A Retrospective Study of Continuous Renal Therapy and Anticoagulation in Patients with Hemorrhagic Fever with Renal Syndrome

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Objective To observe the application of continuous renal replacement therapy (CRRT) and heparin anticoagulation in patients with HFRS, and to explore a more suitable anticoagulant strategy.

Methods Eighty-five severe-type patients (severe group) and 71 critical-type patients (critical group) were enrolled in this study. The frequency of CRRT was compared between the two groups; the frequency of CRRT treated with and without heparin anticoagulation and the frequency of hemorrhage and channel blood clotting induced by the two anticoagulant strategies were observed.

Results The frequency of CRRT in the critical group was higher than that in the severe group ($P < 0.001$). The frequency of CRRT initiated during the overlapping phases in the critical group was significantly higher than that of the severe group ($P = 0.032$). The total times of CRRT was 103, and 70 of them were treated with heparin anticoagulation. The frequencies of hemorrhage induced by heparin anticoagulation and no heparinization were 16 and 0, respectively, and the frequencies of channel blood clotting were 2 and 4, respectively.

Conclusions CRRT has been used extensively in the critical-type patients with HFRS. The heparin anticoagulation and no anticoagulant strategies should be used more rationally in patients treated with CRRT, according to the clinical characteristics of the disease.

Key words: Continuous renal replacement therapy; Anticoagulation; Hemorrhagic fever with renal syndrome; Intermittent hemodialysis

Hemorrhagic fever with renal syndrome (HFRS) is an acute infectious disease transmitted by Hantavirus. China is the most severe endemic area of HFRS in the world, with 30 000-50 000 cases reported annually, which accounts for over 90% of total cases worldwide. Shaanxi Province is one of the most severely affected provinces in China. Xi’an is the center district of Shaanxi Province and had an increased incidence and mortality rate in the last three years. In China, the major pathogens are Hantaan virus (HTNV) and Seoul virus (SEOV) of the genus Hantavirus, with the major natural hosts of Apodemus agrarius and Rattus norvegicus, respectively. Hantavirus is transmitted from its natural hosts (rodents) to humans via inhalation of aerosolized, virus-contaminated excreta, such as urine and feces.

Typical patients progress through the following five successive phases: febrile, hypotensive, oliguric, diuretic and convalescent. In some severe and critical cases, the febrile, hypotensive and oliguric phases can overlap during the acute stage, resulting in acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), acute progressive noncardiogenic pulmonary edema, disseminated intravascular coagulation (DIC) and multiple organ dysfunction syndrome (MODS), with increasing hospital fatality remarkably without effective treatment.

Renal replacement therapy (RRT) is a major supportive treatment for septic patients with AKI, and continuous renal replacement therapy (CRRT)
has been extensively used on the septic patients with hemodynamic instability in the intensive care unit (ICU). Like sepsis, HFRS has general pathophysiologic characteristics of systemic inflammatory response syndrome (SIRS), and the manifestations of the hypotensive phase are similar to those of a typical distributed septic shock. For the critical HFRS patient with evidence of unstable hemodynamic status accompanied with multiorgan injury, ARDS, pulmonary edema, fluid overload, severe electrolyte disturbances, cerebropathy and AKI, CRRT should be considered as the first choice, according to the principle of blood purification in ICU. Furthermore, as an essential element of operation, CRRT anticoagulation should also be used based upon the clinical characteristics of patients with different diseases. The principles of individualization should be followed, and the anticoagulant dose should be adjusted reasonably. During the course of CRRT, patients should be carefully monitored for hemorrhage, channel blood clotting and longevity of filter induced by anticoagulants or no anticoagulants in a timely fashion. Until now, clinical research on CRRT and anticoagulation in patients with HFRS is limited. The aim of this study was to observe the application of CRRT and heparin anticoagulation in patients with the disease, and to explore a more suitable anticoagulant strategy.

METHODS

Study participants

The medical records of 346 typical patients with HFRS treated at the center for infectious diseases, Tangdu Hospital, from January, 2008 to August, 2012 were reviewed. All the cases were diagnosed based upon a positive enzyme-linked immunosorbent assay (ELISA) for specific IgM and IgG antibodies to Hantaan virus in the acute phase serum.

According to the degree of hypotension, renal function, effusion, hemorrhage and edema in the patients, the severity of HFRS was classified into the following four types. (1) mild-type patients had kidney injury without an obvious oliguric stage and without hypotension; (2) moderate-type patients had obvious symptoms of uremia, effusion (bulbar conjunctiva), hypotension, hemorrhaging (skin and mucous membranes), and AKI with a typical oliguric stage; (3) severe-type patients had severe uremia, effusion (bulbar conjunctiva and either

the peritoneum or pleura), hemorrhaging (skin and mucous membranes), hypotension and AKI with oliguria (urine output of 50-500 ml/day) for ≤ 5 days or anuria (urine output of < 100 ml/day) for ≤ 2 days; and (4) critical-type patients usually with one or more of the following complications compared to the severe-type patients: refractory shock (≥ 2 days), visceral hemorrhaging, heart failure, pulmonary edema, brain edema, severe secondary infection, and severe AKI with oliguria (urine output of 50-500 ml/day) for > 5 days, anuria (urine output of < 100 ml/day) for > 2 days. Customarily, the so-called acute stage of the disease was defined as the period of febrile, hypotensive and oliguric phases, and overlapping phase was defined as the period of overlapping febrile, hypotensive and oliguric phase. In total, 85 severe-type patients and 71 critical-type patients met the aforementioned criteria, and were classified as a severe group and a critical group, respectively.

CRRT procedures

According to the Chinese Medical Association’s guideline for blood purification in the ICU, the patients with evidence of unstable hemodynamic status accompanied with multiorgan injury, ARDS, pulmonary edema, fluid overload, severe electrolyte disturbances, cerebropathy and AKI were treated with CRRT. For patients with stable hemodynamic status and less potentially fatal complications during their clinical course, intermittent hemodialysis (IHD) was chosen by clinicians as the first choice. However, over the period of treatment, a minority of critical patients may have lost the option of CRRT due to their critical condition on admission, and some of them even signed informed consents to withdraw CRRT due to poor economic status.

The patients treated with CRRT were catheterized in the femoral vein with a double-lumen catheter. The median duration of catheterization was 12 days, and AN69 Hemofilters were used on patients treated with PRISMA machine with a M100 extra-corporeal circuit. Port prescription was used, and a bicarbonate buffer solution and other fluids were added separately. CRRT (24 h) was provided for most patients during the period of treatment, a minority of critical patients met the aforementioned criteria, and were classified as a severe group and a critical group, respectively.
10 000 IU. Based on the clinical characteristics of HFRS, the patients without a bleeding tendency were defined as those with platelets > 50 × 10^9/L and activated partial thromboplastin time (APTT) < baseline × 120% (reference value: 22-36 s) and without evidence of active bleeding, such as haematemesis, hemafecia, hemoptyisis, petechia at the puncture location and errhysis at the tracheal incision. Heparin was given at an initial dose of 5-10 IU/kg and was maintained at a dose of 5-10 IU·kg^{-1}·h^{-1} in these patients. The patients with a bleeding tendency were defined as those with platelets < 30 × 10^9/L and APTT > baseline × 150% or without evidence of active bleeding, as described above. Heparin was given at an initial dose of 5 IU/kg and was maintained at a dose of 5 IU·kg^{-1}·h^{-1} in these patients. The patients with an obvious bleeding tendency were defined as those with platelets < 30 × 10^9/L and APTT > baseline × 150% or without evidence of active bleeding as described above. No heparinization was used in these patients and frequent washing of the filter with substitution fluid was performed.

The patients treated with IHD were catheterized in the femoral vein with a double-lumen catheter. Ployflux 17 L Capillary Dialyzers were used on the patients treated with hemodialyzer (Gambro AK96S, Sweden). Dialysate flow rate was 400-600 ml/min with bugged fluid employed. All patients were treated with bicarbonate dialysate. The concentration of sodium in the dialysate was 140 mmol/L. All patients were heparinized with low dosage heparin or administered no anticoagulant and dialyzed for 3.0-4.0 hours, according to the patient’s condition.

**Statistical analysis**

Statistical analyses were performed using the SPSS 17.0 software (SPSS Inc, Chicago, IL, USA). The tables were prepared using Excel 2003 (Microsoft). Continuous variables were presented as the mean ± SD and were analyzed by the Kolmogorov-Smirnov’s test for normality of distribution and the Levene’s test for the homogeneity of variance. The variables were compared between groups with the Student’s t-test for normally distributed variables. The frequencies and percentages were given for qualitative variables, and significant differences between groups were tested by the Chi-square test, and Fisher’s exact test was used when numbers were too small to perform the Chi-square test. A two-tailed \( P < 0.05 \) was considered statistically significant.

**Ethics statement**

This study was reviewed and approved by the Institutional Review Board of Tangdu Hospital, and the patients’ medical records were anonymized and de-identified prior to analysis.

**RESULTS**

**Clinical classification and outcome**

Clinical data were recorded for 346 typical HFRS patients. Among these cases, 77 were classified as mild, 113 cases were classified as moderate, 85 cases were classified as severe, and 71 cases were classified as critical. A total of 26 critical-type patients died, with a hospital mortality of 7.5%.

**Application of renal replacement therapy in patients with HFRS**

Among the mild-type patients, only one case was treated with IHD, and no case was treated with CRRT; two cases manifested mild anemia with unknown reason (hemoglobin 90-120 g/L), which was not related to RRT. Among the moderate-type patients, 33 cases were treated with IHD, and no case was treated with CRRT; two cases manifested moderate anemia (hemoglobin 60-90 g/L), which was caused by hematoma on the left groin and iron deficiency anemia (IDA), respectively.

Among the severe-type patients, 11 cases were treated with CRRT, and 61 cases were treated with IHD. Among the critical-type patients, 48 cases were treated with CRRT, and 15 cases were treated with IHD. The age and sex distribution between the two groups were not significantly different, no matter treated with CRRT or IHD (\( P = 0.578 \) and \( P = 0.729 \), respectively) (Table 1). Sixteen patients in the severe group presented with moderate or severe anemia (hemoglobin < 90 g/L or hemoglobin < 60 g/L), and 58 patients presented with moderate or severe anemia in the critical group. There was no significant difference between the two groups on the total frequency of RRT (\( P = 0.463 \) (Table 2). The frequency of CRRT in the critical group was found to be higher than that of the severe group, and the frequency of IHD in the critical group was lower than that of the severe group, both demonstrating statistically significant differences (\( P < 0.001 \) (Table 2). The frequency of CRRT initiated during the overlapping phases in the critical group was significantly higher than that of the severe group (\( P = 0.032 \) (Table 3).
The evolution of risk on heparin anticoagulation and no heparinization treated with CRRT

Among the patients enrolled, the total times of CRRT was 103, and 70 of them were treated with heparin anticoagulation. The frequencies of hemorrhage induced by heparin anticoagulation and no heparinization were 16 and 0, respectively, and the frequencies of channel blood clotting were 2 and 4, respectively.

**DISCUSSION**

This study retrospectively observed the application of CRRT in patients with HFRS and evaluated the risk of hemorrhage and channel blood clotting induced by heparin anticoagulation and no heparinization treated with CRRT, which is the first report on this issue in China.

In this study, no patient with mild or moderate disease was treated with CRRT, and only a minority of moderate-type patients were treated with IHD. According to the pathophysiologic characteristics of HFRS, mild-type patients may go directly through the polyuric phase from the febrile phase directly without obvious hypotensive phase, and the degree of AKI in these patients is usually mild; moderate-type patients usually go through a short hypotensive phase with stable haemodynamic condition or mild AKI, and they all have good outcome by generally supportive treatment. Considering the economic costs and the need to conserve medical resources, IHD may be a better choice than CRRT for the moderate patients with AKI during the oliguric phase.

This study demonstrated that the frequency of CRRT in the critical group was higher than that of the severe group, and the frequency of IHD in critical group was lower than that of the severe group (Table 2); the frequency of CRRT initiated during the overlapping phases in critical group was significantly higher than that of the severe group (Table 3). This observation indicated that CRRT has been widely used in the critical-type patients in our center because of its advantage of improving hemodynamic stability, controlling biochemical status, eliminating the mediators of inflammation and permitting the use of nutritional support, compared with IHD.\(^8,11,15,16\)

By the way, although CRRT is an important supportive therapeutic tool, the influential factors for prognosis of critical patients with HFRS are multiple and complicated. In the actual clinical practice, it should be emphasized that only early monitoring and taking systematically supportive treatment, including mechanical ventilation combined with RRT, vasoactive drugs and nutritional supplement, would

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**Table 1. Demographic characteristics in severe-type and critical-type patients treated with renal replacement therapy**

<table>
<thead>
<tr>
<th></th>
<th>CRRT (n = 59)</th>
<th>IHD (n = 76)</th>
<th>P values (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.47 ± 12.95</td>
<td>50.61 ± 11.31</td>
<td>0.578</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>48 (81.4)</td>
<td>60 (79.0)</td>
<td>0.729</td>
</tr>
</tbody>
</table>

*Notes: CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; \(^a\) CRRT vs. IHD.

**Table 2. Frequencies of renal replacement therapy in severe-type and critical-type patients**

<table>
<thead>
<tr>
<th></th>
<th>Severe group (n = 85)</th>
<th>Critical group (n = 71)</th>
<th>P values (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRT, n (%)</td>
<td>72 (84.7)</td>
<td>63 (88.7)</td>
<td>0.463</td>
</tr>
<tr>
<td>CRRT, n (%)</td>
<td>11 (12.9)</td>
<td>48 (67.6)</td>
<td>(&lt; 0.001)</td>
</tr>
<tr>
<td>IHD, n (%)</td>
<td>61 (71.8)</td>
<td>15 (21.1)</td>
<td>(&lt; 0.001)</td>
</tr>
</tbody>
</table>

*Notes: CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; RRT, renal replacement therapy; \(^a\) Severe group vs. critical group.

**Table 3. Frequencies of CRRT commenced during the acute stage in severe-type and critical-type patients**

<table>
<thead>
<tr>
<th></th>
<th>Severe-type (n = 11)</th>
<th>Critical-type (n = 48)</th>
<th>P values (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotensive phase, n (%)</td>
<td>1 (9.1)</td>
<td>8 (16.7)</td>
<td>0.869</td>
</tr>
<tr>
<td>Oliguric phase, n (%)</td>
<td>7 (63.6)</td>
<td>16 (33.3)</td>
<td>0.130</td>
</tr>
<tr>
<td>Overlapping phases, n (%)</td>
<td>1 (9.1)</td>
<td>24 (50.0)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

*Notes: \(^a\) Severe-type vs. critical-type.

decrease mortality rate more efficiently. Additionally, the critical conditions on admission and the patient’s poor economic status may also influence the clinical applications of supportive instruments and even influence the prognosis directly.

HFRS has its unique pathophysiological characteristics, and the degree of septic shock caused by HTNV may be more severe than that caused by other pathogenic bacteria. Like dengue fever, the critical patients with HFRS typically appear to have a leukemoid reaction, severe plasma leakage, changes in capillary permeability and thrombocytopenia, which could influence the degree of clotting directly and indirectly and increase the probability of multiorgan bleeding and DIC. It has been accepted that thrombocytopenia is most likely the result of decreased platelet production or increased platelet destruction and platelet dysfunction. Heparin is an important anticoagulant in blood purification because of its low cost and easy monitoring, but it is associated with several negative characteristics and adverse effects, such as heparin-induced thrombocytopenia (HIT) and hemorrhage. A reasonable heparin anticoagulation treatment can reduce the risk of channel blood clotting effectively, but in actual clinical practice, the dosage may be influenced by the clinical characteristics of the disease and the subjective judgment of clinicians. Until now, platelet count, APTT, activated coagulation time (ACT) and international normalized ratio (INR) have been considered as important laboratory parameters for evaluating the effect of heparin anticoagulation, and as far as we know, a formulated strategies of heparin anticoagulation according to the clinical experiences and corresponding research in sepsis and AKI patients treated with CRRT in ICU have been applied in a majority of the public hospitals in England.

According to the Chinese Medical Association’s guideline for blood purification in ICU and the clinical characteristics of HFRS, we also stratified the patients treated with CRRT based upon the dosage of heparin anticoagulation used, while in the actual clinical practice, a minority of patients presented still manifested hemorrhage or channel blood clotting regardless of whether heparin or no anticoagulation was used, increasing the difficulty of the following treatment. Until now, there are no guidelines for heparin anticoagulation treatment during CRRT aiming at patients with HFRS. Determining effective heparin anticoagulation strategy suitable for HFRS, exploring the potential value of local anticoagulation with sodium citrate in patients with HFRS, and formulating guidelines for anticoagulant use in CRRT will be the direction of our future research.

There were some limitations in this study. First, as a retrospective study, the statistical power of this study was low because of the relatively small samples enrolled. Second, the treatment principle might be biased by the lack of a standardized protocol and guidelines regarding coagulation for the patients treated with CRRT, which may influence the patients’ condition and prognosis. Third, the clinical classifications of HFRS might also be biased due to the lack of a more standardized protocol for the management of patients with HFRS.

CONCLUSIONS

CRRT has been extensively used in the critical-type patients with HFRS. The heparin anticoagulation and no anticoagulant strategies should be used more rationally according to the clinical characteristics of the disease, in patients treated with CRRT.

ACKNOWLEDGEMENTS

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