Effects of Dexamethasone on Clinical Outcome in Patients with Severe Crimean-Congo Hemorrhagic Fever

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Abstract

Background: Crimean-Congo hemorrhagic fever (CCHF) is an acute viral hemorrhagic disease, and it is currently endemic in Southeastern Iran. The present study aimed at comparing the effect of ribavirin alone and in combination with dexamethasone on clinical outcome of patients with severe form of Crimean-Congo hemorrhagic fever.

Methods: In this clinical trial study, we studied 30 patients with severe form of Crimean-Congo hemorrhagic fever (2 groups with 14 controls and 16 cases), who were admitted to Boo Ali hospital in Zahedan (Southeast of Iran) from July 2015 to April 2016. Patients were selected randomly for each group. The intervention group received dexamethasone and ribavirin, and the control group was treated only with ribavirin. Then, the rate of recovery, mortality rate, blood products used, and duration of hospitalization in both groups were recorded and compared. The distribution of samples and comparison of quantitative variables were evaluated by Kolmogorov Smirnov test, t test, and Man-Whitney test. The comparison of qualitative variables was performed by Chi-square and McNamara's test.

Results: Of 30 patients, 24 (80%) and 6 (20%) were male and female, respectively. A few patients required transfusion of blood products in the intervention group compared to controls, but there was no statistically significant difference between the 2 groups (P < 0.05). The mean duration of hospitalization was 10.87 and 12 days in the intervention and control groups, respectively. No significant difference was obtained between the 2 groups in the duration of recovery (P < 0.05). No patients died in the intervention and control groups.

Conclusions: It seems that high-dose dexamethasone is effective in the treatment of patients with severe form of CCHF. Blood products requirement for severe CCHF patients was reduced after receiving high-dose dexamethasone. Further investigations are necessary to determine the efficacy of corticosteroid and its effect on outcome.

Keywords: CCHF, Clinical Outcome, Dexamethasone, Ribavirin

1. Background

Crimean-Congo hemorrhagic fever (CCHF) is an acute fatal febrile hemorrhagic viral disease, which is common between humans and animals through tick bites caused by a tick-borne virus (Nairovirus) of the Bunyaviridae family, and is transmitted by direct contact with the blood or secretions of patients or infected animal carcasses to healthy people (1-5).

Geographical pervasiveness is one of the important features of the virus and the disease. Crimean-Congo hemorrhagic fever is found in Eastern Europe, particularly in the former Soviet Union, throughout the Mediterranean Region, in Northwestern China, central Asia, Southern Europe, Africa, the Middle East, and the Indian subcontinent (2).

High prevalence of the disease among farmers and people who deal with livestock and hospital workers has also been reported (1, 2).

The disease is endemic in Iran, especially in the Southeast of Iran, and large-scale epidemics have occurred in the spring and summer since 1999 (6, 7). The virus causes severe disease in humans with a mortality rate near 80% and cases of nosocomial outbreaks have also been reported (8, 9). The severe forms of the disease are associated with higher mortality and morbidity, and they are as follow: bleeding presentations, a sharp drop in platelets, decreased level of consciousness, low fibrinogen levels, and prolonged partial thromboplastin time (PTT), and those patients whose total of all mentioned parameters (Severity Scoring Index) equal to 10 or more (10).

Immediate medical actions should be done after the diagnosis of Crimean-Congo hemorrhagic fever suspected cases. The base of the treatment is supportive including

water and electrolytes balance and progressive coagulation disorders. Other protective measures include prophylactic treatment of peptic ulcer and avoiding intramuscular injections, aspirin, and other anti-inflammatory drugs administration (11). In recent decades, re-emergence of this disease has proven the effect of ribavirin in the treatment of disease (12-14). Initiation of the medication as soon as possible has increased the response to treatment and decreased the mortality rate from 22% to 3% in the Southeast of the country in the recent years (15, 16).

Despite the effect of ribavirin in the clinical outcome, sometimes physicians are faced with high mortality rate during the treatment with ribavirin and supportive care. Therefore, physicians need to reduce the complications, morbidity, and mortality using another effective treatment regimens. However, interferon has shown significant antiviral activity against hemorrhagic viruses, and the use of interferon and intravenous immunoglobulin in critically ill patients is recommended, but few studies have been done in this regard, and the results are still under consideration (9).

Limited studies have shown the effect of corticosteroids on increasing platelet count, which is one of the main options for the severe form of this disease (17, 18). A clinical trial evaluated the efficacy of high dose prednisolone in patients with CCHF and severe thrombocytopenia and showed positive effects on increasing platelet count and reduction in the need for blood products in these patients (19). Considering the importance of the disease, the risk of high mortality and lack of assessing the effect of dexamethasone on clinical outcomes, this study aimed at examining the effect of ribavirin in combination with dexamethasone in patients with a severe form of CCHF and comparing the results with those of the patients who took ribavirin alone.

2. Methods

In this clinical trial research, we studied 30 patients with severe form of Crimean-Congo hemorrhagic fever (2 groups with 14 controls and 16 cases), who were admitted to Boo Ali hospital in Zahedan (Southeast of Iran) from July 2015 to April 2016. Patients were selected randomly in each group. Inclusion criteria included having at least 1 criterion of severe forms of Crimean- Congo hemorrhagic fever as severe thrombocytopenia (platelet count less than 20 000 per cubic meter), bleeding presentations as petechial, ecchymosis and obvious bleeding, fibrinogen level less than or equal to 120 mg dL, partial thromboplastin time (PTT) greater than or equal to 60 seconds, and loss of consciousness.

Exclusion criteria were as follow: pregnancy; underlying disease; immunosuppressive treatment; patients who received any antiviral, blood, or blood products after the onset of the symptoms and prior to hospital admission; and patients with no confirmation of Crimean-Congo hemorrhagic fever by serology or PCR. Informed consent was obtained from all participants in the study.

Blood samples for testing as well as for PCR, IgM, and IgG were taken from the patients, and this diagnostic tests were repeated at day 5 and 10.

In the control group, ribavirin was administrated as 30 milligram per kilogram for the first dose, 16 milligram per kilogram every 6 hours for 4 days, and 8 milligram per kilogram every 8 hours for 6 days. In the intervention group, ribavirin was administrated as 30 milligram per kilogram for the first dose, then 16 milligram per kilogram every 6 hours for 4 days, and 8 milligram per kilogram every 8 hours for 6 days in addition to dexamethasone 10 milligram per square meter body. The rate of recovery or death and need for blood products transfusion were recorded in both groups. The distribution of the samples and comparison of quantitative variables were evaluated by Kolmogorov Smirnov test, t test, and Man-Whitney test. The comparison of qualitative variables was performed by Chi-square and McNemar's test. Data were analyzed using SPSS software Version 21.

3. Results

We Studied 30 patients with severe Crimean- Congo hemorrhagic fever, and the demographic features are presented in Table 1.

In the control group, 14 patients were treated with ribavirin; and in the intervention group, 16 patients were treated with ribavirin and dexamethasone. The mean age of the patients in the control group was 30.78 ± 15.73 years (range 20 - 65 years), and it was 37.12 ± 11.84 years (range 25 - 63 years) in the intervention group.

In the control group, 4 patients (28.6%) were female and 10 were (71.4%) male; and in the intervention group, 2 patients (12.5%) were female and 14 (87.5%) were male.

In the control group, 13 patients (92.2%) had headache and backache, 7 had (50%) diarrhea, and 5 (53.7%) had bleeding. In the intervention group, 14 patients (87.5%) had headache and diarrhea, 10 (62.5%) had back pain, 8 (50%) had bleeding.

The mean interval between the beginning of symptoms and treatment initiation of patients in the control group was 3.50 ± 1.78 days, and it was 2.37 ± 1.02 days in the intervention group.

The results revealed that the average number of transfused blood products units (platelets, packed cells, and

Table 1. Descriptive Indicators of the 2 Groups[a]

Variable	Group	
	Control	Intervention
Location		
City	12 (85.7)	2 (14.3)
Vilage	12 (75)	4 (25)
Occupation		
Slaughterhou se workers	7 (50)	6 (37.5)
Farmer	-	2 (12.5)
Butcher	-	2 (12.5)
Self-employed	3 (21.4)	4 (25)
Housewife	4 (28.6)	2 (12.5)
Contact Type		
Meat	5 (35.7)	12 (75)
Live animals	5 (35.7)	-
Livestoc	2 (14.3)	2 (12.5)
Tick Bite	2 (14.3)	2 (12.5)

[a]Values are expressed as No. (%).

FFP) and the days of hospitalization in patients receiving ribavirin alone was more than in patients receiving ribavirin and dexamethasone, although this difference was not statistically significant (P >0.05) (Table 2).

Table 2. Comparison of Transfused Blood Products Administered and Days of Hospitalization in the 2 Groups

Variable	Group	Mean ± Standard Deviation	P Value
Transfused Platelet Units	Control	22.35 ± 13.64	0.04[a]
	Intervention	18.62 ± 18.62	
Transfused Packed Cells Units	Control	0.71 ± 1.26	0.19[b]
	Intervention	0.00 ± 0.00	
Transfused FFP Units	Control	10.57 ± 12.68	0.05[b]
	Intervention	2 ± 3.57	
Days of Hospitalization	Control	12 ± 1.03	0.06[b]
	Intervention	10.87 ± 1.58	

[a]P Value of T-Test.
[b]P Value of Mann-Whitney test.

4. Discussion

In our study, the CCHF disease did not cause death in any of the patients receiving ribavirin or ribavirin plus dexamethasone. The results of Chinikar et al. study (2005) represents about 11% of deaths in patients suffering from CCHF [7]. The mortality rate of CCHF in Metanat (2006) and Izadi et al. (2009) studies were reported to be 16% [10] and 25% [15], respectively. Sharifi-Mood et al. (2009) reported the mortality rate of CCHF in the city of Zahedan between the years 1999 to 2003 and 2007 and 2005, which was 20% and 3%, respectively [11]. These studies also revealed that the death rate among those patients treated with ribavirin during the first 72 hours was less [10, 11, 20]. The considerable reduction in the mortality of CCHF patients in the recent studies and in our research indicates an increased community awareness, especially among those who are at risk for this disease. On the other hand, prompt initiation of the treatment even in the possible cases have led to better outcome in patients. The results of our study revealed that day of hospitalization and number of transfused blood products used in the intervention group was significantly less than in the control group, but this difference was not statistically significant.

Dilber et al. (2010) demonstrated that treatment with high doses of prednisone in CCHF was highly satisfying, and it was especially effective in the increase in platelets count, fever improvement, and reduction in the need for blood products [21]. The results of Mardani et al. study (2013) also revealed the effect of high- dose methylprednisolone on the increase of platelet counts and reduction in the need for blood products in patients with severe CCHF [13]. CCHF prevention is based on 3 important principles including patient screening, timely treatment of patients, and increase in public awareness about the ways of transmission and prevention of the disease. The intersectoral coordination with relevant bodies such as the organization of veterinary medicine, municipalities, and other organizations to combat and control the disease has been done in the recent years. These factors reduce the incidence of disease in the region [2].

We found that lower number of blood products were required in patients receiving dexamethasone compared to those patients receiving ribavirin and ribavirin, although the difference was not significant. However, in a study by Sharifi-Mood et al. when the effect of methylprednisolone and ribavirin was compared with ribavirin, the difference was found to be significant. CCHF virus, like other viruses that cause hemorrhagic fever with cellular disorder, leads to the immune response against the virus in the body [22]. The pathogenesis of the disease could be the result of direct damage of infected tissues and indirect damage resulting from host immune response including cytokine production [23, 24]. It seems that clinical presentations of CCHF are a result of delayed immune response to interlukine-10 production that assists increased

transcription and distribution of the CCHF virus in the body (25). Continued injuries cause an increase in the production of interferon gamma, tumor necrosis factor-alpha (TNF-α), and other cytokines mediated vascular dysfunction, and disseminated intravascular coagulation (DIC) (26, 27).Corticosteroids reduce the production of cytokines and chemokines and act as an antagonist to proinflammatory cytokines activity. Thus, we can direct the impact on the effectiveness of corticosteroids on the clinical improvement of severe form of CCHF with thrombocytopenia and coagulopathy. The results of this study and those of previous studies have been largely limited to confirm this hypothesis.

4.1. Conclusions

Our results demonstrated a satisfying effect of high-dose dexamethasone with ribavirin in combination with supportive care on the reduction of hospitalization days and number of transfused blood products in patients with severe form of CCHF, although this difference was not statistically significant.

Acknowledgments

Footnotes

References

1. Whitehouse CA. Crimean-Congo hemorrhagic fever. *Antiviral Res.* 2004;**64**(3):145–60. doi: 10.1016/j.antiviral.2004.08.001. [PubMed: 15550268].

2. Mardani M, Keshtkar-Jahromi M. Crimean-Congo hemorrhagic fever. *Arch Iran Med.* 2007;**10**(2):204–14. [PubMed: 17367225].

3. Metanat M, Sharifi-Mood B, Masoud S. Crimean-Congo Hemorrhagic Fever: A Reemerging Disease. *Arch Clin Infect Dis.* 2014;**9**(1).

4. Metanat M, Sharifi-Mood B, Alavi-Naini R, Kermansaravi F, Hamzehnezhad M. Crimean-Congo Hemorrhagic Fever and Hypertention: A Case Report. *Arch Clin Infect Dis.* 2014;**9**(1).

5. Rakhshani M, Abedi-poor F, Noori-Jangi M, Khoorgami P, Hajalizadeh A, Kooshki M, et al. A Five-Member Family With Crimean-Congo Hemorrhagic Fever; A Case Series Study. *Int J Infect.* 2014;**1**(1).

6. Tabatabaei SM, Hassanzehi A, Pakzad A, Mohammdi M, Madani A. Factors Influencing Crimean-Congo Hemorrhagic Fever Risk Perceptions in the General Population, Southeast Iran. *Int J Infect.* 2014;**1**(1) doi: 10.17795/iji-18150.

7. Sharifi-Mood B, Metanat M, Hashemi Shahri SM, Salehi M, Khalili M. Crimean-Congo Hemorrhagic Fever in Children in Southeast of Iran. *Int J Infect.* 2014;**1**(3) doi: 10.17795/iji-22259.

8. Hashemi-Shahri SM, Sharifi-Mood B, Metanat M. Risk Factors Associated With Poor Prognosis in Children With Crimean-Congo Hemorrhagic Fever. *Int J Infect.* 2014;**1**(3) doi: 10.17795/iji-21519.

9. Sharifi-Mood B, Mardani M, Keshtkar-Jahromi M, Rahnavardi M, Hatami H, Metanat M. Clinical and epidemiologic features of Crimean-Congo hemorrhagic fever among children and adolescents from southeastern Iran. *Pediatr Infect Dis J.* 2008;**27**(6):561–3. doi: 10.1097/INF.0b013e3181673c28. [PubMed: 18434934].

10. Sharifi-Mood B, Metanat M, Hashemi-Shahri SM, Mardani M, Hashemi SA, Fayyaz-Jahani F. Crimean-Congo hemorrhagic fever following consumption of uncooked liver: case series study. *Iran J Clin Infect Dis.* 2011;**6**(3):128–30.

11. Ergonul O, Celikbas A, Baykam N, Eren S, Dokuzoguz B. Analysis of risk-factors among patients with Crimean-Congo haemorrhagic fever virus infection: severity criteria revisited. *Clin Microbiol Infect.* 2006;**12**(6):551–4. doi: 10.1111/j.1469-0691.2006.01445.x. [PubMed: 16700704].

12. Ergonul O, Celikbas A, Dokuzoguz B, Eren S, Baykam N, Esener H. Characteristics of patients with Crimean-Congo hemorrhagic fever in a recent outbreak in Turkey and impact of oral ribavirin therapy. *Clin Infect Dis.* 2004;**39**(2):284–7. doi: 10.1086/422000. [PubMed: 15307042].

13. Mardani M, Jahromi MK, Naieni KH, Zeinali M. The efficacy of oral ribavirin in the treatment of crimean-congo hemorrhagic fever in Iran. *Clin Infect Dis.* 2003;**36**(12):1613–8. doi: 10.1086/375058. [PubMed: 12802764].

14. Mirazimi A. In: Crimean-Congo Hemorrhagic Fever: A Global Perspective. Ergonul O, Whitehouse CA, editors. Dordrecht: Springer; 2007. Old and new treatment strategies.

15. Metanat M, Sharifi-Mood B, Salehi M, Alavi-Naini R. Clinical outcome in Crimen-Congo hemorrhagic Fever: A five years experience in the treatment of patients in oral Ribavirin. *Int J Virol.* 2006;**2**(1):21–2.

16. Sharifi-Mood B, Metanat M, Ghorbani-Vaghei A, Fayyaz-Jahani F, Akrami E. The outcome of patients with Crimean-Congo hemorrhagic fever in Zahedan, southeast of Iran: a comparative study. *Arch Iran Med.* 2009;**12**(2):151–3.

17. Dilber E, Cakir M, Erduran E, Koksal I, Bahat E, Mutlu M, et al. High-dose methylprednisolone in children with Crimean-Congo haemorrhagic fever. *Trop Doct.* 2010;**40**(1):27–30. doi: 10.1258/td.2009.090069. [PubMed: 20075424].

18. Erduran E, Bahadir A, Palanci N, Gedik Y. The treatment of crimean-congo hemorrhagic fever with high-dose methylprednisolone, intravenous immunoglobulin, and fresh frozen plasma. *J Pediatr Hematol Oncol.* 2013;**35**(1):e19–24. doi: 10.1097/MPH.0b013e3182706444. [PubMed: 23018575].

19. Sharifi-Mood B, Alavi-Naini R, Metanat M, Mohammadi M, Shakeri A, Amjadi A. Efficacy of high-dose methylprednisolone in patients with Crimean-Congo haemorrhagic fever and severe thrombocytopenia. *Trop Doct.* 2013;**43**(2):49–53. doi: 10.1177/0049475513486642. [PubMed: 23796671].

20. Izadi S, Salehi M. Evaluation of the efficacy of ribavirin therapy on survival of Crimean-Congo hemorrhagic fever patients: a case-control study. *Jpn J Infect Dis.* 2009;**62**(1):11–5.

21. Centers for Disease C. Viral hemorrhagic fever: initial management of suspected and confirmed cases. *MMWR Morb Mortal Wkly Rep.* 1983;**32 Suppl 2**:27S–38S. [PubMed: 6422225].

22. Wauquier N, Becquart P, Padilla C, Baize S, Leroy EM. Human fatal zaire ebola virus infection is associated with an aberrant innate immunity and with massive lymphocyte apoptosis. *PLoS Negl Trop Dis.* 2010;**4**(10):e837. .

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23. Weber F, Mirazimi A. Interferon and cytokine responses to Crimean Congo hemorrhagic fever virus; an emerging and neglected viral zonoosis. *Cytokine Growth Factor Rev.* 2008;**19**(5-6):395–404. doi: 10.1016/j.cytogfr.2008.11.001. [PubMed: 19027345].

24. Saksida A, Duh D, Wraber B, Dedushaj I, Ahmeti S, Avsic-Zupanc T. Interacting roles of immune mechanisms and viral load in the pathogenesis of crimean-congo hemorrhagic fever. *Clin Vaccine Immunol.* 2010;**17**(7):1086–93. doi: 10.1128/CVI.00530-09. [PubMed: 20484568].

25. Ergonul O, Tuncbilek S, Baykam N, Celikbas A, Dokuzoguz B. Evaluation of serum levels of interleukin (IL)-6, IL-10, and tumor necrosis factor-alpha in patients with Crimean-Congo hemorrhagic fever. *J Infect Dis.* 2006;**193**(7):941–4. doi: 10.1086/500836. [PubMed: 16518755].

26. Papa A, Bino S, Velo E, Harxhi A, Kota M, Antoniadis A. Cytokine levels in Crimean-Congo hemorrhagic fever. *J Clin Virol.* 2006;**36**(4):272–6. doi: 10.1016/j.jcv.2006.04.007. [PubMed: 16765637].

27. Kaya S, Elaldi N, Kubar A, Gursoy N, Yilmaz M, Karakus G, et al. Sequential determination of serum viral titers, virus-specific IgG antibodies, and TNF-alpha, IL-6, IL-10, and IFN-gamma levels in patients with Crimean-Congo hemorrhagic fever. *BMC Infect Dis.* 2014;**14**:416. doi: 10.1186/1471-2334-14-416. [PubMed: 25066751].