Medical Journal of the
Islamic Republic of Iran

Volume 17
Number 3
Fall 1382
November 2003

THE EFFICACY OF ORAL RIBAVIRIN IN THE TREATMENT OF 81 PROVED CASES OF CRIMEAN-CONGO HEMORRHAGIC FEVER (CCHF) IN IRAN (1999-2001)

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ABSTRACT

Crimean-Congo Hemorrhagic Fever is a fatal viral disease that occurs in some parts of Africa, Asia, Eastern Europe and the Middle-East. Primarily it is a zoonosis but can be seen sporadically in humans. Recently outbreaks have been reported from Pakistan, Afghanistan, Saudi Arabia, United Arab Emirates and Iran. In this retrospective study, we evaluated the efficacy of oral Ribavirin in the treatment of CCHF cases, by comparing the outcome in two groups of treated and non-treated confirmed CCHF cases. 81 confirmed CCHF cases (by serology or viral culture) were evaluated for the incidence of outcome (death or recovery) in the form of an analytic case-control study. 61 out of 69 treated cases and 5 out of 12 non-treated cases survived. Oral Ribavirin with an efficacy of 91% can be an effective medical therapy for management of Crimean Congo Hemorrhagic Fever.
MJIRI, Vol. 17, No. 3, 193-195, 2003.

Keywords: Congo Hemorrhagic Fever, Oral Ribavirin, Efficacy.

INTRODUCTION

Crimean-Congo Hemorrhagic Fever (CCHF) is a fatal viral infection found in parts of Africa, Asia, Eastern Europe and the Middle East. Although it is a zoonosis in nature, certain sporadic cases also occur in human. In recent years several outbreaks from Afghanistan, Pakistan, Saudi Arabia, United Arab Emirates and Iran have been reported. [1]

Up to the last 3 decades there was no appropriate therapy available for patients with CCHF and the only suggested treatment was use of the serum of patients in convalescent phase for treatment of other patients.[3] Ribavirin is a guanosine nucleoside analogue that is active against many RNA and DNA viruses and has been successfully used in the treatment of other viral hemorrhagic fevers, such as Lassa fever.[4] So, due to the similarity of CCHF virus and other viral hemorrhagic viruses (Lassa, Ebola, ...), it may be effective in the management of CCHF. Up to 1994, no reports of treatment of patients with CCHF with ribavirin had been reported, although data have been presented from South Africa suggesting efficacy.[13] However in 1994 a successful management of 3 nosocomial cases of CCHF from Pakistan as well as use of oral ribavirin vitalized this promise in mind that it may be possible to use oral ribavirin for treatment of CCHF.[4]

Since that time this drug has been used for treatment of CCHF in different parts of the world,[5,6,7] but up to now no randomized controlled trial concerning the efficacy of ribavirin in treatment of these patients has been carried out.[8] Based upon this information and 81 confirmed cases of the disease reported by the Ministry of Heath (1999-2001), we attempted to evaluate the effi-

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cacy of ribavirin in the treatment of these patients who by any reason either had received or not received this drug, voluntarily or involuntarily, in a retrospective study.

MATERIAL AND METHODS

This study was conducted in the form of a retrospective case - control study from June 1999 to September 2001 with participation of 81 patients whose disease had been reported to the Ministry of Health and their diagnosis had been confirmed* by hemorrhagic fever reference laboratories of South Africa, Senegal, and Pasteur Institute of Iran using ELISA antibody test, with focus on drug consumption and outcome (death or cure).

It is worth mentioning that in the year 1999 when for the first time some cases of disease had been diagnosed, ribavirin was not accessible in Iran and was not used for therapy. And hence the primary cases (n=12) were not placed on ribavirin.

According to a series of limited reports on the effectiveness of ribavirin in the treatment of CCHF, considering recommendations of the Ministry of Health, since the year 2000 all of the patients were placed on this drug with the recommended dosage.** In 69 proven cases and for determining the efficacy of this drug, two patient groups were compared to each other and the final results obtained.***

Data statistical analysis was carried out using statistical package of STATA and Epi-info.

RESULTS

Of 69 established cases with CCHF being treated with oral ribavirin, 61 patients recovered and 8 patients passed away, whereas among 12 established cases of CCHF who had not received ribavirin, only 5 patients recovered and 7 patients died.

Crude odds ratio of the drug in cure of patients was estimated equal to 0.09, with confidence interval of 95% (0.02-0.44), in that by a statistical test power of greater than 90%, the drug efficacy in cure of patients has been demonstrated to be equal to 91% (1-0.09) (Table I).

DISCUSSION

Ribavirin is an antiviral drug that acts by a relatively unknown mechanism to change the cellular nucleotide chain and inhibits viral mRNA synthesis.[12] It is demonstrated that ribavirin in low concentration (5μg/kg/mL), has antiviral effect for CCHF.[4] Intravenous and oral compound of ribavirin are recommended for CCHF cases, and ribavirin for prophylaxis in nosocomially exposed cases, but its efficacy in this state has not been established.[4]

Up to 3 decades ago, there was no established effective treatment for CCHF. Lazarev in a study of 97 patients reported that 80-200 mL of convalescent serum drawn from those who survived CCHF was effective for treatment of new patients, via intramuscular injection, and demonstrated that the serum is only effective when used during the initial 3 days of infection and led to a decrease in fever as well as severity of hemorrhagic manifestations or even prevention of the hemorrhagic phase. Later, he regarded these primary results as not enough and thus recommended further and continued study in this matter.[9]

Table I. Absolute and relative frequency of patients on the basis of received ribavirin and the outcome in 81 proved cases of CCHF in Iran (1999 - 2001).

Receiving drug / Outcome	Yes		No		To al	
	No.	%	No.	%	No.	%
Death	8	11.6	7	58.4	15	18.5
Recovery	61	88.4	5	41.6	66	81.5
Total	69	100	12	100	81	100

* The established cases of disease were defined as cases in which presence of clinical sings and symptoms were accompanied by positive serologic titer for IgM or IgG by ELISA method.

** The recommended dose was used according to the below mentioned protocol: 30 mg per kg of body weight as initial dose and then 15 mg per kg body weight every 6 hours for 4 days and after that 7.5mg per kg body weight every 8 hr. for the remaining 6 days. The total duration of treatment was 10 days.
After a mean time of 4 days after first clinical signs and symptoms, the drug with mentioned dosage was administered orally for patients in the second group.

*** No data is available on the interval between starting ribavirin and the time of death, in the patients who died inspite of receiving the drug.

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Also Mikhailov and Pak reported similar results but this type of treatment was not satisfactory for severe and fatal cases.[9, 10,11] In 1994, Fisher and co-workers stated in a paper that they used oral ribavirin in the treatment of 3 patients with a dose of 4 g daily for 4 days and then 2.4 grams daily for a period of 6 days and the 3 patients who were not expected to improve based on clinical signs and symptoms, had their lives saved by this drug.[4]

It is necessary to mention that evaluation of drug efficacy necessitates much epidemiologic studies and randomized control trials, but regarding the high fatality rate of this virus, this measure is not possible in terms of moral consideration and ethics. Therefore, some analytic observational studies including case-control studies are under focus of investigators. In the case-control studies, in case of suitable planning, focus on confounding variables data and limiting their effects as well as justifying other biases, they could be a good alternative for assessment of efficacy of drugs.

It is obvious that regarding the unavailability of confounding variable data in our patient's history, the present study fails to respond in the matter of omitting the effect of confounding variables and potential biases as well. It is worth mentioning that available data are the only means available in Iran and/or perhaps in the world, and concerning the above mentioned informational problems, these data were analyzed in the form of a case-control study.

Regarding the test power(>90%) by which drug efficacy had been demonstrated for therapy of patients equal to 91%, we conclude that oral ribavirin is accounted for as an accepted treatment for controlling sings and symptoms and cure of patients suffering from Crimean-Congo Hemorrhagic Fever. However exact judgment about the effectiveness of oral ribavirin requires further investigations through the far corners of Iran and other countries involved with this disease all over the world.

ACKNOWLEDGEMENT

We greatly thank Dr. Abolhassan Nadim, the honorable professor of Epidemiology for his scientific guidance in preparing this paper.

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