

# SIDE EFFECT PROFILE IN CASES TAKING ORAL RIBAVIRIN FOR CRIMEAN CONGO HEMORRHAGIC FEVER VIRUS EXPOSURE PROPHYLAXIS

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## ABSTRACT

**Background:** Crimean Congo hemorrhagic fever virus is a fatal infection that has a very high case fatality rate. It is highly infectious and there is no recommended treatment for it. Oral ribavirin is the most commonly used drug and has variety of side effect profile. **Objective:** To determine the frequency of side effects in cases taking oral ribavirin for post Crimean Congo virus exposure prophylaxis. **Methodology:** This cross sectional study was conducted at Medical & Emergency Department, Sheikh Zayed Hospital, Rahim Yar Khan from 1<sup>st</sup> January to 31<sup>st</sup> December 2016 on suspected cases of Crimean Congo Hemorrhagic Fever (CCHF) virus exposure. The cases were suspected on this basis of signs and symptoms of hemorrhagic fever and negative Dengue serology. Oral Ribavirin was given in 2 grams (gm) loading dose, 4 gm/ day for 4 days and then 2 gm/ day for next 6 days in divided doses. The cases were then followed for development of nausea/ vomiting, anemia, jaundice, generalized aches and pains and insomnia. The results were collected and recorded and analyzed by using SPSS version 22. **Results:** In this study, there were total 32 cases that were started on ribavirin prophylaxis. Two cases quit prophylaxis early. Out of total 30 cases left that completed the prophylaxis, 17 (56.67%) were males and 13 (43.33%) females. The mean age and weight were 32.86± 7.05 years and 45.66± 7.74 kg respectively. Side effect profiles were seen in 24 (80%) cases. The most common side effect was nausea/vomiting seen in 18 (60%) cases, generalized aches and pains in 17 (56.67%), anemia in 12 (40%) cases, jaundice in 11 (36.67%) and insomnia in 4 (13.33%) cases. There was no significant difference of side effects in terms of age, gender, and weight group with p values of 0.63, 0.49, and 0.25 respectively. **Conclusion:** Oral ribavirin is commonly used for CCHF virus exposure prophylaxis and has a very high side effect profile among which GI side effect and generalized aches and pains are the most common.

**Key words:** Crimean Congo, Hemorrhagic Fever, Ribavirin, Side effects.

## INTRODUCTION

Crimean Congo Hemorrhagic Fever (CCHF) is one of the fatal hemorrhagic fevers caused by a virus named as crimean hemorrhagic fever virus.<sup>1</sup> This infection is found almost in every country especially Asia, Middle East, Russia, and Europe. and is thought to spread by tick bite.<sup>2-3</sup> Early summer and spring season are the most reported weathers. The mortality rate of infection by this virus has been from 10 to 50% of the cases.<sup>4</sup>

Clinical symptoms to present include fever, generalized aches and pains, flue like symptoms and are labeled as pre hemorrhagic phase. It is then followed by oozing of the blood from various mucosal and other sites and bruising and is called as hemorrhagic phase.<sup>5-6</sup>

Early diagnosis is crucial step not only to manage such cases, but also to decrease its spread to other cases, which can result in fatal epidemics. It is diagnosed by various ways like antigen and antibody detection test. Both IgG and IgM are required for confirmatory test. Nested and quantitative real-time reverse-transcription (RT)-

PCR are also used.<sup>7-10</sup>

Management mainly relies upon the supportive therapies. This comprises intravenous fluids, painkillers, antipyretics and antibiotics. Blood transfusion can also be done in cases that bleed.<sup>11</sup> Ribavirin is the only drug, which has been sporadically used for this purpose and has shown different success rates ranging from good to no efficacy. However, data has shown that it's better to be used in the early phase. This drug is also used for prophylaxis and different protocols have been used.<sup>12,13</sup>

The side effects like aches and pains, anemia, jaundice, hemolysis, insomnia, irritability, nausea, vomiting and pose another concern. The cases with high dose methylprednisolone and Interferon have also been tried but data is variable. Intravenous immunoglobulin extracted from the survivors of this infection and vaccines to avoid this disease are the future perspectives, which are under research.<sup>14-16</sup> This study conducted to determine the frequency of side effects in cases taking oral ribavirin for post Crimean cango hemorrhagic virus exposure.

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## METHODOLOGY

This cross sectional study was conducted at Medical & Emergency Department, Sheikh Zayed Hospital, Rahim Yar Khan from 1<sup>st</sup> January to 31<sup>st</sup> December 2016. This study was conducted on suspected cases of CCHF virus exposure as per operational definition. The sociodemographic data like age, weight and gender was noted. The cases were assessed for their normal sleep pattern, GI symptoms, scleral examination, Hemoglobin (Hb), serum total bilirubin, platelet count and hepatitis B or C status. Oral Ribavirin was given in 2 grams (gm) loading dose, 4 gm/ day for 4 days and then 2 gm/ day for next 6 days in divided doses. The cases were then followed for development of nausea/ vomiting (two or more episodes), anemia (a decrease in 2gm/dl of Hb from the baseline), jaundice (clinically yellowish discoloration of the eye and serum total bilirubin of more than 2 mg/dl), generalized aches and pains (pain of score 5 or more on visual analogue scale), and insomnia (unplanned delay in sleep for more than 3 hours than normal routine). The results were collected and recorded. Ethical approval was sought from Institutional Review Board.

### Inclusion criteria:

1. All adult cases aged 15 to 50 years.
2. Both genders.
3. Cases with exposure to CCHF virus suspected cases, that was suspected in them on the basis of contact with animals, fever, bleeding from different sites, decreased platelet count and negative serology for Dengue hemorrhagic fever.

### Exclusion criteria:

1. The cases that had hepatitis B or C
2. The cases with platelet count less than 100000 and Hb less than 10
3. The cases with documented history of liver or renal failure

The data was entered and analyzed on SPSS version 22. Mean and standard deviation were calculated for age, weight, Hb. Frequency and percentages were calculated for gender and side effect developed and type of side effect developed. Data was stratified with outcome variable i.e. side effect. Post stratification chi square test was applied to see for significance and p value of  $\leq 0.05$  was taken as significant.

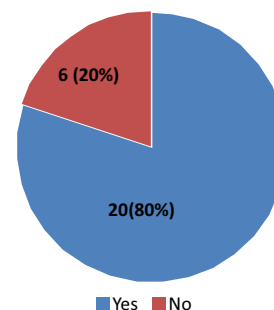
## RESULTS

In this study there were total 32 cases that were exposed and asked to take oral Ribavirin prophylaxis. One case was found positive with hepatitis C and one case quit prophylaxis early. There were total 30 cases left who completed the prophylaxis. Out of the 30 cases, 17 (56.67%) were males and 13 (43.33%) females.

**Table I: Study variables (n=30)**

Variable	Mean	Range
Age	32.86± 7.05	23-41
Weigh	45.66± 7.74	31-71
Hemoglobin	12.61± 1.35	11.20-14.30

**Figure I: Side effect in ribavirin prophylaxis (n=30)**



The mean age was 32.86± 7.05 years while mean weight was 45.66± 7.74 kg as in Table I. Side effect profiles were seen in 24 (80%) cases. The most common side effect was nausea/vomiting seen in 18 (60%) cases, generalized aches and pains in 17 (56.67%), anemia in 12 (40%), jaundice in 11 (36.67%) and insomnia in 4 (13.33%) cases as in Table II.

**Table II: Side effect profile among study subjects. (n=30)**

Side effect	Yes Number (%)	No Number (%)
Nausea/ vomiting	18 (60%)	12 (40%)
Generalized aches	17 (56.67%)	13 (43.33%)
Anemia	12 (40%)	18 (60%)
Jaundice	11 (36.67%)	19 (63.33%)
Insomnia	4 (13.33%)	26 (86.67%)

**Table III: Side effects with respect to variables (n= 30)**

Variables		Yes	No	P value
Gender	Male	10	7	0.63
	Female	8	5	
Age groups	<35 years	11	7	0.49
	>35 years	7	5	
Weight groups	<35 kg	7	4	0.25
	>35 kg	11	8	

There were no significant differences of side effects in terms of age, gender, and weight group with p values of 0.63, 0.49, and 0.25 respectively as in Table III.

## DISCUSSION

CCHF is one of the concerning hemorrhagic fever due to its high number of mortality. Oral Ribavirin is the drug, which is not only used for its treatment, but also for the prophylaxis of the contacts with the diseased personals. However, side effect profile is very common with ribavirin and sometimes leads to quit of the prophylaxis. Not many studies were done to look for the side effect profiles in CCHF prophylaxis. In this study side effects were seen in 24 (80%) of the cases. GI symptoms like nausea, vomiting, abdominal pain and symptoms of generalized aches and pains were the most commonly seen in 18 (60%) and 17 (56.67%) of cases respectively in this study. Similar was observed many studies that also had highest number of these un-wanted effects and found in about two third of the cases. This higher number can be due to both the drug effects as well as due to infection of the cases with CCHF virus, which also presents early with flu like symptoms.<sup>17-18</sup>

Anemia was seen in 12 (40%) of the cases. In one study anemia was seen in 33% of cases while in another study it was observed in about 75% of cases.<sup>19-20</sup> Why this difference was so high in the later study as compared to our and one done by Huggins et al can be explained, because in that study injectable ribavirin was used as compared to oral therapy in our study. Raised bilirubin (jaundice) was seen in 11 (36.67%) of the cases in this study. Similar pattern was seen by other studies as well that had slightly lower number and accounting for less than 30% of cases. This can be explained by the different dosage schedule

criteria, which were higher in our study and it is already been described that the toxicity of bilirubin is directly associated with duration and dose of it.

Furthermore there was no significant association of its toxicity with any of the gender, age and weight groups. However, slightly more side effects were seen in cases with lower weight group where it was seen in 7 out of 11 cases with weight less than 35 kg as compared to 11 out of 19 with more weight with p value of 0.25. This was not significant but thought to be due to higher dosage as Ribavirin prescribed in this study was fixed dose for every cases instead of mg/ kg, which might have resulted in lesser side effects as was seen in other studies.<sup>21-22</sup> There was almost equal distribution among the rest of variables in terms of side effects and there was no significant difference which was also supported by the data of previous studies.<sup>23-24</sup>

There were few strengths of this study as this was probably one of the scarce studies that addressed this range of side effect profiles of oral Ribavirin prophylaxis in CCHF. However, there were few limitations too. First of all, this study was done to see the immediate side effects and did not follow for longer period and secondly this study also did not conclude the outcome of these cases whether they developed the disease or not.

## CONCLUSION

Oral ribavirin is commonly used for post CCHF virus exposure prophylaxis and has a very high side effect profile among which gastrointestinal symptoms and generalized aches and pains are the most common.

### Conflict of interest:

The authors have declared no conflict of interest.

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