Original Article

Efficacy of 5%, 10% Trisodium Citrate and Heparin as Catheter-Locking Solution for Central Venous Hemodialysis Catheters: A Prospective Randomized Controlled Study

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Background: The use of central venous catheter (CVC) is inevitable for hemodialysis in acute kidney injury (AKI) and in end-stage renal disease patients when arteriovenous fistula (AVF) is ineligible. The catheter-locking anticoagulant (CLA) is mandatory for maintaining the patency of CVCs. Trisodium citrate (TSC) is an alternative CLA to unfractionated heparin (UFH). However, the optimal concentration of TSC that yield the best efficacy and safety remains questionable.

Objective: To evaluate the efficacy of 5%, 10% TSC and UFH as CLA for CVCs.

Materials and Methods: The present study was a randomized controlled study of patients with non-tunneled cuffed catheters (NTCC) and tunneled cuffed catheters (TCC). Patients were stratified according to types of CVCs and randomized to receive UFH, 5%, and 10% TSC as a CLA for three months. The primary outcome was the development of catheter dysfunction (CD), defined as a persistent inability to obtain blood flow rate of 250 mL or more per minute despite flushing and repositioning the patient, or the use of recombinant tissue plasminogen activator. The secondary outcomes are the rates of catheter-related bloodstream infection (CRBSI), exit-site infection (ESI), bleeding, and all-cause death.

Results: Three hundred forty patients were randomized, and 249 were analyzed. One hundred thirty-four patients were in the NTCC group , and 115 were in the TCC group. There were 83, 79, and 87 patients in UFH, 5%, and 10% TSC group. The CD rates were 2.2, 1.6, and 1.2 per 1,000 catheter-day in UFH, 5% and 10% TSC groups. Compared to UFH group, the incidence rate ratio (IRR) of CD in 5% and 10% TSC group were 0.74 (p=0.55) and 0.55 (p=0.24). The IRR for CRBSI, ESI, and all-cause death were not significantly different to UFH group in both types of TSC. There was no serious adverse events and major bleeding episodes.

Conclusion: The efficacy and safety of UFH, 5% TSC, and 10% TSC as CLA were not significantly different.

Keywords: Catheter-locking anticoagulant, Citrate, Hemodialysis

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Arteriovenous fistula (AVF) is widely accepted as the optimal vascular access for long-term hemodialysis (HD) because it provides better durability and overall outcomes compare to arteriovenous graft (AVG) and central venous catheters (CVCs)[1]. However, the use of CVCs is inevitable for HD in acute kidney injury (AKI) and in end-stage renal disease (ESRD) patients when AVF contruction is not fully mature or ineligible. About 15% of the patients in the USA and 19.5% of the patients in Thailand used CVCs for long-term HD[2,3]. The use of CVCs is associated with catheter dysfunction (CD)[4] and catheter-related bloodstream infection (CRBSI) that worsen morbidity and mortality rates of the patients[1]. The catheter-locking anticoagulant (CLA) during the interdialytic period is mandatory for maintaining the patency of CVCs. Although, unfractionated heparin (UFH) is widely used for CLA, UFH possibly causes several side effects such as bleeding, heparin-induced thrombocytopenia (HIT), thrombosis, and osteoporosis[5,6].

Trisodium citrate (TSC) is an alternative CLA to

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UFH because of its anti-thrombotic and anti-bacterial properties[7]. The clinical studies showed comparable effect on maintaining catheter patency and reduction of major bleeding episodes[8,9]. However, the systematic review and meta-analysis compared TSC and UFH showed unclear efficacy on maintaining catheter patency and CRBSI prevention[10,11]. These studies used various concentrations of TSC ranging from 4% to 46.7%. The in-vitro study showed superior anti-microbial activity of TSC over UFH, particularly in high concentration[12]. However, the United States Food and Drug Administration issued concerns about safety of using 46.7% TSC as a CLA because it may result in cardiac arrest[13]. Therefore, the lower concentration of TSC for catheter locking is preferred. However, the optimal concentration of TSC that yield the best efficacy and safety remains questionable.

The authors performed a prospective, randomized controlled study to evaluate the efficacy and safety of 5% TSC, 10% TSC, and UFH as a CLA for CVCs.

Materials and Methods

Selection of the patients

The present study was carried out between June and December 2016 at Thammasat University Hospital, a tertiary-care hospital in Pathumthani, Thailand. Patients were eligible for enrollment in the study if they were older than 18 years, had newly placed, well-positioned non-tunnel cuffed catheter (NTCC) or tunnel cuffed catheter (TCC) expected to be needed for more than one week, and had pre-existing TCC without flow problems (a persistent inability to obtain blood flow rate [BFR] above 250 mL/minute).

The exclusion criteria were hemorrhagic diathesis conditions (diagnosis of liver failure, disseminated intravascular coagulopathy, leukemia, vitamin K deficiency, hemophilia, or platelet of less than 100,000/μL), hypercoagulable states (previously diagnosed of deep vein thrombosis, pulmonary embolism, or antiphospholipid syndrome), hematologic diseases (paroxysmal nocturnal hemoglobinuria, myeloproliferative neoplasms, polycythemia vera, essential thrombocytosis, or hemolytic anemia), metastatic cancer, currently using of oral contraceptive pills, currently using one of the following anticoagulants, warfarin, UFH, enoxaparin, rivaroxaban, apixaban, or dabigatran, proven or suspected HIT, allergic to UFH or TSC, pregnant, unable to obtain crucial data, and refused to participate.

The study protocol was approved by The Human Ethics Committee of Thammasat University (COA No.078/2559) and registered in the Thai Clinical Trials Registry with identifier TCTR20170314002. All the patients gave informed consents before enrolling into the study.

Study design

The eligible patients were stratified according to the type of HD catheters (NTCC or TCC) and then randomized into a 1:1:1 ratio to receive UFH, 5% TSC, or 10% TSC, respectively. The list in block of six randomization was computerized created using a random seed number 1 on website https://www.sealedenvelope.com/simple-randomiser/v1/lists. Allocation concealment was performed using opaque, sealed envelopes. Patients and investigators were blinded to the treatment assignments.

Procedures

The eligible patients were randomized to receive either UFH (2,500 U/mL in NTCC or 5,000 U/mL in TCC), 5% TSC, or 10% TSC as CLA in both lumens of their CVCs during the interdialytic period. The TSC solutions were prepared using 5 mL of 30% TSC, then added 25 mL of 0.9% sodium chloride (NSS) for 5% TSC, and 10 mL of NSS for 10% TSC. The UFH 2,500 U/mL solution was prepared by using 1 mL of UFH 5,000 U/mL with 1 mL of NSS. After completing every HD treatment, each lumen of the catheter was flushed with 10 mL of NSS, and then instilled with the assigned CLA equivalent to the priming volume as manufacturer specification noted on each catheter lumen. To prevent accidental infusion of the CLA, the 3-mL syringes or less volume capacity syringes were used. The standard protocol for catheter care were followed for HD treatment including insertion of catheters under strict sterile fashion by experienced operators, and catheter exit-site dressing changes after each HD treatment. The exit sites were inspected before each HD treatment.

The patients' demographics were collected including age, gender, type of renal failure, comorbidities, current antiplatelet use, history of exit-site infection (ESI), history of CRBSI, type of CVCs, site of catheter insertion, date of catheter insertion, and date of initiation of HD treatment. The laboratory data were obtained when enrolled to the study including complete blood count, coagulogram, blood urea nitrogen, creatinine, calcium, phosphate, and liver function test.

Outcomes

The primary outcome was the rates of CD, which

was defined as a persistent inability to maintain BFR above 250 mL/minute despite additional NSS flushing and positional change of the patient, or the use of recombinant tissue plasminogen activator (rTPA) to dissolve the intraluminal catheter clot. The secondary outcomes were the rates of CRBSI, ESI, bleeding episodes type 3a-5 by the Bleeding Academic Research Consortium definition for bleeding[14], and all-cause death. The authors used the criteria for diagnoses of CRBSI, ESI according to the Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection of the Infectious Diseases Society of America 2009[15]. The patients were followed up for 90 days after randomization.

Statistical analysis

Calculation of the required sample size was based on the assumption that the rates of CD would reduce from 8.0 to 5.0 per 1,000 catheter-day in patients who using of TSC instead of UFH[8]. With power of 0.80 and the two-tailed alpha of 0.05, the required sample size is estimated to be 75 patients per treatment arm. Estimating a 10% drop-out rate, this meant that 83 patients were required in each arm, for a total sample size of 249 patients.

Categorical data was presented as frequencies and percentages. Continuous data was presented as means and standard deviations (SDs) or median and interquartile range (IQR) as appropriated. Baseline characteristics were compared using Fischer exact's test for categorical variables. For continuous variables, the one-way analysis of variance (ANOVA) was used in parametric data and Kruskal-Wallis test in non-parametric data. The rate of events was presented in number (%), incident rate per 1,000 catheter-day, and incidence rate ratio (IRR) compared to UFH group. Poisson regression analysis was performed to adjust the IRR for the following baseline factor, age, gender, duration of TCC insertion, diabetes mellitus, hypertension, peripheral arterial disease, current anti-platelet medication, catheter type, site of catheter insertion, hemoglobin level, platelet count, international normalized ratio (INR), partial thromboplastin time (PTT) ratio, and corrected calcium level. The authors performed Kaplan-Meier survival curves to assess CD-free survival and compared between groups with Log-rank test. The analysis of outcomes was performed on an intention-to-treat basis. A p-value of less than 0.05 was considered as statistical significance. The analysis was done using Stata/IC 15.1 software (StataCorp LLC, College Station, TX, USA).

Results

Baseline characteristics of patients

Of the 340 patients enrolled, 91 were excluded and 249 were randomized divided into two groups. One hundred thirty-four patients were in the NTCC group, and 115 were in the TCC group. There were 83 (33.4%) patients in the UFH group, 79 (31.7%) patients in the 5% TSC group, and 87 (34.9%) patients in the 10% TSC group (Figure 1). The reasons for catheter insertion were for HD in ERSD (63.9%), HD in AKI (35.3%), and plasmapheresis (0.8%). The catheter insertion sites were internal jugular vein (IJV) (66.7%) and femoral vein (FV) (33.3%). Subclavian vein (SCV) catheterization was absent in the present study. The major site of catheter insertion in NTCC was FV (57.5%), and in TCC was IJV (94.8%). The baseline characteristics and laboratory results were not significantly different between the three groups, except mildly elevated aspartate aminotransferase (AST) in UFH group (Table 1).

None of the participant switched the intervention group or were loss to follow-up. The mean ± SD duration of participants to receive CLA were 54.6±36.2, 54.1±35.8, and 57.3±35.8 days in UFH, 5%, and 10% TSC group, respectively (p=0.88).

At the end of the study, the catheters were removed from 35 (42.2%), 38 (48.1%), and 36 (41.4%) in UFH, 5% and 10% TSC group, respectively (p=0.65). The causes of catheter removal were catheter malfunction (n=10), suspected of infection (n=15), use permanent vascular access (n=37), recovery from AKI (n=25), and others (n=22).

Catheter dysfunction

The number of CD were 10 (12.1%), 7 (8.9%), and 6 (6.9%) patients in UFH, 5% TSC, and 10% TSC group, respectively (p=0.54). The rate of CD was 2.2 per 1,000 catheter-day in UFH group, 1.6 per 1,000 catheter-day in 5% TSC group, and 1.2 per 1,000 catheter-day in 10% TSC group. Compared to UFH group, the IRR of CD were 0.74 in 5% TSC group (p=0.55, 95% confidence interval [CI] 0.28 to 1.95), and 0.55 in 10% TSC group (p=0.24, 95% CI 0.20 to 1.50). The CD-free survival rates were not different between the three groups (p=0.50) (Figure 2A).

The authors performed subgroup analyses according to the type of catheter and site of catheter insertion. In patients with NTCC, the rates of CD were 5.1, 5.5, and 1.8 per 1,000 catheter-day in UFH, 5% TSC, and 10% TSC, respectively. In patients

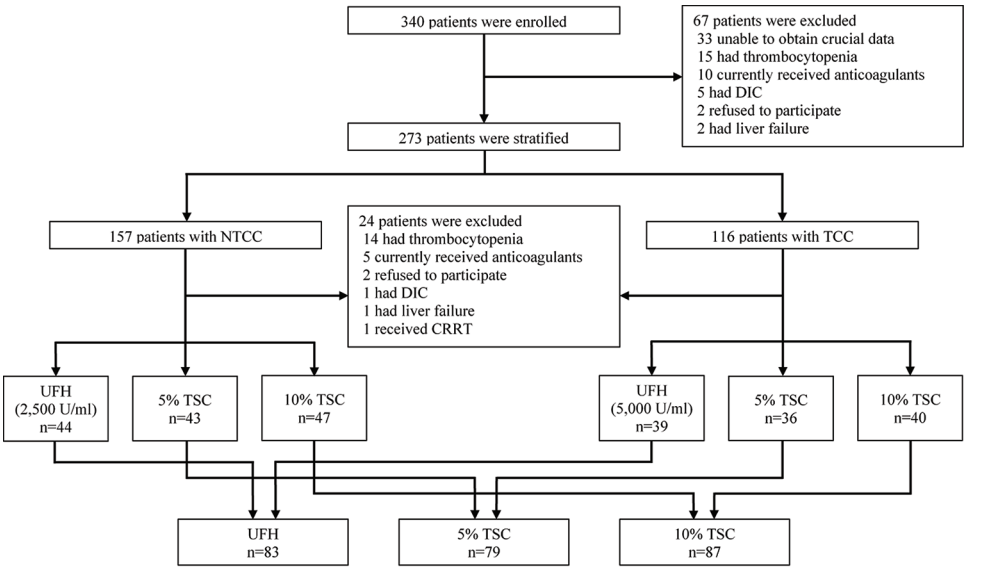

Figure 1. Study flow diagram: Eligibility, stratification, randomization, and analysis.

There were 24 patients with exclusion criteria who were mistakenly randomized and allocated. However, these patients never received the intervention, and were excluded from the analysis.

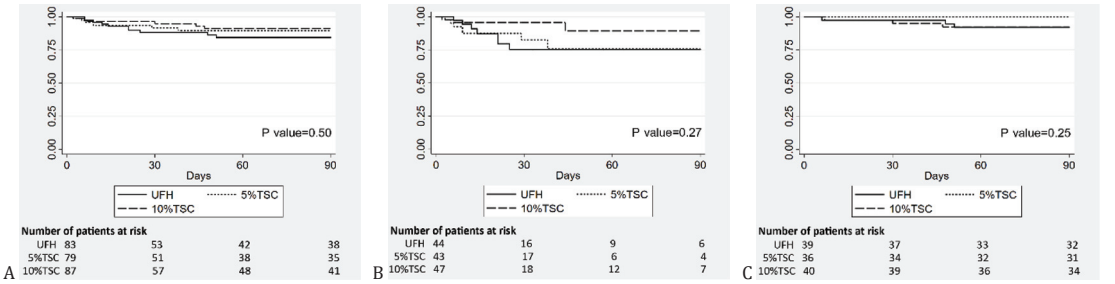

Figure 2. Kaplan-Meier curves for catheter dysfunction-free survival.

(A) In all participants, (B) In patients with non-tunnel cuffed catheters, and (C) In patients with tunnel-cuffed catheters. There was no significant difference of catheter dysfunction-free survival for heparin (UFH), 5% trisodium citrate (TSC), and 10% TSC groups.

with TCC, the rates of CD were 0.9, 0, and 0.6 per 1,000 catheter-day in UFH, 5% TSC, and 10% TSC, respectively. According to subtype of NTCC and TCC, the CD-free survival rates were not different between the three CLA (Figure 2B, C). In patients with catheter site at IJV, the rates of CD were 0.8, 0.3, and 0.5 per 1,000 catheter-day in UFH, 5% TSC, and 10% TSC, respectively. In patients with catheter site at FV, the rates of CD were 11.2, 9.2, and 5.7 per 1,000 catheter-day in UFH, 5% TSC, and 10% TSC, respectively. Compared to UFH group, the IRR of CD were not significantly different in both subgroup analyses by type of catheter and site of catheter insertion. Compared to UFH group, the adjusted IRR for CD was 4.5 for 5% TSC group (p=0.09, 95% CI 0.81 to 25.39), and 0.9 for 10% TSC group (p=0.93, 95% CI 0.15 to 5.68).

Infectious complications

The rate of CRBSI were 1.3, 1.4, and 0.4 per 1,000 catheter-day in UFH, 5% and 10% TSC group, respectively. The IRR of CRBSI in 5% and 10% TSC group compared to UFH group were 1.1 (p=0.91, 95% CI 0.34 to 3.29) and 0.3 (p=0.14, 95% CI 0.06 to 1.50). The rate of ESI were 0.4, 0.5, and 0.2 per 1,000 catheter-day in UFH, 5% TSC and 10% TSC group, respectively. The IRR of ESI in 5% and 10% TSC group compared to UFH group were 1.1 (p=0.95, 95% CI 0.15 to 7.54), and 0.5 (p=0.52, 95% CI 0.04 to 5.01). In the subgroup of CVCs types and sites of CVCs insertion, the rates of CRBSI and ESI were not significantly different among the 3 CLA.

Table 1. Baseline characteristics of the study participants

Characteristics	All (n=249) n (%)	UFH (n=83) n (%)	5% TSC (n=79) n (%)	10% TSC (n=87) n (%)	p-value
Sex: male	114 (45.8)	31 (37.4)	40 (50.6)	43 (49.4)	0.17
Age (years); mean±SD	66.2±16.4	66.9±13.6	65.4±17.9	66.2±17.5	0.89
Tunnel-cuffed catheter	115 (46.2)	39 (47.0)	36 (45.6)	40 (46.0)	0.99
Pre-existing catheter	58 (23.3)	25 (30.1)	15 (19.0)	18 (20.7)	0.20
Duration of TCC insertion (months); median (IQR)	0.1 (6.0)	1.8 (7.3)	0.1 (3.9)	0 (5.3)	0.49
Dialysis vintage (months); median (IQR)	2.2 (20.1)	2.0 (8.0)	1.4 (25.6)	2.8 (45.5)	0.51
Reasons for CVCs insertion					0.84
HD in AKI	15 (6.0)	7 (8.4)	3 (3.8)	5 (5.8)	
HD in AKI on top CKD	73 (29.3)	22 (26.5)	26 (32.9)	25 (28.7)	
HD in ESRD	159 (63.9)	53 (63.9)	50 (63.3)	56 (64.4)	
Plasmapheresis	2 (0.8)	1 (1.2)	0 (0.0)	1 (1.2)	
Comorbidities					
Diabetes mellitus	130 (52.2)	43 (51.8)	40 (50.6)	47 (54.0)	0.92
Hypertension	222 (89.2)	74 (89.2)	71 (89.9)	77 (88.5)	0.97
Dyslipidemia	94 (37.8)	33 (39.8)	26 (32.9)	35 (40.2)	0.56
Ischemic heart disease	56 (22.5)	24 (28.9)	17 (21.5)	15 (17.2)	0.20
Peripheral arterial disease	8 (3.2)	2 (2.4)	3 (3.8)	3 (3.5)	0.91
Stroke	33 (13.3)	14 (16.9)	10 (12.7)	9 (10.3)	0.48
Previous CRBSI or ESI in 1 month	58 (23.3)	25 (30.1)	15 (19.0)	18 (20.7)	0.57
Current antiplatelet					
ASA	61 (24.5)	15 (18.1)	20 (25.3)	26 (29.9)	0.20
Clopidogrel	10 (4.0)	6 (7.2)	2 (2.5)	2 (2.3)	0.26
Cilostazol	1 (0.4)	1 (1.2)	0 (0.0)	0 (0.0)	0.65
ASA+clopidogrel	28 (11.2)	6 (7.2)	12 (15.2)	10 (11.5)	0.29
ASA+clopidogrel+cilostazol	1 (0.4)	1 (1.2)	0 (0.0)	0 (0.0)	0.65
Hemoglobin (g/dL); mean±SD	9.3±1.7	9.3±1.8	9.2±1.7	9.3±1.8	0.90
Platelets (10^3/mcL); mean±SD	220.4±82.3	216.6±82.0	218.1±83.4	226.0±82.6	0.74
INR; mean±SD	1.3±0.3	1.3±0.4	1.2±0.2	1.3±0.3	0.98
PTT ratio; mean±SD	1.3±0.3	1.3±0.3	1.2±0.2	1.3±0.3	0.41
BUN (mg/dL); median (IQR)	74.6 (56.3)	70.3 (51.4)	74.2 (51.5)	79.5 (68.8)	0.73
Creatinine (mg/dL); median (IQR)	6.1 (4.3)	5.4 (4.0)	6.6 (3.8)	6.4 (5.0)	0.14
Corrected Ca (mg/dL); mean±SD	9.4±1.0	9.5±1.1	9.6±1.1	9.3±0.8	0.32
Phosphorus (mg/dL); mean±SD	5.2±2.1	4.8±2.3	5.1±2.0	5.5±2.1	0.07
Albumin (g/dL), mean±SD	2.6±0.7	2.6±0.8	2.5±0.7	2.7±0.7	0.47
TB (mg/dL); median (IQR)	0.6 (0.5)	0.6 (1.0)	0.6 (0.4)	0.6 (0.4)	0.56
AST (U/L); median (IQR)	39 (48)	51 (58)	31 (69)	33 (31)	0.03
ALT (U/L); median (IQR)	30 (31)	37 (30)	30 (44)	26 (22)	0.10
ALP (U/L); median (IQR)	105 (97)	128 (107)	102 (91)	103 (48)	0.42

AKI=acute kidney injury; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASA=aspirin; AST=aspartate aminotransferase; BUN=blood urea nitrogen; Ca=calcium; CKD=chronic kidney disease; CRBSI=catheter-related bloodstream infection; CVCs=central venous catheters; ESI=exit-site infection; ESRD=end-stage renal disease; INR=international normalized ratio; IQR=interquartile range; PTT=partial thromboplastin time; SD=standard deviation; TB=total bilirubin; TCC=tunnel-cuffed catheter; TSC=trisodium citrate; UFH=unfractionated heparin

Table 2. Summary of the primary and secondary outcomes

	UFH	5% TSC	10% TSC
CD; n (%)	10 (12.1)	7 (8.9)	6 (6.9)
Rate (per 1,000 catheter-day)	2.2	1.6	1.2
Incidence rate ratio	Reference	0.7 (p=0.55)	0.5 (p=0.24)
CRBSI; n (%)	6 (7.2)	6 (7.6)	2 (2.3)
Rate (per 1,000 catheter-day)	1.3	1.4	0.4
Incidence rate ratio	Reference	1.1 (p=0.92)	0.3 (p=0.14)
ESI; n (%)	2 (2.4)	2 (2.5)	1 (1.2)
Rate (per 1,000 catheter-day)	0.4	0.5	0.2
Incidence rate ratio	Reference	1.1 (p=0.95)	0.5 (p=0.52)
Bleeding episode type 3a-5; n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Rate (per 1,000 catheter-day)	0	0	0
Incidence rate ratio	Reference	N/A	N/A
All caused mortality; n (%)	12 (14.5)	7 (8.9)	8 (9.2)
Rate (per 1,000 catheter-day)	2.6	1.6	1.6
Incidence rate ratio	Reference	0.6 (p=0.31)	0.6 (p=0.27)

CD=catheter dysfunction; CRBSI=catheter-related bloodstream infection; ESI=exit-site infection; N/A=not available; TSC=trisodium citrate; UFH=unfractionated heparin

Table 3. Bleeding events and causes of death

	All n (%)	UFH n (%)	5% TSC n (%)	10% TSC n (%)	p-value
Bleeding events[14]					
Type 1	1 (0.4)	0 (0.0)	1 (1.3)	0 (0.0)	0.32
Type 2	2 (0.8)	1 (1.2)	0 (0.0)	1 (1.2)	1.00
Type 3a-5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Cause of death					
All infection	19 (7.6)	10 (12.1)	5 (6.3)	4 (4.6)	0.19
CRBSI-related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Myocardial infarction	4 (1.6)	0 (0.0)	1 (1.3)	3 (3.5)	0.27
Cardiac arrhythmia	1 (0.4)	1 (1.2)	0 (0.0)	0 (0.0)	0.65
Stroke	1 (0.4)	0 (0.0)	1 (1.3)	0 (0.0)	0.32
Electrolytes imbalance	1 (0.4)	1 (1.2)	0 (0.0)	0 (0.0)	0.65
Others	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.2)	1.00

CRBSI=catheter-related bloodstream infection; TSC=trisodium citrate; UFH=unfractionated heparin

Bleeding and other complications

There was no bleeding episode type 3a-5 and other serious adverse event that occurred during the present study. Two patients had metallic taste and numbness during instilled 10% TSC in CVCs, and one patient in 5% TSC group had mild headache.

The mortality rates were 2.6, 1.6, and 1.6 per 1,000 catheter-day in UFH, 5% TSC, and 10% TSC group, respectively. The IRR of CRBSI in 5% and 10% TSC group compared to UFH group were 0.6 (p=0.31, 95% CI 0.24 to 1.57) and 0.6 (p=0.27, 95% CI 0.25 to 1.48). The causes of death were not associated with CLA. There was no CRBSI-associated death in the present study. The primary and secondary outcomes are summarized in Table 2. The types of bleeding event and causes of death are shown in Table 3.

Cost

The cost of CLA were calculated according to the price in Thammasat University Hospital on March 2017. The 30% TSC cost 130 Baht/5 mL and UFH (5,000 unit/mL) cost 186 Baht/5 mL. However, when diluted 30% TSC with NSS, the 10% TSC, and 5% TSC cost were 44 and 22.5 Baht, respectively. Although, UFH concentration and cost may be halved when used in NTCC, both 10% TSC and 5% TSC cost less. In order to use these solutions in Thammasat University Hospital, the total approximate annual cost of using 5% TSC and 10% TSC for HD patients with CVCs would be 155,000 and 302,000 Baht, whereas using UFH 5,000 U/mL would be 1,277,000 Baht.

Discussion

The present study is a prospective, randomized controlled trial comparing the efficacy and safety of different concentrations of TSC to UFH as a CLA. The present study included a substantial number of participants with various types of catheter, sites of catheter insertion, types of renal failure, and newly inserted and preexisting TCC, which represented the common situations of kidney disease patients.

The present study's results showed that using UFH, 5% TSC, and 10% TSC as CLA were comparable in both efficacy on CD prevention, and major side effects during 90 days of follow-up. This efficacy was consistent among the subgroups with both types of CVCs and sites of catheter insertion. The efficacy remained persistent after adjusted by multiple variables in regression analysis.

The present study results corresponded with the previous studies. Hendrickx et al[16] showed that locking catheter with 5% TSC and UFH in 19 patients with TCC had no significant difference for prevention of catheter obstruction. Although, there was higher a number of dialysis sessions with clot formation in the 5% TSC group, the need for thrombolytic drug, complete catheter obstruction or infections rate were not different between the two groups. Macrae et al[9] randomized 61 patients with TCC to receive 4% TSC or UFH 5,000 unit/mL. The CD rates were comparable between 4% TSC and UFH group (41% versus 41%, p=0.80). Additionally, the CRBSI rate in the study was slightly higher than the present study (2.2 and 3.3 episodes per 1,000 catheter-day in 4% TSC and UFH group, respectively). Another randomized study in 28 patients with TCC by Meeus et al[17] demonstrated the comparable efficacy of 5% TSC and 10% TSC on prevention of complete catheter obstruction, the need for thrombolytic, and large clot formation. However, there was a slightly higher number of small clot formation in 5% TSC group (12.5% versus 9.5%, p=0.045). The catheter infection rates were not significantly different between the two groups as found in the present study.

In contrast, Weijmer et al[8] demonstrated the lower rate of premature catheter removal in 30% TSC compared to UFH groups (28% versus 46%, p=0.01). However, the infectious complication, not catheter flow problems, was the major contributing factor. This discordant result would be associated with the higher concentration of TSC than in the present study. In a in-vitro study, the TSC at higher concentrations showed superior antimicrobial activity over UFH and less concentrated TSC[12]. The 30% TSC was the only concentration that was able to completely eliminate *Escherichia coli*, *Pseudomonas aeruginosa* and significantly inhibit the growth of *Candida albicans*. Thus, the low to moderate concentration of TSC in the present study may not lessen the infectious complication rates compared to UFH group. Furthermore, there were low CRBSI and ESI rates in the present study, which may be too low to prove the statistical significance. In contrary to the study by Power et al[18], there was no significant difference in infectious complications among patients with TCC who used 46.7% TSC and UFH as CLA. Moreover, the number of thrombolytic locks were greater in 46.7% TSC group (8 versus 4.3 per 1,000 catheter-day, p<0.001). However, there was a concern on systemic leakage of TSC, which was possibly due to catheter design and very high concentration of TSC resulting in attenuation of anticoagulant effect and excessive number of side effects of TSC in the present study.

The NTCC associated with lower catheter patency and higher infectious complication rate[19]. However, few studies included the patients with NTCC for comparing the efficacy of CLA. Correa et al[20] randomized patients with NTCC to receive 30% TSC or UFH 5,000 unit/mL for CLA. The CD-free survival was not different, but the CRBSI-free survival of 30% TSC was shorter. In contrast to the present study, there were approximately a third of the patients who had CVCs at SCV in the present study and these differences possibly resulted in inconsistent outcomes to the present study.

Lorente et al[21] showed the higher rate of CRBSI and catheter-related local infection in patients with CVCs at FV compared to IJV (15.83 versus 7.65 events per 1,000 catheter-day, p<0.001). In the present study, the rates of CRBSI were slightly higher in

patients with CVCs at FV compared to IJV (1.5 versus 0.9 per 1,000 catheter-day). However, the number of sites of CVCs insertion were not different among the three groups of CLA. Thus, the effects from the sites of catheter insertion would be equally distributed among the three groups of patients.

There were few limitations in the present study. First, the short follow-up periods may result in reluctance for determining the type of CLA in patients with TCC, which usually retained for more than three months. The outcome could be different if the follow-up period was longer. Second, the treatment effects of CLA in patients with pre-existing TCC would be contaminated with previous CLA and it was unable to perform the washout period in these participants. However, there was no difference in the duration of TCC insertion and number of patients with the pre-existing catheter among the three groups. Third, the CD rates from the previous study[8], which the authors used for sample size calculation, were much higher than results from the present study. Thus, there is possibility of under power to discrimination of outcomes between these three groups. However, the authors performed power back calculation from the present study results and found that the power for discrimination of the outcomes between UFH group versus 5% TSC and 10% TSC groups were 45% and 97%, respectively. This means that the power for comparing CD rate of UFH group versus 10% TSC group was excellent. Thus, the comparison between UFH and 10% TSC group were strongly reliable. According to this reason and the comparable outcomes of 5% and 10% TSC, the authors prefer 10% TSC over 5% TSC.

Although, there were no significant different outcome between using UFH, 5%, and 10% TSC as a CLA, the TSC can be used as an alternative CLA. Furthermore, TSC was particularly useful in patients with UFH allergy, or HIT. Finally, the lesser cost of TSC would be considered as a factor to determine the type of CLA.

Conclusion

The efficacy of 5% TSC, 10% TSC, and UFH as CLA are comparable in terms of preventing CD and safety during 90 days of follow-up. The lesser cost of TSC would be another advantage of this agent.

What is already known on this topic?

Previous studies showed that TSC can be used as an alternative CLAs to heparin, however, the optimal concentration of TSC remains controversial.

What this study adds?

The 5% and 10% TSC have comparable efficacy and safety to heparin in using as a CLA for either patients with TCC or NTCC.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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