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ORIGINAL RESEARCH

Sivelestat Inhibits Vascular Endothelial Injury Induced by Inflammatory Response and Improves the Prognosis of Hemorrhagic Fever with Renal Syndrome in Children: An Ambispective Cohort Study

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Background: In Asia, Hanta virus (HTNV) results in severe hemorrhagic fever with renal syndrome (HFRS). The efficacy of sivelestat in treating children with HTNV-induced HFRS remains unclear.

Methods: An ambispective cohort study was performed on children diagnosed with HFRS and hospitalized at the Children's Hospital Affiliated to Xi'an Jiaotong University from August 2018 to 2023. Patients who received neutrophil elastin-inhibitor infusion between August 2019 and August 2023 were assigned to the sivelestat group, while patients who did not were assigned to the control group. The independent sample *t* test was used for inter-group analysis. The Chi-square test and Fisher's exact probability test were used for categorical variables. Spearman correlation test was used to evaluate the correlation between two sets of continuous variables. Kaplan-Meier survival curve and Log -Rank test was used to evaluate the difference in cumulative probability of survival between the two groups.

Results: No significant differences were observed between the two groups in gender, age, contact history, body mass index, HFRS severity, clinical indexes at admission. Compared to the control group, the sivelestat group exhibited a significant decrease in the interleukin-8 level at 48 h (28.5±3 vs 34.5±3.5) and 72 h (21.3±4.5 vs 31.5±5.6) ($P<0.05$), as well as the ICAM-1 level at 48 h (553 ±122 vs 784±187) and 72 h (452±130 vs 623±85) ($P<0.05$). The concentration of VCAM-1 in the sivelestat group exhibited a consistent downward trend. Moreover, the level of VCAM-1 was significantly lower than that in the control group at 24 h (1760 ±289 vs 2180±445), 48 h (1450±441 vs 1890±267), and 72 h (1149±338 vs 1500±396) ($P<0.05$). Kaplan-Meier curve analysis revealed a statistically significant difference in the cumulative probability of survival between two groups (P = 0.041). In the secondary outcomes, the sivelestat group demonstrated a decrease in the utilization rate of mechanical ventilation and continuous renal replacement therapy (CRRT).

Conclusion: Sivelestat may suppress neutrophil-mediated inflammatory response to reduce endothelial and organ damage, and improve clinical outcomes in children with severe hemorrhagic fever and renal syndrome.

Keywords: Sivelestat, hemorrhagic fever with renal syndrome, vascular endothelial injury, inflammatory response, cohort study, children

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Introduction

Hantaviruses cause outbreaks of hemorrhagic fever in humans, and mice are the main intermediate hosts.[1] The diseases is predominantly manifested as haemorrhagic fever with renal syndrome (HFRS) in the Eurasia, and haemorrhagic fever with pulmonary syndrome (HFPS) in the Americas.[2,3] Over the past two decades, HFRS has broken out frequently in rural areas of northern China.[4] The cases in China account for roughly 90% of the global total.[5] The pathophysiological mechanism underlying this disease remains obscure, making it urgent to explore specific vaccine candidates or targeted drugs.

Considering the clinical correlation between inflammatory responses and disease severity or prognosis, HFRS has been increasingly thought as a sepsis resulting from an acute inflammatory response triggered by viral infection. Patients with HFRS often exhibit extensive multi-system vascular endothelial injury caused by inflammation, along with increased capillary permeability.[6,7] Abnormal serum levels of pro- and anti-inflammatory cytokines, chemokines, and other mediators are linked to the fatal outcomes of HFRS. Previous studies have found that the high expression of pro-inflammatory factors can enhance inflammatory response in target organs and local organs, and cause organ dysfunction through increasing the permeability of vascular endothelial and epithelial cells. Elevated interleukin-8 and interleukin-10 titers in patients with severe infection are associated with overexpression of endothelial injury markers (intercellular adhesion molecule-1, vascular adhesion adhesion molecule-1), organ dysfunction, and clinical outcomes.[6–10] The cytokine-induced systemic or local inflammatory response syndrome (SIRS), an abnormal immune system reaction, can trigger the activation, chemotaxis, and phagocytosis of immune cells, thus exacerbating endothelial damage and precipitating pulmonary edema, pancreatitis to trigger multiple organ dysfunction syndrome (MODS).[8–10] We observed a clear correlation between the overexpression of proinflammatory cytokines and the severity of the disease in clinically severe patients. By targeting the neutrophil elastase (NE), sivelestat has been proven to reverse amplified neutrophil activation and chemotaxis, thus alleviating inflammation in HFRS. We hope that drug treatment can reduce the damage of inflammatory mediators to children with HFRS and improve the clinical outcome of patients, so as to benefit more children. The study aimed to investigate the effects of sivelestat in countering inflammatory responses and improving its clinical outcomes in children with HFRS.

Materials and Methods

Study Design and Patient Enrollment

We Performed an Ambispective Cohort Study

Inclusion criteria: All subjects were children diagnosed with HFRS and hospitalized at the Children's Hospital Affiliated to Xi'an Jiaotong University from August 2018 to August 2023.

Exclusion criteria: (1) aged >18 years old, (2) had congenital or secondary immune deficiency, (3) developed malignant tumor after chemotherapy myelosuppression stage, (4) were using immune suppressive agents, or (5) died within 72 h after admission.

Ethics

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). It was a study involving de-identified data and no potential risks to participants, and as a result, an informed consent was not required by participants and the Institutional Review Board. The study was approved by the Ethics committee of the Children's Hospital Affiliated to Xi'an Jiaotong University (20240022).

All children were admitted to the hospital during the acute phase and received intravenous infusion of ribavirin. Simultaneously, an individualized treatment was implemented, involving ultrasound-guided assessment of volumetric response, administration of vasoactive agents, and internal environmental balance and stabilization.

Grouping of Subjects

Sivelestat group: This group enrolled patients receiving intravenous infusion of ribavirin (10 mg/kg, twice daily) from August 2021 to August 2023 after diagnosis. Homeostasis and coagulation function indicators were monitored, and

symptomatic treatment was performed. Diagnosis was made within 24 hours and intravenous continuous infusion of sivelestat (0.2mg/kg.h) was performed for no more than 14 days.

Control group: This group enrolled patients receiving intravenous infusion of ribavirin (10 mg/kg, twice daily) from August 2018 to July 2021 after diagnosis. Homeostasis and coagulation function indicators were monitored, and symptomatic treatment was given.

Disease severity was classified. (1) Mild: body temperature below 39°C, petechiae on the skin and mucous membranes, urine protein "+ ~ ++", and no oliguria and hypotensive shock; (2) moderate: body temperature of 39°C to 40°C, marked bulbar conjunctival edema, obvious petechiae on the skin and mucous membranes, systolic blood pressure <90 mmHg or lower by two standard deviations of the mean according to that in the same age group (1 mmHg = 0.133 kPa) or pulse pressure difference < 20 mmHg, oliguria, and urine protein "++~++++" during the course of the disease; (3) severe: temperature above 40°C, neurological symptoms, shock, and oliguria lasting for 5 days, or anuria lasting for ≤ 2 days; (4) critical: at least one of the following conditions, such as refractory shock, bleeding from vital organs, anuria lasting for more than 2 days, and other serious comorbidities (eg, heart failure, pulmonary edema, respiratory failure, coma, and severe secondary infection).[11]

Diagnostic Method Employed for Hanta Virus Infection

Positive hantavirus-specific IgM antibodies can confirm the diagnosis of a current or recent infection. However, a negative result does not exclude the possibility of HFRS. We performed real-time monitoring of antibody titers in pediatric patients with a strong clinical suspicion and documented epidemiological exposure to the epidemic within 7 days. Colloidal gold method was used for the test (Shandong Kanghua).

Acute kidney injury (AKI) was diagnosed and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[12] Thus, children with an increase in serum creatinine (Scr) by ≥0.3 mg/dl (≥26.5 mmol/L) within 48 h or by ≥1.5 times the baseline value within the previous 7 days, or urine output <0.5 mL/kg/h for 6 h was diagnosed as AKI. Stage 1 AKI was defined as an increase in Scr by 1.5–1.9 times the baseline or by ≥0.3 mg/dl (≥26.5 mmol/L), or urine output <0.5 mL/kg/h for 6–12 h. Stage 2 was defined as an increase in Scr by 2.0–2.9 times the baseline or urine output <0.5 mL/kg/h in 12 h; and Stage 3 was classified as an increase ≥3.0 times the baseline or to ≥4.0 mg/dl (≥353.6 mmol/L), decrease of urine output to <0.3 mL/kg/h for ≥24 h or anuria for ≥12 h. We only used Scr as a diagnostic criterion, because the data on urine output were not available in many cases initially on admission. Continuous renal replacement therapy (CRRT) was initiated in stage 2 and 3.

Data Collection

Demographic data, laboratory indexes (blood routine, coagulation, arterial blood gas, renal function, C-reaction protein, serum procalcitonin) were obtained from the electronic medical recording system within 8 h after admission. Meanwhile, relevant important indicators were extracted, including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fib), D-dimer, von Willebrand factor (vWF), platelets count (PLT), lactate (Lac), Scr, neutrophil counts, inflammatory cytokines and biomarkers of vascular endothelial injury, including ICAM-1, (Biolegend, San Diego, CA), VCAM-1, (Biolegend, San Diego, CA) at admission, 24 h, 48 h, 72h after admission. Treatment measures, including CRRT, mechanical ventilation, ECMO and clinical outcomes at 28 d, were also collected.

Outcome Variables

The primary outcome variable was set as the 28-day all-cause mortality, and the secondary outcome variables as ECMO, mechanical ventilation, CRRT use and complication, duration of renal failure.

Statistical Analysis

The data were analyzed using SPSS software (version 21.0). Continuous variables in a normal distribution were presented as mean ± standard deviation. The independent sample *t* test was used for inter-group analysis. The Chi-square test and Fisher's exact probability test were used for categorical variables. Spearman correlation test was used to evaluate the correlation between two sets of continuous variables. Kaplan-Meier survival curve and Log -Rank test were used to evaluate the difference in the cumulative probability of survival between the two groups. Statistical significance was defined at $P<0.05$.

Results

Demographic Baseline Data and General Clinical Characteristics

A total of 132 children were included, with 33 males and 26 females in the sivelestat group, and 34 males and 39 females in the control group. All lived in rural areas, and 34 patients in the sivelestat group and 51 patients in the control group had a history of contact. The differences in gender, age, contact history, body mass index, and severity classification were not significant between the two groups (P>0.05; Table 1).

Clinical Indexes at Admission

There were no significant differences between the two groups in coagulation indexes, including PT, APTT, Fib, D-dimer, vWF, PLT and Scr; inflammatory response markers, including C-reaction protein (78±35 vs 65±41), serum procalcitonin (56±21 vs 61±15), and lactate concentration (6.5±2.1 vs 6±3); as well as blood cell counts (P > 0.05; Table 2).

Dynamic Characteristics of Inflammatory Cytokines

Upon admission, no statistically significant difference was observed in interleukin-1β level between the two groups. However, the sivelestat group exhibited a significantly lower interleukin-1β level at 24 h (12±3.1 vs 15.6±5.9), 48 h (9.5 ±4.3 vs 18.5±5.6), and 72 h (8.5±3.2 vs 12.6±3) (P<0.05; Figure 1A). In both groups, the level of interleukin-2 increased

Table 1 Demographic Baseline Data and General Clinical Characteristics

Variables	Sivelestat Group	Control Group	P value
Patient number	59	73	
Gender (male/female)	33/26	34/39	0.731
Age (years)	11.62±6.14	12.23±5.69	0.555
Contact history, %	57.63 (31/59)	69.86 (51/73)	0.115
Body mass index	21.35±4.51	20.21±5.11	0.182
Severity			
Mild, %	11.86 (7/59)	15.07 (11/73)	0.593
Moderate, %	22.03 (13/59)	28.77 (21/73)	0.653
Severe, %	50.84 (30/59)	46.58 (34/73)	0.861
Critical, %	15.25 (9/59)	9.59 (7/73)	0.119

Notes: Data are presented as mean ± SD, No. (%).

Table 2 Clinical Indexes at Admission

Variables	Sivelestat Group	Control Group	P value
Patient number	59	73	
Coagulation indexes			
PT (s)	36±11	35±16	0.684
APTT (s)	164±34	170±21	0.216
Fib (g/L)	1.6±0.9	1.4±0.7	0.153
D-dimer (mg/L)	12±5	14±5	0.056
vWF (mg/L)	465±103	452±98	0.462
PLT ($\times 10^9$/L)	45±24	49±22	0.325
Inflammatory response markers			
C-reaction protein (mg/L)	78±35	65±41	0.06
Serum procalcitonin (ng/L)	56±21	61±15	0.114
Lactate concentration (mmol/L)	6.5±2.1	6±3	0.281

(*Continued*)

Table 2 (Continued).

Variables	Sivelestat Group	Control Group	P value
Blood cell analysis			
Leukocyte (×10^9/L)	22±15	24±13	0.414
Neutrophil count (×10^9/L)	16±12	18±14	0.386
Neutrophil percentage (×10^9/L)	57±16	61±14	0.128
Lymphocyte count (×10^9/L)	5±4	5±3	0.999
Lymphocyte percentage (%)	18±12	17±9	0.586
Hemoglobin (g/L)	67±23	72±18	0.164
Scr (mmol/L)	286±127	301±143	0.089

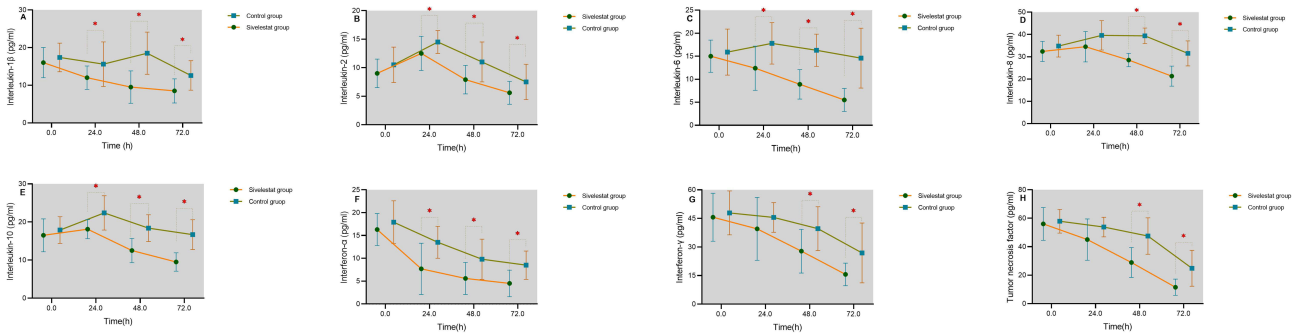
Note: Data are presented as mean ± SD.
Abbreviations: PT, Prothrombin time; APTT, activated partial thromboplastin time; Fib, fibrinogen; vWF, von Willebrand factor; PLT, platelets count; Scr, serum creatinine.

at 24 h (12.6±3 and 14.5±2), and then continuously decreased at 48 h (7.9±2.5 and 11±3.5) and at 72 h (5.6±2 vs 7.6 ±3.1). These differences were statistically significant (P<0.05; Figure 1B). The level of interleukin-6 in the sivelestat group was significantly lower than that in the control group at 24 h (12.4±4.8 vs.17.8±4.5), 48 h (8.9±3.2 vs. 16.3±3.5), and 72 h (5.5±2.5 vs 0.14 0.6±6.5) (P <0.05; Figure 1C). Compared to the control group, the sivelestat group exhibited a significant decrease in the interleukin-8 level at 48 h (28.5±3 vs 34.5±3.5) and 72 h (21.3±4.5 vs 31.5±5.6) (P<0.05; Figure 1D), as well as interleukin-10 at 24 h (18.1±2.5 vs 22.3±4.6), 48 h (12.5±3.2 vs 18.4±3.5) and 72 h (9.5±2.4 vs 17.1±3.1) (P<0.05; Figure 1E).

After admission, there was a continuous decrease in the level of interferon-α in both groups. Notably, the level of interferon-α in the sivelestat group was significantly lower than that in the control group at 24 h (7.7±5.6 vs 13.5±3.5), 48 h (5.8±3.5 vs 9.8±4.4), and 72 h (4.5±2.8 vs.8.5±3.1) (P<0.05; Figure 1F). The level of interferon-γ in the siverestat group was significantly lower than that in the control group at 48 h (27.4±11.5 vs 38.5±11) and 72 h (15.6±5.9 vs 26.9 ±15.7) (P<0.05; Figure 1G). The level of tumor necrosis factor was significantly lower in the sivelestat group at 48 h (28.9±10.5 vs 47.4±12.8) and 72 h (11.5±5.9 vs 24.2±12.6) (P< 0.05; Figure 1H).

Correlation Between Neutrophil and Biomarkers of Vascular Endothelial Injury

The levels of ICAM-1 and VCAM-1 at admission showed a significant and positive linear correlation with the count of neutrophils (r>0.5, P<0.05; Figure 2A and B). Compared to the control group, the sivelestat group demonstrated a statistically significant reduction in neutrophil count at 24 h (16±4.5 vs 21±4.5), 48 h (13±4.5 vs 18±4.7), and 72 h (8±6 vs 13±3.5). (P< 0.05; Figure 2C).



A. Interleukin-1β, B. Interleukin-2, C. Interleukin-6, D. Interleukin-8, E, Interleukin-10, Fnterferon-α, G. Interferon-γ, H.Tumor necrosis factor. The data are expressed as mean±SEM. * P<0.05.

Figure 1 Dynamic characteristics of inflammatory cytokines (**A–H**).

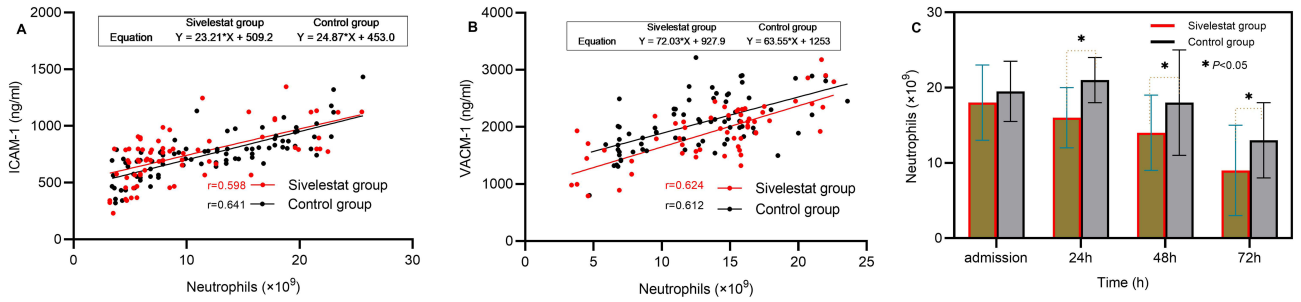


Figure 2 Correlation between neutrophil and biomarkers of vascular endothelial injury (**A–C**).

Vascular Endothelial Injury Related Factors

The ICAM-1 level did not show any significant difference between the two groups within 24 h after admission ($P>0.05$, Figure 3A). Compared to the control group, the sivelestat group exhibited a significant decrease in ICAM-1 level at 48 h (553±122 vs 784±187) and 72 h (452±130 vs 623±85) ($P<0.05$; Figure 3A). The level of VCAM-1 in sivelestat exhibited a consistent downward trend, and was significantly lower than that in the control group at 24 h (1760±289 vs 2180±445), 48 h (1450±441 vs 1890±267), and 72 h (1149±33 vs 1500±396) ($P<0.05$; Figure 3B).

Primary and Secondary Outcomes

The primary endpoint of this study was the 28-day mortality rate. Kaplan-Meier curve analysis revealed a statistically significant difference in the cumulative probability of survival between the sivelestat group and the control group (P=0.041, Figure 4). In the secondary outcomes, the sivelestat group demonstrated a decrease in ECMO and CRRT utilization rates. Additionally, there was a statistically significant reduction in the incidence of complications, such as acute pulmonary edema, acute renal failure, and pancreatitis ($P<0.041$; Table 3).

Discussion

HFRS is characterized by extensive vasculitis as the primary pathological basis. Hanta virus activates the immune system to overproduce interleukin-1 (IL-1), IL-6, chemokine ligand 2 (CCL2), CCL4, and tumor necrosis factor-a (TNF-a), ultimately leading to SIRS.[4,9] The overexpression of inflammatory factors is clearly related to the severity of organ dysfunction and adverse outcomes in patients with HFRS, and especially, the damage of vascular endothelium has been confirmed in a number of studies.[6–10] Cytokines can enhance host defense against viruses and meanwhile induce the reorganization of endothelial cytoskeletons and junctions, causing an increase in endothelial permeability.[13–15] Increased endothelial permeability leads to dysfunction of the vascular endothelial barrier, manifesting cutaneous petechiae, edema,

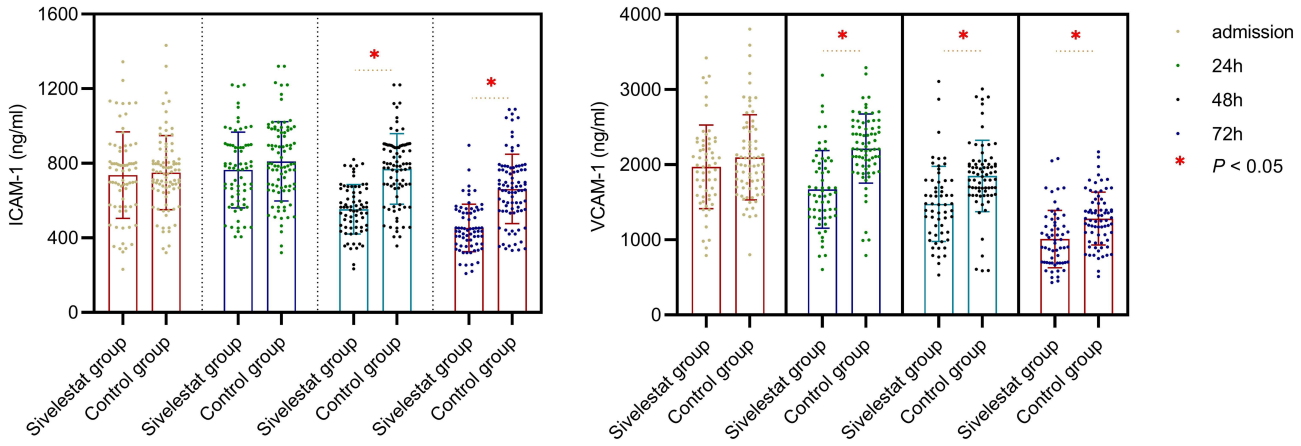


Figure 3 Vascular endothelial injury related factors.

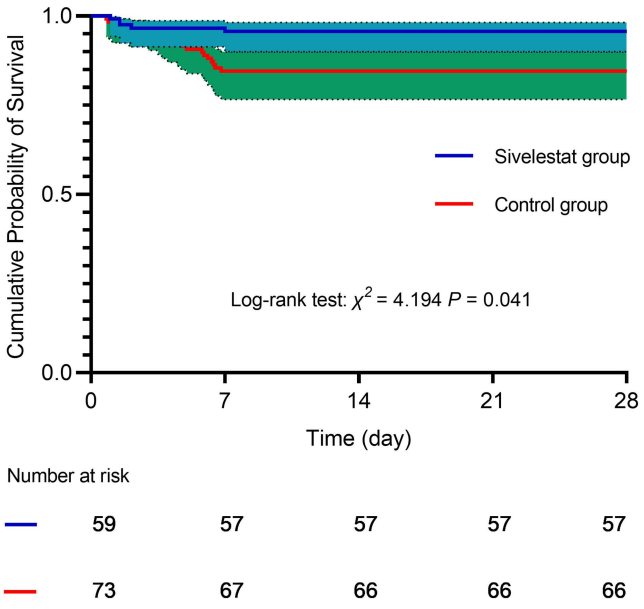


Figure 4 Cumulative probabilities of survival in two groups.

and even hypotension. Previous studies have established a correlation between inflammatory factors and HFRS-related organ dysfunction. Some clinical studies suggest that excessive cytokine expression can result in severe vascular endothelial injury and even death.[15–18]

In this study, we found that in the early stage of HFRS, all enrolled patients exhibited varying degrees of neutrophil elevation and excessive expression of inflammatory factors. The sivelestat group had significantly lower cytokine levels at various time points, compared to the control group. Low-level inflammatory factors effectively suppressed the inflammatory response and prevented endothelial injury, ultimately improving the clinical outcomes. Previous studies have shown that IL-6 and IL-8 down regulation in sepsis can decrease the concentration of ICAM-1 and VCAM-1, thereby reducing the occurrence of multiple organ dysfunction syndrome,[6,7,17–20] which is similar to the finding of the present study in which the sivelestat group exhibited a decrease in either inflammatory factors or anti-inflammatory factor IL-10, a molecule playing a crucial role in suppressing the inflammatory response. In addition, studies have also found that the severity of HFRS is positively correlated with the concentration of IL-10.[6,18] The concurrent reduction in both

Table 3 The Secondary Outcomes and Complications

Variables	Sivelestat Group	Control Group	P value
Patient number	59	73	
Secondary outcomes			
ECMO	3.39 (2/59)	5.48 (4/73)	0.691*
Mechanical ventilation	18.64 (11/59)	35.62 (26/73)	0.034
CRRT	16.95 (10/59)	32.88 (24/73)	0.037
Complication			
Acute pulmonary edema	18.64 (11/59)	38.36 (28/73)	0.014
Acute renal failure	10.17 (6/59)	24.66 (18/73)	0.043
Shock	3.39 (2/59)	6.85 (5/73)	0.687*
Acute pancreatitis	5.08 (3/59)	16.44 (12/73)	0.041
Duration of renal failure	4.5±1.3	6.7±3.5	0.000

Note: Data are presented as mean ± SD, No. (%).
Abbreviations: ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

IL-6 and IL-10 mitigates the impact of the inflammatory response on cellular and tissue function, ultimately enhancing organ functionality.

Sivelestat functions as a highly selective inhibitor of neutrophil elastase. Relevant research has demonstrated that it not only protects against NE at the primary site of infection, but also diminishes the expression of IL-6, IL-8, and TNF-α, thereby inhibiting neutrophil migration and activation, and ultimately the inflammatory response.[21–24] The activation, chemotaxis, and recruitment of neutrophils in injured tissues in HFRS patients can decide the severity of vascular endothelial injury.[15] Furthermore, a significant reduction in neutrophil recruitment and a relatively mild vascular endothelial injury are observed in patients with decreased levels of inflammatory factors.[25–27] Therefore, sivelestat improves the outcomes of HFRS through mitigating neutrophil-mediated inflammatory response and preventing organ dysfunction.

The sivelestat group demonstrated a decrease in neutrophils and cytokines, accompanied by a significant reduction in the biochemical markers of vascular endothelial injury, specifically ICAM-1 and VCAM-1, compared to the control group. Previous studies have indicated that programmed cell death, probably arising from the overexpression of neutrophil extracellular traps (NETs), is correlated with the severity of vascular endothelial injury in HFRS patients.[28–30] Therefore, inhibition on neutrophil-associated inflammatory reactions may potentially mitigate vascular endothelial damage and tissue injury associated with NETs. Mechanisms have been elucidated to explain the correlations between coagulopathy and vascular endothelial injury. In an association study on infection-induced disseminated intravascular coagulation (DIC), sivelestat reduced the incidence of NETs and DIC.[30] This association has also been confirmed in studies related to ARDS.[31,32] Sivelestat effectively alleviates vascular endothelial injury by inhibiting local neutrophil-mediated inflammation. It enhances oxygenation, reduces lung and renal vascular damage, and decreases the 28-d mortality rate. Thus, it can be inferred that sivelestat may attenuate local neutrophil activation and recruitment to suppress inflammatory response and preserve vascular endothelial function, thus improving the outcomes of Hantavirus-induced sepsis.

There are several limitations to our study. First, this was not an experimental study. Therefore, the period/duration of data collection may not be sufficient. Second, this was a single-center study with relatively few patients, which may have skewed the results. Finally, accurate targeted therapy designs are needed for efficacy studies. Future multi-center studies with larger sample sizes are needed to further confirm our findings. The findings of our research indicate that sivelestat exhibits potential therapeutic benefits through its anti-inflammatory properties and ability to mitigate organ dysfunction. This discovery has bolstered our confidence in future investigations.

Conclusion

Sivelestat may suppress neutrophil-mediated inflammatory response to reduce endothelial and organ damage, and improve clinical outcomes in children with HFRS.

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Disclosure

The authors report no conflicts of interest in this work.

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