ORIGINAL RESEARCH

Prevention of Dialysis Catheter Malfunction with Urokinase and Heparin: A Randomized, Controlled Trial

Quan Wang, MM; Nan Jiang, MM; Weidong Chen, MM;
Li Cheng, MM; Shuai Fu, MM; Qiang Li, MM; Hongbo Li, MM

ABSTRACT

Objective • To evaluate the effectiveness of urokinase and heparin in preventing catheter infection and dysfunction in permanent hemodialysis tunneled cuffed catheters.

Methods • We randomized 153 cases of maintenance hemodialysis patients with newly implanted permanent hemodialysis tunneled cannula catheters from November 2018 to November 2021 for this single-center prospective randomized controlled trial The eligible patients were given one of two treatment plans: Patients in the control group (73 patients) were given heparin (6260 U/mL)three times a week after hemodialysis. The intervention group (80 cases) was administered urokinase(25000 U/mL) on the basis of heparin. After six months of maintenance hemodialysis with the above sealing protocols, the primary result was the frequency of catheter malfunction, and the secondary outcome was the frequency of catheter-associated infection.

Results • In the final analysis of 153 patients, catheter malfunctions occurred in 29 of the 80 patients assigned to heparin alone, with an incidence of 36.3%, and 16 of the 73 subjects assigned to urokinase combined with heparin, with a rate of 21.9%. This represents an almost 2-fold increase in the risk of catheter malfunction among patients treated with heparin alone as compared to those treated with urokinase once weekly (hazard ratio, 1.85; 13 patients (16.3%) allocated to heparin alone experienced catheter-related bacteremia, compared to 4 patients (5.5%) assigned to urokinase (hazard ratio, 2.79; 95%CI, 1.08 to 7.22; P = .03). Baseline levels, and adverse events, including bleeding incidents, did not statistically differ between the two groups.

Conclusion • Urokinase can be used as a secondary prevention drug for long-term catheter malfunction and infection based on its cheapness, efficacy, and safety, which can effectively save medical costs, and its sealing protocol is simple and suitable for promotion. (*Altern Ther Health Med.* 2024;30(10):218-224).

Quan Wang, MM; Nan Jiang, MM; Weidong Chen, MM; Li Cheng, MM; Shuai Fu, MM; Qiang Li, MM; Hongbo Li, MM; Department of Nephropathy, Wuhan Hospital of Traditional Chinese and Western Medicine, Wuhan, Hubei, China.

Corresponding author: Hongbo Li, MM
E-mail: wq6395661@163.com

Autologous arteriovenous fistulas (AVF) are recommended as the optimal dialysis access for hemodialysis patients.[1] However, permanent hemodialysis tunneled cuffed catheters (TCC) are applied as crucial vascular access with major complications of thrombosis and catheter-related infection in approximately 20%-40% of the maintenance hemodialysis (MHD) patients due to the extended life expectancy, increased metabolic diseases, and decreased vascular resources for AVF.[2,3] Research has shown that approximately 50% of hemodialysis catheters fail within the first year, and up to two-thirds of the failures are accounts of thrombosis.[3] Moreover, as one of the most feared consequences of hemodialysis catheter use due to its associated higher mortality,[4] the incidence rate of catheter-related infection ranges from 0.67 to 2.7 per 1000 catheter days.[3] Various solutions such as heparin, citrate, recombinant tissue plasminogen activator (rt-PA), antibiotics, and other drugs were instilled into the central venous catheter (CVC) lumens after each hemodialysis session and left in the catheter until the next session (catheter locking solution) to decrease the risk of catheter malfunction and bacteremia in MHD patients,[5] yet the efficacy, health care economy, and adverse effects are still controversial. Numerous pieces of evidence have attested the use of urokinase as a catheter-locking solution could prevent thrombosis and catheter-related infection in critically ill patients and those with cancer.[6,7] In this study, we aimed to explore the preventive effects of hemodialysis catheter malfunction and catheter-related infection of TCC with and without urokinase in catheter locking solution.

METHODS

Study population

Eligible MHD patients with a newly inserted permanent hemodialysis TCC were recruited from November 2018 to November 2021, this experiment adopted a double-blind experimental design, and no member of the research group knew the difference between the two groups of drugs during the experimental process and analysis results. This study has been approved by the Ethics Committee of our institution. Inclusion and exclusion criteria are outlined in Table 1.

Screening

300 patients were recruited, and 170 cases were screened in the study program. According to the principle of simple randomization, odd-numbered patients were allocated to the control group and even-numbered patients were assigned to the intervention group. The eligible participants were randomly allocated into two groups by a 1:1 ratio according to the centralized computerized service, and the screening results were analyzed in the following process (as shown in Figure 1).

Surgical operation and dialysis schedule

Preoperative health status as well as perioperative results were adequately assessed before the operation. All the permanent hemodialysis TCCs were placed in the right jugular internal vein under ultrasound guidance using the Seldinger technique. Before the start of the experiment, the inserted catheters were checked for patency, and chest films were obtained to determine whether the positions of the catheter tip positions were appropriate. Patients underwent hemodialysis on alternating days: Monday, Wednesday, and Friday or Tuesday, Thursday, and Saturday. After a hemodialysis session, the catheter lumens were flushed with 10 milliliter (ml) saline by a 20 ml syringe, and the vascular clamps were clamped, each catheter was subsequently instilled in locking solutions according to the usual standard by a 5 ml syringe. The sealing procedure was prepared and administered by 5 assigned hemodialysis nurses randomly.

Study medication allocation

Patients allocated to the control group received heparin (Jiangsu Wanbang Biopharmaceutical Co., Ltd., State Drug Administration H32020612) locks (6250 U/ml) as the locking solution after each hemodialysis session of the week, while the intervention group received urokinase (Tianjin Biochemical Pharmaceutical Co., Ltd., State Drug Administration H12020492) (25000U/ml) combined with heparin (6250 U/ml) once a week, at the midweek session, and heparin (6250 U/ml) used as locking solution for the other two dialysis sessions that week. Each catheter lock was instilled into the TCC lumen at a volume equivalent to the dead space of the TCC.

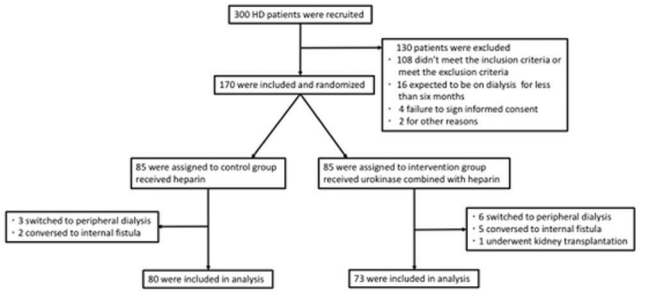
Outcomes definition

The primary outcome was catheter malfunction, and the secondary outcome was catheter-related bacteremia, other outcomes included catheter survival, adverse events as well as censored value.

Table 1. Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
End-stage renal disease patients with newly inserted permanent hemodialysis TCC.	Use of systemic anticoagulation for other comorbidities.
Expected to use the catheter and dialyze at the study center for at least six months.	Insertion of a new permanent catheter into the femoral vein.
The catheter was placed via the right internal jugular vein.	Intra-cranial bleed in the previous 4 weeks.
Frequency of hemodialysis 3 times per week.	Severe thrombocytopenia with spontaneous hemorrhage risk.
Patients who replaced catheters due to catheter-related infections will be eligible if they have completed antibiotic treatment and remained bacteremia-free for 3 hemodialysis sessions.	Major bleeding in the prior 4 weeks, defined as a drop in hemoglobin level greater than 20 g/L, a need for transfusion of packed red blood cells with clinical evidence or suspicion of bleeding.
Patients who have had their catheters removed due to catheter malfunction, recatheterization should be performed under vascular intervention to ensure that the newly inserted catheter is not covered by the fibrous sheath of the former catheter.	Patients with coagulation disorders/ uremic pericarditis are defined by the presence of long-term use of anti-blood platelet accumulation medicine/ pericardial rub.
Baseline INR ≤ 1.3.	Intra-cranial or intra-spinal neoplasm in the past or at present.
Baseline platelet count ≥ 60×10^9/L.	Weight ≤ 30 kg.
Hemoglobin count < 130 g/L.	Presence of a fever as defined by a temperature > 37.3°C.
Patients or their legally authorized representatives must be able to understand and sign the informed consent form, able and willing to participate in the study according to the study protocol.	Allergy or intolerance to urokinase or heparin or its constituents, and those who had a prior history of heparin-induced thrombocytopenia.
	Patients pregnant or lactating, and premenopausal who were not using reliable forms of contraception.
	Patients who inserted catheters during active bacteremia.
	Major surgery in the past 48 hours, or scheduled for major surgery during the study period.

Figure 1. Subject grouping flowchart



Catheter malfunction was defined referred to Chinese Hospital Association's Blood Access Branch[8] by either: 1) a peak blood flow of 200 ml/min or less during two consecutive dialysis sessions, or, 2) when the blood flow rate of higher than 200 ml/min, arterial pressure of less than -250 mmHg, and/or venous pressure greater than 250 mmHg, or, 3) when dialysis prescription completed adequately, dialyzer used reasonably and normally, Kt/v decreases rapidly, and Kt/V less than 1.2 for 2 consecutive dialysis sessions, or inability to initiate dialysis with insufficient blood flow.[9]

Catheter-related bacteremia (CRB), the secondary outcome, met at least one of the conditions according to the Chinese Medical Association's Critical Medicine Branch[10], as outlined in Table 2, both "definite" and "probable" infections were constituted.

Start event, end event, and truncation value[12]

Start event: the patients were followed from trial entry when they underwent 3 consecutive successful hemodialysis sessions (mean blood flow ≥250 ml/min during each treatment) after the insertion of catheters, with heparin used as a locking solution.

Table 2. Definitions for CRB

Definite CRB[11]	Probable CRB[11]
Positive semi-quantitative catheter culture (≥15 CFU per catheter segment), or, positive quantitative catheter culture (≥1000 CFU per catheter segment), with positive peripheral venous blood culture e the same microorganism as the catheter segment, or Quantitative blood culture from both catheter and peripheral vein with a colony count ratio (catheter blood: peripheral blood) ≥ 5:1, or Qualitative blood culture from CVC and peripheral vein simultaneously, positive blood culture from CVC appeared at least 2 hours earlier than positive peripheral blood culture, or Pyogenic fluids culture from peripheral blood and the catheter outlet were both positive for the same strain of microorganism	With clinical signs of severe infection and positive (semi) quantitative blood culture from catheter tip or catheter segment, meanwhile with a negative blood culture and absence of evidence of other infections and symptom improvement occurred within 48 hours of catheter removal without the treatment of new antibiotics, or With bacteremia or fungemia suffered from clinical manifestations such as fever, chills, and/or hypotension, and at least two positive blood cultures, one of which was derived from peripheral blood. The two blood cultures resulted in the same strain of cutaneous commensal bacteria (e.g., diphtheria-like bacteria, Bacillus, Propionibacterium, coagulase-negative staphylococci, micrococci, and Candida, etc.), but negative catheter segment cultures and no other source of blood-related infection to be found.

End event: The follow-up period was six months, end events were the occurrence of catheter malfunction and CRB. If catheter malfunction could continue to be used normally after treatment, CRB could be continued to follow up, but catheter malfunction would not be recorded. When CRB is cured by nephrologists and functions normally during 3 consecutive hemodialysis sessions, the catheter malfunction could continue to be followed up, no longer follow up CRB.

Truncation value: patients were withdrawn from the study at the following points when either: 1) the occurrence of major bleeding events (described in the exclusion criteria), 2) the removal of catheter attributing to catheter-related infection was considered as truncation value for CRB, or 3) removal of catheter attributing to catheter malfunction was considered as truncation value for CRB or 4) death or lost to follow up.

Statistical analysis

GraphPad Prism version 5 software was used to analyze the data, and Kaplan-Meier was applied to estimate the survival curves of the primary outcome and secondary outcome, with a two-sided log-rank test. The measurement data conforming to normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), t test was used to compare the two groups. The count data were expressed as the number of cases (%), and the difference between groups was compared using the chi-squared test or Fisher's exact test. A two-tailed $P < .05$ was set as statistically significant.

RESULTS

Study population

There was no statistical significance between the two groups in terms of gender, age, primary disease, complications, medication use, previous central venous cannulation, or other baseline characteristics ($P > .05$), and the data were comparable (see Table 3).

Primary outcome

The final analysis included 153 patients. Catheter malfunction occurred in 29 of 80 patients assigned to heparin group with an incidence of 36.3%, which was significantly higher compared with 16 of 73 patients (21.9%) in the urokinase combined with heparin group, an almost 2-fold higher risk in the heparin group (hazard ratio, 1.85; 95% confidence interval [CI], 1.03-3.33; $P = .039$). In patients in whom the primary outcome occurred, catheter fracture and abnormal position were ruled out by catheter angiography, and immediate treatment was given. The treatment plan was catheter reversal, pressure suctioning of the catheter and saline flushing, and continued follow-up of catheter-associated blood flow infection after catheter flow was restored. In patients with catheter malfunction, 23 cases (51.1%) were consistent with recurrent arterial pressure less

Table 3. Comparison of baseline characteristics between the two groups

Characteristics	Urokinase group (n = 80)	Heparin group (n = 73)
Female sex-n (%)	42 (52.5)	36 (49.3)
Age-yr (mean ± SD)	60.4±12.8	61.4±13.5
First dialysis access situation (n, %)		
Starting without an internal fistula	43 (53.7)	38 (52.1)
Failure of the fistula or access or waiting for the fistula to mature	14 (17.5)	13 (17.8)
Switch from peritoneal dialysis to hemodialysis	14 (17.5)	12 (16.4)
Kidney graft failure	2 (2.5)	1 (1.4)
Other reasons	7 (8.8)	9 (12.3)
Primary disease (n, %)		
Glomerulonephritis	38 (47.5)	34 (46.6)
Hypertensive nephropathy	9 (11.3)	7 (9.6)
Diabetic nephropathy	18 (22.5)	17 (23.3)
Polycystic kidney	3 (3.8)	2 (2.7)
Gouty nephropathy	2 (2.5)	3 (4.1)
Lupus nephritis	5 (6.3)	4 (5.5)
ANCA - associated nephritis	2 (2.5)	3 (4.1)
Myeloma–associated renal injury	2 (2.5)	1 (1.4)
Others	(1.3)	2(2.7)
Past medical history (n, %)		
Coronary heart disease	38 (47.5)	34 (46.6)
Heart failure	32 (40.0)	30 (41.1)
Cerebrovascular disease	18 (22.5)	17 (23.3)
Diabetes	31 (38.8)	28 (38.4)
Hypertension	64 (80.0)	59 (80.8)
Aortic dissection	5 (6.3)	3 (4.1)
History of gastrointestinal bleeding	6 (7.5)	5 (6.8)
History of deep vein thrombosis or pulmonary embolism	4 (5.0)	3 (4.1)
Malignant tumors	5 (6.3)	3(4.1)
Medication status (n, %)		
Asprin	38 (47.5)	34 (46.6)
Other anti-platelet drugs	9 (11.3)	7 (9.6)
Lipid-lowering drugs	18 (22.5)	17 (23.3)
Chinese herbal medicine and proprietary Chinese medicine	3 (3.8)	2 (2.7)
Glucocorticoids or immunosuppressants	2 (2.5)	3 (4.1)
Erythropoietin	18 (22.5)	18 (21.9)
Biochemical indexes		
Hemoglobin	93.2±13.8	93.2±13.0
Albumin	32.7±4.2	31.9±3.7
Blood platelet	201.8±64.7	210.7±68.9
International Normalized Ratio	0.98±0.14	0.98±0.12
D-Dimer	0.76±0.27	0.75±0.38

Figure 2. Primary outcome analysis chart

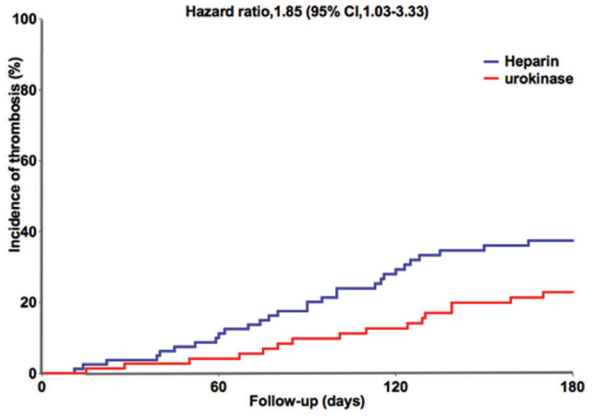


Figure 3. Secondary outcome analysis chart

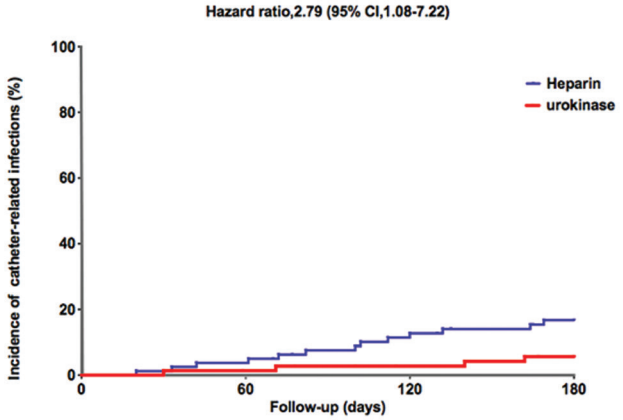
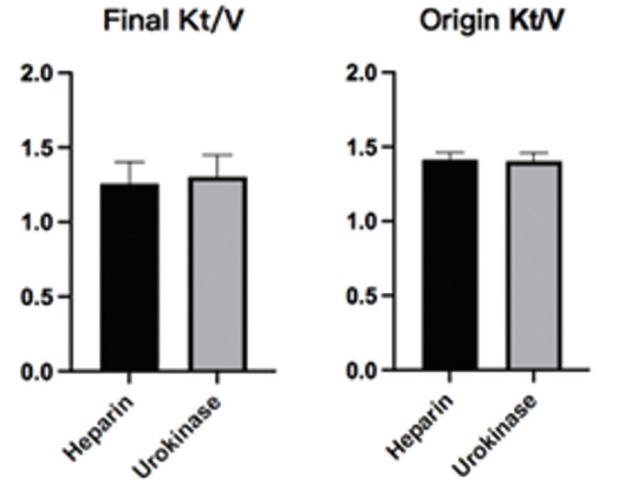


Table 4. Comparison of the occurrence of adverse events between the two groups

Adverse events	Urokinase group (n = 80)	Heparin group (n = 73)	*P* value
Bleeding events(%)			.74
Minor bleeding	6 (7.5)	5 (6.8)	
Clinically significant but not severe Bleeding	2 (2.5)	3 (4.1)	
Severe bleeding	2 (2.5)	2 (2.7)	
Hemorrhage leading to death	1 (1.3)	0 (0.00)	
Inpatient treatment	14 (17.5)	13 (17.8)	.81
Acute coronary syndrome	14 (17.5)	12 (16.4)	
Heart failure	2 (2.5)	1 (1.4)	
Arrhythmia	7 (8.8)	9 (12.3)	
Cerebral infarction(%)			
Non-catheter-associated infections	38 (47.5)	34 (46.6)	
Catheter-associated infections	9 (11.3)	7 (9.6)	
Bleeding	18 (22.5)	17 (23.3)	
Others	3 (3.8)	2 (2.7)	
Deaths	2 (2.5)	3 (4.1)	.83
myocardial infarction	5 (6.3)	4 (5.5)	
Bleeding-related deaths	2 (2.5)	3 (4.1)	
Infection-related deaths	2 (2.5)	1 (1.4)	
Others	(1.3)	2(2.7)	

Figure 4. Comparison of two hemodialysis groups



than -250 mmHg and/or venous pressure greater than 250 mmHg at a blood pump flow rate of 200 ml/min; 11 cases (24.4%) because the average blood flow on two consecutive dialysis sessions was less than or equal to 250 ml/min; 7 cases (15.6%) because they were unable to initiate dialysis; 4 cases (8.9%) with Kt/v less than 1.2. The analysis results are shown in Figure 2.

Secondary outcome

Catheter-associated infections occurred in 13 of 80 patients in the heparin-sealed group, with an incidence of 16.3%, while catheter-associated infections occurred in 4 of 73 patients in the urokinase combined with the heparin-sealed group, with an incidence of 5.5%. The risk of catheter-associated infections in the heparin-sealed group was 2.79 times higher than that of heparin combined with urokinase, with a risk ratio of 2.79 (95% CI,1.08-7.22), P = .03. Due to catheter-associated bloodstream infection, the catheter was removed in three patients, including two in the heparin group and one in the heparin combined with urokinase group, and the remaining patients were cured with normal hemodialysis function for three consecutive sessions and continued to be followed up for catheter malfunction.

Adverse events

There was no significant difference in the incidence of adverse reactions between the two groups. In the heparin group, a total of four patients died, including one patient who died of cerebral hemorrhage, one who died of myocardial infarction, one who died of multiple tumor metastases, and one who died of abdominal infection. In the urokinase combined with the heparin group, one patient died of myocardial infarction, one patient died of pulmonary infection, and one patient died of uremic complications, results can be seen in table 4.

Hemodialysis adequacy

The Kt/V of the enrolled patients all met the standard, and there was no statistical significance between the two groups (P = .16). The last Kt/V was the Kt/V of the last dialysis at the end of the patient's follow-up, and in one case in the heparin group, the patient's blood flow could not be restored after treatment because he could not start dialysis, and the Kt/V recorded was the Kt/V value of the previous dialysis, and the statistical results suggested that the Kt/V of the urokinase group was higher than that of the heparin group (P = .04). During the experiment by real-time detection of Kt/V, two patients in each group had normal blood flow and pressure, but Kt/V decreased significantly, suggesting a poor catheter function, as seen in Figure 4.

Health care economics

The price of urokinase is ¥135(2018-2019), while the price of alteplase is ¥1770.2(2018-2019), and the medical cost of using urokinase to seal the tube is much lower than that of alteplase. Patients in the urokinase group in this experiment added urokinase to seal the tube after the second weekly dialysis, the average weekly dialysis sealing cost was ¥135 more than the heparin group, and the six-month sealing cost was ¥3471.4 more, but among the follow-up costs associated with the management of complications in patients if catheter-related infections and catheter dysfunction occurred, the cost of catheter-related bloodstream infections was ¥32,227.2 according to the China DRGS. The cost of catheter

replacement for catheter dysfunction was ¥18,463.5, and higher if the catheter replacement was performed under intervention.

DISCUSSION

Vascular access is a prerequisite for hemodialysis, and the quality of vascular access directly determines the quality of dialysis and affects the survival time of patients.AVF is recommended as the first choice of vascular access for MHD patients because of its long duration of use and fewer complications.TCC is used for patients with poor vascular conditions, endovascular fistula occlusion, or cardiac insufficiency who are unable to choose an arteriovenous fistula as their vascular access for dialysis . And with the aggravation of population aging and the increase in the incidence of various chronic diseases, the use of TCC is gradually increasing trend.

In our study, the appliance of urokinase as a locking solution once a week (and heparin the other two times) significantly reduces the incidence of catheter malfunction and CRB in patients with newly placed hemodialysis catheters, higher final dialysis KT/V, lower medical costs, and no increase in the frequency of bleeding or other serious adverse events compared with the use of heparin three times a week to seal catheters.

KDIGO guidelines recommend that for hemodialysis patients, vascular access is preferred to an autologous arteriovenous endovascular fistula, followed by an artificial vascular endovascular fistula, with a central venous catheter being the last option, yet for many patients, a central venous catheter may be the last lifeline. After long-term catheter placement with tunneling, the main causes of catheter malfunction are intracatheter thrombosis, fibrous sheath formation, central venous stenosis, and or occlusion after excluding secondary factors such as abnormal catheter position and catheter folding. The decrease in blood flow after the occurrence of catheter malfunction, the increase in recirculation due to catheter reversal, and the shortening of dialysis time due to the cessation of dialysis treatment catheter make patients' dialysis adequacy decrease and complications and mortality increase significantly, and how to detect and intervene early in catheter malfunction is a major challenge in dialysis access management.[13]

The common cause of CRB may include the colonization of skin and catheter tip, contamination of the lumen, as well as hematogenous seeding from the other sites of the body.[14,15]In clinical practice, luminal thrombus, luminal biofilm, fibrous sheath, and central venous stenosis(CVS) are often found when removing malfunctioning catheters or infected long-term tunneled catheters. Studies have shown that venous catheter-associated thrombosis can lead to CVS, and thrombosis and fibrin also promote biofilm formation, which increases the risk of CRB.[16,17] Chen et al have detected neutrophil extracellular traps (NETs) in the fibrin sheaths of dialysis patients without clinical manifestations of infection, and NETs play a crucial role in the formation of catheter-related fibrin sheaths. Moreover, in rat models, transient bacteremia of S. aureus-induced NETs in enlarged fibrin sheaths, and bacteremia could be an initial factor that induces NET-related immune thrombosis enhancing catheter-related CVS.[18] Meanwhile, multiple logistic regression analysis showed that moderate and severe CVS were independent risk factors for catheter microbial colonization, and hemodynamic alterations may affect bacterial colonization, such that local luminal stenosis may lead to reduced blood flow or even blood flow arrest, resulting in microbial colonization of the catheter.[19] Hence, bacteremia and fibrin sheaths are reciprocal causations in catheter dysfunction and sepsis, catheter-related thrombosis and fibrin sheath formation lead to CVS and biofilm formation, while the biofilm generated during catheter infection can cause secondary thrombosis, solutions are urgent need to maintain catheter function and prevent CRB.

Fluid sealing is a crucial step in preventing catheter malfunction. By directly activating fibrinogen in thrombotic substances and lysing fibrin sheaths, thrombus, and bacterial biofilms, thrombolytic medicines have been proven to increase catheter patency, restore the patency of hemodialysis catheters, and lower infection rates.

In a multicenter, randomized, double-blind controlled study, Brenda R et al divided 225 patients undergoing thrice per week dialysis applying CVC into a heparin group and an rt-PA group for dialysis tubing closure.[20] The results revealed that the rt-PA group had a significantly lower rate of catheter embolization and catheter-related infections than the heparin group. The use of weekly rt-PA sealing lowers the incidence of malfunction, according to the findings of several additional research.[21,22] By attaching to fibrin via its lysine residues and promoting the transformation of endogenous fibrinogen into fibrinolytic enzymes, rt-PA exerts its antithrombotic activity.[23] While costly, we utilized urokinase and heparin to seal the tubing after dialysis instead of using rt-PA, which is more expensive. Urokinase is a trypsin-like serine protein hydrolase that is derived from human urine and has properties that are comparable to those of rt-PA. Urokinase directly activates fibrinogen, destroys fibrin and fibrinogen, prevents thrombus growth, as well as dissolves thrombus, the outcomes of our studies support the effectiveness of this article.[24] It is derived from urine, has a high degree of biocompatibility, a short half-life, is primarily processed by the liver, and is appropriate for MHD patients. Al-Ali Fadwa et al compared the newly developed taurolidine citrate/urokinase (Taurolock/U) sealing solution to the currently employed taurolidine citrate/hep solution and assessed its safety and effectiveness, they discovered that only the heparin group experienced recurrent acute catheter thrombosis and even catheter replacement, while the urokinase group did not suffer from this problem and required significantly fewer rt-PA interventions.[25] In a multicenter, double-blind, randomized study, Florence Bonkain et al found that urokinase had a preventive effect on catheter malfunction and that there was a 50% decrease in the rate of thrombosis-related catheter malfunction in the 25 000 U/ml urokinase combined with 4%

citrate group compared to the control group of 500 U/ml heparin combined with 4% citrate.[26] Preventive urokinase catheterization also has been shown to significantly reduce thrombosis in patients who have a history of recurrent catheter malfunction, according to Bonkain Florence. [26] Our trial's findings revealed no catheter removals, one case of catheter removal due to catheter malfunction in the heparin group, and a considerably greater incidence of catheter malfunction in the heparin group than in the urokinase.

Catheter-associated infections are the leading cause of catheter removal and one of the leading causes of death from catheter-related complications, while the topic of catheter infection prevention is currently debatable. Using an antibiotic sealing solution can inhibit the biofilm growth, and lower the risk of CRBSI.[27,28] However, the recent clinical practice guideline published in the American Medical Association Journal of Infectious Diseases did not recommend the technique despite promising results in lowering CRBSIs in HD patients treated with antibiotic blocking solutions, and concerns remain that chronic exposure to antimicrobial agents can result in the emergence of antibiotic-resistant bacteria.[28,29] Additionally, observational research with 404 tunnel catheters and more than 135 000 catheter days reported no discernible decrease in the incidence of CRBSIs when gentamicin to catheters on top of heparin.[30] Currently antibiotic sealing is mainly used for the treatment of bacterial infections.[13] By lowering the incidence of CRBSI, the application of thrombolytic drug seals for newly implanted TCCs may increase catheter survival.[2,20] Within a few months of TCC insertion, the risk of CRBSI and non-infectious complications both significantly declines.[31] The use of anti-platelet medications such as alteplase to seal catheters may lessen the risk of CRBSI, one weekly alteplase seal and two weekly heparin seals were more effective at preventing CRIs than three weekly heparin applications.[20] In this experiment, we used urokinase for catheter sealing together with financial considerations. In comparison to the heparin group, the infection rate of catheters sealed with urokinase was much lower, and catheter survival was higher.

How to define catheter dysfunction varies, which is a major drawback of this study. The Expert Consensus on Vascular Access for Hemodialysis in China (2nd edition) defines catheter dysfunction as catheter recirculation greater than 10%, and we were unable to effectively detect recirculation.[8] Therefore, we may have underestimated the incidence of catheter malfunction events. In addition, the use of hemodialysis catheters has substantially decreased, thus there aren't numerous cases in this study due to the focus on and popularity of peripheral vascular access. The optimum study of the sealing solution is double-blind (such that neither the patient nor the dialysis nurse knows whether the patient is receiving the interventional regimen or standard heparin), but it is more challenging to do so. This reduces bias in the diagnosis of catheter dysfunction.

To minimize possible bias in such studies, there should be an independent data monitoring and safety board (DMSB) to review objective data to assess whether catheter dysfunction is occurring, but currently, our center is not well-equipped to do so.

Blood flow and pressure are mainly used as judgment indicators when preceding standards describe catheter malfunction, nevertheless, if there is significant recirculation, blood flow and pressure as clearance indicators may be deceptive. The equipment was observed online in real time and discovered a substantial decrease in Kt/V in the 4 participants in this trial who had no distinctive anomalies in mean blood flow or pressure. We considered that there might be other catheter malfunctions that pressure or flow alarms might not be able to detect, and this could be a helpful addition to identifying catheter malfunction by catheter blood flow and pressure.

Overall, we believe that urokinase can be used as a secondary prevention drug for long-term catheter malfunction and infection based on its cheapness, efficacy, and safety, which can effectively save medical costs, and that its sealing protocol is simple and suitable for promotion.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

HB. L. designed the project, Q. W. and N. J. wrote and modified the paper. WD. C. and L. C. generated the data. S. F. and Q. L. analyzed the data. Q. W. and N. J. made equal contributions in this work as cofirst authors. All authors read and approved the final submitted manuscript.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

FUNDING

This Work Was Supported By The Scientific Research Project of Wuhan Municipal Health Commission (Grant nos. WX21B20) and The Scientific Research Project of Wuhan Municipal Health Commission (Grant nos. WZ22Q27).

REFERENCES

1. Qian JZ, McAdams-DeMarco M, Ng DK, Lau B. Arteriovenous Fistula Placement, Maturation, and Patency Loss in Older Patients Initiating Hemodialysis. *Am J Kidney Dis*. 2020;76(4):480-489.e1. doi:10.1053/j.ajkd.2020.02.449
2. Winnicki W, Herkner H, Lorenz M, et al. Taurolidine-based catheter lock regimen significantly reduces overall costs, infection, and dysfunction rates of tunneled hemodialysis catheters. *Kidney Int*. 2018;93(3):753-760. doi:10.1016/j.kint.2017.06.026
3. Wathanavasin W, Phannajit J, Poosoonthornsri M, et al. A Randomized Controlled Trial of Comparative Efficacy between Sodium Bicarbonate and Heparin as A Locking Solution for Tunneled Central Venous Catheters Among Patients Requiring Maintenance Hemodialysis. *Can J Kidney Health Dis*. 2021;8:20543581211046077. doi:10.1177/20543581211046077
4. Zhang HH, Cortés-Penfield NW, Mandayam S, et al. Dialysis Catheter-related Bloodstream Infections in Patients Receiving Hemodialysis on an Emergency-only Basis: A Retrospective Cohort Analysis. *Clin Infect Dis*. 2019;68(6):1011-1016. doi:10.1093/cid/ciy555
5. Wang AY, Ivany JN, Perkovic V, Gallagher MP, Jardine MJ. Anticoagulant therapies for the prevention of intravascular catheters malfunction in patients undergoing haemodialysis: systematic review and meta-analysis of randomized, controlled trials. *Nephrol Dial Transplant*. 2013;28(11):2875-2888. doi:10.1093/ndt/gft406
6. Hsieh HC, Hung SC, Huang SY, Huang FL, Chou CM. A prospective, randomized study assessing different modalities for flushing totally implanted vascular access device in children with malignancy. *J Chin Med Assoc*. 2022;85(1):114-119. doi:10.1097/JCMA.0000000000000601
7. van Rooden CJ, Schippers EF, Guiot HFL, et al. Prevention of coagulase-negative staphylococcal central venous catheter-related infection using urokinase rinses: a randomized double-blind controlled trial in patients with hematologic malignancies. *J Clin Oncol*. 2008;26(3):428-433. doi:10.1200/JCO.2007.11.7754
8. Vascular Access Working Group of the Blood Purification Center Branch of the Chinese Hospital Association. Expert consensus on vascular access for hemodialysis in China (2nd ed.). China Blood Purification,2019;18(6):365-381.doi:10.3969/j.issn.1671-4091.2019.06.001.
9. Ying Q, Mao Y, Xie X, et al. Multicenter Investigation of the Initial Hemodialysis Vascular Access and Its Related Factors in Hangzhou of China. *BioMed Res Int*. 2021;2021(6):6628139. doi:10.1155/2021/6628139
10. O'Grady NP, Alexander M, Burns LA, et al; Healthcare Infection Control Practices Advisory Committee (HICPAC). Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis*. 2011;52(9):e162-e193. doi:10.1093/cid/cir257
11. Wu AH. Introduction to the CDC 2011 guidelines for the prevention of vascular catheter-related infections. The 18th National Conference on Hospital Infection Management of China Hospital Association.The 18th National Conference on Hospital Infection Management of the Chinese Hospital Association[C], 2011.

12. Yali ZHU, Chao YANG, Xianghong FAN. Meta-analysis of the effectiveness of sodium citrate versus heparin sealing solution for hemodialysis catheter maintenance. *J Nurs (Luton)*. 2019;26(2):6. doi:10.16460/j.issn1008-9969.2019.02.039
13. Lok CE, Huber TS, Lee T, et al; National Kidney Foundation. 2019 Update. *Am J Kidney Dis*. 2020;75(4)(suppl 2):S1-S164. doi:10.1053/j.ajkd.2019.12.001
14. Gahlot R, Nigam C, Kumar V, Yadav G, Anupurba S. Catheter-related bloodstream infections. *Int J Crit Illn Inj Sci*. 2014;4(2):162-167. doi:10.4103/2229-5151.134184
15. Kawakami Y, Tagami T. Pumping infusions with a syringe may cause contamination of the fluid in the syringe. *Sci Rep*. 2021;11(1):15421. doi:10.1038/s41598-021-94740-1
16. Zhao L, Yang J, Bai M, Dong F, Sun S, Xu G. Risk Factors and Management of Catheter Malfunction During Urgent-Start Peritoneal Dialysis. *Front Med (Lausanne)*. 2021;8(8):741312. doi:10.3389/fmed.2021.741312
17. Ye H, Yang X, Yi C, et al. Urgent-start peritoneal dialysis for patients with end stage renal disease: a 10-year retrospective study. *BMC Nephrol*. 2019;20(1):238. doi:10.1186/s12882-019-1408-9
18. Chen JW, Hsu CC, Su CC, et al. Transient Bacteremia Promotes Catheter-Related Central Venous Thrombosis through Neutrophil Extracellular Traps. *Thromb Haemost*. 2022;122(7):1198-1208. doi:10.1055/a-1695-8612
19. Liang X, Liu Y, Chen B, et al. Central Venous Disease Increases the Risk of Microbial Colonization in Hemodialysis Catheters. *Front Med (Lausanne)*. 2021;8:645539. doi:10.3389/fmed.2021.645539
20. Hemmelgarn BR, Moist LM, Lok CE, et al; Prevention of Dialysis Catheter Lumen Occlusion with rt-PA versus Heparin Study Group. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *N Engl J Med*. 2011;364(4):303-312. doi:10.1056/NEJMoa1011376
21. Manns BJ, Scott-Douglas N, Tonelli M, et al. An economic evaluation of rt-PA locking solution in dialysis catheters. *J Am Soc Nephrol*. 2014;25(12):2887-2895. doi:10.1681/ASN.2013050463
22. Gittins NS, Hunter-Blair YL, Matthews JNS, Coulthard MG. Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial. *Arch Dis Child*. 2007;92(6):499-501. doi:10.1136/adc.2006.100065
23. Zhao HY, Yang GT, Zhang HF, Wang WH. Effect of Alteplase Thrombolysis on Coagulation Function and Nerve Function of Patients with Ischemic Stroke. Dong Z, ed. *Evidence-Based Complementary and Alternative Medicine*. 2022;2022(1):1-5. doi:10.1155/2022/9440271
24. Wang Y, Sun X. Reevaluation of lock solutions for Central venous catheters in hemodialysis: a narrative review. *Ren Fail*. 2022;44(1):1501-1518. doi:10.1080/0886022X.2022.2118068
25. Al-Ali F, Hamdy AF, Hamad A, et al. Safety and efficacy of taurolidine/urokinase versus taurolidine/heparin as a tunneled catheter lock solution in hemodialysis patients: a prospective, randomized, controlled study. *Nephrol Dial Transplant*. 2018;33(4):619-626. doi:10.1093/ndt/gfx187
26. Bonkain F, Van Hulle F, Janssens P, et al. Urokinase-containing locking solution in the prevention of dialysis catheter dysfunction: a double blind randomized controlled trial. *J Vasc Access*. 2017;18(5):436-442. doi:10.5301/jva.5000737
27. Rabindranath KS, Bansal T, Adams J, et al. Systematic review of antimicrobials for the prevention of haemodialysis catheter-related infections. *Nephrol Dial Transplant*. 2009;24(12):3763-3774. doi:10.1093/ndt/gfp327
28. Moghaddas A, Abbasi MR, Gharekhani A, et al. Prevention of hemodialysis catheter-related blood stream infections using a cotrimoxazole-lock technique. *Future Microbiol*. 2015;10(2):169-178. doi:10.2217/fmb.14.116
29. Sohail MA, Vachharajani TJ, Anvari E. Central Venous Catheters for Hemodialysis-the Myth and the Evidence. *Kidney Int Rep*. 2021;6(12):2958-2968. doi:10.1016/j.ekir.2021.09.009
30. Abbas SA, Haloob IA, Taylor SL, et al. Effect of antimicrobial locks for tunneled hemodialysis catheters on bloodstream infection and bacterial resistance: a quality improvement report. *Am J Kidney Dis*. 2009;53(3):492-502. doi:10.1053/j.ajkd.2008.09.019
31. Ravani P, Gillespie BW, Quinn RR, et al. Temporal risk profile for infectious and noninfectious complications of hemodialysis access. *J Am Soc Nephrol*. 2013;24(10):1668-1677. doi:10.1681/ASN.2012121234