Furosemide Stress Test for Evaluating Renal Recovery During Continuous Renal Replacement Therapy: A Protocol-Based Pilot Randomized-Controlled (FST-STOP) Trial

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Abstract

Background: The optimal timing for discontinuing continuous renal replacement therapy (CRRT) remains uncertain. There is limited data on the use of the furosemide stress test (FST) to assess recovery from renal tubular dysfunction. This study aimed to determine whether FST could facilitate earlier discontinuation of renal replacement therapy (RRT).

Methods: Critically ill patients with stage 3 acute kidney injury (AKI) who had received CRRT for at least 48 hours were enrolled and randomized 1:1 to either a protocol-based FST (PB-FST) group or standard care. The primary outcome was successful RRT discontinuation.

Results: Twenty-four patients were enrolled, with a mean age of 70.3±15.6 years and a median baseline estimated glomerular filtration rate (eGFR) of 57.5 mL/min/1.73 m² (interquartile range: 47.5–77). CRRT was successfully discontinued in 6 of 12 patients (50%) in the PB-FST group and 4 of 12 patients (33.3%) in the standard care group (P = 0.408). By day 2, urine output was 990 mL/day in the PB-FST group compared to 372.5 mL/day in the standard care group (P = 0.299); by day 5, it increased to 1427.5 mL/day and 932.5 mL/day, respectively (P = 0.386).

Conclusions: PB-FST may be feasible for assessing renal recovery during CRRT. However, the small sample size may limit the statistical power of the findings.

Keywords: acute renal failure; kidney failure; ARF; oliguria; CVVH renal recovery; ICU

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Received: 1 June 2025; Revised: 13 July 2025; Accepted: 24 July 2025
https://doi.org/10.63555/jnst.2025.280000

การใช้ Furosemide stress test ในการประเมินการฟื้นตัวของไตระหว่างการรักษาบำบัดทดแทนไตแบบต่อเนื่อง: การศึกษานำร่องประเภทการทดลองสุ่มแบบมีกลุ่มควบคุม (FST-STOP)

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บทคัดย่อ

บทนำ: ระยะเวลาที่เหมาะสมในการหยุดการรักษาบำบัดทดแทนไตแบบต่อเนื่อง (continuous renal replacement therapy, CRRT) ยังไม่มีระยะเวลาที่แน่นอน มีข้อมูลไม่มากในการนำ furosemide stress test (FST) มาใช้ในการประเมินการฟื้นตัวของไต การศึกษานี้ได้ทำการสืบค้นว่า FST จะช่วยทำให้หยุดการบำบัดทดแทนไตได้หรือไม่

ระเบียบวิธีวิจัย: การศึกษานี้ได้รวบรวมผู้ป่วยวิกฤตที่มีภาวะไตวายเฉียบพลันระยะที่ 3 ที่ได้รับการรักษาบำบัดทดแทนไตแบบต่อเนื่องมาอย่างน้อย 48 ชั่วโมง ผู้เข้าร่วมการศึกษาจะถูกสุ่ม 1:1 แบ่งเป็นกลุ่มที่ได้รับการทำ protocol-based FST (PB-FST) และกลุ่มที่ได้รับการรักษามาตรฐาน ผลลัพธ์หลักคือจำนวนผู้ป่วยที่สามารถหยุดการบำบัดทดแทนไตได้

ผลการวิจัย: มีผู้เข้าร่วมการศึกษาทั้งหมด 24 รายในการศึกษานี้ โดยมีอายุเฉลี่ย 70.3±15.6 ปี และค่ามัธยฐานของอัตราการกรองของไต (estimated glomerular filtration rate, eGFR) อยู่ที่ 57.5 มล./นาที/1.73 ตร.ม. (ค่าพิสัยระหว่างควอร์ไทล์, 47.5-77) พบว่าสามารถหยุดการบำบัดทดแทนไตได้สำเร็จ 6 ราย จาก 12 ราย (50%) ในกลุ่ม PB-FST และ 4 ราย จาก 12 ราย (33.3%) ในกลุ่มการรักษาตามมาตรฐาน (P = 0.408) ในวันที่ 2 ปริมาณปัสสาวะในกลุ่ม PB-FST มี 990 มล.ต่อวัน และ 372.5 มล.ต่อวัน ในกลุ่มที่ได้รับการรักษามาตรฐาน (P = 0.299) หลังจากนั้นในวันที่ 5 พบปริมาณปัสสาวะ 1427.5 มล.ต่อวัน และ 932.5 มล.ต่อวัน ตามลำดับ (P = 0.386)

สรุป: PB-FST อาจสามารถนำมาใช้ประเมินการฟื้นตัวของไตระหว่างการรักษาบำบัดทดแทนไตแบบต่อเนื่อง ได้ อย่างไรก็ตามจำนวนตัวอย่างที่น้อยอาจส่งผลต่อความเชื่อมั่นทางสถิติของผลการศึกษา

คำสำคัญ: ไตวาย; ไตเสื่อม; ไอซียู; ปัสสาวะน้อย; ฟอกเลือด; ล้างไต

Background

Renal replacement therapy (RRT) is a mainstay treatment for patients with severe acute kidney injury (AKI) and end-stage renal disease. In particular, AKI affects 50-60% of patients in intensive care units (ICU),[1,2] and 10-15% of those need RRT.[3] Continuous renal replacement therapy (CRRT) is one of the modalities used to treat critically ill patients with hemodynamic instability, which covers 70% of acute RRT in the ICU.[4,5]

The optimal time to initiate CRRT has been well established. It has been shown that patients who perform CRRT early experience a similar mortality outcome compared with those who perform late CRRT.[6-9] Conversely, a higher mortality rate was observed in patients who were more delayed in CRRT initiation.[10]

However, prolonged CRRT can cause adverse events,

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including hypotension, electrolyte abnormalities, acid-base disturbances, hypothermia, catheter-related bloodstream infection (CRBSI), new-onset thrombocytopenia, new-onset anemia, and arrhythmia.[11] Little is known regarding the optimal time or criteria to stop CRRT. Urine volume and serum creatinine levels fluctuate gradually in individuals with AKI. As a result, furosemide has been applied in a validated test known as the furosemide stress test (FST) to assess renal tubular function.[12]

The FST is being used to assess whether patients with AKI have the potential to initiate CRRT.[13-15] Nevertheless, no prior study has used this test to assess renal tubular function while the kidney is recovering. In the protocol-based FST versus standard care for evaluating renal recovery during CRRT (FST-STOP) trial, we investigated whether FST enhanced early RRT discontinuation compared to standard care.

Methods

Study design

This prospective, open-label, randomized, placebo-controlled trial was conducted at the Chiang Mai University Hospital, Chiang Mai, Thailand, from June 2023 to February 2024. The study was approved by the Institutional Review Board of the Faculty of Medicine, Chiang Mai University (study code MED-2566-0034). All participants or legally related relatives had written informed consent.

Participants and randomization

Participants were randomized 1:1 to either the protocol-based furosemide stress test (PB-FST) or standard care. Randomization was done using permuted blocks of size four without additional stratification. Eligible criteria included patients age ≥18 years, AKI stage 3 based on kidney disease improving global outcomes classification[16] and CRRT initiation at least 48 hours in the medical or surgical ICU. Non-investigator nephrologists had permission to initiate and adjust the modality of CRRT. Exclusion criteria consisted of high-dose vasopressors (defined as norepinephrine ≥0.5 mcg/kg/min, epinephrine ≥0.5 mcg/kg/min, or dopamine ≥10 mcg/kg/min), severe electrolyte imbalance (defined as serum potassium ≥6.5 mmol/L, serum potassium ≤2.5 mmol/L, serum bicarbonate ≤12 mmol/L, or arterial blood pH ≤7.2), urine output ≥2,100 mL/day, obstructive uropathy, chronic kidney disease (CKD) stage 5 or ESRD, kidney transplantation, RRT during the previous 14 days, require RRT to eliminate drugs or toxins, furosemide administration during CRRT, furosemide allergy, central venous pressure ≤5 mmHg or pulse pressure variation ≥13%, expected death within 24 hours and pregnancy or breastfeeding.

The baseline creatinine value was defined as the lowest value within 365 days before admission in the electronic medical record. In patients without previous creatinine recording, the following formula was applied: creatinine (in mg/dL) = 0.74–0.2 (if female) + 0.08 (if black) + 0.003 × age (in years), presuming normal baseline renal function.[17]

Intervention

The PB-FST group received a furosemide dosage of 1.5 mg/kg intravenously (IV), and urine output was observed for the next 2 hours. Participants with a urine volume greater than 200 mL were allowed to discontinue CRRT; those with less than 200 mL continued the treatment. For the patients who are required to continue receiving CRRT, the dose of furosemide should be raised to 250 mg IV every 6 hours and their urine should be recorded every 2 hours afterward. After receiving furosemide for 48 hours, discontinue the medication if the urine output is less than 200 mL within 2 hours **(Figure 1)**.

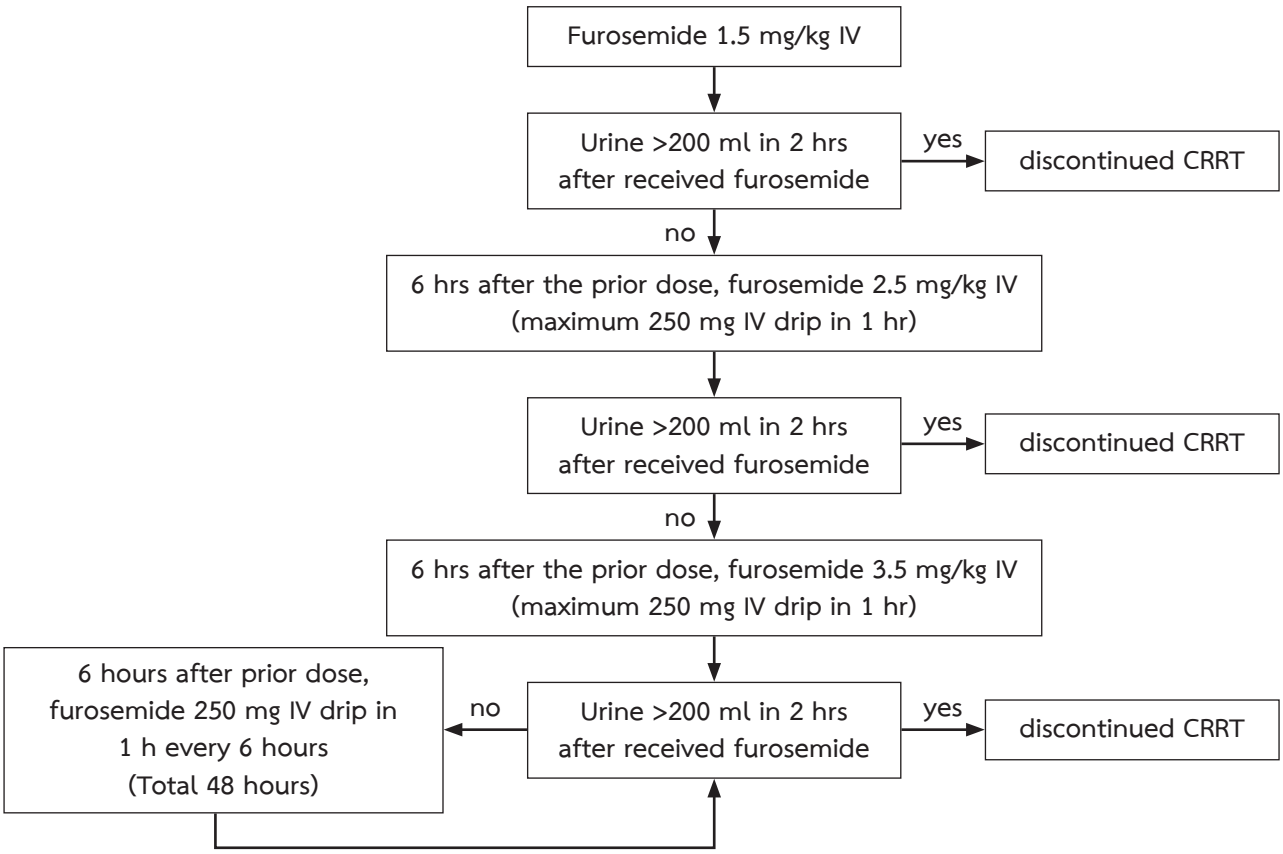

Figure 1 Dose of furosemide and urine output monitoring in the protocol-based furosemide stress test group. CRRT, continuous renal replacement therapy; hr, hour; IV, intravenously

In the standard care group, the nephrologists and critical care physicians provided furosemide at any dose or not at all. Participants in both groups obtained additional treatment according to the guidelines.

Outcomes measurement

The primary outcome was successful discontinuation of RRT, defined as cessation of continuous CRRT within 48 hours after randomization without restarting any form of RRT within the following five days. Secondary outcomes included all-cause mortality at 30 days, RRT dependence at 30 days, total days of RRT use, urine output on days 2 and 5 after randomization, length of hospital stay, length of ICU stay, number of ventilator-free days, the dose of furosemide administered before CRRT discontinuation, and the maximum dose of furosemide that failed to achieve CRRT discontinuation. Safety assessments, including laboratory monitoring, were also conducted.

Statistical analysis

According to the pilot study estimation, the sample size was at least 40 cases among patients with AKI requiring CRRT for at least 48 hours, divided into 20 cases per group. The 95% confidence interval was determined with a power of 80%.[18]

Analysis adhered to the basis of intent-to-treat. Information about patients should be described using descriptive statistics. Continuous variables are summarized with means with the corresponding standard deviation or standard error (mean±SD), median, and interquartile range (IQR) as appropriate. Categorical variables are given as proportions or percentages as appropriate. Continuous variables were compared using the Student's t test or the Mann-Whitney U test, and categorical variables were compared using the Chi-square test or Fisher's exact test. To determine risk factors that differ between groups and either raise or lower the likelihood of RRT discontinuation, we used odds ratios and 95% relative confidence intervals.

Significant variables will be assessed through univariate analysis and multivariate logistic regression to verify the distinct risk factors between groups. A statistically significant correlation in this trial is defined by achieving a P-value of <0.05. All statistical analyses were performed using Stata software, version 17.0 (StataCorp LLC, USA).

Results

Study participants

During the study, 92 participants received CRRT; 59 patients were eligible for inclusion, and 24 underwent randomization **(Figure 2)**. Among the randomized participants, 24 (100%) completed the study. The median follow-up was 30 days (IQR, 19-45) for the patients in the two treatment groups.

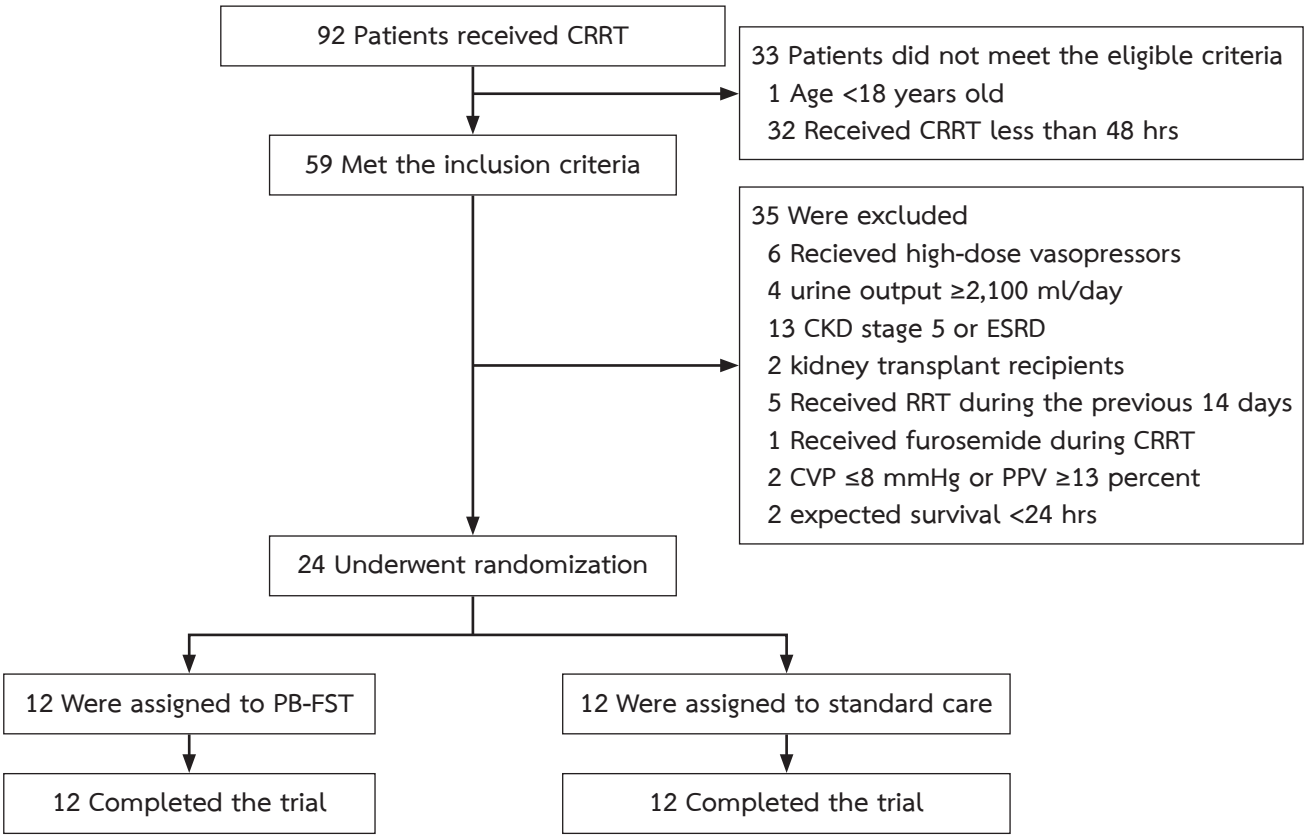

Figure 2 Study Flow Diagram

CRRT; continuous renal replacement therapy; CKD, chronic kidney disease; ESRD, end-stage renal disease; CVP, central venous pressure; PPV, positive pressure ventilation; PB-FST, protocol-based furosemide stress test

Baseline characteristics of all patients are shown in **Table 1**. The primary cause of hospitalization was sepsis (37.5%), with a median sequential organ failure assessment (SOFA) score of 13 (IQR, 12-15). The etiology of AKI was due to hemodynamic acute tubular necrosis (ATN) in all patients (100%). The main indication for initiating CRRT was volume overload (58.3%). The median norepinephrine dose was 0.21 mcg/kg/min (IQR, 0.1-0.44). At the time of randomization, the median urine volume was 117.5 mL/day (IQR, 27.5-447.5), and 90% of patients had a 6-hour urine creatinine clearance of less than 12 mL/min. All baseline characteristics were comparable between the two groups.

Table 1 Baseline characteristics of all patients

Parameters	PB-FST (N = 12)	Standard care (N = 12)
Age, yr	72.8±13.8	67.8±17.6
Male sex, n (%)	9 (75)	8 (66.7)
Body-mass index, kg/m^2	23.2±4.5	22.4±2.9
Serum creatinine before admission, mg/dL	1.1±0.3	1.4±0.6
eGFR before admission - ml/min/1.73 m^2	60 (49.5, 82)	55 (37, 75)
Preexisting conditions, n (%)		
• Cardiovascular disease*	1 (8.3)	4 (33.3)
• Diabetes mellitus	4 (33.3)	5 (41.7)
• Hypertension	6 (50)	9 (75)
• Cancer	3 (25)	0 (0)
• Chronic lung disease	2 (16.7)	1 (8.3)
Medications, n (%)		
• RAS inhibitors	3 (25)	4 (33.3)
• SGLT2 inhibitors	0 (0)	2 (16.7)
• Metformin	3 (25)	1 (8.3)
• Furosemide	1 (8.3)	2 (16.7)
• Spironolactone	0 (0)	2 (16.7)
Admission category, n (%)		
• COVID-19 infection	2 (16.7)	2 (16.7)
• Coronary artery disease	2 (16.7)	2 (16.7)
• Sepsis	5 (41.7)	4 (33.3)
• Surgery	3 (25)	4 (33.3)
SOFA score*	12.5 (11, 13.5)	14.5 (12, 18)
Indication for CRRT, n (%)		
• Acidosis	2 (16.7)	2 (16.7)
• Volume overload	7 (58.3)	7 (58.3)
• Uremia	3 (25)	3 (25)

Table 1 Baseline characteristics of all patients (continued)

Parameters	PB-FST (N = 12)	Standard care (N = 12)
Initial mode for CRRT, no (%)		
• CVVH	1 (8.3)	2 (16.7)
• CVVHD	3 (25)	1 (8.3)
• CVVHDF	8 (66.7)	9 (75)
Initial anticoagulant for CRRT, n (%)		
• None	8 (66.7)	7 (58.3)
• Heparin	3 (25)	2 (16.7)
• Regional citrate	1 (8.3)	3 (25)
Initial prescribed dose of CRRT – ml/kg/hr	30±4.3	30±0
Vasopressor before start of CRRT, n (%)	8 (66.7)	11 (91.7)
• Norepinephrine - mcg/kg/min	0.21 (0.12, 0.49)	0.21 (0.1, 0.3)
• Epinephrine - mcg/kg/min	0.08 (0.01, 0.15)	0.07 (0.07, 0.07)
Vasopressors after 48 hrs of CRRT, n (%)	5 (41.7)	8 (66.7)
• Norepinephrine - mcg/kg/min	0.08 (0.04, 0.1)	0.13 (0.08, 0.23)
Respiratory support after 48 hrs of CRRT, n (%)		
• Non-invasive respiratory support*	0 (0)	2 (16.7)
• Mechanical ventilation	12 (100)	10 (83.3)
CVP after 48 hrs of CRRT ,mmHg	9±2.1	10.2±4.9
Laboratory after 48 hrs of CRRT		
• Blood urea nitrogen, mg/dl	26.5 (17.5, 32)	33.5 (26.5, 51)
• Serum hemoglobin, g/dL	9.1±2	9.2±1.4
• Serum sodium, mmol/liter	137.3±2.5	136.3±3
• Serum potassium, mmol/liter	3.7±0.4	3.9±0.6
• Serum bicarbonate, mmol/liter	22.7±3.3	20.7±2.6

Table 1 Baseline characteristics of all patients (continued)

Parameters	PB-FST (N = 12)	Standard care (N = 12)
Urine volume before start of CRRT, ml/day	845 (517.5, 1117.5)	542.5 (250, 1447.5)
Urine volume after 48 hrs of CRRT, ml/day	295 (22.5, 480)	55 (27.5, 297.5)
6-hour urine creatinine clearance after 48 hrs of CRRT, n (%)[a]		
• <12 ml/min	9 (90)	9 (90)
• ≥12 ml/min	1 (10)	1 (10)

PB-FST, protocol-based furosemide stress test; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; CVP, central venous pressure; eGFR, estimated glomerular filtration rate

Cardiovascular disease was defined as a history of any one or more of the following conditions: valvular heart disease, coronary artery disease, or congestive heart failure.

SOFA scores on the Sequential Organ Failure Assessment (SOFA) range from 0-24, with higher scores indicating more severe disease and a higher risk of death.

Non-invasive ventilation included a nasal oxygen cannula, a non-rebreather oxygen mask with bag, a high-flow nasal cannula, continuous positive airway pressure, and bilevel positive airway pressure.

[a]Data regarding 6-hour urine creatinine clearance were available for 20 of 24 patients (83.3%).

Primary and Secondary Outcomes

Successful RRT discontinuation occurred in 6 of 12 patients (50%) in the PB-FST group and in 4 of 12 patients (33.3%) in the standard care group (P = 0.408) **(Table 2 and Figure 3)**. Deaths at 30 days occurred in 66.7% of the patients in both groups. RRT dependence at 30 days occurred in 41.7% of the PB-FST group and 66.7% of the standard care group (P = 0.219). The duration of RRT was 5 days in the PB-FST group and 6 days in the standard care group (P = 0.336).

The PB-FST group had more urine volume at day 2 (990 mL/day) compared to the standard care group (372.5 ml/day) (P = 0.299) and day 5 (1427.5 mL/day and 932.5 mL/day, P = 0.386) **(Figure 4)**. These differences did not reach statistical significance. The length of hospital and ICU stays and ventilator-free days, were also not statistically different.

The dose of furosemide before stopping CRRT or the maximum dose of furosemide that was unable to stop CRRT was higher in the PB-FST group (1,000 mg/day) than in the standard care group (500 mg/day) (P = 0.182) **(Table 2)**.

Safety outcomes and adverse events

CRBSI occurred in only one patient (8.3%) in the standard care group, whereas polyuria occurred in 2 patients (16.7%) in the PB-FST group. The incidences of hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypomagnesemia, hypermagnesemia, hypophosphatemia, and hyperphosphatemia at day 2 or 5 were similar between the two groups **(Table 3)**.

Discussion

The FST-STOP trial is a pilot randomized controlled study designed to evaluate the feasibility of successful RRT discontinuation. Although the differences were not statistically significant due to the small sample size, the PB-FST group showed a 12% higher rate of successful RRT discontinuation than the standard care group. Additionally, patients in the PB-FST group exhibited greater urine output on days 2 and 5, more ventilator-free days, reduced dependence on RRT, fewer days of RRT use, and shorter hospital stay. However, these trends did not reach statistical significance, likely due to the limited sample size.

Furosemide acts from the lumen to inhibit the sodium/potassium/chloride cotransporter (NKCC2) in the thick ascending limb of the loop of Henle. It also blocks sodium chloride reabsorption via an NKCC2 splice variant in the macula densa, disrupting tubuloglomerular feedback and helping maintain the glomerular filtration rate despite ongoing diuresis. Inhibition of sodium chloride entry into

macula densa cells also triggers volume-independent renin release from the juxtaglomerular apparatus, activating the renin-angiotensin-aldosterone system (RAS). Since the thick ascending limb reabsorbs 20–25% of the filtered sodium load, furosemide is a potent diuretic that effectively promotes urine output.[19]

Table 2 Primary and secondary outcomes

Variable	PB-FST (N = 12)	Standard care (N = 12)	P-value
Primary outcome			
Successful RRT discontinuation, n (%)	6 (50)	4 (33.3)	0.408
Secondary outcome			
Death from any cause at 30 days, n (%)	8 (66.7)	8 (66.7)	1.000
RRT dependence at 30 days, n (%)	5 (41.7)	8 (66.7)	0.219
Duration of RRT, days	5 (4, 7.5)	6 (4.5, 10)	0.336
Urine volume at day 2, mL/day	990 (347.5, 2307.5)	372.5 (67.5, 1372.5)	0.299
Urine volume at day 5, mL/day	1427.5 (135, 2530)	932.5 (140, 1500)	0.386
Length of hospital stay, days	28 (17.5, 70)	30 (18.5, 39.5)	0.583
Length of ICU stay, days	23.5 (11, 29.5)	23.5 (13.5, 37.5)	0.773
Ventilator-free days, days	5 (0, 28.5)	2.5 (0, 6)	0.401
Dose of furosemide before CRRT discontinuation, mg/day*	1000 (525, 1000)	500 (0, 1000)	0.182

*Dose of furosemide before stopping CRRT, or the maximum dose of furosemide, was unable to stop CRRT

RRT, renal replacement therapy; ICU, intensive care unit; PB-FST, protocol-based furosemide stress test

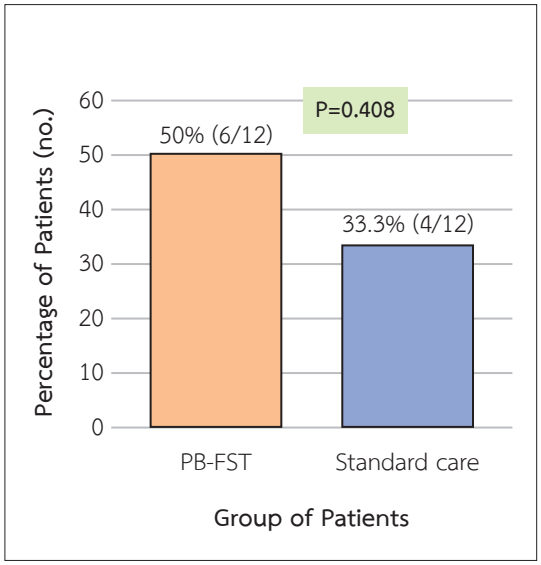

Figure 3 Successful discontinuation of renal replacement therapy

PB-FST, protocol-based furosemide stress test

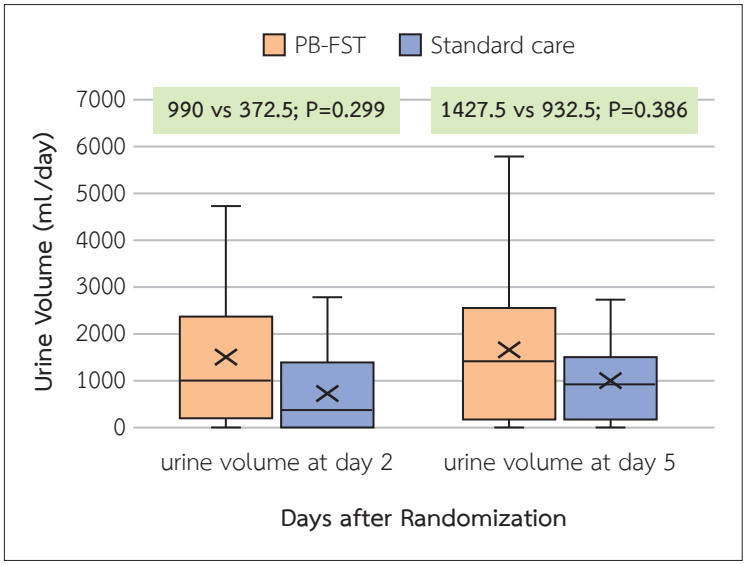

Figure 4 Urine volume at day 2 and day 5

PB-FST, protocol-based furosemide stress test

Table 3 Adverse events

Adverse events	PB-FST (N = 12)	Standard care (N = 12)	P-value
Catheter-related bloodstream infection – no. (%)	0 (0)	1 (8.3)	1.000
Polyuria – no. (%)	2 (16.7)	0 (0)	0.478
Hyponatremia – no. (%) • day 2 • day 5	 3 (25) 3 (25)	 3 (25) 5 (41.7)	 1.000 0.386
Hypernatremia – no. (%) • day 2 • day 5	 2 (16.7) 4 (33.3)	 0 (0) 0 (0)	 0.478 0.093
Hypokalemia – no. (%) • day 2 • day 5	 5 (41.7) 4 (33.3)	 4 (33.3) 1 (8.3)	 0.673 0.317
Hyperkalemia – no. (%) • day 2 • day 5	 0 (0) 0 (0)	 0 (0) 1 (8.3)	 - 1.000
Hypomagnesemia – no. (%) • day 2 • day 5	 1 (8.3) 1 (8.3)	 0 (0) 0 (0)	 1.000 1.000
Hypermagnesemia - no. (%) • day 2 • day 5	 6 (50) 5 (41.7)	 5 (41.7) 6 (50)	 0.682 0.682
Hypophosphatemia – no. (%) • day 2 • day 5	 3 (25) 2 (16.7)	 4 (33.3) 2 (16.7)	 0.653 1.000
Hyperphosphatemia – no. (%) • day 2 • day 5	 0 (0) 1 (8.3)	 2 (16.7) 4 (33.3)	 0.478 0.317

PB-FST, protocol-based furosemide stress test

Prolonged CRRT can cause several adverse events.[11] According to the 2012 KDIGO guidelines for AKI, RRT should be discontinued when it is no longer required.[16] However, this recommendation lacks specific guidance. CRRT weaning involves evaluating hemodynamic stability, volume status, solute control, daily obligate inputs, and the need to improve patients' mobility. Assessing the degree of kidney recovery is essential to CRRT weaning. The response to furosemide serves as a functional test, requiring the integrity of multiple nephron components—from glomerular filtration to proximal tubular secretion and luminal patency.[20]

A previous systematic review and meta-analysis demonstrated that the administration of furosemide at any time was associated with increased urine output and a shorter duration of RRT, findings consistent with our trial.[21] Moreover, a single-center randomized controlled trial investigated patients who received continuous infusions of furosemide (0.5 mg/kg/h) after the completion of continuous venovenous hemofiltration (CVVH). The results showed an increase in urine volume, but no improvement in the rate of renal recovery.[22] In contrast,

our trial provided specific indications of successful RRT discontinuation, which may be attributed to a higher bolus dose of furosemide that produced greater urine output and supported the decision to discontinue CRRT.

Currently, the findings from our trial support those of a recent large retrospective observational cohort study, which showed that furosemide use was associated with increased ventilator-free and RRT-free time.[23] Our trial also demonstrated no major safety concerns with furosemide use, suggesting that PB-FST may be a practical tool in clinical settings.

A key strength of this study is that it is the first randomized controlled trial to utilize furosemide as a PB-FST during CRRT across a broad spectrum of baseline CKD severity, contributing to earlier discontinuation of CRRT. However, the major limitation is the small sample size, due to a short enrollment period, which may have limited the statistical significance of the results. Additionally, other confounding factors common in critically ill patients—such as sepsis or fluid status—can influence mortality, hospital outcomes, and urine output.

In conclusion, this study suggests PB-FST is feasible for assessing renal recovery during CRRT. However, the small sample size may limit the statistical power of these findings.

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