MAJOR ARTICLE

High-Dose Intravenous Methylprednisolone for Hantavirus Cardiopulmonary Syndrome in Chile: A Double-Blind, Randomized Controlled Clinical Trial

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Background. Andes virus (ANDV)–related hantavirus cardiopulmonary syndrome (HCPS) has a 35% case fatality rate in Chile and no specific treatment. In an immunomodulatory approach, we evaluated the efficacy of intravenous methylprednisolone for HCPS treatment, through a parallel-group, placebo-controlled clinical trial.

Methods. Patients aged >2 years, with confirmed or suspected HCPS in cardiopulmonary stage, admitted to any of 13 study sites in Chile, were randomized by study center in blocks of 4 with a 1:1 allocation and assigned through sequentially numbered envelopes to receive placebo or methylprednisolone 16 mg/kg/day (≤1000 mg) for 3 days. All personnel remained blinded except the local pharmacist. Infection was confirmed by immunoglobulin M antibodies or ANDV RNA in blood. The composite primary endpoint was death, partial pressure of arterial oxygen/fraction of inspired oxygen ratio ≤55, cardiac index ≤2.2, or ventricular tachycardia or fibrillation within 28 days. Safety endpoints included the number of serious adverse events (SAEs) and quantification of viral RNA in blood. Analysis was by intention to treat.

Results. Infection was confirmed in 60 of 66 (91%) enrollees. Fifteen of 30 placebo-treated patients and 11 of 30 methylprednisolone-treated patients progressed to the primary endpoint ($P = .43$). We observed no significant difference in mortality between treatment groups ($P = .41$). There was a trend toward more severe disease in placebo recipients at entry. More subjects in the placebo group experienced SAEs ($P = .02$). There were no SAEs clearly related to methylprednisolone administration, and methylprednisolone did not increase viral load.

Conclusions. Although methylprednisolone appears to be safe, it did not provide significant clinical benefit to patients. Our results do not support the use of methylprednisolone for HCPS.

Clinical Trials Registration. NCT00128180.

Keywords. hantavirus; hantavirus cardiopulmonary syndrome; hantavirus pulmonary syndrome; methylprednisolone; clinical trial.

Hantaviruses cause hemorrhagic fever with renal syndrome (HFRS) throughout Asia and Europe and hantavirus cardiopulmonary syndrome (HCPS), also known as hantavirus pulmonary syndrome, throughout the Americas [1–7]. Andes virus (ANDV) is the sole etiologic agent of HCPS in Chile [8] and is unique among hantaviruses in its ability to be transmitted from person to person [9–11]. In Chile, 795 confirmed cases

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have been reported between 1995 and December 2012 with a 35% overall case fatality rate [12].

There are no Food and Drug Administration–approved antivirals, vaccines, or immunotherapeutic agents for HCPS, and competing hypotheses regarding pathogenesis of the capillary leak and cardiogenic shock have prompted evaluation of both antiviral and immunomodulatory agents [13, 14]. Ribavirin has activity against hantaviruses and has shown some benefit in treatment of HFRS [15–17]. Although a randomized, placebo-controlled trial of ribavirin for HCPS in North America was stopped on the basis of a futility analysis, there were no trends suggesting efficacy [18]. The apparent difference in efficacy of intravenous ribavirin in HCPS versus HFRS may result from the rapid progression to fatal cardiogenic shock in severe HCPS as compared to a subacute course in HFRS.

There is evidence suggesting a T-cell–driven pathogenesis of HCPS [19–21]. Circulating activated $CD8^+$ and $CD4^+$ cells appear at the onset of pulmonary edema and shock [22], and the frequency of hantavirus-specific $CD8^+$ T cells is significantly higher in patients with severe versus moderate HCPS [23]. An immunomodulatory strategy was first evaluated during the Korean conflict, when oral or intramuscular cortisone treatment of patients with HFRS reduced deaths during the shock phase but did not decrease overall mortality [24]. In Chile, an uncontrolled, retrospective analysis of 22 HCPS patients at a single center suggested that high-dose methylprednisolone treatment reduced mortality and shock [25] and led to adoption of this treatment in some centers. Here we report a phase 2, randomized, double-blind, placebo-controlled clinical trial to assess the safety and efficacy of intravenous methylprednisolone in patients with HCPS in the cardiopulmonary phase in Chile.

METHODS

Patient Population

We planned to enroll up to 70 subjects with suspected HCPS in the cardiopulmonary phase in order to enroll 60 subjects with confirmed infection in a parallel-group, placebo-controlled clinical trial. We established a research network in 13 hospitals with critical care capability, a physician investigator, research nurse, and pharmacist. Males and females ≥2 years of age with presumptive or confirmed HCPS in the cardiopulmonary phase with hypoxia (oxygen saturation <92% or patient with oxygen treatment) and bilateral infiltrates on chest radiograph were eligible for enrollment. Confirmed diagnosis required a febrile illness <12 days with positive hantavirus immunoglobulin (IgM) serology or genome detection by reverse transcription polymerase chain reaction (RT-PCR). Presumptive diagnosis required a febrile illness <12 days duration with headache; myalgia; nausea and vomiting, abdominal pain, diarrhea; a platelet count $<150 \times 10^3/\mu L$ and, if evaluable, immunoblasts on peripheral smear.

Exclusion criteria included a likely diagnosis other than HCPS; immunocompromised status; systemic corticosteroids equivalent to >0.5 mg/kg prednisone; systemic antiviral medication; any investigational drug within 30 days; gastrointestinal bleeding; extreme bradycardia; or pulseless electric activity. Written informed consent was obtained from participants or next of kin or a parent for children aged <18 years. We amended the protocol in July 2003 and October 2005 eliminating inessential evaluations. All protocol versions and consents were approved by the institutional review boards. Consort guidelines were followed for this report [26].

Grade 3 or 4 adverse events and the number of serious adverse events (SAEs) and proportion of patients experiencing ≥1 SAE were reviewed by a National Institutes of Health (NIH) data safety monitoring board (DSMB) on 7 occasions. The study was halted by the DSMB on 20 May 2005 in response to an imbalance in disease severity at entry and resumed on 2 February 2006. Interim safety and efficacy analysis was performed after enrollment of 60 subjects.

Study Medication

Subjects received either intravenous methylprednisolone (Solu-Medrol 500 mg/8 mL, Pharmacia/Pfizer) 8 mg/kg (up to 500 mg) in 100 cc D5W (or in 50 cc for children <20 kg) or placebo (D5W same volume) by intravenous infusion over 1 hour followed by the same dose administered over 23 hours. On days 2 and 3, 16 mg/kg (up to 1000 mg) methylprednisolone or placebo was diluted in 200 cc D5W (100 cc for children <20 kg) and administered over 24 hours. Infusion bags had identical appearance.

Randomization and Blinding

Subjects were randomized by study center in blocks of 4 with a 1:1 allocation. Sealed, sequentially numbered envelopes with treatment allocation were opened by the study pharmacist after enrollment. All other study personnel remained blinded to therapy.

Primary and Secondary Endpoints

The primary efficacy endpoint was the proportion of subjects who developed 1 or more of the following within 28 days after study entry: death, ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2) ≤55, cardiac index ≤2.2 $L/min/m^2$, pulseless electrical activity, ventricular tachycardia, or fibrillation. Primary safety endpoints were the number of SAEs and number of subjects with ≥1 SAE at least possibly related to study treatment.

Secondary efficacy endpoints included development and duration of shock (median blood pressure <70 mm Hg or systolic

pressure <70 + (2 × age in years) for children aged <16 years) or use of vasoactive drugs; duration of hospitalization and stay in the intensive care unit (ICU); time on mechanical ventilation; and serum creatinine ≥3.0 mg/dL. Serial quantification of viral RNA in blood was an exploratory endpoint.

Serial Clinical and Laboratory Evaluations

Demographic information and medical history were recorded at entry. Interim history, physical examination, complete blood cell count, chemistries, liver function tests, and serum lactate were obtained on days 1–7, 14, 28, 84, and 180; blood gases on days 1–4 and 7; chest radiograph on days 1–4, 7, and 28; urinalysis and a coagulation screening test on days 1, 2, and 4; blood for RT-PCR and viral load on days 1, 3, and 14 and in a subset on days 28, 84, and 180. Adverse events were reported according to NIH guidelines (ICTDR Investigator Manual, 6 February 2003) and the Division of Microbiology and Infectious Diseases adult and pediatric toxicity tables (February 2003).

Serology

Serum samples obtained at admission were tested for immunoglobulin G (IgG) and IgM antibodies to recombinant ANDV antigens by use of an enzyme-linked immunosorbent assay (ELISA) at the Virology Laboratory, Pontificia Universidad Católica, Santiago, Chile [27] and confirmed using an ELISA at the Chilean Institute of Public Health.

RNA Isolation and Complementary DNA Synthesis

Blood samples were separated into plasma and peripheral blood nucleated cells (PBNCs) and tested by a qualitative nested RT-PCR assay, and viral load was determined in PBNCs. Total RNA was extracted from 200 μL of plasma or suspended PBNCs using a High Pure Viral Nucleic Acid Kit (Roche Diagnostics, Mannheim, Germany). RNA (5 μL) was used as a template for cDNA synthesis with the primer S 5′-CACACGAACAACAGCTCGTGA-3′ [11], or ANDV-F primer 5′-GCAGCTGTGTCTACATTGGAGAC-3′ (from the small [S] genomic segment) [28].

Qualitative PCR

Complementary DNA was the template for the first round of PCR using primer S, and primer A 5′-TTAGATGATCATCAGGCTCAA-3′ [11]. The product was used for nested PCR with primer HV-F 5′-AGCTTAAAGATGCCGAGAA-3′ and HV-R 5′-TGAGTTCCCCGAGTTTGGT-3′. LightCycler Fast Start DNA Master SYBR Green I (Roche Diagnostic, Germany) was used according to the manufacturer's instructions. A LightCycler instrument was used for amplification and data acquisition. The specificity of the resulting product was confirmed by melting point analysis using LightCycler software version 3.5.

Quantitative Real-Time PCR (Viral Load)

TaqMan PCR assay was carried out using cDNA, primers, and probes as described [28], and adapted for the LightCycler v3.5 (Roche Diagnostics, Germany). All PCR reactions were performed using the Light Cycler TaqMan Master (Roche Diagnostic, Germany). Amplification products were determined by continuous monitoring of fluorescence. For quantification, serial dilutions of a plasmid containing the PCR target region were used as a standard curve. The viral load was normalized to the amount of PBNCs in the sample. The PBNCs were quantified by amplification of endogenous housekeeping β-globin gene using SYBR green real-time PCR as described [29]. The viral load was expressed as copies of ANDV S-segment per 10^7 PBNCs, calculated as the ratio (ANDV S-segment copy number/[β-globin DNA copy number/2]).

Statistical Analysis

We used descriptive statistics to summarize demographic information, with means and standard deviation for symmetric distributions, median and quartiles for asymmetrical distributions, and *t* tests to compare continuous variables. The numbers of observations and percentages were summarized for categorical data. We used Fisher exact test for categorical data and Mann-Whitney test for difference of medians. For survival analysis we used Kaplan-Meier product estimators and log-rank tests. To evaluate the relative effect of baseline variables of shock, mechanical ventilation, and sequential organ failure assessment (SOFA) score, versus treatment on the primary endpoint, we also used logistic regression analysis, including multivariate logistic regression based on forward variable selection, using a likelihood ratio Wald test. Power and sample size determination. Using a 2-sided Fisher exact test at a significance level of .05, we estimated that we would need 30 patients with confirmed infection in each treatment arm to achieve 78% power to detect a 50% reduction in the number of subjects who reached the primary endpoint. Based on experience in the ribavirin controlled trial [18], we estimated we would need to enroll 70 subjects with suspected HCPS in order to enroll 60 confirmed cases. SAS version 9.2 (SAS Institute Inc, Cary, North Carolina), S-plus 8.0 (Tibco, Palo Alto, California), and PASS 11 (NCSS, Kaysville, Utah) were used for statistical and power analyses.

RESULTS

From January 2003 through April 2010, we enrolled 66 subjects with suspected HCPS, and acute ANDV infection was confirmed in 60 (Figure 1 and Supplementary Figure 1). Thirty-two subjects (30 confirmed ANDV) received methylprednisolone, and 34 (30 confirmed ANDV) received placebo. The demographic characteristics and indicators of clinical severity at study

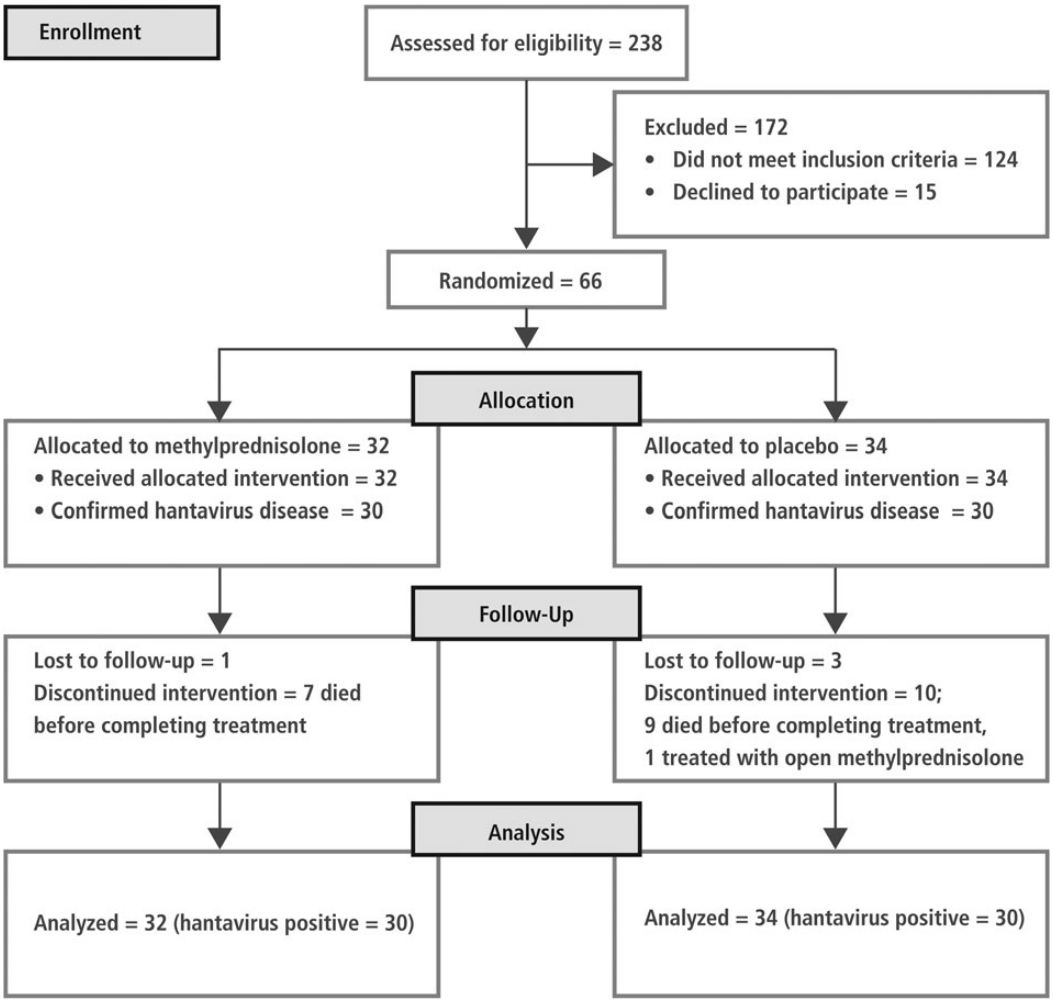


Figure 1. Enrollment, randomization, and follow-up of hantavirus cardiopulmonary syndrome cases.

entry are shown in Table 1. One patient in the placebo group was withdrawn without unblinding 24 hours after entry after reaching a primary endpoint (PaO_2/FiO_2 ratio ≤55). Methylprednisolone was administered, and the patient died 7 hours later. Four patients were lost to follow-up. One failed visits at 28, 84, and 180 days, but was confirmed to be alive on day 180; 3 failed visits on day 180.

Efficacy Outcomes

There was no statistically significant difference in the proportion of patients who died between methylprednisolone recipients (8 of 30 subjects [27%]) and placebo recipients (12 of 30 subjects [40%]) ($P = .41$), nor was there a difference in survival by log rank analysis by treatment group overall or when stratified for disease severity at entry ($P = .272$, Figure 2). Overall, however, the risk of death was significantly higher in subjects who had SOFA scores >8 at entry ($P < .0001$; Figure 2). Extracorporeal membrane oxygenation (ECMO) was unavailable at most centers and no patient received ECMO. No deaths occurred after day 28. The proportion of patients who reached any primary endpoint was 37% and 50% for methylprednisolone and placebo recipients, respectively ($P = .44$; Table 2). The mean number of days in hospital and ICU, days of inotropic support, days on mechanical ventilation, and the proportion developing shock or requiring intubation was also similar in the 2 treatment groups (Table 2).

We also conducted logistic regression analyses to compare the relative contributions of illness severity at entry versus treatment on the primary efficacy endpoint. The odds ratio (OR) for treatment group effect on the primary endpoint was 0.776 (95% confidence interval [CI], .259–2.323) compared with an OR for SOFA score at entry of 2.931 (95% CI, .911–9.432). By multivariate logistic regression analysis, only the SOFA score at entry was a statistically significant variable (OR = 3.141; CI,

Table 1. Demographic and Selected Clinical Parameters at Baseline of Patients With Confirmed Hantavirus Infection by Treatment Arm

Variable	Methylprednisolone (n = 30)	Placebo (n = 30)
Age, y, median (25th–75th percentiles)	40.5 (30.5–51.4)	39.0 (32.2–47.3)
Children		
<18 y	2 (7%)	4 (13%)
<15 y	1 (3%)	1 (3%)
Male	22 (73.3%)	20 (66.7%)
Days from onset of symptoms median (25th–75th percentiles)	6 (5–8)	5 (4–8)
Presence of shock	9 (30%)	15 (50%)
Patient intubated	4 (13.3%)	10 (33.3%)
PaO_2/FiO_2 ratio (missing in 2 cases, 1 from each arm), mean (SD)	204 (±108.6)	170 (±86.0)
SOFA score, mean (SD)	6.1 (±2.3)	7.9 (±3.3)
Platelet count ($\times 10^3/\mu L$)		
>150	2 (7%)	0 (0%)
101–150	3 (10%)	0 (0%)
51–100	15 (50%)	12 (40%)
≤50	10 (33%)	18 (60%)
Hematocrit (%), males, mean (SD)	45 (±7.5)	49 (±9.8)
Hematocrit (%), females, mean (SD)	43 (±4.7)	41 (±6.3)

Data are No. (%) unless otherwise specified. Most HCPS cases do not have significant alterations of liver, renal, or neurological parameters at hospital admission.

Abbreviations: FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SD, standard deviation; SOFA, sequential organ failure assessment.

1.206–8.182; $P = .0492$). Other individual clinical variables and the treatment group assignment were not statistically significant in the multivariate logistic regression analysis.

Safety

In 2 of the 6 subjects with negative hantavirus serologic tests, study drug was discontinued on day 1 when test results became available; 4 subjects completed the study drug before results were available. The number of subjects with at least 1 SAE was higher in the placebo (25/34 [74%]) than in the methylprednisolone group (14/32 [44%]) ($P = .02$), as were the total number of SAEs (Supplementary Table 1). Among the SAEs known to be associated with high-dose corticosteroid treatment, only 1, a ventilator-associated pneumonia, was reported, and it occurred in a patient in the placebo group. Grade 2 or 3 hyperglycemia was more common in methylprednisolone recipients ($P = .03$), but there was no grade 4 hyperglycemia in either group.

Detection of ANDV RNA

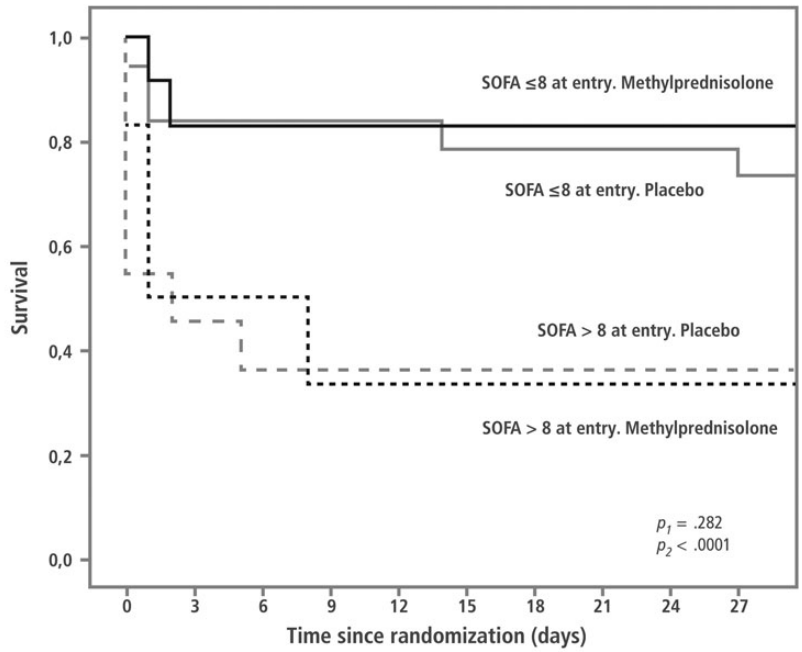
ANDV RNA was detected in PBNCs from most patients in both treatment groups through day 14. We found detectable RNA in PBNCs until day 84 in all 8 cases in the methylprednisolone group and in 4 of 6 in the placebo group, but all were negative by day 180 (Figure 3*A*). In contrast, the proportion of patients with ANDV RNA detected in plasma decreased rapidly over the first 7 days and was similar in the 2 treatment groups (Figure 3*B*).

Quantitative detection of ANDV RNA or viral load was studied in PBNCs, since this blood fraction was shown to have detectable virus in a higher proportion of patients and for a longer period of time than in plasma. ANDV viral load in PBNCs did not vary significantly during the first 14 days of clinical course and was similar between placebo- and methylprednisolone-treated patients (Figure 3*C*). We observed no difference in viral load at admission between patients who developed shock or required mechanical ventilation and those who did not (data not shown) and no difference in viral load in patients who died versus those who survived.

DISCUSSION

This is the largest intervention trial for HCPS in the Americas and the first to reach its target accrual. Methylprednisolone did not improve survival or significantly impact the primary composite endpoint of death, severe respiratory failure, severe shock, pulseless electrical activity, or ventricular tachycardia or fibrillation. Although trends in efficacy outcomes favored methylprednisolone, the multivariate analysis demonstrates that the primary efficacy endpoint was significantly affected by an increased composite disease severity score (SOFA score) at entry whereas treatment had no significant effect on the primary endpoint. As such, our results do not support methylprednisolone treatment for HCPS. Of note, Hammerbeck and Hooper recently questioned the role of T cells in HCPS pathogenesis, as T-cell–depleted Syrian hamsters challenged with ANDV still die from HCPS-like disease [30].

The adverse effects observed in the study were consistent with the clinical evolution of HCPS. Although the number of subjects with 1 or more SAEs and total SAEs were higher in the placebo group, this difference is also explained by more severe disease in the placebo group at entry. No SAE associated with high-dose corticosteroid use occurred in a methylprednisolone recipient, and methylprednisolone did not increase ANDV load or duration of viral detection in plasma or PBNCs. No deaths occurred after day 28, which is in contrast with observations by Steinberg in acute respiratory distress syndrome where methylprednisolone treatment was associated with increased 60- to 180-day mortality rates. This could be explained by shorter exposure to the drug in our study (3 vs 21 days) [31].



Number at risk

Methyl prednisolone	30	27	23	22	22	15	22	22	22	22
Placebo	30	21	20	20	20	20	19	19	19	18

Figure 2. Kaplan-Meier survival analysis by treatment arm and severity at entry. P_1: significance between methylprednisolone and placebo arm. P_2: significance between sequential organ failure assessment (SOFA) >8 and ≤8 at entry. Abbreviation: SOFA, sequential organ failure assessment.

Table 2. Primary and Secondary Efficacy Endpoints by Treatment Group

Endpoint	Methylprednisolone (n = 30)	Placebo (n = 30)	*P* Value	Relative Risk (95% CI)
Primary endpoint (any of the following: death, cardiac index ≤2.2 L/min/m^2, PaO_2/FiO_2 ≤55)	11/30 (37%)	15/30 (50%)	.44[a]	0.73 (.41–1.32)
Deaths	8/30 (27%)	12/30 (40%)	.41[a]	0.67 (.32–1.39)
Cardiac index <2.2 L/min/m^2	1/3 (33%)	2/6 (33%)	1.00[a]	1.00 (.14–7.09)
PaO_2/FiO_2 ratio ≤55	5/28 (18%)	5/30 (17%)	1.00[a]	1.07 (.35–3.31)
Develops shock (only cases without shock at entry)	4/21 (19%)	6/15 (40%)	.26[a]	0.47 (.16–1.40)
Develops respiratory failure requiring mechanical ventilation (only cases not intubated at entry)	6/26 (23%)	10/20 (50%)	.07[a]	0.46 (.20–1.06)
Serum creatinine ≥3.0 mg/dL (only cases <3.0 at entry)	1/29 (4%)	6/30 (20%)	.10[a]	1.21 (1.00–1.46)
Days in hospital, median (25th–75th percentiles)	8.0 (5.3– 11.3)	10.0 (1.0–16.3)	.5476[b]	
Days in ICU, median (25th–75th percentiles)	4.0 (2.0–7.0)	5.0 (1.0–7.0)	.3623[b]	
No. of cases in ICU	27 cases	29 cases		
Days of inotropic support, median (25th–75th percentiles)	2.0 (1.3–2.8)	3.0 (1.0–5.0)	.6299[b]	
No. of patients who received inotropic support	12 cases	20 cases		
Days mechanical ventilation, median (25th–75th percentiles)	2.0 (1.0–5.0)	4.5 (1.0–7.0)	.2687[b]	
No. of cases on mechanical ventilation	11 cases	20 cases		

Abbreviations: CI, confidence interval; FiO_2, fraction of inspired oxygen; ICU, intensive care unit;PaO_2, partial pressure of arterial oxygen.

[a] Fisher exact test.

[b] Mann-Whitney test.

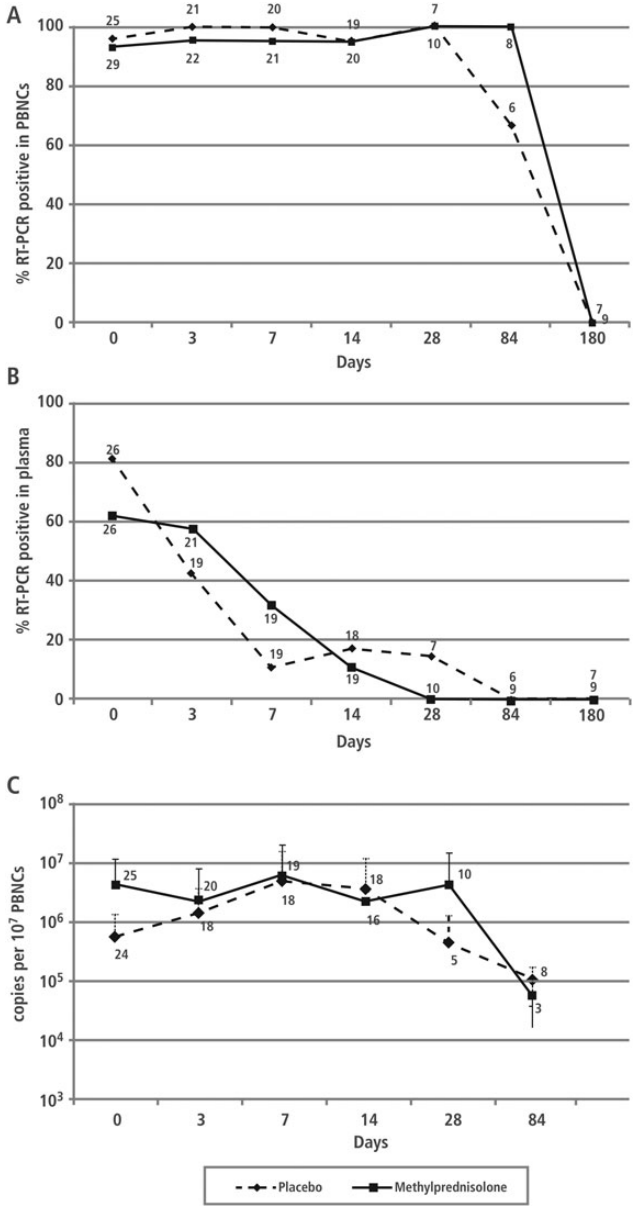


Figure 3. Detection of Andes virus RNA. Percentage of patients with detectable hantavirus RNA by reverse transcription polymerase chain reaction (RT-PCR) in peripheral blood nucleated cells (PBNCs; *A*) and plasma (*B*); numbers above or below graphic points show the number of patients from the placebo branch (above) or the methylprednisolone branch (below) tested at each time point. *C*, Logarithm of mean viral load by quantitative real-time RT-PCR in PBNCs days 0–84 after enrollment. The numbers of subjects tested at each time point are not identical in *A* and *C* because some cases with detectable viral RNA were not quantifiable. Bars = positive standard deviation. Abbreviations: PBNCs, peripheral blood nucleated cells; RT-PCR, reverse transcription polymerase chain reaction.

There are a number of limitations to this study. First, the study was not powered to detect a difference in mortality, a problem inherent to any trial involving a rare disease. Although we were able to enroll 3 times the number of cases enrolled in the North American study of HCPS over a similar time period [18], it took 6 and a half years of active enrollment to reach our target accrual in Chile. Another limitation is that cardiac index could not be measured in most cases, because hemodynamic monitoring was unavailable. Finally, increased disease severity in the placebo group at entry complicated both efficacy and safety analyses. While trends in individual severity indicators were noted by the DSMB in interim analyses, these differences decreased as study accrual continued.

In addition to the challenge of studying a rare disease that occurs in widely dispersed rural areas, in the most severe cases, progression to severe shock and death typically occurs within

hours after the onset of the cardiopulmonary phase. As such, there is little time for an intervention to exert its effect. Although enrollment during the febrile prodrome would offer more time for a treatment to exert its effect, it is difficult to clinically differentiate the prodrome of HCPS from other febrile illnesses. Although patients in the United States and Chile commonly seek medical attention during the febrile prodrome, HCPS is rarely suspected prior to onset of the cardiopulmonary phase.

In the controlled ribavirin trial in North America [18], although hantavirus infection was confirmed in >90% of patients with suspected HCPS in the cardiopulmonary phase based on clinical and routine laboratory findings, no subject enrolled with suspected hantavirus prodrome had infection confirmed. As such, inclusion of subjects with suspected hantavirus prodrome resulted in exposure of subjects without hantavirus infection to high-dose ribavirin. Because attempts to enroll subjects with presumed febrile prodrome would likely have led to exposure of many subjects without hantavirus infection to high-dose methylprednisolone despite entry of few or no subjects with hantavirus, patients with presumed hantavirus febrile prodrome were excluded from the current trial.

One safety concern was that administration of methylprednisolone might impair immune responses, delay clearing of ANDV, and lead to more severe or prolonged disease. However, there was no evidence of more severe or prolonged disease in those who received methylprednisolone, and detection of ANDV RNA in plasma decreased rapidly over the first week in both treatment groups. The latter is likely a result of antibody neutralization of free virus, as high neutralizing antibody titers develop in the first week after hospital admission [32]. However, it was noteworthy that virus was detected in PBNCs in patients through day 84 regardless of treatment group. Detection of viral RNA in the convalescent phase of HCPS by ANDV was also described by Manigold [33]. Finally, in contrast to observations in persons with Sin Nombre virus (SNV) [34, 35], we did not find any correlation between ANDV load at entry and disease severity.

While treatment of HCPS with high-dose methylprednisolone appears safe, treatment did not provide significant clinical benefit and our results do not support the use of methylprednisolone for HCPS. For the present, management of HCPS should be focused on optimizing supportive care, including ECMO where feasible [36]. In addition, there is a need for development of vaccines for prevention of hantavirus infection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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