Original Article

Efficacy and Safety of Sofosbuvir and Ribavirin in Treatment of Chronic Hepatitis C Infection G3 of Multi-Transfused Children Aged 4 to 12 Years; A Single Center Study

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ABSTRACT

Objective: To determine the efficacy and safety of sofosbuvir (SOF) and ribavirin (RBV) in the treatment of chronic Hepatitis C virus (HCV) infection Genotype-3 of multi-transfused children aged 4 to 12 years.

Study Design: A Quasi-Experimental study.

Place and Duration of Study: This study was conducted at the Department of Pediatric Gastroenterology and Hepatology, The Children's Hospital & Institute of Child Health, Multan from July 2021 to October 2022.

Materials and Methods: Children of either gender, aged 4 to 12 years, having HCV genotype-3 and receiving multiple transfusions (> 10 transfusions) were recruited. Children below or equal to 18 kg weight received SOF 200 mg and RBV 15 mg/kg/day while children above 18 kg received SOF 400 mg and RBV 15 mg/kg/day. Efficacy was observed as sustained viral response (SVR) after 12 weeks therapy.

Results: In a total of 28 children, 18 (64.3%) were boys and 10 (35.7%) girls. The mean age was 8.38±3.51 years ranging between 4 to 12 years. Treatment was initiated and children were followed over 12 weeks. None of the children had cirrhosis. The mean hemoglobin and Fibro scan scores were 9.81±0.54 g/dl and 6.98±1.93 respectively. Transfusion requirement was not increased during treatment. On follow up, combination treatment ensured, readjusted and completed for 12-weeks. In both groups, all 28 (100%) children achieved SVR-12. During the course of the study, none of the children reported any serious treatment related side effects. None of the children experiencing treatment related side effects required any kinds of additional drugs.

Conclusion: Treatment of multi-transfused children aged between 4-12 years having HCV genotype-3 with SOF and RBV was highly effective, safe and well tolerated.

Key Words: Body aches, multiple transfusions, ribavirin, sofosbuvir, transfusion.

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INTRODUCTION

Hepatitis C virus (HCV) RNA virus affects about 1.8 million population worldwide.[1] HCV is estimated affect between 2 to 5 million children below 15 years of age.[1,2] Moreover, it is estimated to affect around 68% in children receiving multiple transfusions suffering with conditions like thalassemia, or hemophilia.[3]

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Thalassemia Major is the most common genetic hemoglobinopathy in Pakistan while carrier rate is about 6-7% among various ethnic groups.[4] Blood transfusion is the traditional treatment and usually required after 2-5 weeks interval in these patients. Iron overload, transfusion transmitted infections like hepatitis B virus (HBV), HCV, and human immunodeficiency virus (HIV) are common complications.

Clinical spectrum of chronic HCV in children has variety and presents in different forms, ranging asymptomatic to decompensated liver disease (DCLD), requiring liver transplant.[5] Primary source of HCV infection is by perinatal transmission from infected mother.[5] Despite best available screening modalities in the recent decades, risk of HCV infection is still quite high and creates anticipatory dilemmas and fear of transfusion transmitted HCV infection. Treatment of HCV infection with Pegylated interferon and Ribavirin (RBV) poses challenges like poor compliance, fear of parental administration, and long duration of treatment.

The "European Medicines Agency (EMA)" approved the 1st "direct acting antivirals (DAAs)" regimens in 2017 for adolescents aged 12-17 years with chronic HCV. These drugs included a "fixed-dose combination (FDC)" of sofosbuvir/ledipasvir and sofosbuvir (SOF) with RBV.[6,7]

Limited studies are available regarding outcomes of chronic HCV in children below 12 years age. This study was aimed to determine the efficacy and safety of SOF and RBV in the treatment of chronic HCV infection Genotype-3 of multi-transfused children aged 4 to 12 years.

MATERIALS AND METHODS

This quasi-experimental study was carried out at the department of Pediatric Gastroenterology and Hepatology, "The Children's Hospital & Institute of Child Health", Multan, Pakistan from July 2021 to October 2022. Approval from "Institutional Ethical Committee" was obtained. We acquired informed as well as written consents from parents/caregivers. Children of either gender, aged between 4 to 12 years, having HCV infection genotype-3 and receiving multiple transfusions (> 10 transfusions) were considered. Children who had history of previous HCV treatment were also not included. Patients were excluded from study with DCLD, severe cardiopulmonary disease, malabsorption / chronic diarrhea (drug absorption problem), co-morbid HBV, combs positive receiving steroid and not willing to enroll. Twenty-eight children fulfilled the inclusion/exclusion criteria and were selected for study after PCR estimation of HCV RNA virus (quantitative and qualitative). All 28 children had HCV RNA level above 1000 IU/ml according to criteria and had genotype-3.

At the time of enrollment, demographic and clinical information was noted in all children. All enrolled patients received SOF and RBV for 12-week according to age and weight. SOF was advised to children between 4 to 6 years weighing below 18 kg as 200 mg/day, and 400 mg/day to children aged between 7 to 12 years weighing above 18 kg. RBV was advised as 15 mg/kg/day in 2 divided doses to all children (maximum of 600 mg per day up to 50 kg). Patients visited at day 1, week 1, 4, 8 and 12 and evaluated at each follow up with complete blood count, compliance, palatability, complaints and physical examination. PCR HCV was advised at day 1 and week-12. HCV RNA was quantified by Global Molecular system (lower limit of quantification of 15 IU/ml). Figure-1 is showing study algorithm. Efficacy was defined as 100% SVR sustained viral replication at 12-weeks (SVR 12). Safety was defined as no significant side effects that interfered with the treatment.

The data analysis was conducted utilizing "Statistical Package for Social Sciences (SPSS)", version 26.0. For numeric data, the mean and standard deviation (SD) were calculated. Categorical data were presented in terms of numbers and percentages. To compare the data, either a Chi-square test or Fisher Exact test was employed, considering a p-value < 0.05 as significant.

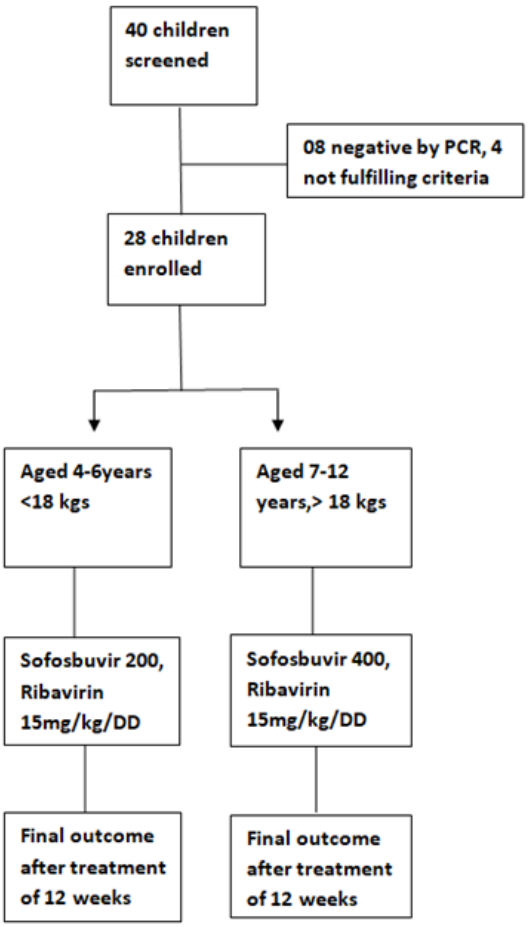

Figure No. 1: Study Algorithm

RESULTS

In a total of 28 children, 18 (64.3%) were boys and 10 (35.7%) girls.

Table No. 1: Efficacy with respect to age groups (N=28)

Interval	Age group 4to 6 years n=10	Age group 7to 12 years N=18
1st Weeks	SOF 200 mg + RBV 15mg/kg/day	SOF 400 mg +RBV 15mg/kg/day
4th Week,	Compliance and laboratory parameters all good	Compliance and laboratory parameters all good
8th Week	Compliance and laboratory parameters all good	Compliance and laboratory parameters all good

SVR-12	Achieved in all 10 (100%) children	Achieved in all 18 (100%) children

The mean age was 8.38±3.51 years ranging between 4 to 12 years. Treatment was initiated and children were followed over 12 weeks. None of the children had cirrhosis. The mean hemoglobin and Fibro scan scores were 9.81±0.54 g/dl and 6.98±1.93 respectively. Transfusion requirement was not increased during treatment. On follow up, combination treatment ensured, readjusted and completed for 12-weeks. In both groups, all 28 (100%) children achieved SVR-12 as shown in Table-1.

During the course of the study, no child reported any serious treatment related side effects. None of the children experiencing treatment related side effects required any kinds of additional drugs. Table-2 is showing details of treatment related side effects.

Table No. 2: Safety of Sofosbuvir and Ribavirin (N=28)

Side effects/ changes	Age 4- 6 years (n=10)	Age 7-12 years (n=18)	P-value
Flue like symptoms	1 (10%)	-	0.3571
Vomiting	1 (10%)	-	0.1716
Headache	-	1 (5.6%)	0.4478
Body aches	1 (10%)	1 (5.6%)	1
Fatigue	1 (10%)	1 (5.6%)	1

DISCUSSION

SOF with ledipasvir/Valpatasvir is recommended for HCV infection for adults and adolescent in certain countries.[10,11] "American Association for the Study of Liver Diseases (AASLD)" clearly defined the combination treatment with SOF and RBV in Genotype-3 above 12 years old for 24 weeks.[12] Limited studies on young children aged below 12 years with SOF and RBV are reported. In the present study, we noted 100% SVR after 12-week treatment which is aligned with what has been described by other researches from other parts of the world as 99%,[11] and 97.14%.[8] As 100% SVR was observed in children with Genotype-3, other researchers have shown that to be 94% when noted among adolescent and adults[13] while in another study it was 67% with SOF and ribavirin.[14] All these studies show that the combination of SOF and RBV is highly efficacious among children having HCV genotype-3 and be recommended to children aged between 4-12 years as was exhibited in this study. A study done by Rosenthal et al analyzing SOF and RBV in the pediatric age groups between 3-12 years of age with HCV Genotype 2 or 3 infection reported that 98% children achieved SVR and the treatment regimens were well tolerated.[15] The findings of Rosenthal et al seem consistent with the revelations of the present study.

Most common side effect found in study were flue like symptom, body ache, and headache that were managed without medicine, and these findings are pretty consistent with what has been described in the literature previously.[13-15] Transfusion needs remained the same during the study period. RBV induced hemolysis was not seen in any of the cases. Early therapy may prevent infected children from developing cirrhosis. Goal 2030 of eradicating HCV infection, a major public health problem described by WHO, can be achieved. In a developing country like Pakistan, there is a need to develop more government centers for the early diagnosis and timely treatment of HCV. Best donor screening of blood products after treatment of HCV in multi-transfused children is advised.

The present study is among the first of its kind from Pakistan adding important insights about the effectiveness, safety and tolerability of SOF and RBV among children aged 4-12 years having HCV genotype-3 infection. Given that our study was conducted at a single center and involved a small sample size, it is important to note that our findings should be validated through additional large-scale prospective trials.

CONCLUSION

Treatment of multi-transfused children aged between 4-12 years having HCV genotype-3 with SOF and RBV was highly effective, safe and well tolerated.

Author's Contribution:

Concept & Design of Study:	Muhammad Aslam Sheikh
Drafting:	Ghazi Khan Khosa, Sara Rubab
Data Analysis:	Zunaira Hameed
Revisiting Critically:	Muhammad Aslam Sheikh, Ghazi Khan Khosa
Final Approval of version:	Muhammad Aslam Sheikh

Conflict of Interest: The study has no conflict of interest to declare by any author.

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