Nephrol Dial Transplant (2017) 1–7
doi: 10.1093/ndt/gfx187

ndt
Nephrology Dialysis Transplantation

ORIGINAL ARTICLE

Safety and efficacy of taurolidine/urokinase versus taurolidine/heparin as a tunneled catheter lock solution in hemodialysis patients: a prospective, randomized, controlled study

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ABSTRACT

Background. Taurolidine citrate with heparin (Taurolock/Hep) is a promising central venous catheter lock solution. Despite its universal use among our hemodialysis patients, the prevalence of catheter malfunction was high. We aimed to compare Taurolock/Hep and taurolidine citrate with urokinase (Taurolock/U) as a catheter lock solution in order to identify whether either solution could reduce catheter-related dysfunction.

Methods. In this prospective, randomized, controlled trial, patients were randomized to receive either Taurolock/Hep or Taurolock/U and were followed for 6 months. Episodes of acute catheter thrombosis, requirement of recombinant tissue plasminogen activator (rt-PA) and incidence of catheter-related blood stream infection (CRBSI) were recorded, along with dialysis adequacy (Kt/V), blood flow rates (BFRs) and adverse events.

Results. There were 93 inclusions (85 patients) in the Taurolock/Hep group and 84 inclusions in the Taurolock/U group (79 patients). Three catheters were removed in the Taurolock/Hep group because of acute thrombosis, while no catheter was removed for the same reason in the Taurolock/U group. The total number of all-causes catheter exchange (acute thrombosis and CRBSI) was significantly lower in Taurolock/U group ($P = 0.028$). rt-PA was used significantly less often in the Taurolock/U group than in the Taurolock/Hep group ($P = 0.006$). Moreover, higher BFR and Kt/V were noted in the Taurolock/U group than in the Taurolock/Hep group, although the differences were not uniformly significant.

Conclusion. Taurolock/U is a safe and effective tunneled dialysis catheter lock solution, with a low rate of catheter exchange.

Keywords: catheter lock solution, catheter-related dysfunction, hemodialysis, taurolidine/heparin, taurolidine/urokinase

INTRODUCTION

The use of tunneled catheters in hemodialysis is one of the leading causes of morbidity and mortality among dialysis patients [1]. The drawbacks include recurrent thrombosis, which decreases the delivered dose of dialysis and increases the rate of catheter-related blood stream infection (CRBSI) [2]. Although The National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) guidelines [3] have recommended that not >10% of chronic kidney disease patients on dialysis should be maintained on catheters, the prevalence of tunneled catheters is still high in most countries, including the USA, where the prevalence is ∼18–19% according to the United States Renal Data System 2010 annual report [4]. Among dialysis units in the state of Qatar, the prevalence of tunneled catheter use is high at ∼27%, which can be attributed mainly to patient refusal for the creation of an arteriovenous fistula (AVF), as well as the high number of medically unfit patients [5]. Catheter malfunction due to thrombosis is considered as the most frequently encountered complication and is responsible for about two-thirds of all cases of catheter removal among tunneled catheter patients [6].

Studies have shown that recombinant tissue plasminogen activator (rt-PA) is an efficient treatment to restore the patency of the clotted catheter with a high safety margin [7], and this was further confirmed in a meta-analysis [8]. Recently, the incidences of malfunction and bacteremia were shown to be significantly lower with the use of rt-PA once weekly than with the use of heparin thrice weekly as a lock solution for central venous catheters [9]. However, the use of rt-PA will add a further burden on dialysis resources as rt-PA is both expensive and not commonly available in all dialysis units.

Taurolidine citrate in combination with heparin (TauroLock Hep500) is an emerging antimicrobial catheter lock solution

with broad-spectrum activity and a property of eradicating pathogens from the catheter biofilm [10, 11]. In a randomized trial, taurolidine citrate use was associated with a decreased rate of CRBSI caused by Gram-negative microbes; however, there was a high need for thrombolytic treatment [12]. In a retrospective study, the addition of 500 U of heparin/mL to taurolidine citrate appeared to reduce thrombosis in comparison with the use of taurolidine citrate alone, without increasing the bacteremia rate [13].

Recently, after the application of 'TauroLock Hep500' as a standard lock solution in our dialysis patients, we noticed that the prevalence of CRBSI ranged from 0.57 to 0.83/1000 catheter days; however, the prevalence of catheter malfunction, including thrombosis, poor blood flow, high venous pressure, etc., was as high as 50% of our patients per year.

Several small studies have suggested the use of periodic fibrinolytic agents, such as urokinase, for decreasing tunneled catheter-related complications [14]. TauroLock U25.000 is a new catheter lock solution, which contains urokinase in addition to (cyclo)-taurolidine and citrate (4%). In an attempt to reduce the catheter malfunction and thrombosis rates further and to identify the best catheter lock solution, we performed a comparative study between Taurolock/Hep (TauroLock Hep500®) and Taurolock/U (TauroLock U25.000®).

The primary objective of this study was to identify the best catheter lock solution in order to decrease the incidences of catheter malfunction and thrombosis through assessment of the following:

(i) Number of catheter exchanges owing to acute or recurrent episodes of thrombosis that interrupt dialysis.
(ii) Time to the first episode of catheter thrombosis that leads to catheter exchange.

The secondary objective was to evaluate the effectiveness of each catheter lock solution by measuring the following:

(i) Amount of rt-PA used to treat acute catheter thrombosis or to lock catheters.
(ii) Incidence of CRBSI that required catheter exchange.
(iii) Number of catheter exchanges.
(iv) Hospitalization days related to catheter malfunction or CRBSI.
(v) Impact of catheter lock solution on adequacy of dialysis, as measured by monthly *Kt*/*V*.
(vi) Impact of catheter lock solution on the blood flow rate (BFR) as an estimate of catheter patency.

MATERIALS AND METHODS

This prospective, randomized, controlled and comparative study was approved by the local ethics committee at Hamad Medical Corporation in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The study was conducted at three dialysis units in the state of Qatar between November 2013 and April 2015. All patients undergoing tunneled catheter hemodialysis thrice weekly were included in the study after obtaining signed informed consent from the patients or their guardians, as specified in the ICMJE Recommendations.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) age $\geq$18 years; (ii) hemodialysis via a tunneled hemodialysis catheter; and (iii) BFR of $\geq$250 mL/min at the start of the study. The exclusion criteria were as follows: (i) catheter malfunction defined by a BFR of $<$250 mL/min; (ii) allergy to used drugs; and (iii) major hemorrhage in the previous 4 weeks.

Study design

This study was single-blinded as patients were blinded to the treatment administered, but the administering clinician was not blinded. Computer-generated randomization was followed with allocation concealment. All patients who were undergoing regular tunneled catheter hemodialysis and met the inclusion criteria were included. Patients were randomized on a 1:1 basis to either the Taurolock/Hep or Taurolock/U group.

In the Taurolock/Hep group, patients underwent catheter lock with TauroLock™-HEP500 at the end of all hemodialysis sessions (thrice weekly). The active ingredients in TauroLock™-HEP500 are (cyclo)-taurolidine, citrate (4%) and heparin (mucosa, 500 IU/mL).

In the Taurolock/U group, patients underwent catheter lock with TauroLock™-U25.000 at the end of the third hemodialysis session before the end of the week. The first two weekly hemodialysis sessions were followed by catheter lock with TauroLock™-HEP500. The active ingredients in Tauro Lock™-U25.000 are (cyclo)-taurolidine, citrate (4%) and urokinase (25 000 IU).

Long-term TYCO® cuffed double lumen central venous catheters were used in this study. The catheters are made of poly-tetra-fluoro-ethylene (PTFE). The French size of the catheters varied from 11 to 14, with variable venous lumen sizes between 1.4 and 2.4 and arterial lumen volumes between 1.3 and 2.3 mL. The lock solution was administered according to the volume of each catheter lumen. All patients were followed up for 6 months after randomization.

Episodes of acute catheter thrombosis that interrupted dialysis or resulted in malfunction, with a maximum catheter delivered BFR of $<$150 mL/min, were treated with rt-PA catheter installation (1 mg/mL as per catheter fill volume) along with reassessment of catheter function after 60 min to check for restored patency. Failure to restore catheter patency after second rt-PA catheter installation was considered as primary endpoint and the patient was referred for catheter exchange.

Episodes of catheter dysfunction with a reduced BFR of $<$200 mL/min during most of the dialysis session were treated with rt-PA lock of the catheter at the end of the session, which was left *in situ* until the next session.

The BFR from the dialysis machine monitor reading was taken four times on an hourly basis for each patient at every session, and then the mean BFR is calculated for every session. The mean BFR reading was then entered for every session three times weekly, for a total of 24 weeks, which is the total study duration for every included patient.

Table 1. Demographic characteristics of the study patients

	Taurolock/Hep	Taurolock/U	P-value
Included catheters, *n*	93	84	
Enrolled patients	85	79	
Single-enrolled patients	77	74	
Twice-enrolled patients	8	5	
Age (years), mean ± SD	56.7 ± 14.7	55.3 ± 15.6	0.6
Gender, *n* (%)			
Male	49 (52.7)	47 (56)	0.6
Female	44 (47.3)	37 (44)	
Cause of ESRD, *n* (%)			
Diabetes mellitus	47 (50.5)	47 (55.9)	0.7
Hypertension	10 (10.7)	8 (9.5)	
Chronic GN	7 (7.5)	8 (9.5)	
Advanced GS	3	4	
IgA nephropathy	2	2	
FSGS	1	1	
MCGN	0	1	
MPGN	1	0	
Reflux nephropathy	0	1 (1.2)	
Single kidney	0	1 (1.2)	
Unknown	29 (31.1)	19 (22.6)	
Comorbidities, *n* (%)			
Diabetes mellitus	54 (58)	49 (58.3)	0.8
Hypertension	67 (72)	67 (79.7)	0.6
Heart failure	6 (6.4)	6 (7.1)	0.9
Connective tissue disease	1 (1.1)	1 (1.2)	0.7
Medications, *n* (%)			
Aspirin	39 (41.9)	45 (53.5)	0.1
Clopidogrel	16 (17.2)	16 (19)	0.2
Warfarin	8 (8.6)	7 (8.3)	0.3
Censored, *n* (%)	20 (21.5)	10 (11.9)	0.089
Follow-up period (days), mean ± SD	124 ± 77.2	135.3 ± 68.4	0.305

Dialysis adequacy was calculated for every patient on a monthly basis using *Kt*/*V*, using the Daugirdas formula with the single pool method of blood urea measurement [15]. Patients with clinical signs suggestive of CRBSI had 10 mL of blood obtained from each catheter lumen and from a peripheral vein, and all samples were split equally between the anaerobic and aerobic blood collection bottles. Diagnosis of CRBSI was made if the same organism was obtained from blood aspirated through the catheter hub and from blood sample obtained from peripheral vein with no other identifiable cause of infection [16].

Statistics

Collected data were entered into the SPSS 22 statistical package (IBM Corp., Armonk, NY, USA) for analysis. Descriptive statistics were performed for all continuous and categorical variables, as appropriate. Parametric and non-parametric statistical techniques were applied to determine the significance of differences between the groups. Repeated-measures ANOVA was used to measure and compare the impact of time on changes in the BFR in each group. A $P \leq 0.05$ was considered statistically significant. Statistics were performed with intention-to-treat analysis.

RESULTS

A total of 177 eligible (single and twice enrolled) patients were included in the present study. Of these patients, 93 and 84 were randomized to the Taurolock/Hep and Taurolock/U groups, respectively. Eight and five patients were twice enrolled in the Taurolock/Hep and Taurolock/U groups, respectively (they finished the study duration or reached the endpoint and then inserted a new catheter). The patients in the two groups were homogenously distributed with regard to age, sex, cause of end-stage renal disease (ESRD), comorbidities and associated relevant medications. A total of 30 patients were censored in both groups during the study mainly because of AVF cannulation (Table 1, Figure 1).

Most catheters were inserted through the right internal jugular vein, while three catheters involved the iliac veins. Both groups were comparable with regard to catheter age, pre-study BFR and venous pressure (Table 2).

The primary endpoint was met thrice in the Taurolock/Hep group and was not met in the Taurolock/U group ($P = 0.078$). Three patients in the Taurolock/Hep group were referred for catheter exchange after a mean period of 90.6 days owing to acute catheter thrombosis not responding to rt-PA intervention.

For secondary objectives, catheter exchange because of CRBSI was more common in the Taurolock/Hep group than in the Taurolock/U group (four episodes versus one episode, respectively). The overall CRBSI rate was 0.3 incidence/1000 catheter days in the Taurolock/Hep group versus 0.08 incidence/1000 catheter days in the Taurolock/U.

Total catheter exchanges was significantly more common in the Taurolock/Hep group than in the Taurolock/U group (seven episodes versus one episode, $P = 0.028$) (Table 3).

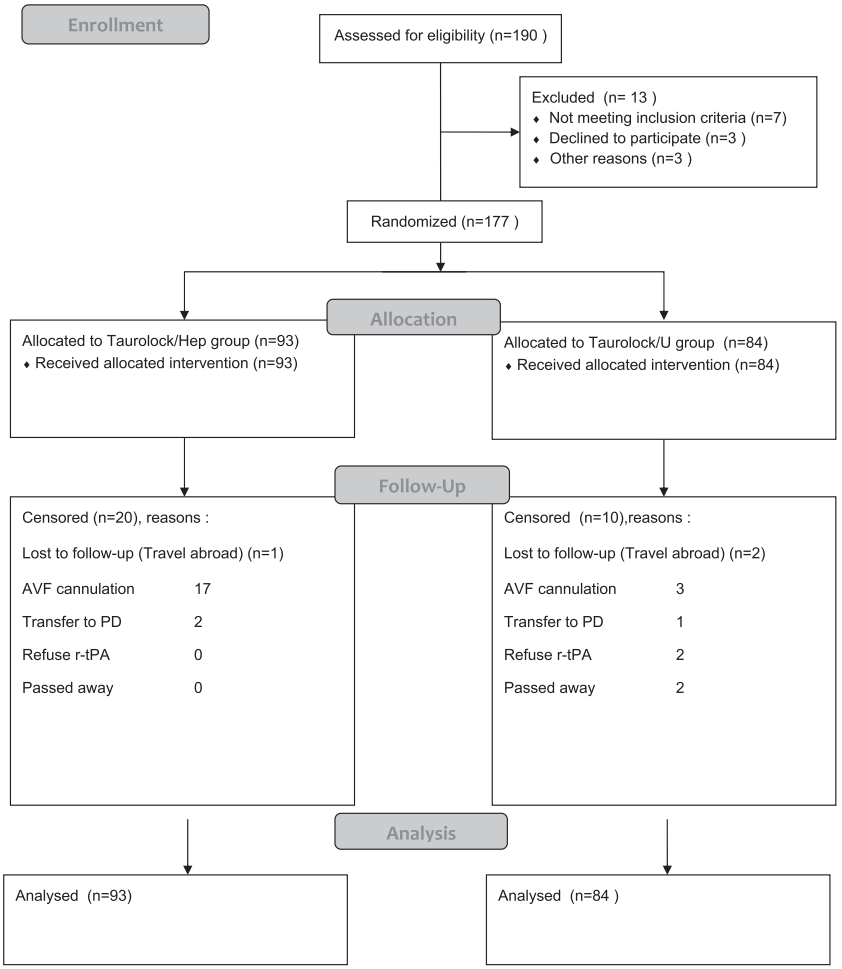

FIGURE 1: Consort diagram. PD, peritoneal dialysis.

Table 2. Tunneled catheter characteristics

Tunneled Catheters	Taurolock/Hep ($n = 93$)	Taurolock/U ($n = 84$)	P-value
Site, *n*			
Right internal jugular vein	91	83	
Right external iliac vein	1	0	
Left external iliac vein	1	1	
New catheters (0–90 days)	37	39	
Catheter age at start (days), mean ± SD	218.4 ± 306.7	291.2 ± 431.9	0.237
Pre-study, BFR (mL/min), mean ± SD	262.8 ± 21.6	265.0 ± 26.0	0.541
Pre-study venous pressure (mmHg), mean ± SD	143.0 ± 16.4	141.9 ± 19.1	0.686

The number of patients who required rt-PA intervention (both for catheter installation to restore patency and as catheter lock) was higher in the Taurolock/Hep group than in the Taurolock/U group; however, the difference was not significant (P = 0.083). Further analysis revealed that a higher number of patients in the Taurolock/Hep group required rt-PA repeatedly, with 12 patients requiring rt-PA intervention five times or more (Figure 2). Therefore, repeated rt-PA use was compared between the two groups, and we found that rt-PA use was significantly higher in the Taurolock/Hep group than in the Taurolock/U group (4.3 times versus 2.1 times, P = 0.006) (Table 4).

To estimate the possible impact of a catheter lock solution on dialysis adequacy, we measured the delivered dialysis adequacy as expressed by *Kt*/*V* in both study groups on a monthly basis. The *Kt*/*V* values were found to be uniformly higher in the Taurolock/U group than in the Taurolock/Hep group; however, the difference reached statistical significance only once at the first month estimation (P = 0.050) (Table 5).

Tunneled catheter patency can be expressed by the delivered BFR during dialysis sessions. Therefore, the measured BFRs during each hemodialysis session for all studied patients were evaluated. The mean BFR per week was persistently higher in the Taurolock/U group than in the Taurolock/Hep group for all

Table 3. Catheter-related complications and management

Catheter Exchange	Taurolock/Hep ($n = 93$)	Taurolock/U ($n = 84$)	P-value
Exchange due to malfunction			
Number	3		0.078
Time to removal (days), mean ± SD	90.6 ± 15.3		
Hospital stay (days), mean ± SD	7.3 ± 10.1		
Exchange due to CRBSI			
Number	4	1	0.167
Hospital stay (days), mean ± SD	170 ± 71.5	62	0.613
Hospital stay (days), mean ± SD	6.2 ± 4.5	5	0.823
Total number of catheter exchanges	7	1	0.028*

*$P \leq 0.05$.

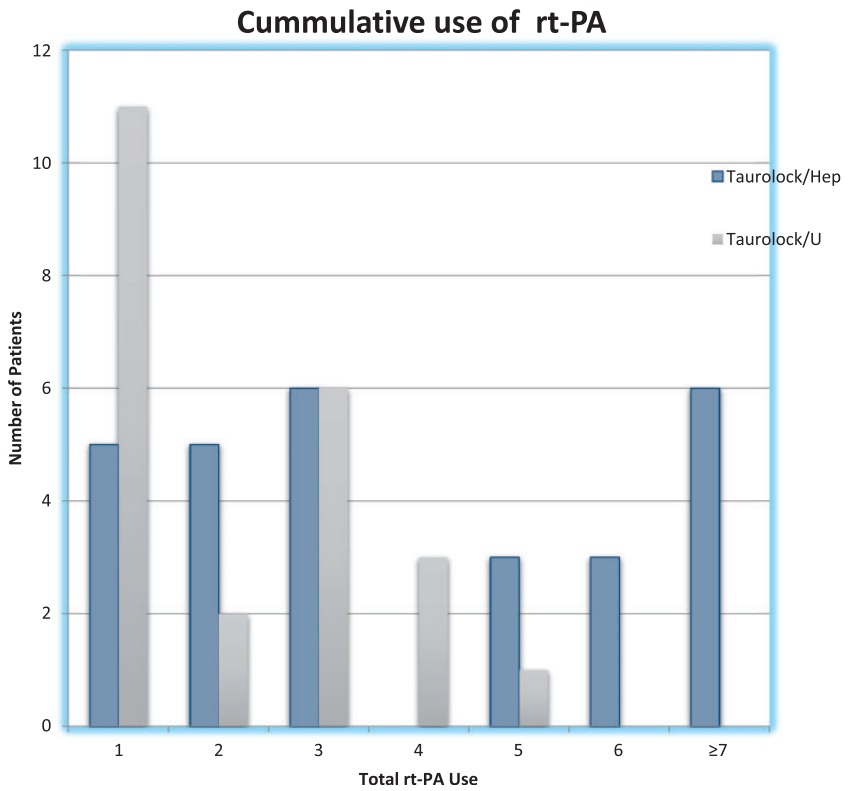

FIGURE 2: Cumulative use of rt-PA.

Table 4. Use of rt-PA for the treatment of catheter thrombosis/malfunction

Use of rt-PA	Taurolock/Hep ($n = 93$)	Taurolock/U ($n = 84$)	P-value
Use of rt-PA installation to restore catheter patency			
Number of patients	12	5	0.612
Repeated treatments, mean ± SD	2.50 ± 2.11	1.20 ± 0.44	0.200
Use of rt-PA for catheter lock			
Number of patients	27	21	0.113
Repeated use, mean ± SD	3.26 ± 2.3	2.10 ± 1.2	0.032*
Use of rt-PA for both treatment and catheter lock			
Number of patients	27	23	0.083
Repeated use, mean ± SD	4.37 ± 3.58	2.17 ± 1.30	0.006*

*$P \leq 0.05$.

studied weeks; however, the difference did not reach statistical significance (P = 0.144; data not shown). As Taurolock/U was used for catheter lock after the third weekly session before the end of the week (as per the protocol), we were interested to determine if there was any improvement in the BFR in subsequent sessions (particularly the first session of the following week). As shown in Figure 3, the mean BFR for the first hemodialysis sessions per week was persistently higher in the Taurolock/U group than in the Taurolock/Hep group for all studied weeks, and the difference approached statistical significance in the repeated-measures ANOVA test (P = 0.066). Further, weekly comparison using the independent *t*-test showed that the BFR in the first weekly session was significantly higher in the Taurolock/U group than in the Taurolock/Hep group at many of the measured time points (Figure 3).

Table 5. Impact of catheter lock solution on dialysis adequacy as measured by *Kt/V*

Time	Taurolock/Hep (mean ± SD)	Taurolock/U (mean ± SD)	P-value
Pre-study	1.31 ± 0.19	1.32 ± 0.24	0.941
First month	1.36 ± 0.17	1.43 ± 0.27	0.050*
Second month	1.39 ± 0.23	1.43 ± 0.29	0.360
Third month	1.40 ± 0.22	1.46 ± 0.28	0.170
Fourth month	1.40 ± 0.20	1.48 ± 0.30	0.134
Fifth month	1.44 ± 0.18	1.47 ± 0.33	0.586
Sixth month	1.46 ± 0.22	1.52 ± 0.37	0.335

*P ≤ 0.05.

DISCUSSION

A catheter lock solution is used to prevent thrombosis during the period between dialysis sessions and guard against catheter-related infection. However, evidence supporting the use of various lock solutions to achieve these objectives is limited. Heparin has been the traditional locking solution. The addition of 500 U of heparin/mL to taurolidine citrate (Taurolock/Hep) was found to further reduce thrombosis when compared with that with heparin alone [13].

However, in view of the persistently high rate of thrombotic complications with currently used tunneled catheters among our dialysis patients, there was a need to use new catheter lock solutions with better anticoagulant properties. In this context, the new taurolidine citrate/urokinase (Taurolock/U) solution was assessed for safety and efficacy as a novel catheter lock solution in comparison with currently used taurolidine citrate/heparin (Taurolock/Hep).

In this study, repeated episodes of acute catheter thrombosis that required catheter removal were encountered only in the Taurolock/Hep group, with no removed catheters for the same reason from the Taurolock/U group. Furthermore, a greater anticoagulant benefit of Taurolock/U was evidenced by a significantly lower number of rt-PA interventions to restore catheter patency in this group.

CRBSI is a serious complication, with an estimated incidence of 2.5–6.5 per 1000 catheter days [17]. In a recent systematic review and meta-analysis that included 13 randomized controlled trials (1770 patients, 221 064 catheter days), it was found that an antimicrobial-containing citrate lock is better than a heparin lock for the prevention of catheter-related infection, while citrate alone

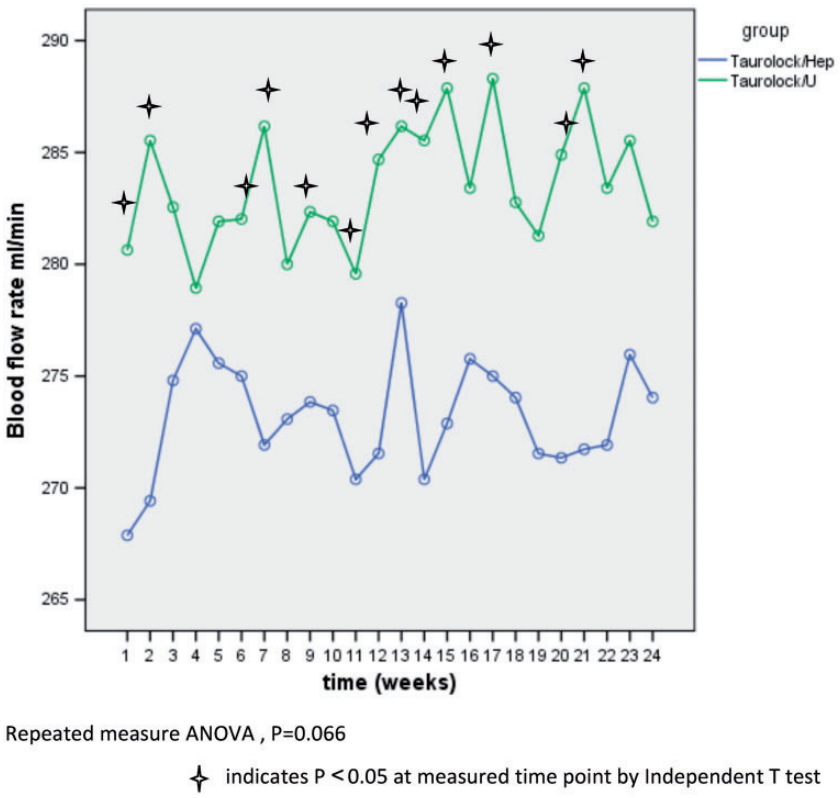

FIGURE 3: BFR at the first dialysis session/week.

fails to show a similar advantage [18]. In our study, catheter removal because of CRBSI was more common in the Taurolock/Hep group than in the Taurolock/U group, although the difference was not significant, likely due to low event rate in both groups, which was 0.3 versus 0.08 incidence/1000 catheter days in the Taurolock/Hep and Taurolock/U group, respectively.

On estimation of the possible impact of the catheter lock solution on dialysis adequacy, *Kt*/*V* values were found to be uniformly higher in the Taurolock/U group than in the Taurolock/Hep group, a finding that further confirms better catheter performance in Taurolock/U group.

Furthermore, the tunneled catheter-delivered BFR during dialysis sessions was measured and evaluated as an indicator of catheter patency in both groups. It was found that mean BFR was significantly higher in the Taurolock/U group than in the Taurolock/Hep group at many of the measured time points, a finding that adds further evidence of better tunneled catheter performance with Taurolock/U lock solution, most probably due to its higher anti-thrombotic benefit.

No reported serious adverse event or bleeding related to the lock solution was encountered during the study period in either group.

Our study strengths include being the first randomized clinical trial to assess the safety and efficacy of taurolidine citrate with urokinase as a tunneled catheter lock solution; in addition, it provided direct comparison with currently used taurolidine citrate with heparin. The limitations of the study included the relatively small number of patients, short follow-up period and being a single-center study, and further confirmation in a larger multicenter clinical trial is needed.

CONCLUSION

The use of taurolidine citrate/urokinase once a week as a tunneled dialysis catheter lock solution (with taurolidine citrate/heparin used the other two times), as compared with taurolidine citrate/heparin administered three times a week, led to reduced incidence of catheter exchanges and decreased the need for emergency thrombolysis with rt-PA.

FUNDING

This study was funded by the Medical Research Center, Hamad Medical Corporation and was approved by the IRB committee of Hamad General Hospital under the title 'Vascular Management of Tunneled Catheter Thrombosis in Hemodialysis Patients' (protocol #12180/12).

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Hoen B, Paul-Dauphin A, Hestin D *et al.* EPIBACDIAL: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol* 1998; 9: 869–876
2. Krishnasami Z, Carlton D, Bimbo L *et al.* Management of hemodialysis catheter-related bacteremia with an adjunctive antibiotic lock solution. *Kidney Int* 2002; 61: 1136–1142
3. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 Updates: Hemodialysis Adequacy, Peritoneal Dialysis Adequacy and Vascular Access. *Am J Kidney Dis* 2006; 48(Suppl 1): S1–S322
4. U.S. Renal Data System, USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010
5. Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. *Kidney Int* 2002; 62: 1109–1124
6. Trerotola SO, Johnson MS, Harris VJ *et al.* Outcome of tunneled hemodialysis catheters placed via the right internal jugular vein by interventional radiologists. *Radiology* 1997; 203: 489–495
7. Daeihagh P, Jordan J, Chen J *et al.* Efficacy of tissue plasminogen activator administration on patency of hemodialysis access catheters. *Am J Kidney Dis* 2000; 36: 75–79
8. Clase CM, Crowther MA, Ingram AJ *et al.* Thrombolysis for restoration of patency to haemodialysis central venous catheters: a systematic review. *J Thromb Thrombolysis* 2001; 11: 127–136
9. Hemmelgarn BR, Moist LM, Lok CE *et al.* Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *N Engl J Med* 2011; 364: 303–312
10. Zwiech R, Adelt M, Chrul SA. Taurolidine-citrate-heparin lock solution effectively eradicates pathogens from the catheter biofilm in hemodialysis patients. *Am J Ther* 2016; 23: e363–e368
11. Shah CB, Mittelman MW, Costerton JW *et al.* Antimicrobial activity of a novel catheter lock solution. *Antimicrob Agents Chemother* 2002; 46: 1674–1679
12. Solomon LR, Cheesbrough JS, Ebah L *et al.* A randomized double-blind controlled trial of taurolidine-citrate catheter locks for the prevention of bacteremia in patients treated with hemodialysis. *Am J Kidney Dis* 2010; 55: 1060–1068
13. Solomon LR, Cheesbrough JS, Bhargava R *et al.* Observational study of need for thrombolytic therapy and incidence of bacteremia using taurolidine-citrate-heparin, taurolidine-citrate and heparin catheter locks in patients treated with hemodialysis. *Semin Dial* 2012; 25: 233–238
14. Ray CE, Jr, Shenoy SS, McCarthy PL *et al.* Weekly prophylactic urokinase installation in tunneled central venous access devices. *J Vasc Interv Radiol* 1999; 10: 1330–1334
15. Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for hemodialysis adequacy. Update 2006. *Am J Kidney Dis* 2006; 48 (Suppl 1): S2–S90
16. Mermel LA, Allon M, Bouza E *et al.* Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 49: 1–45
17. Little MA, O'riordan A, Lucey B *et al.* A prospective study of complications associated with cuffed, tunnelled haemodialysis catheters. *Nephrol Dial Transplant* 2001; 16: 2194–2200
18. Zhao Y, Li Z, Zhang L *et al.* Citrate versus heparin lock for hemodialysis catheters: a systematic review and meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2014; 63: 479–490

Received: 8.5.2016; Editorial decision: 7.4.2017