treatment) was noted in 86 (96.7%) children. A similar study from Lahore noted PCR negative at 12 weeks after starting the treatment in all the studied cases which is exactly the same which we found in the present research.[18] The same study also noted that SVR was impressive as 97.1% achieved it which is again very similar to the current findings where we noted it to be 96.7%.[18] A multi-centric trial assessing the effectiveness of Sofosbuvir plus ribavirin amongst children with HCV noted SVR as 98% which again confirms our findings that this regimen seems to be really effective in children with HCV infection.[21] In the past, virological response such as 86% have been reported with Pegylated interferon α-2a and ribavirin which quite below than what has been found by us.[24] Studies analysing interferon-free DAA regimens are being conducted around the world among children and we may expect more uptake of DAA that may preserve HCV infected children by lessening the burden of this infection. It is also hypothesized that DAAs may minimize cases with vertical and horizontal transmission of HCV.[23]

In our study, none of the children were withdrawn from the treatment because of side effects. Headache was the commonest side effect, reported by 24 (27.0%) followed by nausea in 15 (16.9%). Overall, the tolerability of sofosbuvir and ribavirin proved to be high. Interferon free regimens have been shown to have significantly fewer side effects which make them a popular choice.

The present work also highlights excellent efficacy of sofosbuvir and ribavirin amongst children having HCV genotype 1 which was thought to have poor prognosis in the past. The current results may entice other researchers to experience the studied regimen in their patients which could turn the tide amongst children having HCV infection.

There were few limitations of this study as well. We had a relatively small sample size in this research while not much regarding cirrhosis assessment was done in our study population. It is still not fully understood that how a combination of sofosbuvir and ribavirin affects outcome of HCV treatment among children with cirrhosis. Studies involving multiple sets of children population with larger sample size will further shed led regarding outcome and safety profile of new options considered for the treatment of HCV infection.

CONCLUSION

Regardless of the genotype, sofosbuvir and ribavirin combination therapy was noted to have excellent efficacy amongst children with HCV infection. Headache and nausea were the commonest side effects of the treatment while no major side effects were experienced by an of the treated case. History of blood and blood product transfusion was the commonest risk factor found.

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AUTHORS' CONTRIBUTION

GK: Data collection, drafting. MTA: Literature review, supervision. HS: Study design, proof reading. IH: Data analysis. MAT: Data interpretation. SJJ: literature review.

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