The evaluation of ribavirin use in patients with Crimean-Congo hemorrhagic fever

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Objective

Crimean Congo hemorrhagic Fever (CCHF) is an important viral hemorrhagic disease caused by CCHF virus belonging to the Nairovirus genus of Bunyaviridae family.

Primary mode of transmission to humans is by *Hyalomma* ticks or by direct contact with the blood or infected tissues of infected humans or domestic animals. The disease was first recognized in Turkey in 2002, since then to the end of 2011, more than 6000 cases were detected with approximately 6% mortality rate. Although in some region it is under control, geographic distribution of disease is widened.

Since there is no other effective drug, the World Health Organization currently recommends ribavirin as a potential therapeutic drug for CCHF. While supportive care, mainly with blood products, is the basic treatment, ribavirin usage as antiviral treatment is a debate because of conflicting results.
The aim of this study is to investigate the effect of oral ribavirin on mortality and morbidity in the patients with CCHF treated in our hospital.

Methods

A case control study was retrospectively conducted between the years 2007 and 2011. Our hospital is a tertiary referral hospital and there were two independent infectious diseases departments. One of the departments had ribavirin in the treatment protocol of CCHF patients. Supportive care protocol (mainly hematological support with fresh-frozen plasma, thrombocyte suspension, erythrocyte suspension when needed according to the homeostatic values) was similar in both of the departments.

Patients: CCHF diagnosis was confirmed with PCR and/or ELISA IgM in all patients with compatible clinical presentation and epidemiological history. The patients who had received at least 48 hours of ribavirin and/or supportive therapy were included in the study. Ribavirin group were monitored in the sense of probable adverse effects.

Ribavirin therapy: Ribavirin was used according to the protocol described by Turkish Ministry of Health. Patients were treated initially loading dose of 2g oral ribavirin, then 4x1g/day for four days, then 4x500 mg/day, totally 10 days. Ribavirin was not used in the patients with active bleeding or renal insufficiency or severe diarrhea.

***Statistical analysis*:** The two groups were compared according to clinical course, laboratory findings and hematological product requirement. SPSS 15.0 package program was used for statistical analysis. The Chi-square and the Wilcoxon–Mann–Whitney U test were used when appropriate to compare proportions.

Results

Crimean Congo Hemorrhagic Fever (CCHF) is an important viral hemorrhagic disease caused by CCHF virus The study was conducted with 243 patients (122 male, 121 female) after excluding 7 deaths because of less than 48 hours hospitalization. The ribavirin group was composed of 91 patients (37.4%). Both of the groups were similar upon admission in terms of age, gender and initial laboratory findings, except PT and aPTT mean values

(Table). For blood and blood products requirement, there was no statistically significant difference between the groups. One patient (1.1%) in ribavirin group (ribavirin was started on fifth day of disease) and eight patients (5.3%) in the other group died (p=0.096, OR=5.0). No adverse effect was observed in the ribavirin group during treatment.

Table. Comparison of age, gender distributions and laboratory findings of both groups

	Ribavirin group	**Control group**	**p value**
Gender M/F (n)	**47/44**	**75/77**	**0.728**
	Mean (±SD)	**Mean (±SD)**	**p value**
Age (years)	**48 (±17)**	**51 (±18)**	**0.261**
Hgb (10^3/µL)	13.6 (±1.8)	13.5 (±1.9)	0.646
PLT (10^3/µL)	54644 (±40924)	56204 (±34946)	0.267
WBC (10^3/µL)	2459 (±1494)	2837 (±2134)	0.259
AST (U/L) (N: 5–35 U/l)	254 (±246)	316 (±640)	0.650
ALT (U/L) (N: 0–45 U/l)	110 (±103)	137 (±161)	0.254
LDH (U/L) (N:0–248 U/l)	733 (±566)	747 (±729)	0.783
CK (U/L) (N: 0-145 U/l)	623 (±700)	606 (±1140)	0.056
PT (s) (N: 11–14 s)	13.1 (±3.4)	12.0 (±2.7)	**0.001**
aPTT (s) (N:25-36 s)	43.2 (±11.0)	40.3 (±13.2)	**0.004**
Mortality n (%)	1 (1.1%)	8(5.3%)	0,096(**OR=5**)

Conclusion

Although no statistical significance was detected in our study, ribavirin seems noteworthy in survival of CCHF patients. Besides, as we did not observe any adverse effects, ribavirin should not be excluded from the CCHF treatment protocol until convincing studies performed.