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Ribavirin: An Effective Drug for Treatment of Children with Crimean-Congo Hemorrhagic Fever: A Seven-years Experience

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Abstract: Crimean-Congo Hemorrhagic Fever (CCHF) is a tick-borne disease caused by the arbovirus which is a member of the Nairovirus genus and has a high mortality rate if the patients don't take treatment. This study was conducted to detect the clinical outcomes of treatment with oral ribavirin in children with CCHF. In this study, we evaluated the recovery rate and mortality rate among children with confirmed CCHF, who were treated with oral ribaririn within the three days of onset of disease and the patients who were treated after this time or had not been treated. Out of 29 children with Crimean-Congo hemorrhagic fever (18 Male, 11 Female with age range 5 to 17 years) 25 patients had been treated by oral ribavirin within the initial three days, two patients were treated after three days of the onset of disease and two cases had not been treated with ribavin. Nearly all the patients except two children were treated with ribavirin. Both these two children not treated with ribavirin died. One patients who was treated six days after the onset of disease was expired. Sixteen percent of children who were treated during the initial 72 h of disease died. Fatality rate was 24.1% in all of the patients. The recovery rate was higher in the children who were treated during the initial 3 days than children who were treated after this time or were not treated (84 versus 25%). We conclude that oral ribavirin is an effective treatment for children 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, children, recovery rate, Iran

INTRODUCTION

Crimean-congo hemorrhagic fever is an acute viral hemorrhagic disease and is usually transmitted to humans by infected tick bite and contact with domestic livestock and freshly slaughtered meat and contaminated blood of human and animal or via blood transfusion (Chinikar *et al.,* 2001; Khalili and Sharifi-Mood, 2005; Chapman *et al*., 1991). However, nosocomial transmission may also occur (Van Eeden *et al*., 1985; Mardani *et al*., 2003). CCHF virus infection was rarely reported in Iran before 1999. Since spring 1999 epidemic of this infection has been occurred in some regions of Iran especially in Sistan and Baluchistan, southeast of Iran (Chinikar *et al*., 2001; Izadi, 2004). Many cases have been reported from the countries surrounding Iran, including Pakistan, Afghanistan, Iraq, Turkey and Russia (Tikriti *et al*., 1981; Tantawi *et al*., 1980). The disease usually occurs in young or middle age men and it shows that male risk factors, primarily associated with herding activities (Chapman *et al*., 1991). Crimean-Congo hemorrhagic fever is not usual in children. The route of transmission in children is similar to adults (Alavi-Naini *et al*., 2006). The disease is characterized by a febrile illness with headache, myalgia, petechial rash and epistaxis which is usually followed by necrotic hepatitis (Metanat *et al*., 2006). 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 clinialy apparent cases. Despite this high mortality rate, up to 80% of the infection may be subclinical (Metanat *et al*. 2006; Mardani *et al*., 2003; Warts *et al*., 1989). Ribavirin has shown to have a good activity against CCHF *in vitro* and *in vivo* (Warts *et al*., 1989). Although, the intravenous preparation is recommended for treatment but oral ribavirin has also shown to be effective in patients with CCHF (Mardani *et al*., 2003; Metanat *et al*., 2006; Sheikh *et al*., 2004). There is only one report about affectivity of this drug in children (Alavi-Naini, 2006). The purpose of present study was to emphasized the importance of treatment with oral ribavirin in the children with CCHF, because in the Iran especially in Sistan and Baluchistan Province, it is now as a public health problem in all age groups and treatment can increases recovery rate.

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MATERIALS AND METHODS

This study was conducted at Departments of Infectious Diseases, Boo-Ali hospital in Zahedan and Imam-Ali hospital in Zabol. Sistan and Baluchistan province, a subtropical area in the southeast of Iran, has an estimated population of 2,200,000 inhabitants and disease now endemic in this area. Most of our source population which is about half of this, reside in Zabol and Zahedan situated in northern part of this province. We evaluated all children with confirmed CCHF, who were admitted in two hospitals during June 1999 to Feb 2006 and we evaluated the clinical outcome in our patients. Center for disease control and prevention in this province recommend several criteria for probable diagnosis. A probable case was defined as an acutely ill person with (1) clinically observed signs and symptoms of acute onset of fever, myalgia and bleeding, (2) epidemiological risk factors (history of tick bite, contact with suspected cases of CCHF, contact with domestic animals and travel to or residence in an area of endemicity for CCHF) and laboratory data consisting of a platelet count of <150,000 platelets/mm^3 and a leukocyte count of below 4000. With the availability of the final laboratory results, the case definition for confirmed (definite) cases of CCHF was revised as individuals who met the criteria for a probable case and positive serological test results for Enzyme Linked Immunoassay (ELISA) of IgM and/or rising of IgG antibodies or having a positive test for RT-PCR. Here in, we selected all the patients who had an age under 18 years and the disease was confirmed. They were retrospectively evaluated in means of sex, living environment (rural versus urban), past history of tick bite, contact history with livestock and fresh meat, the date of tick bite, contact with cattle or suspected persons and the most common clinical symptoms and laboratory results and clinical outcome.

RESULTS

Among the 179 confirmed patients who were treated with Ribavirin, we evaluated all patients under 17 years of age. Out of 29 children with Crimean-Congo hemorrhagic fever (18 Male, 11 Female with age range 5 to 17 years) 25 patients had been treated by oral ribavirin within the initial three days, 2 patients were treated after three days of the onset of disease and two cases had not been treated with ribavirin. Nearly all the patients except two children were treated with ribavirin. Both these two children who had not been treated with ribavirin, died. Fatality rate was 24.1% in all of the patients. The recovery rate was higher in the children who were treated during the initial 3 days than children who were treated after this time or were not treated (84 versus 25%). Several demographic, clinical characteristics and laboratory results of 29 patients under 17 years old are presented in Table 1. The most common observed symptoms were fever (95.8%), bleeding (91.7%) and myalgia (75%). The most common site of bleeding was oral-nasal mucosa (69%) and then gastrointestinal tract (18%). Serologic test for Crimean-congo hemorrhagic fever was performed on all patients. Seventeen (58.6%) patients were serologically proved and 12 patients (41.4%) were cases who had a positive test for PCR.

Table 1: Epidemiological data, clinical manifestation and laboratory results in 29 children with CCHF

Variable	No. of patients	(%)
Sex		
Male	18	62.0
Female	11	37.0
Environment		
Urban	12	42.0
Rural	17	58.0
History of		
Animal contact	21	75.0
Tick bite	3	10.3
Tick in the living area	14	48.0
Contact with freshly slaughtered meat	11	37.0
Contact with wool	4	13.0
Clinical findings		
Fever	24	95.8
Myalgia	18	75.0
Bleeding	22	91.7
Petechia and purpura	11	45.8
Laboratory data		
Thrombocytopenia (Plt $\leq 150\times10^9$ μL^{-1})	29	100.0
Leukopenia (WBC $\leq 3,000$ μL^{-1})	14	49.0
Anemia (Hb ≤ 10 g dL^{-1})	15	51.0

DISCUSSION

Present study showed that 16.2% of all patients with CCHF who were admitted to infectious diseases during 1999-2006 in Sistan and Baluchistan province were children less than 17 years old. Fatality rate was 24.1% in all of our patients. Ribavirin had been given in a suggested dose 30 mg kg^{-1} as initial dose then 15 mg kg^{-1} every 6 h for 4 days, then 7.5 mg kg^{-1} every 8 h for 6 days. Treatment is more effective if started within the three initial days of the onset of fever (Mardani *et al*., 2003; Metanat *et al*., 2006). CCHF is rare in children and in our study, the children were infected in several ways but the most routes of infection in our patients were contact with livestock and fresh meat and then tick bite. Sometimes there route of transmission is not quite clear-cut but the epidemiological factor of living in an endemic area is one of the important criteria to suspect to this life threatening disease. There are a few reports about the CCHF in children in Iran and other countries (Khalili and

Sharifi-Mood, 2005; Alavi-naini *et al*., 2006). Saijo *et al.* (2004) described a child with Crimean-Congo Hemorrhagic Fever (CCHF) presumably infected with CCHF virus from her 27 year old mother. The child developed fever on the 5th day after the mother's onset. The child's genome sequence of virus was identical to that of the mother, indicating possible transmission of the virus from mother to child (Saijo *et al*., 2004). Other study by Alavi-Naini *et al.* (2006) in Sistan and Baluchistan showed that 11% of total patients who were evaluated during 1999-2004, were children less than 15 years. In recent study mortality rate was 22.2% in children and was higher in patients who were not treated or were treated late (Unpublished data). In our study mortality rate was higher than Alavi report (24.1 versus 22.2%). As Alavi study, fever, bleeding and myalgia were the most common clinical manifestations. Although, we found a few reports about affectivity of oral ribavirin in adults ((Mardani *et al*., 2003; Metanat *et al*., 2006; Sheikh *et al*., 2004) but we could not find any report except Alavi report about clinical outcome in children who had been treated with ribavirin. Studies by Mardani *et al.* (2003) and Metanat *et al.* (2006), in adults, showed that mortality rate was higher in untreated group. Efficacy of oral ribavirin in the treatment of patients with CCHF in Mardani survey was 91%. We should be aware that as long as endemic areas are afflicted with ecological change, poverty and social instability, Crimean-congo hemorrhagic fever are likely to remain a threat especially for children.

Since, Crimean-congo hemorrhagic fever is an endemic infection in Iran especially in the southeast of Iran and this disease also has high mortality rates among children especially among untreated children, awareness of physicians is important for early diagnosis and treatment. Oral ribavirin can increase recovery rate in children as adults.

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