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Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea

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Abstract

Background—In the wake of the recent outbreak of Ebola virus disease (EVD) in several African countries, the World Health Organization prioritized the evaluation of treatment with convalescent plasma derived from patients who have recovered from the disease. We evaluated the safety and efficacy of convalescent plasma for the treatment of EVD in Guinea.

Methods—In this nonrandomized, comparative study, 99 patients of various ages (including pregnant women) with confirmed EVD received two consecutive transfusions of 200 to 250 ml of ABO-compatible convalescent plasma, with each unit of plasma obtained from a separate convalescent donor. The transfusions were initiated on the day of diagnosis or up to 2 days later. The level of neutralizing antibodies against Ebola virus in the plasma was unknown at the time of administration. The control group was 418 patients who had been treated at the same center during the previous 5 months. The primary outcome was the risk of death during the period from 3 to 16 days after diagnosis with adjustments for age and the baseline cycle-threshold value on polymerase-chain-reaction assay; patients who had died before day 3 were excluded. The clinically important difference was defined as an absolute reduction in mortality of 20 percentage points in the convalescent-plasma group as compared with the control group.

Results—A total of 84 patients who were treated with plasma were included in the primary analysis. At baseline, the convalescent-plasma group had slightly higher cycle-threshold values and a shorter duration of symptoms than did the control group, along with a higher frequency of eye redness and difficulty in swallowing. From day 3 to day 16 after diagnosis, the risk of death was 31% in the convalescent-plasma group and 38% in the control group (risk difference, −7 percentage points; 95% confidence interval [CI], −18 to 4). The difference was reduced after adjustment for age and cycle-threshold value (adjusted risk difference, −3 percentage points; 95% CI, −13 to 8). No serious adverse reactions associated with the use of convalescent plasma were observed.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Conclusions—The transfusion of up to 500 ml of convalescent plasma with unknown levels of neutralizing antibodies in 84 patients with confirmed EVD was not associated with a significant improvement in survival. (Funded by the European Union's Horizon 2020 Research and Innovation Program and others; ClinicalTrials.gov number, NCT02342171.)

The recent outbreak of Ebola Virus Disease (EVD) in West Africa has been the worst ever witnessed. By September 9, 2015, a total of 28,183 cases and 11,306 deaths had been reported.1 The high case fatality rate (40 to 60%)2,3 highlights the need for effective EVD-specific treatments, which would also provide an incentive for patients to present to treatment centers early. Such interventions would facilitate the rapid tracing of contacts of patients and the implementation of measures to control the spread of an outbreak.

The World Health Organization (WHO) has prioritized the evaluation of treatment with convalescent whole blood or plasma derived from patients who have recovered from EVD.4 Such treatment has been used successfully for other serious infectious diseases with appropriate safeguards.5,6 Data on previous use of convalescent whole blood or plasma for the treatment of EVD are limited. The largest case series involved eight patients who were treated with convalescent whole blood during the Kikwit outbreak of EVD in 1995; of these patients, seven survived.7 However, it was not possible to assess whether the low case fatality rate was due to treatment with convalescent whole blood or other factors, such as characteristics of the patients or the period during the illness at which treatment was given.7 Because of uncertainty about the therapeutic value of convalescent blood products in the treatment of EVD, we conducted the Ebola-Tx trial to assess the safety and efficacy of convalescent plasma for the treatment of EVD in Conakry, Guinea. We did not evaluate the use of convalescent whole blood since convalescent plasma was available at the onset of the trial.

Methods

Study Design, Patients, and Intervention

From February 17, 2015, to August 3, 2015, we conducted a nonrandomized, comparative study at the Ebola Treatment Unit (ETU), which was supported by Médecins sans Frontières (MSF), in Conakry, Guinea. We determined that the randomization of patients was locally unacceptable in the volatile setting of the EVD outbreak.8 All eligible patients (of any age and including pregnant women) who had symptomatic, laboratory-confirmed EVD were enrolled. Written informed consent was obtained from the patients or their surrogates.

Exclusion criteria were a history of allergic reaction to blood or plasma products, a medical condition in which the infusion of additional fluid was contraindicated (e.g., decompensated congestive heart failure or renal failure with fluid overload), the futility of treatment according to a consensus among members of the clinical team, and the presence of a condition associated with a substantial risk to staff members (e.g., agitation). The criteria for futility included the presence of shock that was unresponsive to fluid challenge or that was accompanied by signs of multiorgan failure (defined as the presence of oliguria or anuria and impaired consciousness or the presence of oliguria or anuria and jaundice).

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Eligible patients received a transfusion of convalescent plasma as soon as ABO-compatible plasma was available to the treatment center. It was planned that the control group would consist of patients who had been admitted to the ETU during the preparatory period for the study while the system for apheresis and pathogen reduction was being set up and those for whom ABO-compatible convalescent plasma was not available during the study. At the start of recruitment, there was a sufficient amount of convalescent plasma available to treat all the patients, so a protocol amendment was approved for the control group to consist of patients who were treated at the same ETU before the initiation of the trial. Additional details regarding the conduct of the study are provided in the protocol, available with the full text of this article at NEJM.org.

In accordance with WHO guidance,4 patients received two consecutive transfusions of 200 to 250 ml of ABO-compatible convalescent plasma (i.e., 400 to 500 ml of convalescent plasma in total), with each unit of plasma obtained from a separate convalescent donor; small adults and children weighing less than 45 kg received two transfusions of 10 ml of convalescent plasma per kilogram of body weight. Each transfusion was administered over a 20-minute period, with a 15-minute interval between the two transfusions.

Study Oversight

The study protocol was approved by the national ethics committee in Guinea, the institutional review board of the Institute of Tropical Medicine, and the ethics committees of the Antwerp University Hospital, the London School of Hygiene and Tropical Medicine, MSF, and the WHO. The European Union's Horizon 2020 Research and Innovation Program and the other funders of the study had no role in the study design, the collection, analysis, or interpretation of the data, or the writing of the report. The first author had full access to all the study data and had final responsibility for the decision to submit the manuscript for publication. (Details are provided in the Methods section in the Supplementary Appendix, available at NEJM.org.)

Procedures

The participation of convalescent donors was organized through the Ebola survivor association of Conakry (Table S1 in the Supplementary Appendix). For patients with EVD, the determination of blood group was made with the use of the Beth–Vincent method or the MDmulticard (Medion Grifols Diagnostics), and ABO-compatible plasma was ordered. Supportive care for all patients was based on MSF guidelines for the treatment of EVD, including intravenous hydration and shock management (see the Methods section in the Supplementary Appendix).9

Blood samples were obtained from study patients on three occasions: at the time of diagnosis for use in a real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for Ebola virus (EBOV), blood-group typing, and point-of-care laboratory testing (i-STAT); at 24 hours after transfusion for an RT-PCR assay; and at the time of discharge to ascertain EVD cure on RT-PCR. Each RT-PCR assay provided a cycle-threshold value, which is the number of cycles required for the fluorescent signal to cross the threshold for a positive test. A lower value is correlated with a higher viral load.

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Laboratory testing for EBOV was performed on whole-blood samples at the Guinean national laboratory for hemorrhagic fever viruses with the use of the QIAamp Viral RNA Kit (Qiagen) for nucleic acid extraction and the LightMix Ebola Zaire rRT-PCR Test (TIB MOLBIOL) and a SmartCycler (Cepheid) for genomic amplification, according to the manufacturer's recommendations. Patients were discharged after a negative result for EBOV on RT-PCR.

Outcome Measures and Definitions

The primary outcome was the risk of death in the 14 days after the administration of convalescent plasma. Included in the analysis were all deaths that occurred up to 16 days after PCR confirmation of EVD in the two groups to allow for plasma administration up to and including the second day after PCR confirmation (by which time plasma administration had started in all the patients). Patients in the convalescent-plasma group were contacted by telephone after discharge to confirm survival up to day 30. Patients in the control group who had been discharged before day 16 and who had not been followed up were assumed to be alive on day 16.

Adverse events and serious adverse events that were considered by the treating clinician to be reactions that were related to the receipt of convalescent plasma were recorded from the start of treatment until 4 hours after the end of the intervention (see the Methods section in the Supplementary Appendix). During transfusion, patients were under continuous supervision, with vital signs checked every 15 minutes until 15 minutes after the administration of the second plasma unit and at 4 hours after the end of the intervention. Safety risks to health workers who were administering the transfusions were also assessed.

Statistical Analysis

We determined that a risk of death that was 20 percentage points lower among patients receiving convalescent plasma than among patients in the control group was clinically important, on the basis of discussions by international experts during two teleconferences organized by the WHO and an estimate of the minimum effect necessary to justify the substantial investment in infrastructure, risk to health care workers, and mobilization of resources to organize widespread convalescent-plasma treatment in affected countries (Wood D, WHO: personal communication). We calculated that enrollment of up to 130 patients per group would provide a power of 90% to detect an absolute between-group difference of 20 percentage points, assuming a risk of death of 40 to 80% in the control group, at a two-sided alpha level of 0.05. Since convalescent plasma was available for all the patients and no concurrent controls were enrolled, comparative analyses included data from patients who were treated at the same ETU during a period that was prespecified in the analysis plan as September 2014 through January 2015. During this period, 507 patients with confirmed EVD were treated. The data and safety monitoring board advised the termination of the study on July 7, 2015, because of the low caseload. At that time, 102 patients with confirmed EVD had been enrolled. Although fewer than 130 patients had been enrolled in the convalescent-plasma group, the increased sample size in the control group meant that the study was still powered to detect an overall absolute difference of 20 percentage points in the risk of death.

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We used the chi-square test, Fisher's exact test, or the Wilcoxon rank-sum test to compare the clinical and demographic characteristics of the patients at baseline. The primary analysis population, as prespecified in the analysis plan, excluded patients who had died before the third day after confirmation of EVD on RT-PCR (i.e., on the day of diagnosis or on the two following days) in order to provide a similar starting point for measuring survival, given that the patients in the convalescent-plasma group started treatment at various times up to and including the second day after confirmation on RT-PCR. Patients who received other experimental treatments (e.g., favipiravir) were also excluded.

We used logistic-regression methods to compare risks of death in the two study groups. Adjustments for age and cycle-threshold value were prespecified in the statistical analysis plan on the basis of published data.10,11 We used logistic regression to estimate the probability of death for each patient and calculated adjusted risk differences and 95% confidence intervals as the differences in the averages of these probabilities.12

Patients were divided into four age groups (<5 years, 5 to 15 years, 16 to 44 years, and ≥45 years).10 Mortality in the control group was originally categorized according to five intervals for the cycle-threshold values. However, in the convalescent-plasma group, the cycle-threshold value was less than 20 in the case of only one patient and more than 35 in the case of only four patients, so we further categorized the cycle-threshold values into three groups (<25, 25 to 29.9, and ≥30 cycles) for analysis to avoid sparse data. Patients who received incomplete transfusions of convalescent plasma were included. We used adjusted logistic-regression models with interaction terms to perform subgroup analyses according to age group and cycle-threshold value.

Results

Patients

A total of 514 patients were assessed at the ETU during the study period; the diagnosis of EVD was confirmed in 114 of those patients. Twelve patients died before enrollment could take place. Compatible convalescent plasma was available for all 102 patients who were enrolled in the trial and was administered to 99 patients, of whom 84 were included in the primary analysis (Fig. 1). Of the 114 patients with confirmed EVD, 19 (17%) died before the third day after EVD diagnosis. Five children under the age of 5 years were treated with convalescent plasma, including 4 children who were under 1 year of age.

A total of 507 patients with confirmed EVD were admitted and treated with supportive care in the 5 months preceding the trial; of these patients, 87 (17%) died before the third day after EVD diagnosis. Two patients were excluded because of missing data with respect to outcome and age, which left 418 patients to be evaluated in the primary analysis.

On average, patients in the convalescent-plasma group had slightly higher cycle-threshold values and a shorter duration of symptoms at baseline than did patients in the control group. The frequencies of difficulty in swallowing and eye redness were higher in the convalescent-plasma group than in the control group (Table 1). Otherwise, the characteristics of the patients were generally similar in the two groups at baseline.

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Primary Analysis

From day 3 to day 16 after diagnosis, 26 of 84 patients (31%) in the convalescent-plasma group died and 158 of 418 patients (38%) died in the control group, for a risk difference of −7 percentage points (95% confidence interval [CI], −18 to 4). After adjustment for age and cycle-threshold value, mortality remained lower in the convalescent-plasma group, but the difference was not significant; the adjusted risk difference was −3 percentage points (95% CI, −13 to 8), and the adjusted odds ratio was 0.88 (95% CI, 0.51 to 1.51), as compared with the unadjusted odds ratio of 0.74 (95% CI, 0.45 to 1.22) (Table 2).

Of the measured factors that were not balanced in the two study groups, a longer duration of symptoms and difficulty in swallowing were associated with an increased risk of death in the control group. Additional adjustment for these factors had little effect on results (adjusted odds ratio, 0.90; 95% CI, 0.50 to 1.67). The between-group difference in the risk of death was greater among younger patients than among older patients after adjustment for cycle-threshold value, but the subgroups were small and the differences according to age were not significant (Tables 2 and 3).

Among the 84 patients in the convalescent-plasma group who were included in the primary analysis, there was 1 major protocol deviation in which a patient received less than 90% of the recommended volume of convalescent plasma, and there were 14 minor deviations involving 11 patients (Table S2 in the Supplementary Appendix). The exclusion of the patient with the major protocol deviation had a negligible effect on the between-group results. One day after the transfusion of convalescent plasma, the median cycle-threshold value increased by 3.5 cycles (Table S3 in the Supplementary Appendix).

Adverse Reactions

No serious adverse reactions were observed in the 99 patients who received convalescent plasma. Eight patients (8%) had an adverse reaction during or early after the transfusion. These reactions resolved spontaneously with treatment of the symptoms or a reduced rate of transfusion (Table 4, and Table S4 in the Supplementary Appendix). No safety events related to convalescent-plasma transfusion were reported among health care staff members.

Discussion

We observed no serious adverse reactions associated with the transfusion of convalescent plasma, and the procedure was acceptable to both donors and patients. In the adjusted analysis, the risk of death was slightly lower in the convalescent-plasma group than in the control group, but the difference was not significant. The prespecified clinically relevant difference (mortality that was lower by 20 percentage points in the convalescent-plasma group than in the control group) could be excluded (adjusted risk difference, −3 percentage points; 95% CI, −13 to 8). Mortality was analyzed up to day 16, since most patients with EVD have either recovered or died before this time. We did not have 30-day follow-up on the control patients, and 1 patient in the convalescent-plasma group died between day 16 and day 30 after being discharged as EVD-free and transferred to another medical facility for the management of another condition.

The level of EBOV-neutralizing antibodies in donor plasma could be important for the effectiveness of this intervention, as has been shown in studies involving nonhuman primates.13,14 However, we could not determine the level of neutralizing antibodies in the donor plasma before transfusion. EBOV plaque-neutralization assays require access to biosafety level 4 laboratories, which are currently unavailable in the affected countries, and shipment of blood samples abroad for sample testing was not possible at the time of this report. Consequently, unless convalescent plasma has been stockpiled during an EVD outbreak (in which case, anti-EBOV titers would already be known), it will probably be available without information regarding antibody levels at the time of administration until simple, field-adapted assays become available. Antibody levels are often low in some patients during early convalescence, which may have diluted the effect of convalescent plasma. Analyses of the level of EBOV-neutralizing antibodies in plasma donations and the correlation between such levels and the survival of patients will need to be performed. It is possible that high-titer convalescent plasma or hyperimmune globulin might be more potent. In addition, we do not know the most effective frequency of administration of convalescent plasma, and repeated administration with higher total volumes than those used in our study might be required.

We cannot exclude the possibility that some patients will benefit more than others from treatment with convalescent plasma. Of possible interest is that children younger than 5 years of age with EVD, who are known to have a poor prognosis,10 had the highest risk of death in the control group (Table 3). However, four of the five patients in this age group who were treated with convalescent plasma survived. Although pregnant women with EVD also have a poor prognosis,15 six of the eight pregnant women who were treated with convalescent plasma survived. These patients might also have benefited from the coagulation factors present in the plasma. Unfortunately, pregnancy was incompletely recorded in the control group.

The lack of obvious identified safety issues with the transfusion of convalescent plasma in an ETU is reassuring, since there was concern that serious adverse reactions might occur more frequently than they did. However, it is difficult to distinguish complications such as transfusion-related acute lung injury from EVD progression.16

In our comparative design, the control group was supposed to consist of patients who had presented before ABO-compatible plasma was available. However, with many survivors volunteering to donate, there was no shortage of convalescent plasma during the trial, so all the control patients were historical patients. There are clear limitations with respect to the use of a historical control group, and we cannot exclude the possibility that unmeasured confounding factors may have biased the mortality comparison. We also included the cycle-threshold value as a surrogate marker for viral load. Although there was variation in the risk of death during the 5-month historical period, there was no clear trend; our conclusions remained unchanged when the comparison was restricted to patients who were treated during the 3 months preceding the administration of convalescent plasma. We also conducted an intention-to-treat analysis in which we compared the risk of death among all the patients in whom EVD was diagnosed during the period of the convalescent-plasma trial with the risk of death among all historical patients; this analysis yielded results that were

similar to those in the primary analysis (see the Results section in the Supplementary Appendix).

The adjusted analyses that we conducted are unlikely to account for any variability in supportive care, such as the introduction of the point-of-care test, or for differences in caseload over time. Moreover, the administration of convalescent plasma requires intravenous access, which could have resulted in an increased administration of intravenous fluid beyond the plasma transfusion. Such factors (e.g., possible variability in supportive care and in administration of intravenous fluids) could have contributed to lowering the mortality in the convalescent-plasma group, but despite this fact, we did not find significantly lower mortality among the patients who received convalescent plasma than among patients who did not. The assessment of a dose–response relationship between the level of neutralizing antibodies in donor plasma and changes in viral load after transfusion or changes in survival could be important in determining any direct effect of antibody therapy.

We found that treatment with convalescent plasma was feasible to organize and administer and was acceptable to donors, patients, family, and health care providers in the middle of an EVD outbreak. Although uncertainty remains about our findings because of the nonrandomized nature of the study and the use of historical controls, we could not detect a marked survival effect of the administration of a dose of 200 to 250 ml of convalescent plasma twice daily. It remains to be assessed whether plasma with high levels of EBOV-neutralizing antibodies, possibly administered repeatedly, would show efficacy and whether subgroups of patients, such as young children and pregnant women, would be more likely to benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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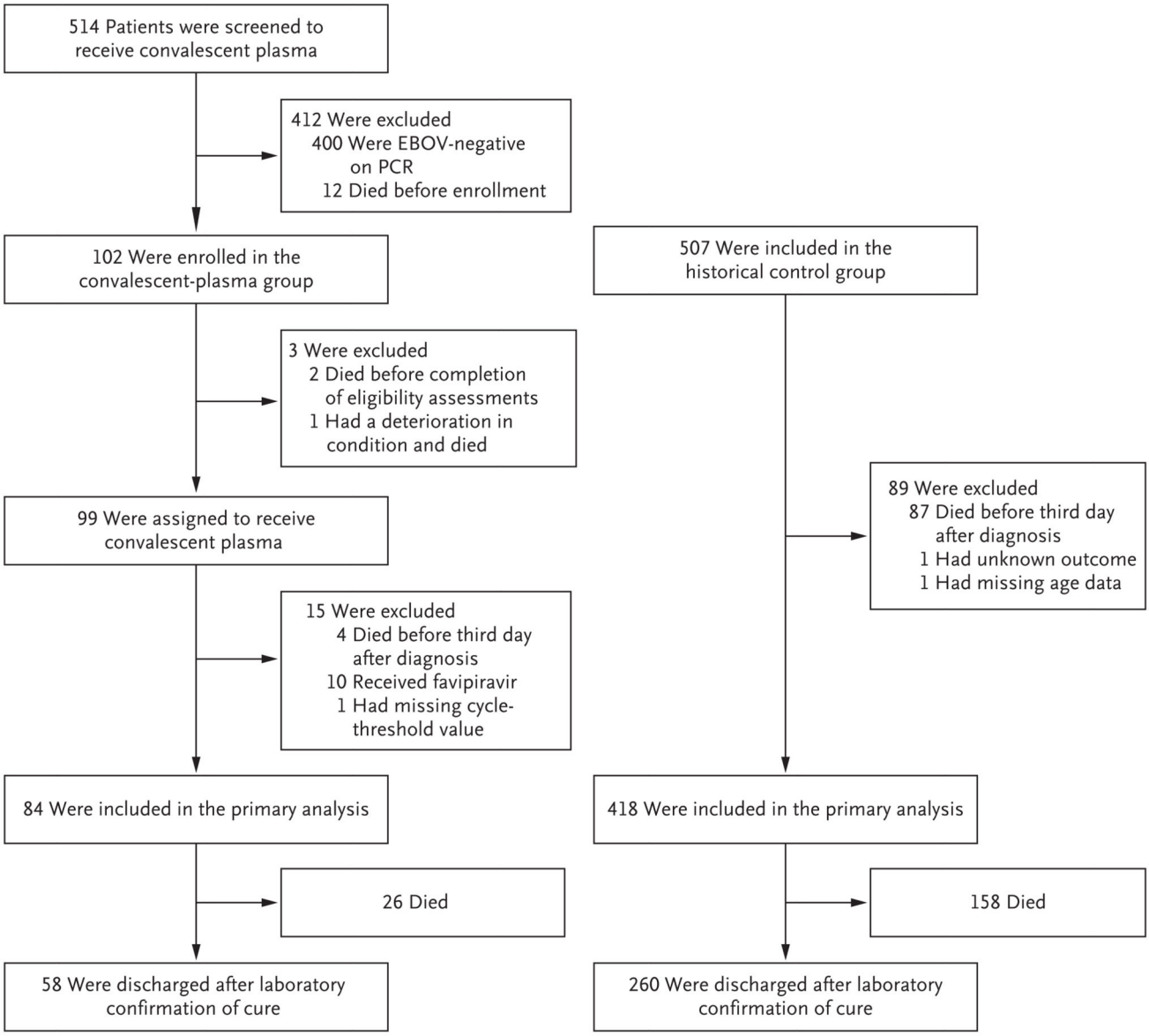

Figure 1. Enrollment and Outcomes.

Of the 514 patients who were screened, 412 were excluded, which left 102 patients who were eligible to be enrolled and assessed for eligibility to receive convalescent plasma. During screening, 400 patients were found to be negative for Ebola virus (EBOV) on polymerase-chain-reaction (PCR) assay. Of the remaining 114 patients with confirmed EVD, 19 (17%) died before the third day after EVD diagnosis. During the 5 months preceding the trial, 87 of the 507 patients with confirmed EVD (17%) in the historical control group died before the third day after EVD diagnosis. In the convalescent-plasma group, 10 patients who were health care workers were subsequently referred to a center dedicated to the care of such workers, where they received favipiravir in a different trial; of these patients, 7 survived.

Table 1
Characteristics of the Patients at Baseline.

Characteristic	Convalescent Plasma (N = 84)	Control (N = 418)	P Value
Sex — no. of patients (%)			0.25
Male	36 (43)	208 (50)	
Female	48 (57)	210 (50)	
Age			
Median (range) — yr	29 (0–75)	28 (0–87)	0.71
Distribution — no. of patients (%)			0.79
<5 yr	5 (6)	23 (6)	
5–15 yr	8 (10)	53 (13)	
16–44 yr	56 (67)	258 (62)	
≥45 yr	15 (18)	84 (20)	
Cycle-threshold value on PCR *			
Median no. of cycles (range)	27.3 (19.2–35.8)	26.0 (15.2–39.4)	0.007
Distribution — no. of patients (%)			0.05
<25 cycles	21 (25)	159 (38)	
25.0–29.9 cycles	41 (49)	183 (44)	
≥30 cycles	22 (26)	76 (18)	
Symptom on admission — no. of patients (%)			
Nausea and vomiting	42 (50)	203 (49)	0.81
Diarrhea	29 (35)	155 (37)	0.66
Weakness or asthenia	77 (92)	353 (84)	0.09
Pain	73 (87)	342 (82)	0.26
Cough	11 (13)	40 (10)	0.33
Difficulty breathing	4 (5)	11 (3)	0.29
Difficulty swallowing	15 (18)	39 (9)	0.02
Hiccups	7 (8)	38 (9)	0.82
Eye redness †	34 (40)	83 (20)	<0.001
Unusual bleeding ‡	5 (6)	21 (5)	0.79
Disorientation or agitation	0	2 (<1)	1.00
Anuria	1 (1)	1 (<1)	0.31
Seizures	0	1 (<1)	1.00
Duration of symptoms >6 days — no./total no. (%) §	14/73 (19)	203/412 (49)	<0.001
Coexisting chronic medical condition — no. of patients (%)			
Infectious ¶	1 (1)	2 (<1)	0.42
Noninfectious ‖	1 (1)	3 (1)	0.52

[*] The cycle-threshold value is the number of cycles required for the fluorescent signal to cross the threshold for positive results on polymerase-chain-reaction (PCR) assay. Thus, the values are inversely proportional to the amount of target nucleic acid in the sample (i.e., a lower value indicates a higher viral load).

[†] Eye redness includes both conjunctivitis and conjunctival bleeding.

[‡] Conjunctival bleeding is excluded from this category.

[§] The binary categorization of the duration of symptoms was based on the mean duration obtained from published data.2

[¶] Listed infectious conditions include tuberculosis and human immunodeficiency virus infection.

[‖] Listed noninfectious conditions include diabetes mellitus and chronic cardiac, pulmonary, and renal disease.

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Table 2

Primary Outcome Analysis.*

Variable	Convalescent Plasma (N = 84)	Control (N = 418)	P Value for Interaction†
Death 3 days to 16 days after diagnosis — no. (%)	26 (31)	158 (38)	
Odds ratio for death (95% CI)			
Unadjusted	0.74 (0.45–1.22)	1.00	
Adjusted for age and cycle-threshold value	0.88 (0.51–1.51)	1.00	
Adjusted for cycle-threshold value according to age group			0.92
<5 yr	0.18 (0.02–2.12)	1.00	
5–15 yr	0.75 (0.08–7.41)	1.00	
16–44 yr	0.86 (0.44–1.68)	1.00	
≥45 yr	1.52 (0.48–4.88)	1.00	
Adjusted for age according to cycle-threshold value			0.43
<25 cycles	0.87 (0.34–2.22)	1.00	
25–29.9 cycles	0.81 (0.37–1.76)	1.00	
≥30 cycles	1.11 (0.31–3.97)	1.00	

* The primary outcome was the risk of death in the 14 days after the administration of convalescent plasma. Included in the analysis were all deaths that occurred up to 16 days after PCR confirmation of EVD on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay in the two groups to allow for plasma administration up to and including the second day after RT-PCR confirmation. Patients who had died before the third day after confirmation of EVD on RT-PCR were excluded from the analysis to provide a similar starting point for measuring survival. The unadjusted between-group difference in the convalescent-plasma group was −7 percentage points (95% confidence interval [CI], −18 to 4), and the adjusted between-group difference was −3 percentage points (95% CI, −13 to 8).

† P values, calculated with the use of likelihood ratio tests, are for the comparison of models that included terms for the interaction of study group with the factor of interest with models that did not include interaction terms.

Table 3

Primary Outcome, According to Cycle-Threshold Value and Age.*

Age and Cycle-Threshold Value	Convalescent Plasma (N = 84)		Control (N = 418)	
	Patients	Death	Patients	Death
	no. (%)	*no./total no. (%)*	*no. (%)*	*no./total no. (%)*
All ages				
<25 cycles	21 (25)	11/21 (52)	159 (38)	90/159 (57)
25–29.9 cycles	41 (49)	11/41 (27)	183 (44)	56/183 (31)
≥30 cycles	22 (26)	4/22 (18)	76 (18)	12/76 (16)
Age <5 yr	5 (6)	1/5 (20)	23 (6)	15/23 (65)
<25 cycles	1 (1)	1/1 (100)	12 (3)	10/12 (83)
25–29.9 cycles	3 (4)	0	10 (2)	5/10 (50)
≥30 cycles	1 (1)	0	1 (<1)	0
Age 5–15 yr	8 (10)	1/8 (12)	53 (13)	10/53 (19)
<25 cycles	2 (2)	0	19 (5)	5/19 (26)
25–29.9 cycles	3 (4)	1/3 (33)	23 (6)	3/23 (13)
≥30 cycles	3 (4)	0	11 (3)	2/11 (18)
Age 16–44 yr	56 (67)	16/56 (29)	258 (62)	90/258 (35)
<25 cycles	15 (18)	8/15 (53)	97 (23)	50/97 (52)
25–29.9 cycles	28 (33)	5/28 (18)	112 (27)	34/112 (30)
≥30 cycles	13 (15)	3/13 (23)	49 (12)	6/49 (12)
Age ≥45 yr	15 (18)	8/15 (53)	84 (20)	43/84 (51)
<25 cycles	3 (4)	2/3 (67)	31 (7)	25/31 (81)
25–29.9 cycles	7 (8)	5/7 (71)	38 (9)	14/38 (37)
≥30 cycles	5 (6)	1/5 (20)	15 (4)	4/15 (27)

* Each RT-PCR assay provided a cycle-threshold value, which is the number of cycles required for the fluorescent signal to cross the threshold for a positive test. A lower value is correlated with a higher viral load.

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Table 4

Adverse Reactions among 99 Patients Receiving Convalescent Plasma.*

Adverse Reaction	Patients *no. (%)*
Serious adverse reaction	0
Any adverse reaction	8 (8)
Increase in temperature	5 (5)
Itching or skin rash	4 (4)
Nausea	1 (1)
Reaction requiring reduction in infusion rate	2 (2)
Reaction requiring temporary or permanent interruption of infusion	0

*Two patients had two adverse reactions each (fever and nausea in one patient and fever and itching in another).