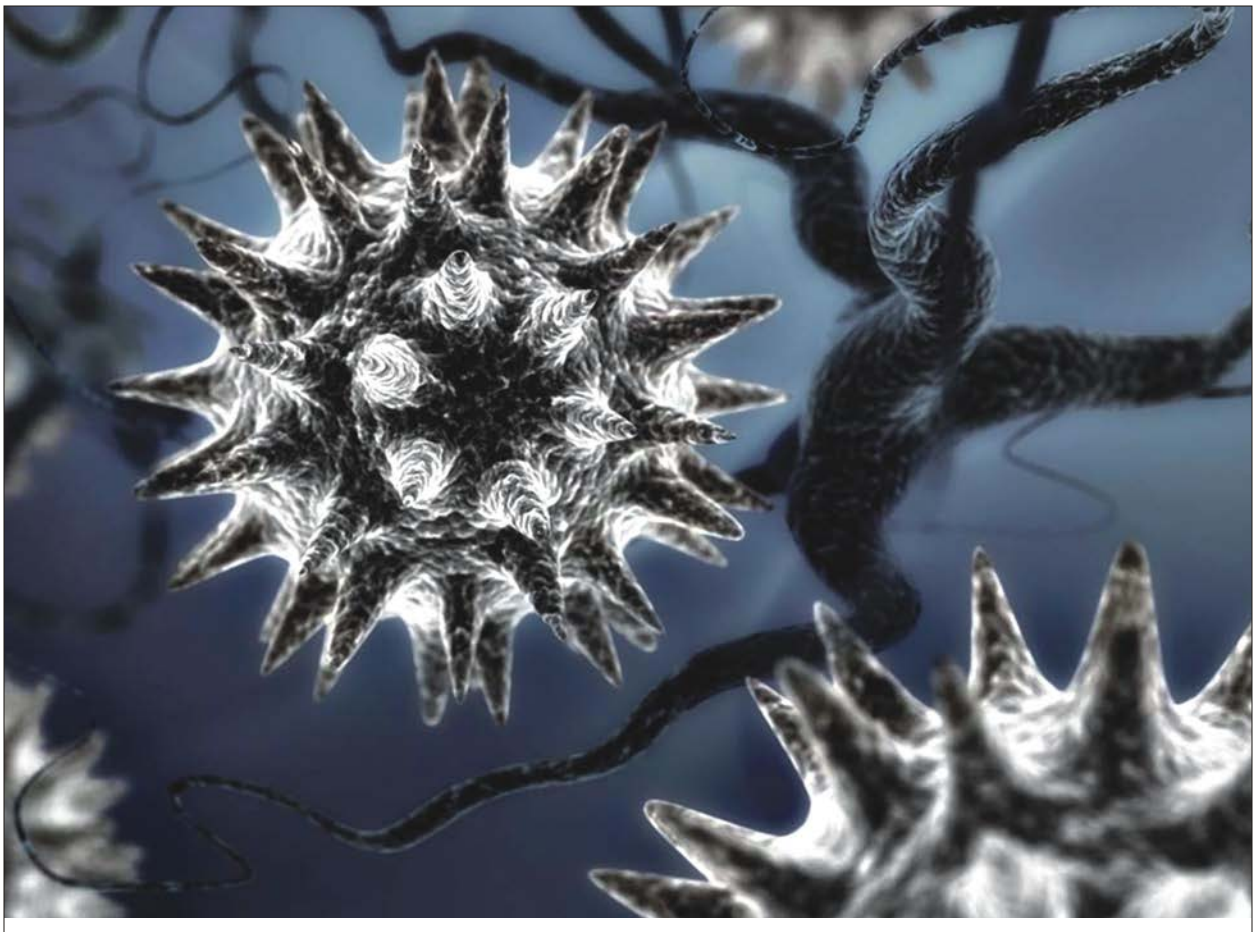

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Clinical Outcomes in Crimean-Congo Hemorrhagic Fever: A Five-years Experience in the Treatment of Patients in Oral Ribavirin

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Abstract: In order to determine the clinical outcomes of treatment with of oral Ribavirin in the patients with Crimean-Congo Hemorrhagic Fever (CCHF), we conducted this study.In this case-control survey, we compared the recovery rate and mortality rate among patients with confirmed CCHF, who were treated with oral ribavirin within the 3 days of onset of disease with the patients who were treated after this time. Eighty nine of (48.5%) of 184 cases were treated during the initial 72 h of disease. In this group 75 patients (84%) survived and 14 cases (16%) expired. Out of 95 patients who were treated after 3 days of the onset of disease, 71 cases (74.8%) survived and 24 cases (25.2%) died.The recovery rate was higher in the patients who were treated during the initial 3 days (Relative risk = 1.75; 95% confindence interval[CI] = 0.96-3.2; p = 0.06; absolute risk increased = 0.09). We conclude that oral Ribavirin is an effective treatment for patients with CCHF, especially when it is used within 72 h of the onset of disease and as soon as it is possible.

Key words: Crimean-Congo hemorrhagic fever, oral Ribavirin, mortality rate, Iran

Introduction

Crimean-Congo Hemorrhagic Fever (CCHF) is caused by *Nairovirus,* genus *Bunyavirus* in family of bunyaviridae and is spread by the tick *Hyalomma* spp or via blood transfusion and contaminated blood of human and animal (Metanat *et al*., 2003; Mardani, 1999). CCHF virus infection was rarely reported in Iran before 1999. From January 1st 1999 to October 1st 2004 nearly 440 confirmed sporadic CCHF cases reported from many provinces of Iran (Chinikar *et al*., 2001). The virus enters the blood and its target organs are liver, lungs and lymphoid tissue. The disease is characterized by a febrile illness with headache, myalgia, petechial rash and epistexis which is usually followed by necrotic hepatitis (Steel, 1996; Fisher *et al*., 1995; Peters, 2000). In severe cases complications frequently reported are hepatorenal and pulmonary failure; coagulation is impaired leading to hemorrhage. The bleeding manifestations are the result of severe thrombocytopenia. CCHF virus can produce a severe human disease with high mortality rate (up to 60% of clinically apparent cases) making CCHF amajor public health concern. Despite this high lethality rate, up to 80% of the infections may be subclinical (Whitley, 2000; Flick *et al*., 2003; Chinikar, 2004). Ribavirin has been shown to have activity *in-vitro* against CCHF virus in concentrations as low as 5 μg mL^{-1} (Watts *et al*., 1989; Sheikh *et al*., 2004; McCormik *et al*., 1986). The intravenous preparation is recommended for treatment of Viral Hemorrhagic Fevers and the oral form for post-exposure prophylaxis. Oral Ribavirin has also shown to be effective in patients with less severe disease. Few

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Table 1: The outcome in the patients with CCHF in Zahedan

	Patients		
	Recovery	Death	Total
Group 1	75 (84%)	14 (16%)	89 (48.5%)
Group 2	71(74.8%)	24 (25.2%)	95 (51.5%)
Total	146 (79.3%)	38((20.7%)	184 (100%)

The recovery rate was higher in group1 (relative risk = 1.75; 95% confidence interval [CI] = 0.96-3.2; p = 0.06; absolute risk increased = 0.09)

data is available about the time of starting of Ribavirin and it's efficacy (Watts *et al*., 1989; Sheikh *et al*., 2004; Anonymous, 2003).

This study was conducted in order to compare the outcome of the treatment with oral Ribavirin in confirmed CCHF patients who are treated within the intial 3 days of onset of illness with patients who are treated after this time.

Materials and Methods

The study was conducted at Department of Infectious Diseases, Boo-Ali Hospital, a teaching hospital in the province of Sistan and Baluchestan, in Southeast of Iran. We evaluated all patients with confirmed CCHF, who were admitted during 6 years from Jan. 2000-Sep. 2005 and were treated with oral Ribavirin. In this study, we evaluated the outcome of the treatment with oral Ribavirin in the patients, by comparing the recovery rate and mortality rate in 89 patients who were treated within 3 days of onset of disease (Group 1) with the 75 cases who were treated after 3 days of onset of disease (Group 2). The recommended dose was according to the below protocol: 30 mg kg^{-1} of body weight as initial dose and then 15 mg kg^{-1} body weight every 6 h for 4 days and thereafter 7.5 mg kg^{-1} body weight for 6 days. From patients medical records, information was extracted regarding recovery or death. Then statistical analysis system (SSPS) was used for all statistical analysis.

Result

Out of 184 confirmed cases who were treated with Ribavirin, 146 cases (79.3%) recovered and 38 cases (20.7%) died. Among the 184 cases, 89 cases (48.5%) were treated within the 3 days of onset of disease (Group 1). In this group 75 patients (84%) survived and 14 cases (16%) died. Ninety five patients who were treated after 3 days of onset of illness (Group 2), 71 cases (74.8%) survived and 24 cases (25.2%) died. The recovery rate was higher in the patients who were treated during the initial 3 days (Table 1).

Discussion

Present study showed that recovery rate was higher in the patients who were treated during the initial 3 days. It is reported that in patients with CCHF who don't receive any treatment, mortality rate is to eighty percent (Mardani *et al*., 2003). In our patients who were treated during the initial 72 h, mortality rate was less than patients who were treated after 3 days of onsent of disease (16% versus 25%). The treatment of hemorrhagic fevers is primarily symptomatic. However, ribavirin has been reported to reduce mortality in this patients. Ribavirin is a purine nucleoside analog that inhibits the replication *in vitro* of a wide range of RNA and DNA viruses, including myxoviruses,

paramyxoviruses, arenaviruses, bunyaviruses, retroviruses, herpesviruses, adenoviruses and poxviruses (Chinikar, 2004; Watts *et al*., 1989). For treatment of CCHF, Ribavirin has been given orally in a suggested dose of 2 g initially, then one gm every 6 h for 4 days, then 500 mg every 8 h for 6 days (Sheikh *et al*., 2004; McCormik *et al*., 1986). Treatment is most effective if started within days of the onset of fever(Mardani, 1999). For prophylaxis, a dose of ribavirin 600 mg by mouth 4 times daily for 10 days has been suggested for adults. With the exception of a dose -related reduction in circulating red-blood cell numbers, no significant adverse effects have been reported (Watts *et al*., 1989). Few data is available on the efficacy of ribavirin and time of onset of this drug. Ribavirin has been reported to be useful in the management of south African and pakistani CCHF cases (Kelly *et al*., 2004). In 1994, fisher and co-workers reported that they used oral ribavirin in the treatment of 3 patients with a dose of 4 grams daily for 4 days and then 2.4 g daily for a period of 6 days (Fisher *et al*., 1995). In fisher study, the patients became afebrile and their hematological and biochemical abnormalities returned to normal within 48 h of ribavirin treatment. Efficacy of oral Ribavirin in the treatmen of patient withCCHF was 91% (Mardani *et al*., 2003). A mean period of 2.30±0.69 days of treatment with ribavirin, the clinical as well as the laboratory parameters started improving and returned to normal levels after 10 day course of treatment (Watts *et al*., 1989). Due to the non avability of intravenous form, oral ribavirin was given to the patients, although usually oral ribavirin has been used for post-exposure prophylaxis for CCHF infection. When administered orally or intravenously, ribavirin causes anaemia due to extravascular hemolysis and suppression of the bone marrow (W atts *et al*., 1989; Mardani *et al*., 2003). Ribavirin is well absorbed from the gastrointestinal tract and would be expected to attain levels in the blood comparable with *in vitro* sensitivity of CCHF to Ribavirin (Watts *et al*., 1989; Sheikh *et al*., 2004). But in our patients, due to the non avability of this test, it was not checked.

In this study, of 89 cases were treated within the 3 days of onset of disease, 75 patients (84%) survived and 14 cases (16%) died and recovery rate was higher in the patients who were treated during the initial 3 days. Regarding present results, oral Ribavirin can be an effective medical therapy for management of Crimean-Congo hemorrhagic fever, especially if the patients were treated within the first days of the onset of disease. Althougth present finding, did not have significant difference between two groups but, the results showed that recovery rate was higher in patients were treated during the first days.

Therefore, we would recommend use of oral Ribavirin within the first 3 days of onset of illness in a dose of 2 g as a loading dose, then 15 mg kg^{-1} in four doses, for four days; dropping to 7/5 mg kg^{-1} in four doses for six days, completing 10 day course. The oral treatment is cheaper and easier to administer, is of remarkable efficacy and is usually well tolerated with mild gastrointestinal symptoms. This would certainly shorten the protracted convalescence and would result in a much better outcome of this fatal disease.

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