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The efficacy of oral ribavirin on clinical and laboratory parameters in Crimean–Congo hemorrhagic fever: an observational study from Turkey*

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Background/aim: In this observational study, the effects of oral ribavirin on clinical and laboratory parameters and blood products use in patients with Crimean–Congo hemorrhagic fever (CCHF) were evaluated.

Materials and methods: CCHF patients (n = 100) who were hospitalized between 2007 and 2010 were included. Oral ribavirin was administered to 56 patients with symptom duration less than 5 days. Forty-four patients did not receive ribavirin (control group). The patients that received ribavirin in the first 3 days following the initiation of symptoms were designated as Group 1 (n = 29) and the others were designated as Group 2.

Results: Ribavirin-treated and untreated groups were similar in terms of demographic and most clinical characteristics. Leukocyte and platelet counts were lower in the ribavirin group than in the control group, but values of prothrombin time, activated partial thromboplastin time, aspartate aminotransferase, creatinine phosphokinase, and lactate dehydrogenase were higher (P = 0.011, P = 0.015, P = 0.001, P = 0.001, P = 0.021, P = 0.019, P = 0.004, respectively). Platelet concentrates use was greater in the ribavirin group (P = 0.01).

Conclusion: No positive effects of oral ribavirin on blood products use or clinical or laboratory parameters of CCHF patients were observed. Moreover, no difference was shown between early and late initiation of ribavirin.

Key words: Crimean–Congo hemorrhagic fever, ribavirin, clinical parameters, laboratory parameters

1. Introduction

Crimean–Congo hemorrhagic fever (CCHF) is a viral hemorrhagic disease with high fatality. The CCHF virus infects people by tick bites and contact with the blood or tissue of infected people or viremic livestock (1). The first case in Turkey was reported in 2002. Later cases have been reported from Eastern and Central Anatolia and the Central-Eastern Black Sea Region (2,3). The number of confirmed cases was 9069 at the end of 2014 (Data of Ministry of Health of Turkey; obtained by personal communication).

Today, there is no specific treatment for CCHF. Monitoring of the patient and supportive treatment consisting of replacement of blood products are the main principles of treatment (4,5). Although use of ribavirin is suggested by the World Health Organization and Centers for Disease Control and Prevention, the efficacy of ribavirin as an antiviral drug is controversial (available http://www.who.int/mediacentre/factsheets/fs208/en and at: http://www.cdc.gov/vhf/crimean-congo/treatment/index.html). Ribavirin, which is used for the treatment of viral hemorrhagic fever syndromes, was shown to inhibit the growth of CCHF virus in animal models and in vitro (6,7). Many observational and case-control studies were reported in Turkey, Iran, and Pakistan in which oral and intravenous ribavirin was used for treatment (8,9–20). Recently, two systemic reviews and meta-analyses were published evaluating the efficacy of ribavirin (21,22). Yet, whether ribavirin is effective has not been clarified. The aim of the present study was to evaluate the effects of oral

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ribavirin on clinical and laboratory parameters and blood products use in CCHF patients who were followed in a tertiary care center.

2. Materials and methods

This retrospective study was conducted in the 670-bed Ankara Training and Research Hospital in Central Anatolia. All patients with CCHF hospitalized between 2007 and 2010 at the First Department of Infectious Diseases and Clinical Microbiology were included in the study. The study group comprised severe patients who were transferred from rural areas according to regulations on CCHF by the Health Ministry of Turkey. Diagnosis was confirmed by CCHF IgM and/or RT-PCR positivity in serum samples taken on admission and 1 week later. Tests were run at the Reference Laboratory of the Public Health Institute of Turkey.

According to requirements all patients received supportive therapy including fluid, fresh frozen plasma (FFP), and platelet and erythrocyte concentrates. Informed consent was obtained from the patients. At the time of admission, oral ribavirin was administered to the patients whose symptoms were shorter than 5 days and who had no contraindications such as renal failure. The patients whose symptoms were longer than 5 days did not receive ribavirin because viremia is decreasing in the second week of the disease. These patients were defined as the control group. Dosage of oral ribavirin was 2 grams as an initial loading dose, then 1 g q.i.d. for 4 days, and then 0.5 g q.i.d. for 6 days (11,23).

The patients who were treated with ribavirin were grouped according to receiving ribavirin within 3 days of the onset of symptoms (Group 1) or after the 3rd day (Group 2). The patients' clinical symptoms, signs, and laboratory findings [aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), leukocyte, hemoglobin (Hb), platelet, activated partial thromboplastin time (APTT), prothrombin time (PT)] were recorded. Various clinical findings were compared to evaluate the efficacy of ribavirin. Moreover, the differences between the laboratory values on the 1st and 5th days of admission were compared. Statistical analysis was performed using SPSS (Chicago, IL, USA). Comparisons of categorical variables were performed by chi-squared test. According to results of the normality test, Student's t-test, Mann–Whitney U test, or Kruskal–Wallis test were used to compare the means or medians of continuous variables. P values < 0.05 were considered significant.

3. Results

The number of the patients was 100 (56 in the ribavirin group and 44 in the control group) and 15 of them was diagnosed by IgM and 85 by RT-PCR positivity. The mean duration between onset of symptoms and admission to our hospital was 3.7 ± 2.2 days. The ribavirin-treated and untreated groups were similar in terms of age, sex, history of tick contact, location of residence, and duration of symptoms (P > 0.05) (Table 1). Myalgia, fever, headache, vomiting, and bleeding were the most frequent symptoms. Both groups were similar at the time of admission in terms of symptoms and findings except nausea and abdominal pain. Nausea and abdominal pain were more frequent in the ribavirin group (P = 0.01 and P = 0.037, respectively) (Table 1). Initial laboratory values at the time of admission were significantly more deteriorated in the ribavirin group than they were in the controls. Leukocyte and platelet counts were lower and values of APTT, PT, AST, CPK, and LDH were higher in the ribavirin group than in the control group (P = 0.011, P = 0.015, P = 0.001, P = 0.001, P = 0.021, P = 0.019, P = 0.004, respectively). The differences for the remaining laboratory values were statistically insignificant (P > 0.005 for all comparisons). Duration of hospitalization was longer in the ribavirin group compared to the control group (8 vs. 7 days, P < 0.001). The median duration from onset of symptoms to hospital admission was longer in Group 2 than in Group 1 (5 vs. 2 days, P = 0.000). Diarrhea was more frequent (P = 0.038) and the median PT values were longer in Group 2 (11.4 vs. 13.2 s, P = 0.028) (Table 2). The overall case fatality rate was 2%. One of the 2 patients who died received ribavirin but the other did not (P = 0.689).

When evaluating the efficacy of ribavirin, fever decreased earlier in the control group than in the ribavirin group (1 day vs. 2 days, P = 0.001), but there was no statistical significance for duration of bleeding cessation between the groups. The difference for platelet counts was less in the ribavirin group compared to the control group (P = 0.031). No significant difference was found between the groups in terms of other laboratory parameters. Use of platelet concentrates was greater in the ribavirin group (P = 0.01). However there was no statistical difference for use of FFP (P > 0.005) (Table 3).

When the efficacy of early or late initiation of ribavirin was evaluated, fever decreased earlier in the control group than in both Group 1 (1 day vs. 2.5 days, P = 0.015) and Group 2 (1 day vs. 2 days, P = 0.001). No statistical significance was found between Groups 1 and 2 for resolution of fever. Moreover, there was no statistical significance for duration of bleeding cessation between Group 1, 2, and the control group. Platelet counts increased most rapidly between the 1st and 5th days of admission in the control group (P = 0.027). A significant difference was found between Group 2 and the control group for platelet counts (P = 0.007). Prothrombin time values decreased most rapidly in Group 2 (P = 0.007). A significant difference was detected between Group 1 and Group 2, and between Group 2 and the control group for

Table 1. Demographic and baseline clinical and laboratory findings of the patients with CCHF.

	Ribavirin group (n = 56)	Control group (n = 44)	P
Demographic characteristics			
Age (years) (mean ± SD)	46.88 ± 17.46	46.27 ± 17.36	0.864
Female sex, n (%)	33 (57.9)	21 (48.8)	0.181
Tick bite history, n (%)	36 (64.3)	28 (63.6)	0.556
Living in rural area, n (%)	51 (91.1)	35 (79.5)	0.088
Median (range) duration from onset of symptoms to hospital admission	4 (1–8)	3 (1–12)	0.658
Median (range) duration of hospitalization	8 (4–24)	7 (1–12)	<0.001
Symptoms and signs, n (%)			
Bleeding	18 (32.1)	11 (25)	0.289
Fever	43 (76.8)	35 (79.5)	0.467
Confusion	3 (5.4)	1 (2.3)	0.405
Myalgia	46 (82.1)	32 (72.7)	0.188
Headache	26 (46.4)	14 (31.8)	0.101
Abdominal pain	12 (21.4)	3 (6.8)	0.037
Diarrhea	10 (17.9)	5 (11.4)	0.17
Nausea	44 (78.6)	24 (54.5)	0.01
Vomiting	20 (35.7)	11 (25)	0.176
Maculopapular rash	5 (8.9)	5 (11.4)	0.469
Hepatosplenomegaly	2 (3.6)	2 (4.5)	0.649
Laboratory findings, median (range)			
Leukocytes (/mm^3)	1800 (157–11,200)	2500 (100–10,000)	0.011
Hb (g/dL)	13.4 (6.6–18.2)	14.1 (6.8–17.5)	0.128
Platelets (×10^3)	44.5 (5–150)	65 (6–314)	0.015
APTT (s)	41.2 (31.3–82.3)	34.95 (23.9–105.8)	0.001
PT (s)	12.3 (9.7–34.5)	10.7 (8.9–17)	0.001
ALT (U/L)	93.5 (10–734)	78 (10–1089)	0.309
AST (U/L)	232 (29–1055)	91.5 (21–657)	0.021
CPK (U/L)	319 (55–3796)	206 (37–1920)	0.019
LDH (U/L)	576.5 (190–2781)	367 (139–6105)	0.004

SD, standard deviation; Hb, hemoglobin; APTT, activated partial thromboplastin time; PT, prothrombin time; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatinine phosphokinase; LDH, lactate dehydrogenase.

Table 2. Demographic, baseline clinical and laboratory findings of the patients treated with ribavirin.

	Group 1 (n = 29)	Group 2 (n = 27)	P
Demographic characteristics			
Age (years) (mean ± SD)	47.7 ± 15.1	46.5 ± 18.6	0.825
Female sex, n (%)	16 (55.2)	17 (63)	0.554
Median (range) duration from onset of symptoms to hospital admission	2 (1–5)	5 (4–8)	0.000
Median (range) duration of hospitalization	8 (4–16)	9 (4–24)	0.078
Symptoms and signs, n (%)			
Bleeding	10 (34.5)	8 (29.6)	0.698
Fever	22 (75.9)	21 (48.8)	0.865
Confusion	1 (3.4)	2 (7.4)	0.511
Myalgia	22 (75.9)	24 (88.9)	0.299
Headache	12 (41.4)	14 (51.9)	0.432
Abdominal pain	4 (13.8)	8 (29.6)	0.149
Diarrhea	2 (6.9)	8 (29.6)	0.038
Nausea	25 (86.2)	19 (70.4)	0.199
Vomiting	12 (41.4)	8 (29.6)	0.359
Maculopapular rash	2 (6.9)	3 (11.1)	0.664
Hepatosplenomegaly	0 (0)	2 (7.4)	0.228
Laboratory findings, median (range)			
Leukocytes (/mm^3)	1800 (157–3600)	1900 (800–11,200)	0.131
Hemoglobin (g/dL)	13.4 (6.6–16)	13.4 (9.4–18.2)	0.844
Platelets (×10^3)	44 (7–123)	48 (5–150)	0.617
APTT (s)	39.2 (31.3–74.6)	42.1 (32.5–82.3)	0.207
PT (s)	11.4 (9.7–34.5)	13.2 (10.1–33.3)	0.028
ALT (U/L)	96 (10–734)	88 (14–438)	0.528
AST (U/L)	217 (37–1055)	242 (29–790)	0.646
CPK (U/L)	311 (55–3796)	327 (74–1817)	0.863
LDH (U/L)	569 (247–2781)	615 (190–1693)	0.922

SD, standard deviation; Hb, hemoglobin; APTT, activated partial thromboplastin time; PT, prothrombin time; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatinine phosphokinase; LDH, lactate dehydrogenase.

Table 3. Comparison of clinical and laboratory characteristics and blood products use in ribavirin-treated and untreated patients.*

	Ribavirin group (n = 56)	Control group (n = 44)	P
Duration of fever resolution[a] (days)	2 (1–7)	1 (1–4)	0.001
Duration of bleeding cessation[b] (days)	3 (1–4)	1 (1–6)	0.127
Difference between laboratory values on the 5th and 1st day[c]			
Leukocytes (/mm^3)	1350 (–6700–11,400)	2050 (–4400–8400)	0.147
Hb (g/dL)	–0.25 (–4.2–3)	–0.6 (–9.7–4.6)	0.157
Platelets (×10^3)	14 (–56–144)	58.5 (–41–175)	0.031
APTT (s)	–6.35 (–33.5–25.1)	–7.45 (–48.9–9)	0.59
PT (s)	–0.68 (–17.3–4.2)	–0.3 (–5.5–9.1)	0.255
ALT (U/L)	4 (–571–326)	0.5 (–576–250)	0.997
AST (U/L)	–35.5 (–648–470)	–12.5 (–416–240)	0.576
CPK (U/L)	–156 (–3666–495)	–127.5 (–1845–4941)	0.234
LDH (U/L)	–156.5 (–2631–567)	–90 (–2069–143)	0.361
Given blood product (units)			
Platelet concentrates	1 (0–15)	0 (0–61)	0.01
FFP	0 (0–20)	0 (0–19)	0.401

*Data were presented as median (range).
[a]Analysis was performed for patients with fever (n = 78).
[b]Analysis was performed for patients with bleeding (n = 29). [c]Negative values indicate descending laboratory findings on the 5th day.
SD, standard deviation; Hb, hemoglobin; APTT, activated partial thromboplastin time; PT, prothrombin time; ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatinine phosphokinase; LDH, lactate dehydrogenase; FFP, fresh frozen plasma.

PT values (P = 0.011 and P = 0.004, respectively). However, there was no difference between the three groups in terms of the other laboratory parameters. Use of platelet concentrates was least in the control group (P = 0.037). A significant difference was detected between Group 1 and the control group, and between Group 2 and the control group for platelet concentrates use (P = 0.025 and P = 0.031, respectively). There was no significant difference between the three groups in terms of need for FFP (Table 4). Erythrocyte concentrates could not be compared due to limited use. No adverse reactions were detected due to ribavirin.

4. Discussion

Ribavirin was given to CCHF patients who were admitted to a tertiary care hospital and had symptoms that had started less than 5 days earlier. Oral ribavirin is used because there is no intravenous form of ribavirin in Turkey. In this study, no effect of ribavirin on the improvement of clinical and laboratory parameters and blood products use was detected. The longer duration of hospitalization in the patients who received ribavirin could be related to the poorer laboratory findings of these patients, even though the clinical characteristics were similar. Additionally, patients who received ribavirin were discharged later depending on the duration of treatment.

Many observational and case-control studies in which ribavirin has been used for treatment have begun to increase by taking in vivo and in vitro studies as examples (8–20). In some of these studies no positive effect of ribavirin was shown on the prognosis of the disease compared to the control group (9,16,18). These three studies included patients who were transferred to tertiary centers because of severity of the disease as in our study. In the quasi-experimental, multicenter study by Elaldi et al. (9) no decline in fatality attributable to ribavirin was found. Only the need for platelet concentrate and FFP was lower in the patients who received ribavirin. In our study, use of platelet concentrates was greater in Groups 1 and 2. This may be related to the low platelet values in the ribavirin-treated patients. The transferred patients were severe cases. Furthermore, duration of symptoms until admission to the

Table 4. Comparison of clinical and laboratory characteristics and blood products use in early, late, and untreated patients.*

	Group 1 (n = 29)	Group 2 (n = 27)	Control group (n = 44)	P
Duration of fever resolution[a] (days)	2.5 (1–6)[c]	2 (1–7)[c]	1 (1–4)[d]	0.002**
Duration of bleeding cessation[b] (days)	2 (1–4)	3.5 (2–4)	1 (1–6)	0.148
Difference between laboratory values on the 1st and 5th days[e]				
Leukocytes (/mm^3)	1600 (–200–3300)	1000 (–6700–11,400)	2050 (–4400–8400)	0.26
Hb (g/dL)	0.1 (–4.2–2)	–0.4 (–4.2–3)	–0.6 (–9.7–4.6)	0.274
Platelets (×10^3)	20 (–54–144)	7 (–56–108)[c]	58.5 (–41–175)[d]	0.027**
APTT (s)	–6.3(–33.5–20.1)	–6.5 (–33.1–25.1)	–7.45 (–48.9 – 9)	0.632
PT (s)	–0.13 (–17.3–2.6)[d]	–1.6 (–13–4.2)[c]	–0.3 (–5.5–9.1)[d]	0.007**
ALT (U/L)	2000 (–571 – 326)	6 (–362–193)	0.5 (–576–250)	0.953
AST (U/L)	–65 (–648–153)	–25 (–598–470)	–12.5 (–416–240)	0.484
CPK (U/L)	–169 (–3666–254)	–142 (–1493–495)	–127.5 (–1845–4941)	0.333
LDH (U/L)	–166 (–2631–191)	–109 (–1132–567)	–90 (–2069–143)	0.625
Given blood product (units)				
Platelet concentrates	1 (0–8)[c]	1 (0–15)[c]	0 (0–61)[d]	0.037**
FFP	0 (0–20)	0 (0–20)	0 (0–19)	0.697

*Data were presented as median (range).
[a]Analysis was performed for patients with fever (n = 78).
[b]Analysis was performed for patients with bleeding (n = 29).
[e]Negative values indicate descending laboratory data on the 5th day.
**There is a significant difference between c and d.
For duration of fever resolution; P = 0.015 (Group 1 and the control); P = 0.001 (Group 2 and the control)
For PLT, P = 0.007 (between Group 2 and the control).
For PT, P = 0.011 (Group 1 and Group 2); P = 0.004 (Group 2 and the control).
For PLT concentrates, P = 0.025 (Group 1 and the control); P = 0.031 (Group 2 and control)

hospital was long [median: 3.5 (1–12) days]. The delay of initiation of ribavirin in these patients could be one of the parameters affecting the antiviral response.

The studies that examined the positive effects of ribavirin on clinical and/or laboratory parameters have mostly been reported from Turkey, Iran, and Pakistan (8,10,12,14,15,17,19,20). In their retrospective cohort study, Fisgin et al. (14) reported that laboratory values improved earlier in the group that received ribavirin earlier compared to both of the groups that did not receive or received it later. The efficacy of early or late initiation of ribavirin was not assessed in our study. Additionally, platelet counts increased rapidly in the control group. This condition may have been caused by unfavorable laboratory parameters in the patients that received ribavirin. Moreover, early decline of platelet counts in the patients who received ribavirin late may be due to clinical progress of the disease.

Because there is no definite recommendation about the effect of ribavirin in CCHF, some centers in Turkey give ribavirin but some use only supportive treatment. In a study about the epidemiology of CCHF, it was determined that although the use of ribavirin decreased from 67.9% to 21.8% between 2004 and 2007 in Turkey, the fatality rates did not change (5.2% in 2004, 4.6% in 2007) (24). According to data from the Ministry of Health of Turkey, the fatality rate was 4.8% in 2014. The effect of ribavirin on fatality could not be evaluated in our study because two patients died.

To date, only one randomized study about ribavirin use in CCHF patients has been conducted, by Koksal et al. (13). In their study (n = 136 patients), no positive effect of ribavirin was determined on clinical or laboratory findings. The two meta-analyses and a systemic review reported to date were not sufficient to clarify the discussions. The authors pointed out the inadequate level of evidence, the

high risk of bias, the heterogeneity of the patients, and the time of ribavirin initiation as common problems (21,22). However, Soares-Weiser et al. (22) suggested that ribavirin treatment could reduce mortality by 44% according to the results of selected observational studies. In a review about the treatment of CCHF, ribavirin is recommended in suspected cases until new data are provided, even though its efficacy has not been fully confirmed (25).

Our study has some limitations. First of all, this was an observational study including a small sample size. Application of supportive treatment to all patients may be considered a confounding factor in the study. In addition, it was not possible to choose case and control groups with all characteristics similar. Unfortunately this increased the risk of bias. Ribavirin could be administered late because the study was conducted with transferred patients. The effect of ribavirin on mortality was not evaluated, which is another limitation. Moreover, detection of viral load as an independent predictor of mortality could not be performed.

In conclusion, in our observational study, no positive effects of oral ribavirin on blood products use or clinical or laboratory parameters in CCHF patients were determined. Considering the risk of fatal prognosis in severe cases, we suggest that well-designed randomized trials should be planned to evaluate the efficacy of ribavirin in CCHF.

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