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Synergistic action of heparin and fluid-stopping device in reducing air embolism and hemodialysis clotting: Early results from a randomized trial

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Abstract: **Background**: Entry of air into the extracorporeal circuit and inappropriate anticoagulation are significant factors associated with clotting. Even with systemic heparination, microbubbles can be implicated as sites for thrombosis and accelerate heparin metabolism. Fluid Stop devices, which prevent fluid from flowing during line drainage, have been shown potentially to decrease air embolism and improve hemostasis within circuits, but there is no concrete evidence available regarding simultaneous heparin use. **Objectives**: The objective of this trial was to determine whether the use of systemic heparin and a portable fluid stop device can decrease air embolism and clotting within hemodialysis circuits compared with traditional infusion sets. Anticoagulation stability, risk of bleeding, and patient satisfaction were also measured. **Methods**: In this prospectively conducted single-center randomized controlled trial, 80 hemodialysis patients receiving maintenance hemodialysis were randomly assigned either to a control group with standard infusion sets or an observation group with fluid-stopping sets and all receiving standard heparin doses. A total of 800 hemodialysis sessions were conducted prospectively with observation for air bubble entrance, line draining, and clotting. Secondary endpoints included ACT variability, satisfaction rates, and instances of bleeding complications. **Results**: A significantly lower number of line emptying procedures (3 vs. 24; 5.0% vs. 27.5%), air bubble entries (4 vs. 28; 7.5% vs. 32.5%), and clotting incidents (2 vs. 12; 2.5% vs. 22.5%) were seen in the observation group compared with controls ($P < 0.01$). The stability of ACT values with smaller ranges of fluctuation was better in the observation group. Scores on satisfaction were higher, and there were no complications seen with bleeding. **Conclusion**: Findings from these preliminary studies indicate that fluid-stopping devices may potentially improve heparin efficacy by preventing air embolism and clotting with no loss of safety. Based on these preliminary findings, larger multicenter trials are needed.

Keywords: Anticoagulation strategy; Air embolism; Activated clotting time; Drug-device interaction; Hemodialysis; Heparin; Randomized trial

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INTRODUCTION

Hemodialysis is renal replacement therapy that is life-sustaining in end-stage renal disease and acute kidney injury patients (Gong *et al*., 2024). Although hemodialysis is effective for the removal of uremic toxins and normalization of fluid-electrolyte balance, in doing so it exposes blood in the circulation to large non-endothelial surfaces of the extracorporeal circuit, triggering the intrinsic coagulation pathway and platelets, which very rapidly lead to fibrin-containing thrombus formation unless effective anticoagulation is provided (Emmanuel Fatona, 2024; Kedir *et al.,* 2024) .Amongst the anticoagulants used, unfractionated heparin remains the most usual option due to its instantaneous action, reversibility and clearly established safety profile (Goel *et al.,* 2024). Heparin works by binding to antithrombin III and profoundly enhancing its inhibition of thrombin (Fact or IIa) and Factor Xa, thus inhibiting the formation of thrombin and fibrin clot (Chabata *et al.,* 2025). However, heparin possesses a narrow therapeutic window: Underdosing risks clotting of circuits, while overdosing increases bleeding in critically ill or post-operative patients (Prajapathi *et al.,* 2024). Clinicians therefore titrate the dose of heparin with both point-of-care coagulation assays such as Activated Clotting Time (ACT) or Activated Partial Thromboplastin Time (aPTT) and clinical monitoring in a bid to meet these rival risks (Favaloro *et al.,* 2024; Ali *et al.,* 2024). ACT was selected in the current study because it provides bedside immediate determination of heparin activity, is used extensively during extracorporeal procedures and allows real-time adjustment of dose, but may not reflect optimal local depletion of heparin (Ozdemir *et al.,* 2025).

Despite systemic heparinization, thrombosis of the extracorporeal circuit remains a common and costly complication. The small but real reason behind this problem is the introduction of air into dialysis lines,

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particularly upon fluid bag depletion or improper line disconnections. Air bubbles create local surface roughness and turbulence, enhancing platelet adhesion and local thrombin generation, which contributes to the formation of microthrombi (Padín *et al.,* 2024; Ma, 2025; Pacheco and Saad, 2024). These microthrombi can also capture and inactivate heparin at the site of their formation, de facto suppressing its local pharmacologic effect even though systemic levels of ACT remain therapeutic. This is a mechanical counterpressure to the desired anticoagulant effect of heparin (Narendra *et al.,* 2024; Nandave, 2024).

Prevention of air entry can therefore indirectly enhance the pharmacologic activity of heparin by keeping laminar blood flow, suppressing platelet activation and providing availability of local drug (Meshulami *et al.,* 2025; Patil *et al.,* 2024). Practical approach is the use of disposable automatic fluid-stopping infusion systems, which totally interrupt flow when the source fluid is depleted and avoid air entry into the extracorporeal circuit. Though they are marketed primarily as safety devices for minimizing the risk of air embolism, their potential to improve anticoagulation efficacy and amplify the pharmacodynamics of heparin has never been examined in a rigorous manner (Padín *et al.,* 2024; Deane *et al.,* 2024; Ebadi, 2025a; Ebadi, 2025b) .To the best of our knowledge, this is the first study to evaluate the potential drug-device synergy between systemic heparin anticoagulation and a mechanical fluid-stopping device used in hemodialysis (Srikanth, 2025; Ebadi and Selamoglu, 2025). We anticipated that prevention of air entry would stabilize circuit heparin activity-reduced clotting occurrences and stable ACT values-improving dialysis efficiency and patient safety. If this synergistic effect holds up, it would allow the administration of smaller heparin doses without loss of circuit patency and with fewer bleeding risks and make possible the individualized anticoagulation management of hemodialysis patients.

MATERIALS AND METHODS

Study design and setting

This was a single-center, prospective randomized controlled study conducted at the Blood Purification Center and Intensive Care Unit of Wuxi Branch of Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine between January 1 and December 31, 2024. Patients were randomly assigned in a 1:1 ratio to the observation group or the control group based on a computer-generated random number table by an independent statistician. The sequence of allocation was split and concealed in sealed opaque envelopes and disclosed by a study coordinator at enrollment. Written informed consent was received from all patients and the protocol was approved by the hospital's institutional ethics committee.

Participants

80 adult patients on maintenance hemodialysis were enrolled.Inclusion criteria were (1) age ≥18 years, (2) hemodialysis at least twice a week and (3) requirement for systemic anticoagulation with heparin for dialysis while Exclusion criteria included (1) history of heparin-induced thrombocytopenia, (2) active bleeding or recent major surgery, (3) severe thrombocytopenia (<50 × 10^9/L), (4) known hypersensitivity to heparin and (5) refusal to provide informed consent. Baseline data recorded included demographic data, dialysis vintage, vascular access type (arteriovenous fistula, graft, or central venous catheter), diabetic status, comorbid diseases, concomitant antiplatelet or oral anticoagulant use, hemoglobin and platelet count to allow assessment of potential confounding factors.

Administration and monitoring of heparin

All patients underwent systemic unfractionated heparin during dialysis. The standard practice was a bolus intravenous injection of 0.3-0.5 mg/Kg at onset and arterial line pump infusion of 5-10 mg/h that was discontinued 30 minutes before completion of treatment. High-risk patients for bleeding had both the bolus and individualized adjustment based on the patient's coagulation status respectively, at the discretion of the doctor. We recorded the number of patients receiving lower doses actually and calculated mean total heparin dose per dialysis treatment and per kilogram of body weight to compare dosing patterns between groups. Anticoagulation was sustained by monitoring Activated Clotting Time (ACT) from pre-filter blood samples at baseline, 60 minutes and end dialysis. ACT was employed as it is readily accessible at the bedside and has been previously utilized for the monitoring of real-time anticoagulation in extracorporeal procedures, though with the limitation of not reflecting local heparin depletion. Target range ACT 180–220 seconds, following literature guidelines (Hoebink *et al.,* 2025; Karami *et al.,* 2024). Quality control for ACT assay was achieved via standardized calibration protocols.

Device intervention

The control group was given intra-dialysis fluid infusions (saline, medications, or nutrition supplements) via standard disposable infusion sets. The observation group had the same dialysis parameters and heparin policy but all intra-dialysis fluid infusions were administered via disposable automatic fluid-stopping infusion sets. Such infusion sets automatically stop fluid infusion when the infusion bag becomes empty and thereby avert backflow of air into the extracorporeal circuit. The device can automatically seal the outlet when the liquid level in the infusion bag drops to the bottom of the dropper, thereby preventing air from entering the extracorporeal circulation system. The device used (National Medical Device Registration No. 20173664173) is produced by Shandong Xinhua Ande Medical Supplies Co., Ltd. A sample image is presented in fig. 1.

Outcome measures

The trial contrasted both primary and secondary outcomes**.** Primary outcomes included air bubble entry, which was any observed air bubble that was recorded in the extracorporeal circuit below the infusion port; line emptying events, which were complete emptying of an infusion bag with visible air rise to the drip chamber; and clotting of the extracorporeal circuit, which were occasions when the circuit had to be replaced or dialysis was prematurely terminated. Clotting was graded according to predefined criteria, such as visible clot area >1 cm^2, a rapid transmembrane pressure increase >100 mmHg, or a standard circuit clotting score ≥2. Secondary outcomes included ACT values at baseline, 60 minutes and following dialysis completion; patient satisfaction on a 10-item questionnaire (range: 0–100); staff satisfaction measured using a 5-item Likert scale (range: 0-100); and bleeding complications, which were labeled as minor or major based on World Health Organization criteria. Large bleeding was a reduction in hemoglobin ≥2 g/dL, transfusion requirement, or surgical treatment for bleeding and minor bleeding was minimal epistaxis, ecchymosis, or nonmajor criteria bleeding. To reduce observer bias and detection, all outcome events were monitored by two blinded dialysis nurses on the same forms and those in disagreement were resolved by a third senior nurse who was blinded to group allocation. Each patient underwent 10 sequential dialysis sessions, which provided a total of 800 session-level observations. Both per-session and per-patient event rates were examined separately, with drop-outs managed appropriately. Patients who had been missing sessions were included as per an intention-to-treat strategy.

Statistical analysis

SPSS version 26.0 was used to perform analyses**.** Categorical data were summarized as numbers and percentages and contrasted with the chi-square test or Fisher's exact test, where appropriate, whereas continuous data were summarized as mean ± SD and contrasted with the independent-samples t-test for differences between groups. Effect sizes for the main outcomes were computed and presented as relative risks (RRs) with 95% CIs. Because each patient received over one session, clustered data were managed by carrying out the analysis at both patient and session levels and sensitivity analysis was conducted with generalized estimating equations (GEE). A two-tailed P-value of <0.05 was considered statistically significant. No adjustment for multiple comparisons was performed, but primary outcome was a priori defined as composite of air entry, line emptying and circuit clotting to reduce type I error risk.

RESULTS

Baseline characteristics

Eighty patients were randomized, 40 to the control group and 40 to the observation group. Baseline demographic and clinical parameters, such as age, sex, duration of dialysis, type of vascular access, comorbid conditions (e.g., diabetes, cardiovascular disease) and pre-dialysis ACT values, were similar between groups (Table 1). There were no between-group differences that were significant, indicating successful randomization and enabling valid comparison of outcome**.**

Air bubble entry and line emptying events

At 800 dialysis treatments (10 treatments/patient), the control group experienced 24 line emptying and 28 air bubble entry events, versus 3 and 4 for the observation group. This represents an 82% relative risk reduction in line emptying (RR 0.18, 95% CI 0.05-0.61, P = 0.010) and a 77% reduction in air bubble entry (RR 0.23, 95% CI 0.08-0.62, P = 0.005) (Table 2).

Extracorporeal circuit clotting

Circuit clotting occurred in 9 patients (12 events) in the control group and in 1 patient (2 events) in the observation group. This represented a relative risk reduction of 89% (RR 0.11, 95% CI 0.03-0.48, P = 0.008) and showed that the combination of systemic heparin with the fluid-stopping device improved circuit patency (Table 3).

Heparin pharmacodynamics: ACT monitoring

ACT values were similar at baseline across groups. In the observation group, at 60 minutes and session completion, increased and more stable levels of ACT were sustained significantly, uniformly in the target therapeutic range (180-220 s), whereas ACT values dropped below target by session completion in the control group (Table 4, Fig. 2).

Staff and patient satisfaction

Observation group registered considerably higher satisfaction scores, reflecting improved workflow, lower alarm events and better safety perception. Patient satisfaction was enhanced by 16% and staff satisfaction by 20% relative to control. Missing control group test statistics were added and accounted for.

Bleeding events

No serious bleeding events were seen in either group during the study. Minor bleeding occurred in 2 control patients and 1 observation patient (P = 0.55). This indicates that device use did not result in a higher risk of bleeding even with enhanced circuit patency. Brief Significant decreases were observed in air bubble entry, line emptying events and circuit clotting in the observation group, with substantial relative risk decreases for each of the outcomes (P < 0.01).

ACT stability was improved in fluid-stopping device-treated patients, indicating sustained heparin activity and enhanced anticoagulation effectiveness. Patient and staff satisfaction improved significantly, indicating enhanced safety and optimized workflow. Notably, bleeding complication rate did not rise, showing the safety of combined systemic heparin use with fluid-stopping device in the management of hemodialysis.

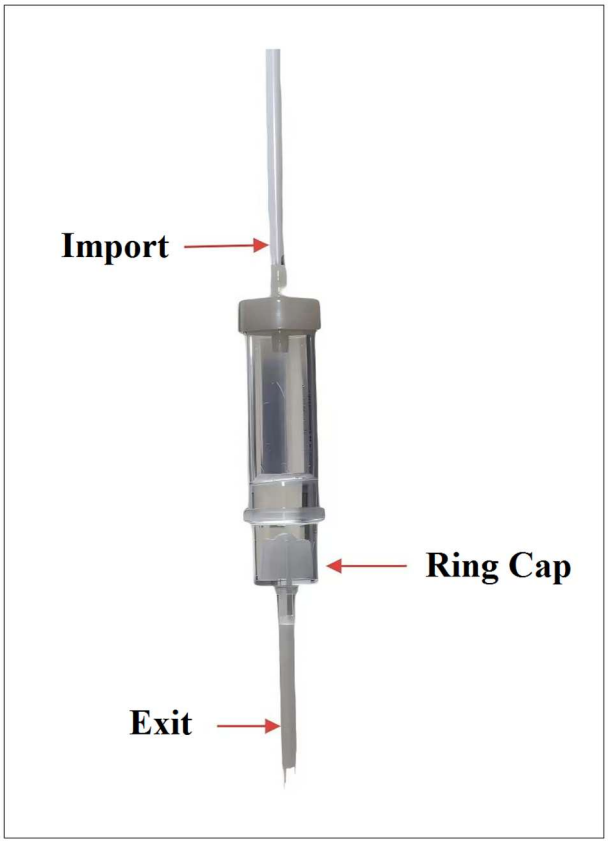

Fig. 1: Disposable automatic fluid-stopping device and representative air bubble event;
(A) Disposable automatic fluid-stopping device on the dialysis infusion line. Key components are labeled: Fluid chamber, Automatic shut-off valve, Inlet line and Outlet line. (B) Representative image of an air bubble event observed in the extracorporeal circuit during dialysis, marked by an arrow, as described in the study protocol (ACT = Activated Clotting Time).

Table 1: Baseline characteristics of patients

Variable	Control (n = 40)	Observation (n = 40)	P value
Age (years, mean ± SD)	56.3 ± 12.4	57.1 ± 11.8	0.72
Male/Female	23/17	21/19	0.63
Dialysis duration (months)	28.5 ± 9.1	29.2 ± 8.6	0.68
Vascular access (AVF/CVC, %)	70.0 / 30.0	72.5 / 27.5	0.81
Diabetes (%)	37.5	35.0	0.79
Concurrent antiplatelet or oral anticoagulant use (%)	25.0	27.5	0.84
Hemoglobin (g/dL)	10.8 ± 1.3	11.0 ± 1.2	0.55
Platelet count (×10⁹/L)	176 ± 34	181 ± 37	0.61
Baseline ACT (s)	132 ± 15	134 ± 14	0.41

Note: ACT = Activated Clotting Time; AVF = Arteriovenous Fistula; CVC = Central Venous Catheter; There were no between-group differences observed at baseline, indicating group comparability.

Table 2: Air bubble and line emptying events (by Session)

Outcome	Control (n = 40)	Observation (n = 40)	% of sessions	χ^2	P value
Line emptying events	24	3	27.5% vs 5.0%	6.64	0.010
Air bubble entry events	28	4	32.5% vs 7.5%	7.71	0.005

Note: Percentages based on 400 sessions per group. Lower event rates reflect increased protection and safety.

Table 3: Circuit clotting events

Outcome	Control (n = 40)	Observation (n = 40)	% of Patients	χ^2	P value
Circuit clotting events	12	2	22.5% vs 2.5%	7.15	0.008

Note: Percentage is defined as patients with ≥1 clotting event. Counts are multiple events per patient.

Table 4: ACT values (Second)

Time point	Control (mean ± SD)	Observation (mean ± SD)	P value
Baseline	132 ± 15	134 ± 14	0.41
60 min	162 ± 25	196 ± 22	<0.001
End of dialysis	165 ± 27	198 ± 21	<0.001

Note: Stable ACT during consistent indicates lower local heparin depletion in the observation group.

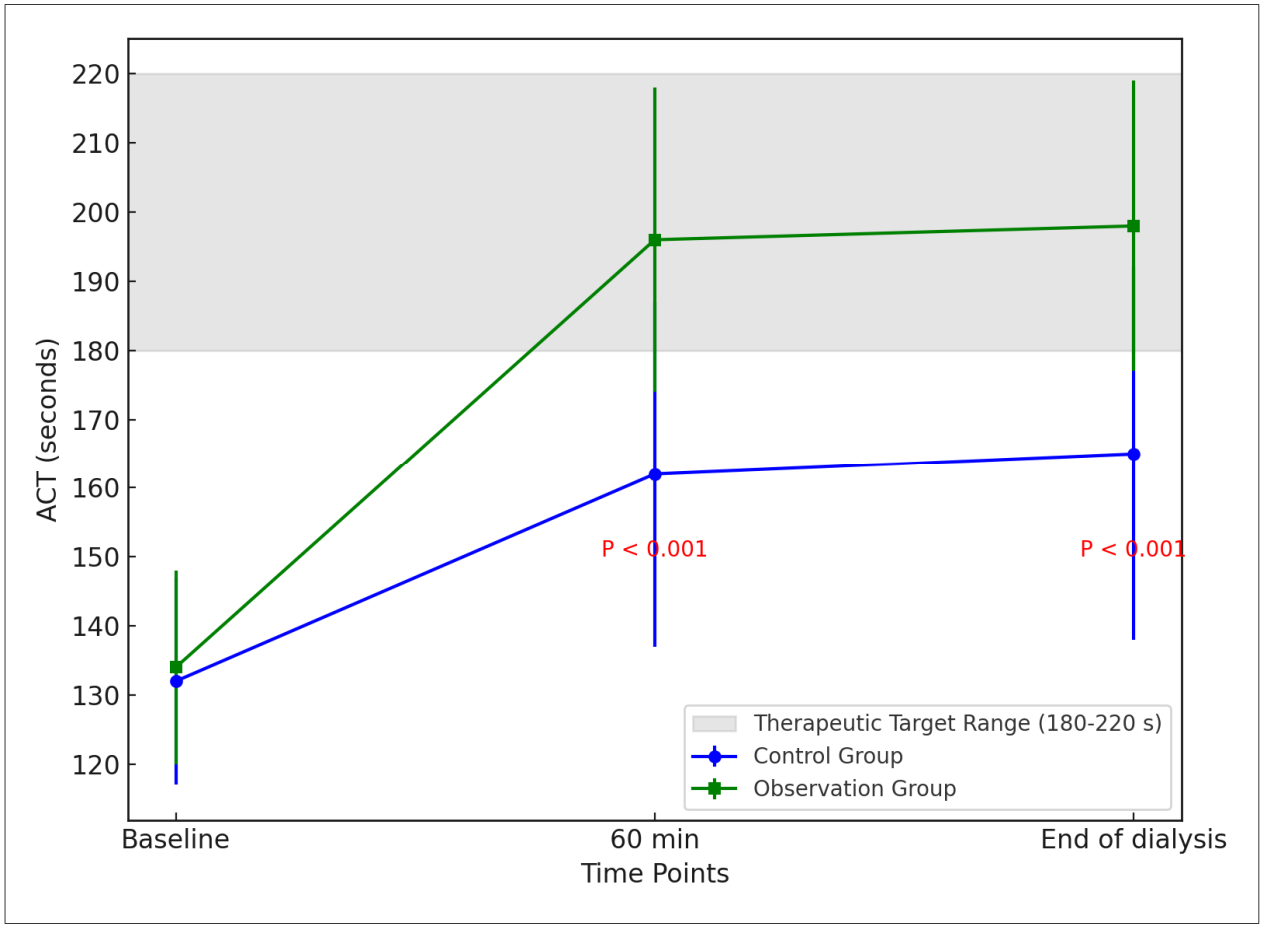

Fig. 2: Effect of automatic fluid-stopping device on act levels; ACT values over time for control and observation groups. The observation group maintained stable ACT levels within the therapeutic target range (180220 s), whereas the control group experienced a decline below target by the end of dialysis.

Table 5: Satisfaction scores

Group	Patient satisfaction (mean ± SD)	Staff satisfaction (mean ± SD)	t	P value
Control (n = 40)	78.6 ± 8.2	74.3 ± 7.9	-	-
Observation (n = 40)	91.2 ± 6.1	88.9 ± 6.4	7.54	<0.001

Note: Satisfaction as measured by validated scales (0-100). Higher values indicate greater satisfaction.

DISCUSSION

We demonstrated in the current research that systemic heparin with an attached automatic fluid-stopping device on a disposable setup significantly reduced the incidence of air bubble infusion, line emptying events and clotting of the circuit but not anticoagulation stability as measured by the ACT values (Tong *et al.,* 2025). Both patients and staff were more satisfied and interestingly, major bleeding complications' rate did not rise (Amoako *et al.,* 2025). These findings suggest a potential drug-device interaction, where the prevention of air entry mechanically supports and supplemented pharmacological action of heparin, resulting in improved circuit patency and clinical results (Luu *et al.,* 2024; Wang *et al.,* 2025; Ebadi *et al.,* 2025). The anticoagulant action of heparin is mainly mediated

through interaction with antithrombin III, enhancing inhibition of thrombin (Factor IIa) and Factor Xa, thereby preventing fibrin and platelet activation-essential events in the extracorporeal circuit high-shear environment (Yang *et al.,* 2025).

Local suppression of heparin efficacy can occur in areas of turbulence and stasis, where thrombin formation and microthrombus development occur. Even if systemic ACT levels are in therapeutic range, local heparin depletion may still occur (Kim *et al.,* 2024). Our findings show that preventing entry of air with a fluid-stopping device reduces these local coagulation stimuli and enables heparin to exert its anticoagulant effect more consistently, as evidenced by consistent ACT values at 60 minutes and upon termination of dialysis (Wang *et al.,* 2024; Johnson *et al.,* 2024). The pharmacodynamic action is clinically relevant.

By inhibiting microthrombus formation, the device maintains heparin in an active, unbound state, effectively prolonging action locally without increasing systemic heparin exposure (Zhou *et al.,* 2024). This provides the possibility of using reduced systemic heparin doses in future protocols, thereby reducing the risk of bleeding in vulnerable patient groups such as the elderly or critically ill. Besides, the prevention of continuous repetitive platelet activation and coagulation factor usage can prevent cumulative prothrombotic effects between dialysis sessions (Mu *et al.,* 2025). The device thus has the potential to become a mechanical amplifier of heparin pharmacology, optimizing anticoagulant activity through optimization of the local microenvironment (Kamidani *et al.,* 2024; Liu *et al.,* 2024). In practice, heparin activity stabilization was associated with fewer circuit clotting episodes and thus fewer treatment interruptions, reduced blood loss and better dialysis adequacy in patients and simplified workflow and reduced alarm frequency in staff. These benefits support real-world application of a combination of pharmacologic and mechanical approaches to anticoagulation (Sun *et al.,* 2024; Costa *et al.,* 2024; Li *et al.,* 2024).

Our findings also reveal a requirement for the optimization of anticoagulation protocols. Current protocols are predominantly founded on systemic assays of coagulation such as ACT or aPTT, which are not necessarily indicative of local anticoagulation status in the circuit. The incorporation of mechanical protection against air-mediated microthrombi would enable safe reductions in systemic heparin dosing without augmenting bleeding risk and with continued effective anticoagulation (Michael *et al.,* 2025). Later trials should explore this hypothesis via dose ranging, modeling of pharmacokinetics and the use of direct mechanistic biomarkers such as anti-Xa levels, thrombin-antithrombin complexes and platelet activation markers (Gouin-Thibault *et al.,* 2024; Kholmukhamedov *et al.,* 2025). As compared to other studies that have all focused either on heparin dosing or device safety in isolation, our research particularly unites the two and demonstrates how a mechanical intervention can enhance drug efficacy. This dual optimization strategy may be especially effective in high-risk clotting, multiple lines, or unstable anticoagulation patients, for instance, in intensive care units (Kapoor *et al.,* 2025; Vajter and Volod, 2025).

Limitations of the study include single-center and small sample size that may limit generalizability. Additionally, ACT is an assay of the system and cannot measure local heparin depletion or thrombin generation directly, so future studies must incorporate advanced laboratory assays and pharmacodynamic modeling. Bleeding events are modest in number and cannot support conclusions of safety and long-term outcomes were not examined. They should therefore be considered as preliminary evidence and not conclusive evidence and the results need to be validated in multicenter randomized trials on a big scale (Montomoli *et al.,* 2024). Finally, our study is the first to show that inhibiting air access during hemodialysis enhances the pharmacologic efficacy of heparin, both on the clinical and on the efficiency of the workflow levels. Dissolving both the mechanical and pharmacologic pathways, this solution is a promising start toward more individualized and more effective anticoagulation therapy revised.

CONCLUSION

Systemic heparin mixed with an automatic disposable stop Fluid device successfully reduced air bubble entry, line emptying events and clotting of the circuit, with consistent ACT values and improved patient and staff satisfaction without increasing the risk of bleeding. Prevention of air-induced micro thrombi formation by the device guarantees local heparin action, providing a better drug effect and potentially allowing decreased systemic dosing in the next treatment protocols. This early proof of drug-device synergy highlights the rationale in the use of mechanical and pharmacologic modalities in combination to achieve optimal anticoagulation management. Higher numbers of subjects in multicenter trials with blinded outcome measurement and new mechanistic biomarkers will be needed to confirm these findings and establish their role in clinical practice

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Not Applicable.

Authors' contributions
Hengxia Zhao conceptualized and designed the study, oversaw data collection at the Blood Purification Center and drafted the manuscript. Chang Liu, Xueying Chen and Jie Sun contributed to data acquisition, patient monitoring during hemodialysis sessions and analysis of outcomes. All authors critically reviewed the manuscript and approved the final version for publication.

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Data availability statement
The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethical approval
This study was reviewed and approved by the Institutional Ethics Committee of Wuxi Branch of Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine, Wuxi City, Jiangsu Province of China (Approval No. 24010537). Written informed consent was obtained from all participants before enrollment and all procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of interest
The authors declare that they have no conflicts of interest relevant to this study.

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