The role of nafamostat mesylate anticoagulation in continuous kidney replacement therapy for critically ill patients with bleeding tendencies: a retrospective study on patient outcomes and safety

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Background: Continuous kidney replacement therapy (CKRT) is crucial in the management of acute kidney injury in intensive care units (ICUs). Nonetheless, the optimal anticoagulation strategy for patients with bleeding tendencies remains debated. This study aimed to evaluate patient outcomes and safety of nafamostat mesylate (NM) compared with no anticoagulation (NA) in critically ill patients with bleeding tendencies who were undergoing CKRT.

Methods: This retrospective study enrolled 2,313 patients who underwent CKRT between March 2013 and December 2022 at the third affiliated hospital in South Korea. After applying the exclusion criteria, 490 patients were included in the final analysis, with 245 patients in the NM and NA groups each, following 1:1 propensity score matching. Subsequently, in-hospital mortality, incidence of bleeding complications, agranulocytosis, hyperkalemia, and length of hospital stay were assessed.

Results: No significant differences were observed between the groups regarding the lengths of hospital and ICU stays or the incidence of agranulocytosis and hyperkalemia. The NM group showed a smaller decrease in hemoglobin levels during CKRT (–1.90 g/dL vs. –2.39 g/dL) and less need for blood product transfusions than the NA group. Furthermore, the NM group exhibited a survival benefit in patients who required transfusion of all three blood products.

Conclusion: NM is an effective and safe anticoagulant for CKRT in critically ill patients, especially those requiring transfusion of all three blood products. Although these findings are promising, further multicenter studies are needed to validate them and explore the mechanisms underlying the observed benefits.

Keywords: Acute kidney injury, Anticoagulants, Continuous kidney replacement therapy, Intensive care units, Continuous renal replacement therapy

Introduction

Acute kidney injury (AKI) is observed in 5% to 70% of critically ill patients admitted to the intensive care unit (ICU) [1-4], including 14% to 30% of patients with stage 3 disease requiring kidney replacement therapy [1,2,5]. Despite continuous advancements in intensive care, the mortality rate of ICU patients with AKI remains high [1,6], underscoring...
the need for AKI prevention [1,7], early nephrology consultations [8], and more proactive therapeutic approaches. Continuous kidney replacement therapy (CKRT) is frequently applied to ICU patients with AKI, especially to those with hemodynamic instabilities [9,10].

Effective CKRT requires anticoagulation therapy to the extracorporeal circuit [10]. However, while regional citrate anticoagulation is recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) Organization [11], it is not always feasible because of national or institutional circumstances [12,13]. Systemic heparin anticoagulation is an alternative for patients without bleeding tendencies; in cases with bleeding tendencies, no anticoagulation (NA) is suggested because both systemic and regional heparin should be avoided [12]. However, with NA, the filter life is short [14,15]; thus, an anticoagulation strategy is required [11].

Nafamostat mesylate (NM) is a low-molecular-weight synthetic inhibitor of serine proteases that include coagulation factors such as factors VIIa, IXa, Xa, XIIa, and thrombin [16–18]. Due to the short half-life of NM (8–10 minutes) [16,19], it is rapidly eliminated from the blood upon infusion termination. This property allows the use of NM as a circuit anticoagulant for CKRT in patients with bleeding tendencies [20]. In South Korea, NM has been approved as an anticoagulant for CKRT since 2005 and is widely used in patients with bleeding tendencies.

Nevertheless, the 2012 KDIGO guidelines do not recommend NM anticoagulation during CKRT because of possible side effects such as agranulocytosis, hyperkalemia, and anaphylactoid reactions [12,21,22]. To date, several randomized controlled trials (RCTs) and retrospective studies have shown the benefits of NM compared with NA regarding filter life [14,15,23–25]; however, studies exploring the safety of these modalities have not been performed. Herein, we evaluated the safety of NM and NA in critically ill patients undergoing CKRT.

**Methods**

**Study design and population**

This retrospective study included data from consecutive adult patients (aged >18 years) who underwent CKRT between March 2013 and December 2022 at the third affiliated hospital in South Korea. Patients with end-stage kidney disease undergoing maintenance dialysis, those with missing information regarding anticoagulation, those who received heparin-based anticoagulation, and those with hospital stays >90 days since the start of CKRT were excluded.

The study protocol was approved by the Institutional Review Board of Pusan National University (No. 2305-023-127), which waived the requirement for informed consent.

**Data collection and definition**

The parameters examined included patient demographics, comorbidities, disease severity at CKRT initiation, and laboratory findings during CKRT. Demographic information was obtained from nurses’ charts, and comorbidity information was obtained from physicians’ notes. Disease severity was assessed using the Sequential Organ Failure Assessment (SOFA) score [26]. Baseline laboratory parameters at the time of CKRT initiation, laboratory parameters such as hemoglobin and potassium levels and platelet counts, and transfusion records of any blood products during CKRT were extracted from the electronic medical records.

Bleeding complications were indirectly assessed through the delta change of hemoglobin (lowest hemoglobin – initial hemoglobin at start of CKRT, g/dL) and transfusion requirements during CKRT. Hyperkalemia was defined as a serum level of potassium exceeding 5.5 mg/dL at the start of CKRT, and severe hyperkalemia was defined as potassium exceeding 7.0 mg/dL [27]. Absolute neutrophil count (ANC) was calculated in the following way: ANC (cells/µL) = total white blood cell count (×10³/µL) × percentage of segmented neutrophils [28]. Neutropenia or severe neutropenia was defined as an ANC <1,000 cells/µL or <500 cells/µL, and agranulocytosis as an ANC <100 cells/µL [29].

CKRT data included the mode, prescribed and delivered doses, the anticoagulation method, downtime, actual CKRT time, and the number of filters used. Filter life was defined as the actual CKRT time (in hours) divided by the total number of filters used [30]. Downtime was calculated in the following way: downtime (%) = [1 – (actual CKRT time/total intended CKRT time)] × 100 [31]. Information regarding in-hospital mortality was collected by reviewing the medical charts.
Continuous kidney replacement therapy and nafamostat mesylate anticoagulation

Details of the CKRT procedure have been reported in a previous study [32]. In short, CKRT was initiated at the discretion of the attending physician and implemented and managed by a specialized CKRT team. The decision to terminate CKRT or switch to conventional hemodialysis was made by the attending physician or an experienced nephrologist. A Baxter Prismaflex instrument with an AN69ST membrane (Baxter International Inc.) was used to deliver CKRT, using heparin as the primary anticoagulant. In the event of bleeding tendencies, either NM or NA was chosen. The NM infusion was prepared by dissolving 100 mg NM in 5% dextrose, resulting in a total volume of 20 mL (5 mg NM/mL). The NM solution was administered at an infusion rate of 2 mL/hr (10 mg NM/hr) using an anticoagulant infusion device mounted on the Prismaflex. If filter clotting was frequently observed, the NM concentration was doubled (10 mg NM/mL) and infused at a rate of 2 mL/hr (20 mg NM/hr). In the NA group, the anticoagulant was replaced with 20 mL of normal saline.

Outcomes

The primary outcome was in-hospital mortality. Because not all deaths in hospitals are directly associated with CKRT-anticoagulation methods, we additionally evaluated the deaths observed during CKRT operation (CKRT mortality) and ICU stay (ICU mortality). Secondary outcomes were the safety of NM; incidences of bleeding complications, agranulocytosis, and hyperkalemia; overall length of hospital stay; length of ICU stay; CKRT duration; and filter life.

Statistical analysis

The normality of the data was determined using the Kolmogorov-Smirnov test. Continuous variables are expressed as medians and interquartile ranges or means ± standard deviations. The differences between the two groups were compared using the Student t test, chi-square test, or Mann-Whitney U test, as appropriate. A non-parsimonious multivariate logistic regression model was used for 1:1 propensity score matching (PSM). Rigorous adjustments for significant differences in the patients’ baseline characteristics, including SOFA scores, serum hemoglobin levels, platelet counts, and prothrombin times (PTs) at CKRT initiation, were performed based on a caliper width of 0.05 standard deviations of the propensity score and no replacement. The Kaplan-Meier survival curves were plotted to compare in-hospital mortality. The proportion of patients who received transfusions and the incidence rates of agranulocytosis or hyperkalemia were compared using the Pearson chi-square test. Differences in the time from hyperkalemia to normokalemia between groups were compared using a t test of means. Statistical significance was set at p < 0.05. IBM SPSS version 28.0 (IBM Corp.) was used for statistical analysis.

Results

Patient characteristics

Between January 2013 and December 2022, 3,475 adult patients underwent CKRT at the third affiliated hospital. After excluding 519 patients (14.9%) with end-stage kidney disease, 24 patients (0.7%) without information regarding anticoagulation, 221 patients (6.4%) who underwent heparin anticoagulation, and 79 patients (2.3%) with a hospital stay >90 days after CKRT initiation, the study population consisted of 2,632 patients (Fig. 1), including 1,850 patients (70.3%) who received NM and 782 patients (29.7%) who received NA. In the primary cohort, patients in the NM group were older and had lower SOFA scores, higher serum platelet counts, and shorter prothrombin times compared to those in the NA group; however, after 1:1 PSM, the two groups were well-balanced regarding all baseline characteristics, including comorbidities, disease severity, and laboratory test results, except for the slightly higher proportion of surgical patients in the NA group compared to that of the NM group (Table 1). In the 1:1 PSM model, each group included 245 patients (65.8% males) with a mean age of 63.2 years; 35.6% had diabetes mellitus and 18.4% had cancer. At the time of CKRT initiation, the mean SOFA score was 12.4; sepsis was present in 54.7% and anuria in 68.0% of the patients. Details of the parameters before and after PSM are provided in Table 1, and a specific score for each SOFA parameter is described in Supplementary Table 1 (available online). In both groups, CKRT was performed.
Among the 3,475 patients who required continuous kidney replacement therapy (CKRT), 1,162 patients were excluded based on the exclusion criteria. After 1:1 propensity score matching, 490 patients were included; 245 in the no anticoagulation group and 245 in the nafamostat mesylate group. ESKD, end-stage kidney disease.

using the continuous venovenous hemodiafiltration mode with a mean delivered dose of 34.0 mL/kg/hr for a mean of 5.5 days.

**Patient outcomes**

Information regarding the survival status was available for 489 (99.8%) of the 490 patients. The in-hospital mortality was significantly lower in the NM group (143 of 245, 58.4%) than in the NA group (169 of 244, 69.3%; \( p = 0.012 \)). The Kaplan-Meier survival plot indicated better survival in patients who received NM than in patients who received NA (Fig. 2).

In the NM group, 121 patients (49.4%) died during CKRT compared with 128 patients (52.7%) in the NA group; the difference was significant (\( p = 0.003 \)). Deaths in the ICU were less common in the NM group (135 of 245, 55.2%) than in the NA group (164 of 244, 67.4%; \( p = 0.009 \)).

The lengths of ICU and hospital stays were similar for both groups. The mean length of ICU stay was 12.63 ± 16.40 days for the NM group and 10.80 ± 12.05 days for the NA group (\( p = 0.16 \)), while the mean length of hospital stay was 25.29 ± 28.24 days for the NM group and 21.46 ± 23.45 days for the NA group (\( p = 0.11 \)).

**Incidence of bleeding complications, agranulocytosis, and hyperkalemia**

The delta change in hemoglobin was -2.39 ± 2.14 and -1.90 ± 1.90 g/dL in the NA and NM groups, respectively, being significantly higher in the NA than in the NM group (\( p = 0.009 \)). During CKRT, any kind of blood product transfusion was required in 353 patients (72.0%), with transfusion being less frequent in the NM group (164 of 245, 66.9%) than in the NA group (189 of 245, 77.1%; \( p = 0.01 \)). By specific blood product component, the requirements for each red blood cells (RBC), platelet concentrate, or fresh frozen plasma transfusion were significantly higher in the NA group than in the NM group, and the proportion of patients requiring all three types of blood components was significantly higher in the NA group than in the NM group (Fig. 3; Supplementary Table 2, available online).

During CKRT, agranulocytosis (ANC <100 cells/µL) developed in 34.6% (\( n = 47 \)) of patients; the difference between the two groups was not significant (NM vs. NA, 35.0% vs. 34.1%; \( p = 0.85 \)). The incidence of neutropenia or severe neutropenia (ANC <1,000 cells/µL or <500 cells/µL) was also similar between the two groups (Fig. 4).

At the time of CKRT initiation, hyperkalemia (serum potassium [serum K] >5.5 mmol/L) and severe hyperkalemia (serum K >7.0 mmol/L) were observed in 19.2% (\( n = 94 \)) and 5.3% (\( n = 26 \)) of the patients, respectively. During CKRT, serum K levels gradually decreased in both groups, without any differences between days 2 and 3 of CKRT. The mean time from hyperkalemia (serum K >5.5 mmol/L) to normokalemia (serum K <4.5 mmol/L) was 19.2 ± 13.3 hours in the NM group and 17.9 ± 14.8 hours in the NA group; the difference was not significant (\( p = 0.72 \)). Similarly, the mean time required to correct severe hyperkalemia (serum K >7.0 mmol/L) to normokalemia (serum K <4.5 mmol/L) showed no significant difference between the two groups (Fig. 5; Supplementary Table 3, available online).

The mean filter life was 21.25 ± 12.01 hours in the NM group, which was not statistically different from the 19.67
Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before PSM</th>
<th>After PSM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>782 (29.7)</td>
<td>1,850 (70.3)</td>
<td>245</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
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<td></td>
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<tr>
<td>Age (yr)</td>
<td>62.62 ± 14.82</td>
<td>66.49 ± 14.05</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Male sex</td>
<td>65.9</td>
<td>62.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 ± 0.10</td>
<td>1.63 ± 0.08</td>
<td>0.45</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.32 ± 14.53</td>
<td>63.12 ± 22.38</td>
<td>0.02*</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>24.17 ± 4.46</td>
<td>23.47 ± 9.24</td>
<td>0.07</td>
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<td><strong>Comorbidity</strong></td>
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<tr>
<td>Diabetes mellitus</td>
<td>30.5</td>
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<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36.2</td>
<td>57</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Cancer</td>
<td>26.9</td>
<td>18.7</td>
<td>&lt;0.001*</td>
</tr>
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<td><strong>Department</strong></td>
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<tr>
<td>Medical</td>
<td>65.6</td>
<td>87.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Surgical</td>
<td>34.4</td>
<td>12.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Disease severity</strong></td>
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<td></td>
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</tr>
<tr>
<td>SOFA score</td>
<td>12.48 ± 3.66</td>
<td>9.85 ± 3.81</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>SOFA score ≥10</td>
<td>78.9</td>
<td>52.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sepsis</td>
<td>44.6</td>
<td>41.7</td>
<td>0.33</td>
</tr>
<tr>
<td>Anuria</td>
<td>65.0</td>
<td>70.0</td>
<td>0.02*</td>
</tr>
<tr>
<td><strong>CKRT treatment mode</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CVVHDF</td>
<td>100</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Prescribe dose (mL/kg/hr)</td>
<td>38.46 ± 11.46</td>
<td>38.53 ± 12.68</td>
<td>0.89</td>
</tr>
<tr>
<td>Delivered dose (mL/kg/hr)</td>
<td>33.61 ± 6.60</td>
<td>33.44 ± 6.38</td>
<td>0.57</td>
</tr>
<tr>
<td>Downtime (%)</td>
<td>4.69 ± 9.95</td>
<td>5.69 ± 11.01</td>
<td>0.04*</td>
</tr>
<tr>
<td>Days on CKRT</td>
<td>6.00 ± 7.43</td>
<td>5.47 ± 6.16</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Laboratory test</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>WBC (×10³/μL)</td>
<td>12.83 ± 12.13</td>
<td>14.28 ± 14.05</td>
<td>0.01*</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.86 ± 3.39</td>
<td>10.68 ± 4.99</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Platelet (×10³/μL)</td>
<td>101.88 ± 86.05</td>
<td>170.65 ± 113.66</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>5.02 ± 1.21</td>
<td>5.83 ± 3.83</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.96 ± 2.88</td>
<td>3.13 ± 0.97</td>
<td>0.03*</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>3.57 ± 5.59</td>
<td>1.66 ± 3.49</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>50.82 ± 33.02</td>
<td>58.87 ± 35.96</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.88 ± 3.53</td>
<td>4.34 ± 5.93</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.71 ± 3.45</td>
<td>7.76 ± 3.71</td>
<td>0.86</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>7.87 ± 1.35</td>
<td>8.22 ± 1.31</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>5.85 ± 2.67</td>
<td>5.72 ± 2.61</td>
<td>0.52</td>
</tr>
<tr>
<td>PT, INR</td>
<td>2.20 ± 2.00</td>
<td>1.53 ± 0.98</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>65.07 ± 42.21</td>
<td>52.52 ± 36.27</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Data are expressed as number (%), number only, mean ± standard deviation, or percentage only.

aPTT, activated partial thromboplastin time; BUN, blood urea nitrogen; CKRT, continuous kidney replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; INR, International normalized ratio; PSM, propensity score matching; PT, prothrombin time; SOFA score, Sequential Organ Failure Assessment score; WBC, white blood cell.

*Departments refer to the units to which patients were admitted. Medical department includes Departments of Internal Medicine, Emergency Medicine, Neurology, Rehabilitation Medicine, and Pediatrics. Surgical department includes Departments of General Surgery, Neurosurgery, Thoracic Surgery, Obstetrics And Gynecology, Orthopedic Surgery, Urology, Ophthalmology, and Dental Surgery.

*p < 0.05, statistically significant.
± 12.67 hours value in the NA group (p = 0.19) (Fig. 6). The downtime per 24 hours was similar (Table 1).

Differences in the beneficial effect of nafamostat mesylate on patient outcome by transfusion requirement

A total of 149 (30.4%), 114 (23.3%), and 90 patients (18.4%) required transfusion of three, two, and one blood product, respectively. In the Kaplan-Meier survival analysis, the survival benefit of NM was the highest in patients who required transfusion of all three blood products (log-rank p = 0.01, Fig. 7A), whereas no significant differences were observed in patients requiring less than three kinds of blood products (any combination of two blood product types: log-rank p = 0.30, Fig. 7B; just one blood product type: log-rank p = 0.74, Fig. 7C).
Differences in the beneficial effect of nafamostat mesylate on patient outcomes between medical and surgical patients

Of 490 patients, 369 (75.3%) were medical and 121 (24.7%) were surgical patients. Surgical patients more frequently required transfusions of all three blood products (63 of 121, 52.1%) compared to medical patients (86 of 369, 23.3%). In the Kaplan-Meier survival analysis, surgical patients showed a higher survival benefit of NM at hospital mortality (log-rank p = 0.03), while the benefit was less pronounced in medical patients (log-rank p = 0.29). CKRT mortality and ICU mortality showed the same trend (Supplementary Fig. 1, available online).

Discussion

Herein, the outcomes of patients treated with NM anticoagulation for CKRT and the safety of NM were evaluated. Both in-hospital mortality and incidences of bleeding complications were significantly lower in the NM group than in the NA group. The incidence of agranulocytosis during CKRT did not differ between the groups, and the time from hyperkalemia to normokalemia was not significantly prolonged by NM anticoagulation therapy. To our knowledge, this is the first study to assess the safety of NM anticoagulation for CKRT following the publication of the KDIGO 2012 anticoagulation guidelines [12].

The survival benefits conferred by NM compared with NA can be attributed to a decrease in the incidence of bleeding complications in patients administered NM. Both the hemoglobin changes during CKRT and transfusion requirements were significantly lower in the NM group than in the NA group. A potential criticism of this result could be selection bias due to the retrospective design of this study. The primary cohort without PSM indicated that younger patients with higher SOFA scores and more pronounced laboratory abnormalities (lower platelet count, longer PT or activated partial thromboplastin time) received NA, whereas patients with milder conditions received NM. Im-
importantly, we controlled these baseline differences using a PSM model, and analysis was performed with the same baseline characteristics, which strengthened the novelty of our findings. In previous RCTs and meta-analyses, NM did not have a significant effect on patient mortality or bleeding complications [24,25,33]. However, in these studies, in-hospital mortality or bleeding complications were not the primary outcomes, and the study populations were relatively small (20–30 patients per group). In addition, there were differences in the definitions of bleeding complications, RBC transfusion requirements [25,34], or incidences of bleeding events [14,24], which limited the power of evidence in these studies. In contrast, our study included a large number of patients (245 per group), and bleeding complications were objectively determined based on blood product transfusion requirements.

As a serine protease inhibitor, NM has been demonstrated to affect disseminated intravascular coagulation (DIC) [35], which might contribute to better patient outcomes. In our study, 30.4% of patients required transfusions of all three types of blood products; these patients had a greater survival benefit than those who required only one or two types of blood products. We speculate that the group requiring transfusion of all three types of blood products included a larger number of patients with DIC than did the group requiring transfusion of one or two types of blood products; moreover, the survival benefit seen in the NM group might be associated with the DIC treatment effects of NM. Both the higher transfusion requirements in surgical compared to medical patients and the stronger benefit of NM over NA in surgical patients strengthen the likelihood of DIC as a link between NM and improved patient outcomes, considering that surgery itself can cause DIC [36]. This speculation was supported by a study by Kamijo et al. [37] who used data from the nationwide retrospective DIC registry in Japan (J-Septic DIC registry) to evaluate the in-hospital and in-ICU mortality of patients with sepsis who underwent blood purification in the ICU. The patients in the group administered NM had lower in-hospital and in-ICU mortality than those in the NA group. Further RCTs are required to determine the beneficial effects of NM anticoagulation for CKRT on the survival of critically ill patients with DIC.

Hyperkalemia is a well-known side effect of NM [12,21], as both NM and its metabolites (p-guanidinobenzoic acid

**Figure 6.** Mean continuous kidney replacement therapy filter life.
CI, confidence interval; NA, no anticoagulation; NM, nafamostat mesylate.

**Figure 7.** Kaplan-Meier survival curves for all-cause mortality according to the number of blood product types transfused during continuous kidney replacement therapy. (A) All three types of products, (B) any two types of products, and (C) any one type of product. NA, no anticoagulation; NM, nafamostat mesylate. *p < 0.05, statistically significant.
and 6-amidino-2-naphthol) inhibit the inward sodium current in the renal collecting duct, thus reducing the driving force for the diffusion of potassium from cells into the lumen, which in turn inhibits urinary potassium secretion [21]. However, in patients receiving CKRT, potassium is eliminated by dialysis and hyperkalemia is less likely to occur. Nevertheless, the speed of hyperkalemia correction may differ. Our study evaluated the effects of NM on the speed of hyperkalemia correction. Hyperkalemia (serum K >5.5 mmol/L) at CKRT initiation was present in 19.2% of the patients, and the time to normokalemia (serum K ≤4.5 mmol/L) in the NM group was 19.2 hours, which was approximately 1 hour (7.3%) longer than that in the NA group (17.9 hours). In patients with severe hyperkalemia (serum K >7.0 mmol/L), the time to normokalemia was 20.3 hours in the NM group and 18.1 hours in the NA group, a difference of approximately 2 hours (12.2%). As the number of patients with hyperkalemia was relatively small, these differences were not statistically significant, and further studies on this issue are required. Therefore, until additional data regarding this becomes available, a higher dose of CKRT may be considered when initiating NM anticoagulation in patients with hyperkalemia.

Herein, agranulocytosis (ANC <100 cells/µL) developed in 34.6% of the patients, without a significant difference between the NM and NA groups. Additionally, there were no cases of anaphylaxis; however, owing to the retrospective nature of this study, relevant records may have been missing. Although infrequent, anaphylaxis is a fatal complication and careful observation is warranted [38].

Unlike previous RCTs, in our study, NM administration did not result in a longer filter life than NA. The mean filter life in our study was 21.25 ± 12.01 hours, which is shorter than those reported in previous RCTs (31.7 ± 24.1 hours [14], 26.63 ± 21.14 hours [25], and 28.73 ± 12.67 hours [33]). This difference might be attributed to our center’s unique CKRT implementation strategies. As the Korean national reimbursement system covers one filter per day for CKRT, we routinely changed the filter every 24 hours, even without evidence of clotting. Therefore, in our center, the filter life is not an appropriate parameter for assessing the efficacy of anticoagulation therapy.

Our study has several limitations. Owing to its retrospective design, there is a potential for systematic error or bias. Despite the use of PSM, unmeasured confounding variables may have remained. In addition, as the study population consisted exclusively of Koreans, the results may not be generalizable to other populations or healthcare settings. Moreover, long-term patient and kidney outcomes in patients administered NM have not been evaluated. Thus, whether NM has other nephroprotective or systemic protective effects in addition to its anticoagulant action should be explored. Some studies have suggested that serine protease inhibitors have anti-inflammatory properties that may be beneficial for critically ill patients [39,40]. Finally, although the in-hospital mortality and adverse events analyzed in our study are important outcomes, long-term sequelae in survivors, including NM-induced renal recovery and long-term mortality, should also be evaluated.

In conclusion, this study provides strong evidence supporting the use of NM as an effective and safe anticoagulant for CKRT in critically ill patients, especially those requiring transfusion of all three blood products. Although our results are promising, they should be interpreted with caution. Multicenter trials, especially in patients with DIC, are still needed, together with an in-depth exploration of the mechanisms underlying the observed benefits. While the quest to find the ideal anticoagulant for CKRT for patients with bleeding tendencies continues, NM may be a step in the correct direction.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors’ contributions

Conceptualization, Formal analysis: TK, DWK, HJK, EYS, SHS, HR


