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Comparison of regional citrate anticoagulation and nafamostat mesylate anticoagulation during plasma exchange for children at high bleeding risk: a retrospective study

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Abstract

Background There is currently no established optimal anticoagulation protocol for plasma exchange (PE) in pediatric patients at a high risk of bleeding. Therefore, we aimed to evaluate the efficacy and safety of regional citrate anticoagulation (RCA) and nafamostat mesylate (NM) for PE anticoagulation in this patient group.

Methods This retrospective study analyzed data from 66 children with high bleeding risk who underwent PE in the Pediatric Intensive Care Unit of Hunan Children's Hospital between June 2018 and January 2023. Patients were divided into two groups: RCA-PE ($n=45$) and NM-PE ($n=21$), and filter performance and adverse reaction rates were compared. Statistical analysis utilized SPSS 25.0, comprising two-sample t-tests, chi-square or Fisher's exact tests, and Mann–Whitney U tests, as appropriate. Data visualization was performed using ggplot2 in R-studio. $P<0.05$ was considered statistically significant.

Results No statistically significant differences were found between the two groups in initial transmembrane pressure (TMP) [17.0 (14.0, 21.5) mmHg vs. 16.0 (14.0, 19.5) mmHg, $P=0.614$], maximum TMP [46.0 (42.0, 49.5) mmHg vs. 43.0 (41.5, 49.5) mmHg, $P=0.689$], and final TMP [40.0 (35.5, 45.0) mmHg vs. 38.0 (35.0, 42.0) mmHg, $P=0.298$]. Filter grade distribution and bleeding events also showed no statistically significant difference between the groups. However, the NM-PE group had significantly lower overall adverse reaction and metabolic alkalosis rates (both $P<0.05$) compared to the RCA-PE group.

Conclusions NM demonstrates similar efficacy but superior safety compared with RCA, making it a more suitable anticoagulation strategy for children with high bleeding risk. Study limitations include single-center design, selection bias, and uncertain NM dosage.

Keywords Pediatric intensive care, Bleeding risk management, Anticoagulant efficacy, Transmembrane pressure, Metabolic alkalosis, Adverse reaction rates

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Background

Plasma exchange (PE) is an extracorporeal blood purification technique used in treating critical illnesses such as autoimmune diseases, liver failure, certain poisonings, thrombotic microangiopathies, and cytokine storms. Effective anticoagulation is crucial during PE, but poses challenges, especially for patients at high bleeding risk. The standard method, systemic anticoagulation with heparin [1], increases bleeding risks in such patients. Therefore, identifying a suitable PE anticoagulation strategy for this patient group is essential. Regional citrate anticoagulation (RCA) provides local anticoagulation in extracorporeal circulation with minimal impact on the overall coagulation function of the body. RCA mitigates bleeding risk and can significantly extend filter life, making it widely preferred in continuous renal replacement therapy (CRRT) [2, 3]. However, RCA is less utilized in PE due to concerns regarding citrate-related metabolic complications, such as metabolic alkalosis and hypocalcemia, when PE is performed without CRRT.

Nafamostat mesylate (NM) is a serine protease inhibitor that acts independently of antithrombin. It inhibits coagulation factors IIa, Xa, XIIa, kallikrein, and plasmin, while also suppressing complement and platelet activation. NM's short half-life of about 5–8 min, owing to rapid degradation by hepatic carboxylesterase in the blood, makes it suitable for local anticoagulation in extracorporeal circulation [4]. Although both RCA and NM are local anticoagulation techniques, no studies have compared their application in PE anticoagulation. This study aims to evaluate the efficacy and safety of these two anticoagulation methods in PE for children at high bleeding risk, to improve the anticoagulation strategies for PE in such patients.

Methods

Study participants

In this retrospective study, we analyzed the medical records of children at high bleeding risk who underwent PE in the Department of Critical Care Medicine, Hunan Children's Hospital, from June 2018 to January 2023. High bleeding risk was defined according to the following criteria [5]: (1) activated partial thromboplastin time (aPTT) > 60 s; (2) platelet count $< 50 \times 10^9$/L; (3) active bleeding, such as gastrointestinal bleeding or intracranial hemorrhage; and (4) surgical history within 48 h before PE. The inclusion criteria were: (1) PE anticoagulation with either sodium citrate or NM alone; and (2) no other forms of blood purification before PE. The exclusion criteria were: (1) termination of PE for reasons unrelated to the procedure (e.g., patient discharge or death); and (2) potential citrate metabolism disorders, such as liver failure, refractory shock, or uncorrectable hypoxemia. We analyzed only the first PE session, regardless of the number of PE sessions performed during hospitalization in the pediatric intensive care unit (PICU). We divided the study participants into two groups based on the anticoagulation method used during PE: the RCA-PE group (using sodium citrate) and the NM-PE group (using NM). This study, being a retrospective observational study, involved data extracted from the electronic medical record system without involving patient privacy or commercial interests. Therefore, the requirement for informed consent was waived and the study was approved by the Ethics Committee of Hunan Children's Hospital (Ethics No.: HCHLL-2024-269).

PE procedure

At the study center, we performed PE using either the MultiFiltrate (Fresenius Medical Care, Bad Homburg, Germany) or PrismaFlex© (Gambro, Lund, Sweden) devices, along with corresponding tubing and filters. During the procedure, we placed a dual-lumen central venous catheter in the femoral or internal jugular vein under ultrasound guidance. We selected appropriate plasma separators and tubes based on the patient's weight. The target replacement volume for PE was 1–1.5 times the plasma volume, calculated as plasma volume = 65 × weight (kg) × (1 - hematocrit). We exchanged 40–60 ml/kg of plasma per session, using fresh frozen plasma as the replacement fluid. For children weighing less than 10 kg, we primed the tubing with a mixture of 50 ml 10% albumin and 0.9% saline in a 1:1 ratio to prevent hypotension. Prior to the successful implementation of RCA-PE, anticoagulation for PE was either absent or predominantly involved heparin. Since 2018, RCA has been used for PE in patients with a high bleeding risk, with NM introduced in 2020.

PE anticoagulation management

For the RCA-PE group, we infused a 4% sodium citrate solution (Qingshan Likang Pharmaceutical Co., Ltd., Chengdu) into the blood inlet port via a three-way pump. We set the initial citrate flow rate (ml/h) to (1.1–1.3) × blood pump flow rate (ml/min), with the initial blood pump flow rate set at 3 ml/(kg·min), adjusted according to hemodynamic conditions. We measured ionized calcium concentrations both in vivo and in the extracorporeal circuit half an hour following PE initiation. We further rechecked calcium levels after the procedure if the targets were met; otherwise, we adjusted the citrate dose and rechecked calcium levels every half hour until the target was reached. The target ionized calcium levels were 1.0–1.2 mmol/L in vivo and 0.2–0.4 mmol/L in the extracorporeal circuit.

For the NM-PE group, we dissolved 20 mg of injectable NM (Durui Pharmaceutical Co., Ltd., Jiangsu) in 2–5 ml of 5% glucose injection solution. Subsequently, we added

this to 500 ml of 0.9% sodium chloride for tubing priming. After PE initiation, we infused NM continuously at an initial rate of 0.25 mg/kg/h. Half an hour later, we measured the activated clotting time (ACT) of whole blood post-filter and adjusted the NM infusion rate based on the result, aiming to achieve a target ACT of 180–250 s. If targets were met, ACT was rechecked after the procedure; otherwise, the NM dose was adjusted, and ACT was rechecked every half hour until the target was reached.

Data collection

We collected demographic characteristics, clinical data, PE parameters, and outcomes of the study participants. The primary outcome was filter performance, assessed through the evaluation of the filter's performance during PE to determine anticoagulation efficacy. Filter performance indicators included transmembrane pressure (TMP) during PE, which encompassed initial TMP, maximum TMP, and final TMP, as well as the filter grade after PE. The criteria for filter grading [6] were: Grade 0 - no coagulation or minimal fibrous coagulation; Grade 1 - less than one-third fibrous coagulation; Grade 2 - one-third to two-thirds fibrous coagulation; Grade 3 - more than two-thirds fibrous coagulation leading to significant increases in venous pressure and TMP, necessitating filter replacement. Secondary outcomes included the incidence of new bleeding events and metabolic disorders during PE. Key metabolic disorder indicators included metabolic alkalosis, hypocalcemia, metabolic acidosis, hyperlactatemia, hyperkalemia, hypernatremia, and hyponatremia.

Statistical analysis

Statistical analyses were conducted using SPSS 25.0 (IBM Corp., Armonk, NY). We presented normally distributed data as mean ± standard deviation (x ± s) and performed between-group comparisons using the two-sample t-test. Conversely, count data are presented as the number of cases [n (%)]and performed comparisons using the chi-square test or Fisher's exact test. Non-normally distributed data were expressed as median (quartile) [M (P25, P75)], and between-group comparisons were performed using the independent-samples Mann–Whitney U test. A P-value < 0.05 was considered statistically significant. We performed data visualization using ggplot2 in R-studio (version 4.2.1, Integrated Development for R. RStudio, Inc., Boston, Massachusetts, USA).

Results

Comparison of baseline characteristics

Based on the inclusion and exclusion criteria, 66 children were enrolled in the study, with 45 in the RCA-PE group and 21 in the NM-PE group. The patient selection process is illustrated in Fig. 1. Among these patients, 63.6% required mechanical ventilation before PE, 39.3% needed vasopressor support, 6% had active bleeding before PE, and 7.6% had a surgical history within 48 h before PE. The most common reason for PE was hemophagocytic lymphohistiocytosis, accounting for 31.8% of all patients. The median aPTT values for the RCA-PE and NM-PE groups were 58.4 s and 65.3 s, respectively, and the median platelet counts were 40×10^9/L and 38×10^9/L, respectively. Baseline characteristics between the two groups were similar, with no statistically significant differences observed (Table 1).

Comparison of anticoagulant efficacy

There was no statistically significant difference observed between the RCA-PE and NM-PE groups in terms of initial TMP [17.0 (14.0, 21.5) mmHg vs. 16.0 (14.0, 19.5) mmHg, Z = -0.504, P = 0.614], maximum TMP [46.0 (42.0, 49.5) mmHg vs. 43.0 (41.5, 49.5) mmHg, Z = -0.675, P = 0.500], and final TMP [40.0 (35.5, 45.0) mmHg vs. 38.0 (35.0, 42.0) mmHg, Z = -1.042, P = 0.298]. Additionally, the filter grades after PE in the RCA-PE and NM-PE groups were: 0-grade filter at 24.4% and 28.6%, 1-grade filter at 73.3% and 66.7%, and 2-grade filter at 2.2% and 4.8%, respectively. No grade 3 filters were observed in either group. No statistically significant difference was observed in filter grades (P > 0.05) between the two groups (Fig. 2; Table 2).

Comparison of anticoagulant safety

Adverse reactions occurred in both groups, with those in the RCA-PE group primarily manifesting as metabolic alkalosis. Compared to the RCA-PE group, the NM-PE group exhibited a significantly lower total incidence of adverse reactions (64.4% vs. 23.8%), as well as metabolic alkalosis (48.9% vs. 4.8%) (P < 0.05 in both cases). The incidence of severe metabolic alkalosis in the RCA-PE group was 15.6%. Among 22 patients who developed metabolic alkalosis following RCA-PE, 13 received sequential CRRT, while 9 did not undergo CRRT. In the non-CRRT patients, 6 patients still exhibited metabolic alkalosis at 12 h post-PE but with reduced severity compared to immediate postoperative levels. Two cases remained unresolved at 24 h post-PE, with no clinical interventions administered. Notably, all patients receiving sequential CRRT therapy achieved complete resolution of metabolic alkalosis within 12 h post-procedure. However, there was no statistically significant difference observed in the incidence of bleeding events between the two groups (4.4% vs. 4.8%) (Table 3).

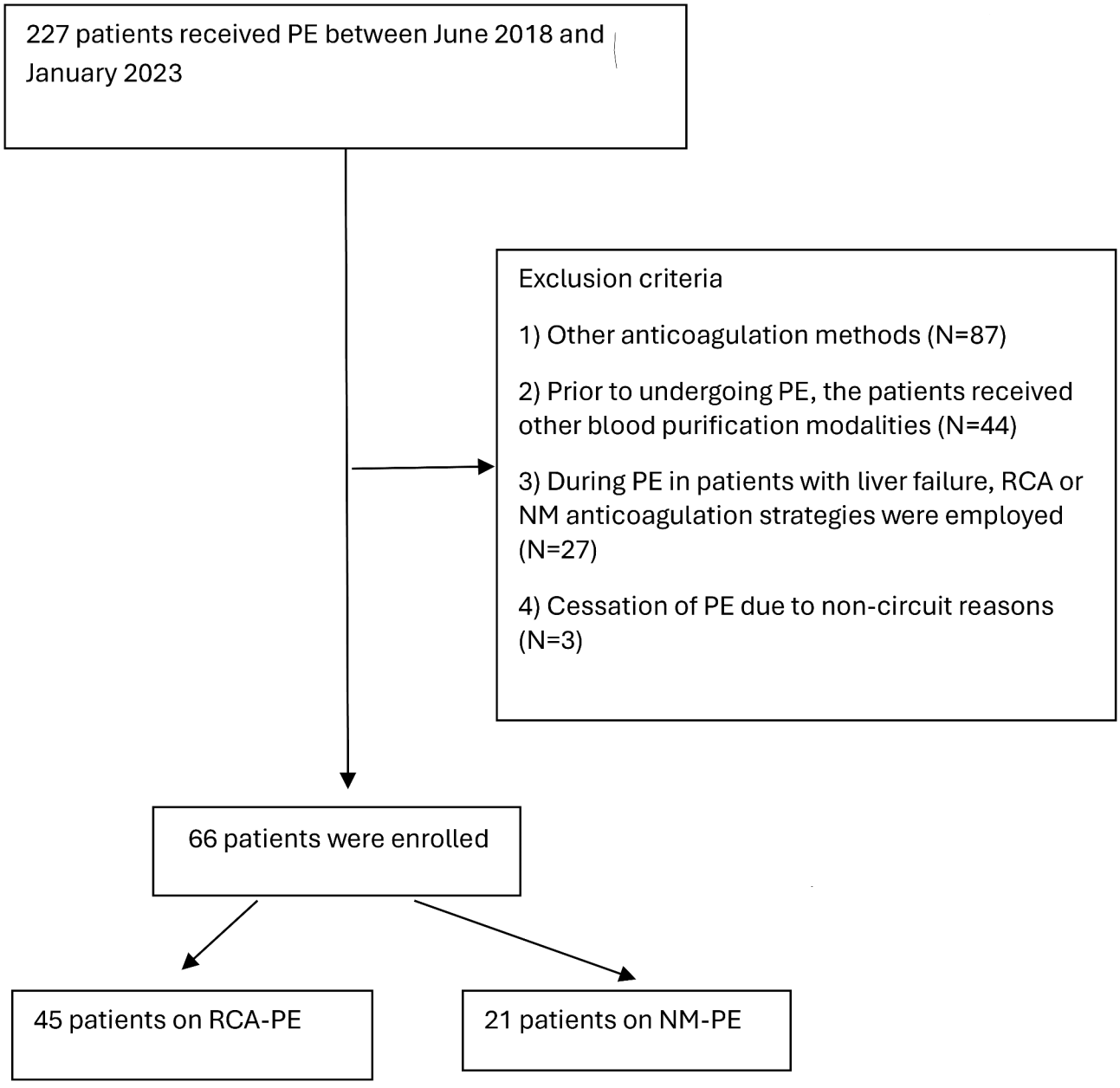

Fig. 1 Overview of patient selection. PE: plasma exchange; RCA: regional citrate anticoagulation; NM: nafamostat mesylate

Discussion

To our knowledge, this is the first cohort study evaluating the anticoagulant efficacy and safety of RCA versus NM in children with a high risk of bleeding during PE. Through retrospective analysis performed at a single center, we compared filter performance and the incidence of adverse reactions during PE with different anticoagulation methods, finding that NM achieves comparable anticoagulant efficacy to RCA, while demonstrating significantly lower incidences of metabolic complications, indicating superior safety and efficacy in this patient population.

For children with a high bleeding risk, the choice of anticoagulant during PE must balance achieving effective anticoagulation with minimizing bleeding risks. Before the successful application of RCA in PE, options for anticoagulation in high-risk pediatric patients were limited, often involving either no anticoagulation or the risky use of heparin. The absence of anticoagulation during PE, while avoiding bleeding risks, increases the likelihood of clot formation in the extracorporeal circuit, shortening the filter lifespan [7–9]. Systemic anticoagulation with heparin, on the other hand, increases bleeding risk, with a bleeding incidence of up to 16.4%. Additionally, it increases the need for transfusions within 24 h

Table 1 Comparison of baseline characteristics in the two groups

Indicator	RCA-PE Group	NM-PE Group	*P*-value
No. of Cases	45	21	
Age [*M (P25, P75)*, months]	45 (25.5, 85.5)	63.0 (31.0, 103.5)	0.256
Gender (Male/Female, n)	24/21	11/10	0.942
Weight [*M (P25, P75)*, kg]	17.5 (11.7, 21.8)	19.0 (12.7, 27.1)	0.332
PCIS [*M (P25, P75)*, points]	78 (72, 84)	78 (76, 83)	0.777
Mechanical Ventilation [n (%)]	29 (64.4)	13 (61.9)	0.842
Vasopressor Support [n (%)]	16 (35.6)	10 (47.6)	0.350
Platelets [*M (P25, P75)*, $x10^9$/L]	40 (27, 71.5)	38 (25, 72.5)	0.967
Hemoglobin [*M (P25, P75)*, g/L]	78 (71.5, 81.0)	77.0 (69.5, 84.5)	0.756
pH [*M (P25, P75)*]	7.35 (7.24, 7.42)	7.40 (7.24, 7.44)	0.874
HCO_3^- [*M (P25, P75)*, mmol/L]	20.7 (18.3, 23.6)	18.8(17.2,21.8)	0.164
Ionized Calcium In Vivo (_x ± S, mmol/L)	1.19 ± 0.10	1.22 ± 0.13	0.291
Blood Lactate (_*x* ± *S*, mmol/L)	2.1 ± 1.1	2.4 ± 1.5	0.449
Blood Sodium (_*x* ± *S*, mmol/L)	133.3 ± 6.1	131.9 ± 5.7	0.408
Blood Potassium [*M(P25,P75)*, mmol/L]	4.4 (3.8, 5.1)	4.2 (3.7, 4.7)	0.606
aPTT [*M (P25, P75)*, s]	58.4 (50.6, 72.3)	65.3 (55.6, 81.0)	0.500
Active Bleeding [n (%)]	3 (6.7)	1 (4.8)	> 0.999
Surgical History within 48 h	3 (6.7)	2 (9.5)	0.650
Etiological Factors [n (%)]			0.939
Severe Sepsis	13 (28.9)	4 (19.0)	
Acute Poisoning	8 (17.8)	5 (23.8)	
Hemophagocytic Lymphohistiocytosis	14 (31.1)	7 (33.3)	
Hemolytic Uremic Syndrome	7 (15.6)	3 (14.3)	
Drug Hypersensitivity Syndrome	2 (4.4)	1 (4.8)	
Systemic Lupus Erythematosus	1 (2.2)	1 (4.8)	

PCIS: Pediatric Critical Illness Score; RCA: regional citrate anticoagulation; NM: nafamostat mesylate; PE: plasma exchange; aPTT: Activated partial thromboplastin time

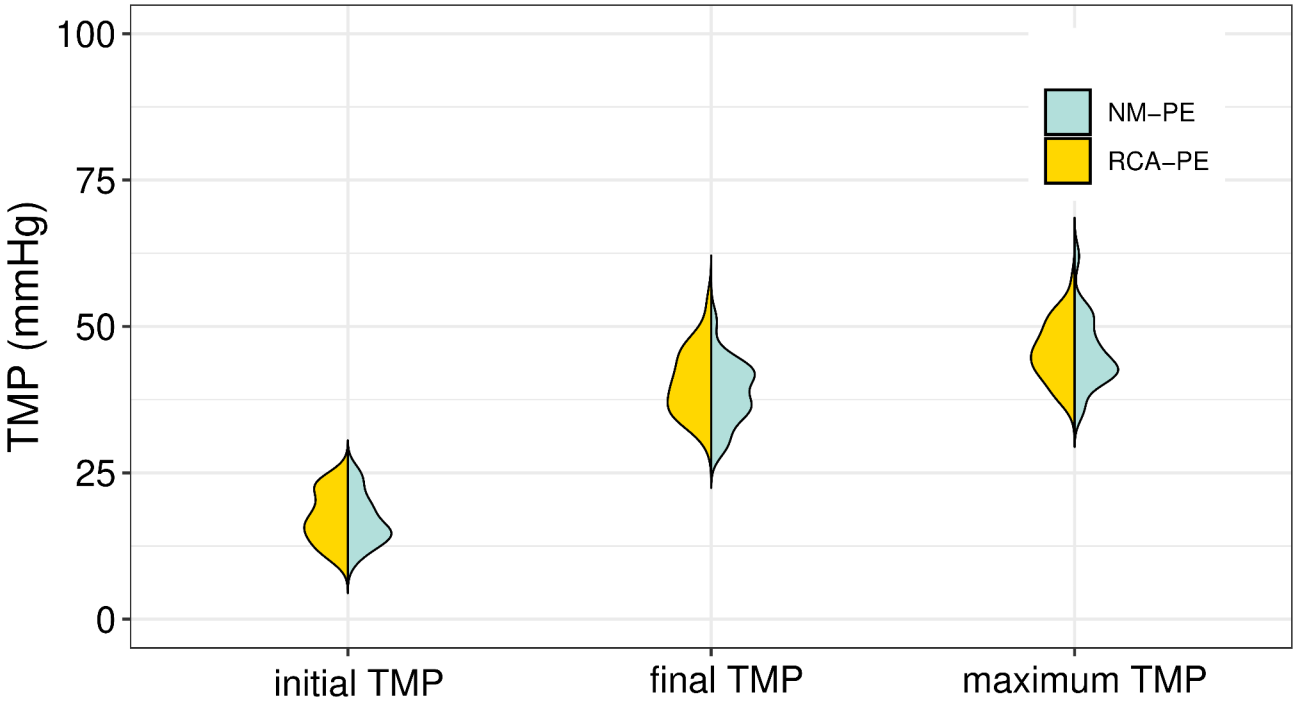

Fig. 2 TMP during PE in the RCA-PE and NM-PE groups. TMP: transmembrane pressure; PE: plasma exchange; RCA: regional citrate anticoagulation; NM: nafamostat mesylate

Table 2 Comparison of filter grades after PE

Group	No. of Cases [*n* (%)]	Filter Grade			
		0	1	2	3
RCA-PE Group	45	11 (24.4)	33 (73.3)	1 (2.2)	0
NM-PE Group	21	6 (28.6)	14 (66.7)	1 (4.8)	0
P-value	0.687				

RCA: regional citrate anticoagulation; NM: nafamostat mesylate; PE: plasma exchange

Table 3 Comparison of adverse reaction rates between the two groups

Adverse Reaction [*n* (%)]	RCA-PE Group *n* = 45	NM-PE Group *n* = 21	*P*-value
Total Adverse Reactions	29 (64.4)	5 (23.8)	0.003
Bleeding Events	2 (4.4)	1 (4.8)	> 0.999
Metabolic Alkalosis	22 (48.9)	1 (4.8)	< 0.001
Severe Metabolic Alkalosis[a]	7(15.6)	0(0)	-
Hypocalcemia	2 (4.4)	1 (4.8)	> 0.999
Hypercalcemia	0(0)	0(0)	-
Lactic Acidosis	2 (4.4)	1 (4.8)	> 0.999
Hyperkalemia	1 (2.2)	1 (4.8)	0.538
Hypernatremia	0(0)	0(0)	-
Hyponatremia	0(0)	0(0)	-

RCA: regional citrate anticoagulation; NM: nafamostat mesylate; PE: plasma exchange

[a] pH > 7.50 and bicarbonate concentration > 30 mmol/L

post-PE [8, 10]. In contrast, RCA does not affect coagulation within the body, thereby reducing bleeding risk [11]. However, the metabolism of sodium citrate releases a large amount of bicarbonate, raising the risk of metabolic alkalosis [12].

NM is an ultra-short-acting anticoagulant that does not increase bleeding risks during blood purification in critically ill patients, making it commonly used for extracorporeal anticoagulation therapy in South Korea and Japan [9, 13–16]. Its introduction in China for blood purification anticoagulation is relatively recent (2020), with limited clinical experience. Existing research on NM for extracorporeal anticoagulation has primarily focused on CRRT and extracorporeal membrane oxygenation (ECMO) [5, 17–21], with no clinical studies comparing RCA and NM for anticoagulation during PE in pediatric patients with high bleeding risk.

In a large animal model study [22], NM and heparin were compared for ECMO anticoagulation, revealing prolonged aPTT in both groups compared to baseline values. Thromboelastography parameters were similar, and the NM group exhibited a smaller reduction in hemoglobin levels than the heparin group. In line with our study findings, this preclinical study suggests that NM provides an anticoagulant efficacy comparable to that of regular heparin but induces fewer bleeding complications, indicating its potential as an alternative for extracorporeal anticoagulation therapy. In an observational study of 101 patients undergoing CRRT [23], no significant difference was observed in median filter lifespan between NM and heparin groups; NM significantly mitigated the risk of bleeding complications (3.3% vs. 27%). Additionally, a retrospective study by Liu et al. found NM to be as effective as RCA in high-risk bleeding patients undergoing CRRT anticoagulation, with comparable safety profiles [5]. Another study comparing pediatric CRRT anticoagulation [20] between a Japanese and an American children's hospital reported a significantly longer filter lifespan in the NM group than in the RCA group (NM: 38 [22, 74] hours vs. RCA: 36 [17, 66] hours; $P = 0.02$) with no significant difference in bleeding incidence between the two groups (NM: 5% vs. RCA: 9%). In a study by Jiao J et al., [10] the treatment had to be terminated in 4.1% of high-risk bleeding patients undergoing PE with heparin anticoagulation due to grade III filter coagulation. Our data indicates that, while using NM or RCA, filter performance during pediatric PE therapy was good, with no cases of treatment interruption due to filter coagulation. This finding suggests that both NM and RCA provide reliable anticoagulation.

TMP reflects the relative permeability of the side holes in the hollow fibers of the filter, serving as a crucial indicator for monitoring the coagulation status of the filter [7]. However, studies on TMP during PE are relatively scarce. In a study by Chavda et al., which analyzed 674 PE procedures, high TMP was reported as the most common circulatory complication during PE, occurring in approximately 8.3% of cases [24]. Another PE study recorded average TMP [7] and found that in PE treatments where filter coagulation occurred, the average TMP was 54.5 mm Hg, compared to 43.7 mm Hg in treatments without filter coagulation ($P < 0.001$). The risk of filter

Table 4 Comparative analysis of anticoagulation strategies for pediatric PE

Feature	Heparin-PE	RCA-PE	NM-PE
Filter Efficacy	Weaker than RCA	Good	Comparable to RCA
Advantages	Easy availability	Does not increase the risk of bleeding	Does not increase the risk of bleeding
Risk of adverse events	High bleeding risk, Heparin-induced thrombocytopenia	Metabolic alkalosis (common), Hypocalcemia	Hyperkalemia (rare)
Operational challenges	Needs aPTT/ACT monitoring	Requires simultaneous monitoring of systemic and extracorporeal circuit ionized calcium levels, leading to a substantial increase in clinical workload.	Needs aPTT/ACT monitoring
Half-life	1–5 h (dose-dependent)	5 min	5–8 min
Exclusion criteria	High bleeding risk, Heparin-induced thrombocytopenia	Severe liver dysfunction PO_2<60 mmHg	Hypersensitivity history
Cost	The costs of heparin and coagulation function tests; Low cost	The costs of citrate along with intravascular and extracorporeal ionized calcium monitoring as well as coagulation function tests; The highest cost	The costs of nafamostat mesylate and coagulation function tests; Moderate cost
Availability	Universally available	Limited to specialized centers	Restricted (China, Japan, and Korea mainly)

PE: plasma exchange; RCA: regional citrate anticoagulation; NM: nafamostat mesylate; aPTT: activated partial thromboplastin time; ACT: activated clotting time

coagulation was notably increased when TMP exceeded 50 mm Hg, with an odds ratio of 2.10 ($P=0.006$) [7]. Another study suggested that for every 1 mm Hg increase in TMP, the risk of coagulation increased by 1.5% (95% CI 1.0–2.0%) [25], while maintaining TMP below 60 mm Hg effectively prevented filter rupture [26]. In the present study, the average maximum TMP was 45 mm Hg. TMP remained at appropriate levels during PE in both the RCA-PE and NM-PE groups, indirectly reflecting the effectiveness of both anticoagulation strategies.

Possible adverse reactions during NM anticoagulation include hyperkalemia, hyponatremia, severe allergic reactions, and bone marrow suppression. Hyperkalemia has been reported in approximately 15–18% of cases during ECMO anticoagulation with NM, but is typically mild [27, 28]. There have been no reports of hyperkalemia during CRRT, and other potential adverse reactions have not been documented [9, 18, 29]. Nonetheless, given the complex conditions of patients in the PICU, some potential adverse reactions may have been missed. By inhibiting amiloride-sensitive sodium conductance, NM metabolites suppress potassium secretion and urinary potassium excretion, ultimately leading to hyperkalemia [30].

Compared to CRRT, RCA-PE lacks the acidic replacement fluid necessary to neutralize the alkalinity produced by citrate metabolism. Consequently, using sodium citrate as an anticoagulant during PE can lead to metabolic alkalosis. The reported incidence of metabolic alkalosis in RCA-PE varies across different studies, with bicarbonate levels ranging from high normal to levels as high as 93% [8, 10, 31]. In the present study, the incidence of metabolic alkalosis in RCA-PE was 48.9%, significantly higher than the 4.8% observed in the NM group. This difference may be attributed to variations in several factors, such as the citrate-to-blood pump flow ratio, PE duration, and PE volume, which lead to different alkalinity loads from citrate metabolism entering the body.

Based on our study findings, we have systematically compared Heparin, RCA, and NM in terms of filter efficacy, risk of adverse events, operational challenges, half-life, exclusion criteria, cost, and availability (Table 4). This table integrates both general characteristics and our original data to guide clinical decision-making.

This study has certain limitations. Firstly, as a single-center retrospective observational study, the sample size was relatively small, and the anticoagulation strategy was determined by PICU physicians, introducing potential selection bias. Secondly, there is no consensus on the optimal dosage of NM for PE, which could impact its anticoagulant efficacy in extracorporeal circulation during PE. Further prospective clinical studies are needed to establish the optimal NM dosage for PE anticoagulation in pediatric patients.

Conclusions

In children with high bleeding risk undergoing PE, NM and RCA show comparable effectiveness in terms of extracorporeal anticoagulation and similar incidences in bleeding events. However, NM is associated with fewer metabolic complications, making it a safer option than RCA. Future studies with larger sample sizes are encouraged to determine the optimal NM dosage for PE anticoagulation in this patient group to provide more definitive clinical guidance.

Abbreviations

ACT	Activated clotting time
aPTT	Activated partial thromboplastin time
CRRT	Continuous renal replacement therapy
NM	Nafamostat mesylate

PE Plasma exchange
RCA Regional citrate anticoagulation
TMP Transmembrane pressure

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Author contributions
DP: study design and manuscript writing; ZC: research guidance and data analysis; JH: data analysis and visualization; WD: data compilation and analysis; XZ: study design and guidance and manuscript revision.

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Data availability
All data generated or analyzed during this study are included in this published article. Further inquiries may be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Hunan Children's Hospital (Ethics No.: HCHLL-2024-269). The requirement for informed consent was waived owing to the retrospective observational study design, involving data extracted from the electronic medical record system without involving patient privacy or commercial interests. All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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