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Research Article

**INSTEAD OF INTERFERON THERAPY, AN UN-CONTROLLED TRIAL AND OPEN LABEL STUDY OF SOFOSBUVIR AND RIBAVIRIN COMBINATION THERAPY ON CHILDREN WITH NATURAL HEPATITIS C DISEASE**<sup>1</sup>Dr. Habib ur Rehman, <sup>2</sup>Dr. Usman Asghar, <sup>3</sup>Dr. Farjad Naveed Ahmed<sup>1</sup>Tianjin Medical University, China<sup>2</sup>Govt. Eye Cum General Hospital, Gojra, Toba Tek Singh<sup>3</sup>Medical Officer, Basic Health Unit Rurki Kalan, Sialkot**Abstract:**

**Objective:** To define the efficiency and effects of sofosbuvir and ribavirin combination therapy in children with natural HCV illness.

**Study design:** Open label and uncontrolled trial.

**Place and Duration of study:** Present research paper was completed in the period of one year from April 2017 to March 2018 at the venue of Institute of Child Health, Lahore and as well as hepatology department of Children hospital, Lahore.

**Material and Methods:** In this study selected the children on the age criteria of 5 years to 17 years who infected by hepatitis C virus and did not carry out any treatment. Following consecutive non-probability sampling technique used for these selection criteria. Carried out clinical tests such like serum ALT and PCR, PT, bilirubin and blood CP and noted down the symptoms and signs. For the period of six month medicated the children with ribavirin 10mg to 15mg within 24 hours and sofosbuvir 400mg daily. Subsequently, as the treatment started, observed the patients on regular basis of 4 weeks. After first four weeks carried out PCR and patients who found with positive results, repeated it after the duration of 3 months. Again when treatment was completed and after the period of 3 months of completion of treatment, PCR was carried out. IBM SPSS Statistic V.25 used for analyses of data.

**Results:** Selection was made gender wise as girls were 26 boys were 44 a total number of 70. As per percentage 37.14 % and 62.86 % respectively. HCV genotype-3 was the most common and on the top of the list, as it was observed amongst 77.15 % (54) patients, on the second number it was genotype-1 as it was found in 17.14 % (12) patients, whereas, patients who haven't fall in any type were only 5.71% (4). 14.28 % (10) patients produced early virological response and 85.71% (60) patients responded to Rapid virological. At the end of treatment, all patients were PCR negative and well tolerated treatment. 16 (22.86%) patients complained headache, however they recovered quickly.

**Keywords:** Ribavirin, Sofosbuvir, untreated children, Hepatitis C Virus (HCV).

**Corresponding author:**

**Dr. Habib ur Rehman,**  
Tianjin Medical University,  
China

QR code



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**INTRODUCTION:**

The main purpose of this research study was to govern about the effectiveness of sofosbuvir and ribavirin combination therapy in children from 5 years to 17 years of age, as available research data is very less regarding effectiveness of this course of therapy in children. One of the most common deadly viruses in the whole world is hepatitis C virus and it primarily damages the liver. It results in chronic liver inflammation further leading to cirrhosis or hepatocellular carcinoma. In children above 3 years of age medicine used against hepatitis C is Pegylated interferon  $\alpha$ -2a and  $\alpha$ -2b with ribavirin. This treatment gave positive results in almost every genotypes, as healing percentage of it is almost sixty percent. Inverse effects observed due to interferon therapy were depression, myalgias, thrombocytopenia, and flue like symptoms, fever and headache. Symptoms of hypothyroidism and anemia are associated to combined treatment of interferon and ribavirin but these can diminished by using proper reductive medication. By matching the various results of the patients such as genotypes, cirrhosis, previous treatment response and baseline viral load it found that response to interferon-based regimens differs. Various drawbacks of ribavirin and interferon therapy are side effects mentioned above, weekly injections and less effectiveness against genotype 1 and 4. Because less research data is available regarding effectiveness of this regimen in children so this study was aimed to determine the effective use of ribavirin and sofosbuvir combination therapy in children from 5 to 17 years old.

**METHODOLGY:**

This research study was completed in the period of twelve months from April 2017 to March 2018 and the venue was Institute of Child Health and department of hepatology, Children hospital, Lahore with the prior permission of ethical committee of said hospital. Base of the study was open label and un-controlled trial so with the written permission by guardians or parents of children, all data was collected. Selection of the children for current study was made on the base of age group starting form 5 years to 17 years who were infected by hepatitis C virus as checked and confirmed through PCR and didn't carried out any medical treatment of it. All those were not included in this study who already got clinical treatment or under going from carcinoma, End Stage Renal Disease (ESRD), liver transplant surgery, decompensated liver disease or procuring chemotherapy.

After analyses Chronic Liver Disease (CLD) symptoms were found such as palmar erythema,

hepatosplenomegaly, digital clubbing, ascites and spider angiomas. Carried out clinical tests such like serum ALT, PCR, PT, bilirubin and blood Complete Picture. For the period of six month medicated the patients selected for the study with ribavirin 10mg to 15mg within 24 hours and sofosbuvir 400mg daily. After the start of proper treatment, observed the patients on regular monthly intervals. Every time inquired the patients about any side effects and took certain clinical test such as bilirubin, ALT, blood CP and PT for observations. After the period of first four weeks conducted the PCR and children who were found with positive effects, repeated the process after the duration of four weeks. Again carried out PCR when treatment was finished and after the period of 12 weeks of completion of treatment.

According to HCV RNA, the efficiency of therapy was defined by using real time qualitative PCR against genotype. Negative result of PCR, taken on the fourth week of treatment was nominated as Rapid Virological Response. Positive result of PCR, taken on the fourth week of treatment and later on it turned into negative on 12<sup>th</sup> week was nominated as Early Virological Response. At the 12<sup>th</sup> week after completion of 24<sup>th</sup> week of treatment process negative PCR results was called Sustained Virological Response. That medical treatment was called safe treatment in which protection from the appearance of any negative reactions of medicines

that will result as suspension of clinical treatment. Analyses of data were carried out by using SPSS Statistic V.25. Displayed the data in the shape of frequencies and percentages. Statistics were derived from different variables such as side effects of drugs, virological responses, genotype of hepatitis C virus, gender of patients, stigmata of CLV etc. general quantities like bilirubin, ALT, prothrombin time, platelet count, hemoglobin and TLC were tested through normality testing by using Shapiro-Wilk test. Normally distributed presentation method was used to display mean  $\pm$  standard deviations. Whereas to present interquartile range or median range non parametric variables were used. Before and after medical treatment serum ALT levels were matched by means of Wilcoxon Signed Rank Test. Paired sample T-Test was selected for the comparison of Hb levels of patients before and after medical treatment. Significant considered P value was less than 0.05 (<0.05).

**RESULTS:**

70 patients were chosen for this study as female were 26 and male were 44 and their age was between 8 years to 14 years. Percentage calculated was as 37.14

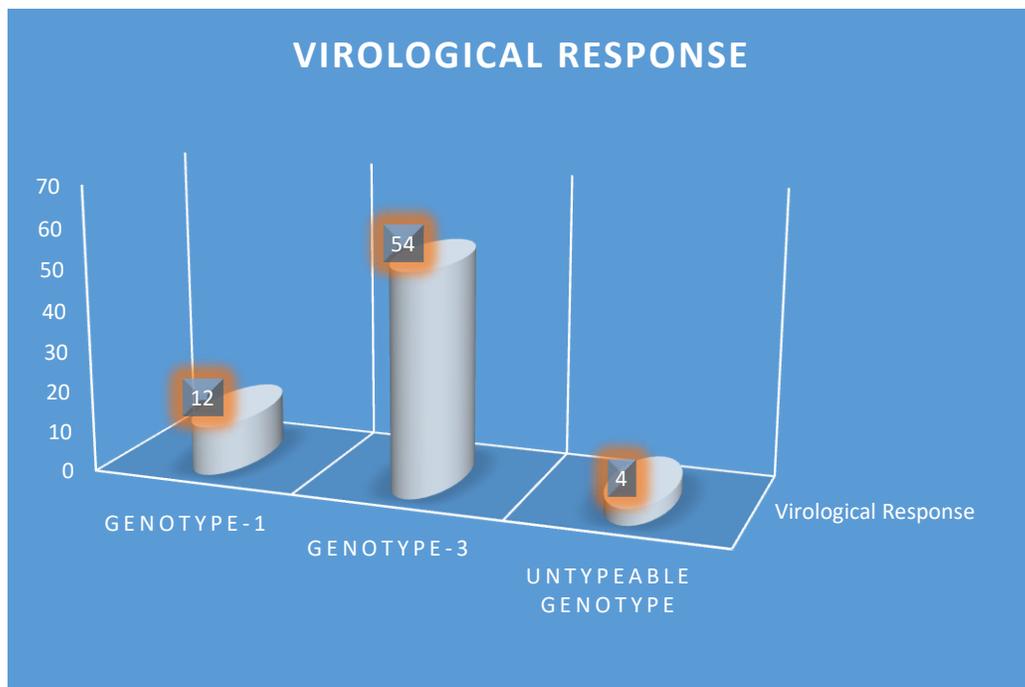
% of female and 62.86 % male. The most common was HCV genotype-3 and on the top of the list, as it was observed amongst 77.15 % (54) subjects, on the second number it was genotype-1 as it was found in 17.14 % (12) subjects, on the other hand, patients who haven't fall in any type were only 5.71% (4). 14.28% (10) patients produced early virological response and 85.71% (60) subjects responded to Rapid virological. At the end of treatment all patients were PCR negative and well tolerated treatment. Headache was complained by 16 (22.86%) patients, however they recovered quickly. Previously diagnosed for von- willibrand and hodgkins disease were only 2.85% (2). Acute lymphoblastic leukemia

found in 5.71% (2) children and non-hodgkins lymphoma also present in 5.71% (2) patients. Rhabdomyosarcoma and Wilson's disease was found in 2.85% patients.

Early virological response was observed in 10 (14.29%) patients and after 3 months of treatment were detected as PCR negative, and just after one month of treatment 60 (85.71%) patients showed rapid virological response as checked results of PCR. Three months after the completion of treatment, sustained virological response was achieved by 68 (97.14%) patients. Tabular and graphical shape of results are shown below.

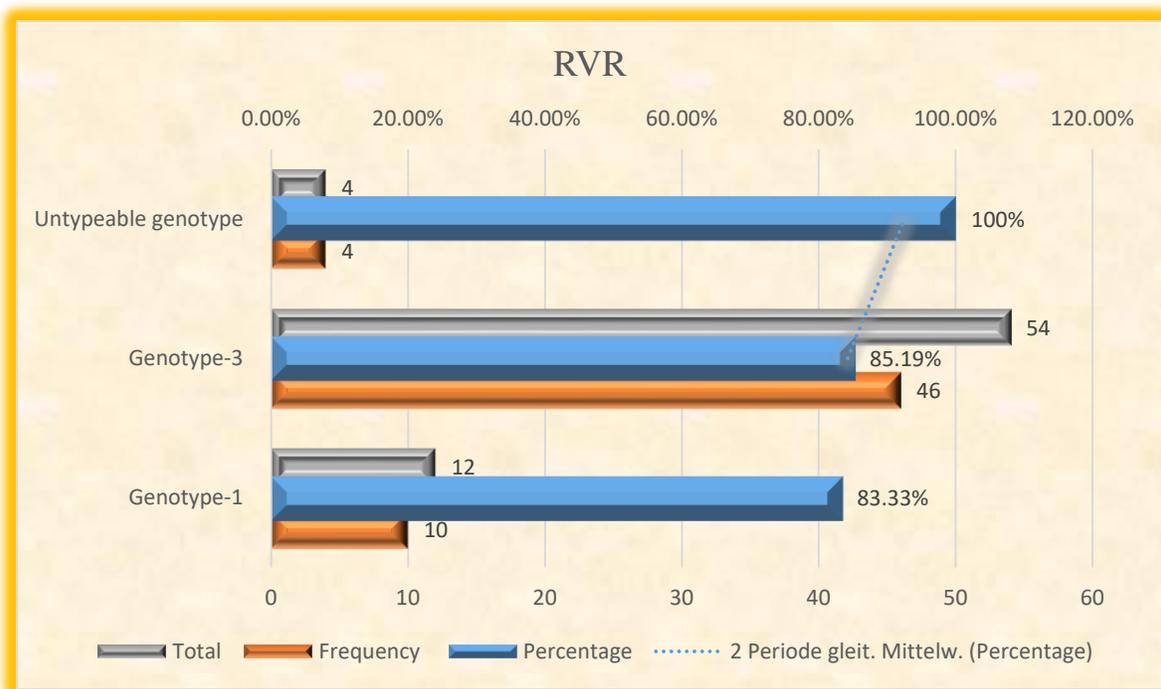
**Table No1: Virological response according to HCV genotype**

<i>Genotype</i>	<b>Frequency N = 70 (%)</b>
<i>Frequency of genotype-1</i>	12 (17.14%)
<i>Frequency of genotype-3</i>	54 (77.15%)
<i>Frequency of untypeable genotype</i>	04 (05.71%)

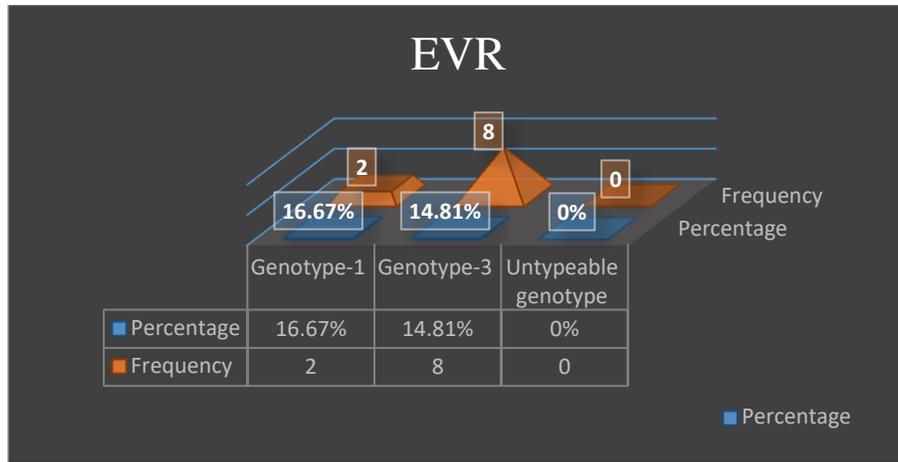


**Table No2: Rapid Virological Response (RVR) according to HCV genotype**

	Percentage	Frequency	Total
<b>Genotype-1</b>	83.33%	10	12
<b>Genotype-3</b>	85.19%	46	54
<b>Untypeable genotype</b>	100%	04	04

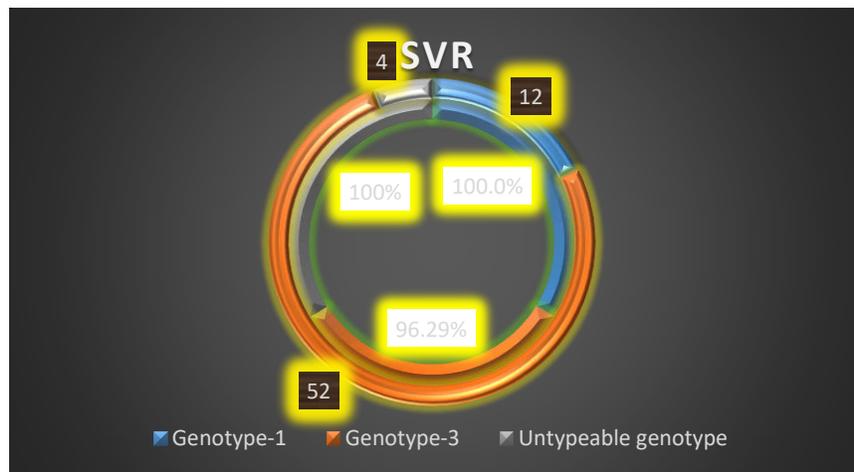
**Table No3: Early Virological Response (EVR) according to HCV genotype**

	Percentage	Frequency	Total
<b>Genotype-1</b>	16.67%	02	12
<b>Genotype-3</b>	14.81%	08	54
<b>Untypeable genotype</b>	0%	00	04



**Table No3: Sustained Virological Response (SVR) according to HCV genotype**

	Percentage	Frequency	Total
<b>Genotype-1</b>	100%	12	12
<b>Genotype-3</b>	96.29%	52	54
<b>Untypeable genotype</b>	100%	04	04



**DISCUSSION:**

In the present research paper included 70 children who were infected by HCV. The ratio of gender was 2:1 as male to female. Inquired common mode of transmission of hepatitis C, results were tattooing, past surgical history, blood transfusion and perinatal transmission. Comparing with another study by Elise Roy *et.al* found similarity in the results. Pre-transfusion screening process is not efficient in

developing countries like Pakistan. Injections and blood transfusion is still most frequent cause of HCV. Therapy for clinical treatment of HCV being used was interferon based but now a day it is being replaced by such antiviral medicine which are non-injectable due to the negative effects of interferon therapy. Medicines used for HCV currently include paritapavir, ladipasvir, daclatasvir, sofosbuvir, ombitasvir and dasabuvir. Due to less side effects and

excessive effectiveness as matched to interferon therapy these medicines are quickly replacing interferon treatment. Several combined dosage methods are under trial for the use of these medicines. Most common combinations which are under trial are of ledipasvir and sofosbuvir, ribavirin and sofosbuvir. In a previous research study held by Kris V. Kowdley, et al. in previous treatment failure, the effectiveness of non-injectable antivirals was found to be almost 96% in hepatitis C infected patients.

The main purpose of this study was to calculate the efficiency and find safe usage method of such a medicine combo which is not used as injection like ribavirin and sofosbuvir in children as less data is available on this subject in this paediatric age group. New treatment has described a vital role in treatment of genotype 1, amongst all other genotype which was considered as difficult to treat. However, lot more research work is yet needed to be done to find out the efficacy of these medicines for children and how to reduce occurrence rate of HCV in children by use of these medications.

#### CONCLUSION:

Selection was made gender wise as girls were 26 boys were 44 a total number of 70 on the age criteria of 5 years to 17 years. There were very minor side effects associated with the Sofosbuvir and Ribavirin combined medication method. That is the reason this combo therapy mode was found highly useful and effective in children.

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