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Effect of taurolidine citrate and unfractionated heparin on inflammatory state and dialysis adequacy in hemodialysis patients

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Abstract

Background and aim: HD patients using dialysis catheters have been associated with chronic inflammatory state. In Egypt 6.6% of HD patients use catheters, of which short term catheters represent 59.6% and 40.4% with long-term catheters. In this study, we **aimed** to assess the effect of Taurolidine citrate and unfractionated heparin combination (Taurolock-hep500™) as a lock solution compared to unfractionated heparin alone on inflammatory markers, incidence of catheter related blood stream infections (CRBSI) and dialysis adequacy in HD patients with temporary HD catheters only, for 4 weeks duration.

Methods: Sixty ESRD patients from hemodialysis units in Ain-Shams University hospitals (ASUH) at the time of catheter insertion we enrolled in our study. They were randomized into two groups: **Group 1**: Thirty patients received Taurolock-hep500™ as a catheter lock solution at the end of each hemodialysis session. **Group 2**: Thirty patients received unfractionated heparin as a catheter lock solution. hsCRP and IL-6 were measured at baseline and 1 month after using the lock solutions. Blood cultures were done in patients who developed symptoms of catheter related infections.

Results: At the end of the study, Inflammatory markers were significantly higher in group 2 (p-value: 0.045, 0.001, and 0.018 for WBCs, hsCRP and IL-6, respectively). Group 1 had better dialysis adequacy assessed by URR (p-value: 0.007 and 0.001, respectively). CRBSI were demonstrated in nine patients in group 2 (30%) in contrast to one patient only in group 1(3.3%) (p-value: 0.006) with pseudomonas being the most common isolated organism (27.7%).

Conclusion: Use of (Taurolock-hep500™) for temporary hemodialysis catheters was associated with lower levels of inflammation markers and lower incidence of CRBSI and better catheter performance.

Keywords

Catheters, CRBSI, taurolidine, inflammation, dialysis adequacy

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Introduction

Hemodialysis depends on long term and effective vascular access. The vascular access of choice is the arteriovenous fistula (AVF) while, vascular grafts and central venous catheters (CVC) are considered second and third options, due to the greater risk of infection, thrombosis, need of rescue procedures, and higher mortality and hospitalization rates.[1] AVF is the best access for longevity and has the lowest association with morbidity and mortality.[2] Short-term catheters should be used for acute dialysis and for a limited duration in hospitalized patients.[3,4] All indwelling vascular catheters develop a biofilm on internal and external surfaces with subsequent bacterial colonization that induces chronic inflammatory state shown to

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have multiple adverse effects, including resistance to erythropoietin.[5] Moreover, the use of a CVC is the major risk factor for bacteremia in HD and can result in life-threatening complications such as septic shock, endocarditis, septic arthritis, osteomyelitis, and epidural abscesses. Furthermore, the relative risk of hospitalization for infection and death is 2–3 times greater in patients using CVC compared with patients with AVF or vascular graft.[1] Heparin is the most frequently used substance in lock solutions. Antibiotic lock solutions have been presented as a potential strategy to reduce infectious complications and catheter dysfunction. The addition of antibiotics as gentamicin or taurolidine to heparin decreases CRBSI by 60%–70%, according to five recent meta-analyses.[1] Taurolidine, a broad-spectrum, antimicrobial, nontoxic agent that reduces the development of biofilm is a non-antibiotic lock alternative that does not cause bacterial resistance and has no adverse effects, even if it leaks into circulation.[6] Studies with taurolidine–citrate locks (a combination of taurolidine with 4% citrate) in tunneled catheters resulted in a reduction of CRI rates.[7,8] The addition of heparin to taurolidine–citrate has been shown to strengthen its efficiency regarding catheter patency.[9] We evaluated the effect of Taurolock-hep500™ in comparison to standard heparin locks on the inflammatory response, incidence of CRBSI and HD adequacy in HD patients with CVCs.

Patients and methods

This randomized single blinded control study included 60 adult stable HD patients from hemodialysis units at (ASUH). The randomization was simple random sampling. Patients recruited in the study were on waiting list for AVF. All patients were receiving conventional HD, 3 sessions/week, 4 h long, using standard dialysate containing bicarbonate and biocompatible low flux HD polysulfone membrane with surface area 1.4 m^2. Patients were recruited to our study at the time of catheter insertion. Dual–lumen polyurethane non-cuffed non tunneled HD catheters (Amecath® Ameco medical Industries, Egypt) were inserted under strict asepsis and sutured to the skin. The jugular insertion site was preferred as the first choice followed by the subclavian site. Catheters were placed ultrasound guided; fluoroscopy was used in some patients. Catheters were fixed with stitches and covered with steripad. Two percent chlorohexidine cleaning solution was used for exit site care. Patients with intercurrent infections, sepsis, patients receiving drugs affecting immune system like immunosuppressive drugs and patients on antibiotics during the study period were all excluded. All patients received oral and written information and signed an informed consent form. The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki and its revisions. The study was registered at ClinicalTrials.gov with reference n.: NCT03539718. Reference number for local ethics committee approval: FWA 000017585.

Study design

Patients were randomized into two groups: **Group 1** (Taurolock group); with 30 patients who received Taurolock-hep500™ (Taurolidine, 4% citrate and 500 IU/mL heparin are combined in this solution), used as a catheter lock solution at the end of each hemodialysis session and **Group 2** (heparin group); 30 patients who received unfractionated heparin (5000 i.u/mL) after hemodialysis sessions as a catheter lock solution.

Instillation of TauroLock™-HEP500: (by manufacture labeling)[10]

- Flush the device with 10 mL of saline.
- Withdraw TauroLock™-HEP500 from the container using an appropriate syringe.
- Instill TauroLock™-HEP500 slowly (not more than 1 mL per second) into the access device in a quantity sufficient to fill the lumen completely. The volume must be strictly respected. TauroLock™-HEP500 will remain inside the access device until the next treatment (for a maximum of 30 days).
- Prior to the next treatment, TauroLock™-HEP500 must be aspirated and discarded according to the institution's waste policy. Prior to initiation of the next treatment, TauroLock™-HEP500 must be withdrawn from the access device and discarded according to the institution's waste policy.
- Flush the device with 10 mL of saline.

Standard aseptic techniques were strictly followed in handling with catheters. Catheters were instilled by 10 mL of normal saline in both opening followed by either taurolock hep 500™ or unfractionated heparin 5000 iu/mL. Patients were followed up for 1 month and were monitored for clinical symptoms and signs of CRBSI (fever, rigors, hypotension, sweating) on the hemodialysis sessions.

Laboratory assessment at baseline (on catheter insertion) and after 1 months of catheters use or if any signs and symptoms of infection were present which included:

CBC, **highly sensitive CRP (hsCRP)** that was measured by high Sensitivity Enzyme Immunoassay test kit. It was measured by mg/L, with expected range in healthy adults: 0.068–8.2 mg/L, **Interleukin 6 (IL-6)** that was measured by a high-sensitivity immunoenzymatic enzyme-linked immunosorbent assay (ELISA) method with minimum detectable concentration was 2 pg/mL, **blood cultures** that were collected from peripheral vein and catheter tips in patients who developed symptoms of CRBSI, **Urea reduction ratio (URR) and blood flow rate** measured by hemodialysis machine blood pump in (mL/min). URR It is calculated as:

Table 1. Characteristics of the study population.

	Group 1 ($n=30$)	Group 2 ($n=30$)	p-value
	No. (%)	No. (%)	
Gender (*N*/%)*			
Male	14 (46.7%)	18 (60%)	0.301
Female	16 (53.3%)	12(40%)	
Age (mean ± SD)**	39.57 ± 14.30	39.30 ± 14.83**	0.944
Cause of renal failure*			
DM	6 (20%)	9 (30%)	0.542
HTN	3 (10%)	4 (13.3%)	0.353
ADPKD	0 (0%)	2 (6.7%)	0.492
Reflux	2 6.7%)	1 (3.3%)	1.000
Idiopathic	9 (30%)	3 (10%)	0.053
Stones	1 (3.3%)	3 (10%)	0.612
Chronic GN	3 (10%)	5 (16.7%)	0.424
Analgesics	4 (13.3%)	2 (6.7%)	0.671
Post-partum HGE	2 (6.7%)	1 (3.3%)	1.000

*Chi square test.
**t: Student t-test.

URR = 100% × (predialysis BUN−postdialysis BUN)/ predialysis BUN.[11]

Statistical analysis

We used SPSS (statistical package for social science) version 24 to analyze the data. Categorical data was described in terms of frequencies and percentages. Numerical data was described in terms of means and standard deviation if normally distributed. Kolmogorov–Smirnov test was used to test the normality of data. Chi square test was used to test the association between qualitative variables. Independent t test was used to measure the statistical significance of difference in means between both groups. ANOVA was used to test the statistical significance of difference between more than two groups with Bonferroni post hoc test. Pearson correlation was used to test the association between numerical variables.

Results

Characteristics of the patients are detailed in Table 1. Patients in both groups were age and sex matched (with mean age 39.57 ± 14.30 years in group 1 and 39.30 ± 14.83 years in group 2), with nearly similar duration of HD (median of 2.0 years in group 1 and 1.75 years in group 2). Diabetes mellitus was the most common cause of ESRD in both groups. As regard inflammatory markers, initially, there was no significant difference between the two groups as regard the hsCRP, IL-6 levels and TLC (p-value: 0.366, 0.90, and 0.988, respectively). While *1 month later after* catheter insertion, a significant rise in hsCRP, IL-6, and TLC in heparin group (G2) was found (p-value: 0.001, 0.018, and 0.045 for hsCRP, IL-6, and TLC, respectively), which indicated higher inflammatory/ infections state in the heparin group (G2) (Table 2). Catheter performance was assessed by URR measured and compared weekly throughout the study between the two studied groups. URR was comparable between both groups through the first 3 weeks of the study, however, the degree of change in URR showed a significant change by the fourthweek of the study in favor of Taurolock group (G1) patients (p-value: 0.008). Similarly, the weekly change of the blood flow rate turned to be significantly different between both groups by the fourth week of the study (p-value: 0.006) owing to the significant decrease in the blood flow rate in heparin group (G2) patients throughout the study (Figures 1 and 2), suggesting better catheter performance in patients using Taurolock-hep500™ as anticoagulant catheter lock solution. Catheter related blood stream infections were demonstrated by presence of fever and positive blood and catheters' cultures. During follow up, nine patients developed CRBSI in heparin group (G2) (30%) versus one patient only in Taurolock group (G1) (3.3%), (three patients in third week and six patients in fourth week) with a significant difference between both groups (p-value: 0.006). As shown in Table 3. Organisms isolated from the blood cultures are shown in Figure 3, with pseudomonas being the most common isolated organism (27.7%) followed by Coagulase-negative staph (25.9%). Weekly comparison between the two studied groups as regard weekly Blood flow (mL/min) during study period is shown in Table 4.

Table 2. Inflammatory markers in the study population (at baseline and at the end of the study).

CRP mg/L	Group 1 ($n=30$)	Group 2 ($n=30$)	U*	p
Baseline				
IQR	2.50–10.0	2.70–10.50	389.0	0.366
Median	8.0	7.35		
End of the study				
IQR.	2.70–115.0	4.30–175.0	227.5	0.001
Median	7.90	9.50		
p**	0.530	<0.001		
IL6 pg/mL				
Baseline				
IQR.	7.0–36.0	6.0–31.0	441.5	0.900
Median	16.0	17.0		
End of the study				
IQR.	9.0–175.0	10.0–275.0	290.0	0.018
Median	16.50	24.50		
p**	0.231	<0.001		
WBCs* 1000				
Baseline				
IQR.	3.20–10.0	3.40–9.20	449.0	0.988
Median	6.15	6.35		
End of the study				
IQR.	3.60–22.0	4.20–25.0	314.5	0.045
Median	6.10	8.0		
p**	0.750	0.001		

*U: Mann–Whitney test.
**Wilcoxon signed ranks test.

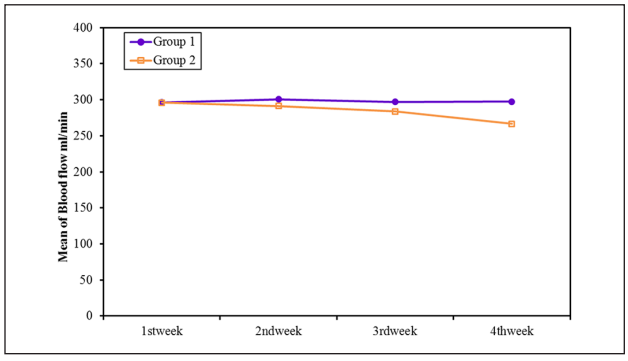

Figure 1. Changes in blood flow rate in the study population throughout the study.

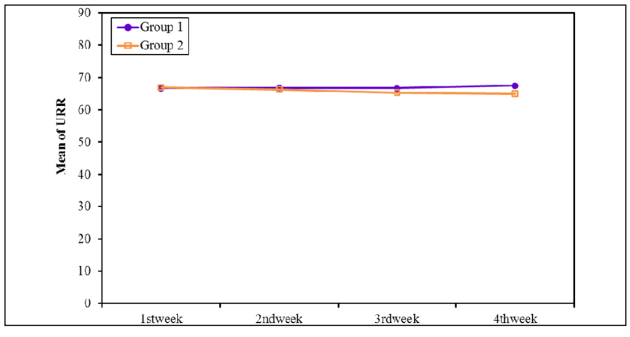

Figure 2. Changes in urea reduction ratio in the study population throughout the study.

Discussion

We found that using (taurolock-hep500™ for temporary hemodialysis catheters was associated with lower levels of inflammation and lower incidence of CRBSI in comparison to the standard heparin lock. Moreover, our results suggested better catheter performance and HD adequacy with the use of (taurolock-hep500™) compared to standard heparin lock. In Egypt, a study done by Elsharkawy et al. involved 241 hemodialysis centers from 19 Egyptian governorates, data of 16,820 patients out of 23,981 patients investigated, were assessed by 49 field investigators. The vascular access data showed 92.7% of patients were using AVF, 1.6% using AVG, and 6.6% with catheters, of which short term catheters represent 59.6% of those with catheters and 40.4% with long-term catheters.[12] Our study was conducted to evaluate the potential effects of taurolidine citrate based lock solution in comparison to standard heparin lock solution on inflammatory profile and incidence of CRBSI in ESRD patients on hemodialysis through temporary catheters being still commonly used in our hemodialysis patients. To the best of our knowledge, this was the first study to compare between (taurolock-hep500™) and unfractionated heparin in temporary hemodialysis catheters. Baseline data of the study showed that 26 patients (43.3%) (14 in group 1 and 12 in group 2) had high levels of hsCRP, while 36 patients (60%) (15 in group 1 and 19 in group 2) had high levels of IL6 but with no

Table 3. Catheter related blood stream infections (CRBSI) in the study population.

	Group 1 ($n=30$)		Group 2 ($n=30$)		χ^{2*}	p
	No.	%	No.	%		
Catheter related blood stream infections (CRBSI)	1	3.3	9	30.0	7.680	0.006

*Chi square test.

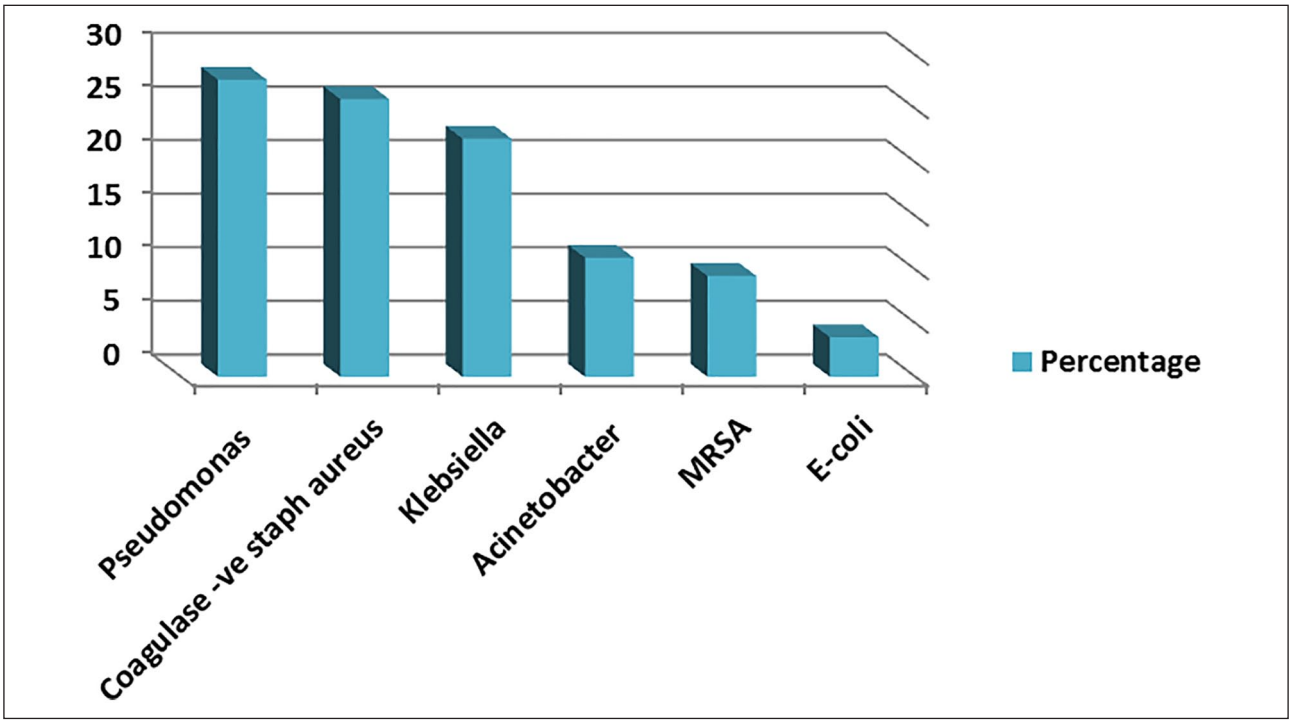

Figure 3. Different organisms isolated from blood cultures in the study population.

significant difference between both groups ($p=0.366$, 0.900, respectively), however patients had no overt symptoms or signs of infection and normal total leucocytic count. These results were in favor with the chronic sub-inflammatory state present in ESRD, as stated by Dai et al.,[13] who concluded that dialysis-related factors such as use of catheters for vascular access, poor dialyzer membrane biocompatibility, dialysate contamination, exposure to endotoxins, and back-leak of dialysate across the dialysis membrane in hemodialysis (HD) may promote a persistent, low-grade inflammatory response. At the end of the study period our results showed a significant difference in levels of inflammatory markers hsCRP and IL6 between both groups ($p=0.001$, $p=0.018$, respectively) in favor of group 1 whose patients showed lower levels of these markers. Also, on comparing the WBCs count at baseline and 1 month after using lock solutions in both groups, we found a significant rise in WBCs count in heparin group 2 ($p=0.001$), with significant difference between the two groups ($p=0.045$).These results could be explained by increase WBCs in patients who got CRBSI despite within normal range result (Table 2), suggesting a potential beneficial effect of taurolidine citrate heparin locks in reducing inflammation in comparison to standard heparin lock. These results agreed with Fontseré et al.,[14] study that compared between taurolidine citrate heparin lock solution (TCHLS) and unfractionated heparin lock solution on levels of inflammatory markers in tunneled dialysis catheters showing lower levels of hsCRP, IL6, IL10, and TNF-α with TCHLS. In addition, their study showed a significant reduction in these values 3 months after using TCHLS compared to baseline within the same group, unlike our results. This may be attributed to shorter duration in our study or the use of temporary catheters.[14] Our results were consistent with the results of Wurster et al., in their study on catheter lock solutions where they stated that the ranked risk of CRBSI is lowest with taurolidine use, then alteplase/urokinase, then citrate, then heparin. They stated that if the local risk of CRBSI is high the TCHLs should be used.[15] Our results also agreed with the results of the study by Filiopoulos et al., that was conducted to compare gentamicin/heparin (group A) and taurolidine/citrate (group

Table 4. Weekly comparison between the two studied groups as regard weekly blood flow (mL/min) during study period.

Blood flow mL/min	Group 1	Group 2	Test of sig.	*p*
First week	*n* = 30	*n* = 30		
Mean ± SD	296.3 ± 31.46	296.0 ± 29.78	*t** = 0.042	0.967
Second week	*n* = 30	*n* = 30		
Mean ± SD	300.7 ± 24.49	291.3 ± 22.55	*t** = 1.536	0.130
Third week	*n* = 30	*n* = 30		
Mean ± SD	297.0 ± 21.84	283.7 ± 33.27	*t** = 1.835	0.072
Fourth week	*n* = 30	*n* = 27		
Mean ± SD	297.3 ± 30.16	266.7 ± 39.86	*t** = 3.360	0.001
Change first week/fourth week	*n* = 30	*n* = 27		
Min.–max.	−50.0 to 100.0	−50.0 to 150.0	*U*** = 280.50	0.006
Median	0.0	0.0		
IQR	2.50	50.0		
% of change	*n* = 30	*n* = 27		
Change first week/fourth week				
Min.–max.	−33.33 to 20.0	−42.86 to 20.0	*U*** = 277.50	0.006
Median	0.0	0.0		
IQR	0.93	16.07		

B), as catheter-lock solutions, in 119 chronic hemodialysis patients and found that both antimicrobial lock solutions were superior to standard heparin-alone lock in CRBSI prevention. They concluded that gentamicin/heparin and taurolidine/citrate equally prevented CRBSI and catheter thrombosis.[16] Comparing weekly URR between both groups throughout the duration of the study, we noticed a significant difference between both groups during the fourth week ($p = 0.007$) with the difference being in favor of taurolock group (G1). We also noticed a significant gradual decline in URR in heparin group (G2) from first week toward fourth week ($p = 0.008$) suggesting better hemodialysis adequacy in group 1. During our study, blood flow measured in mL/min during midweek sessions was noticed to be significantly different between both groups during the fourth week ($p = 0.001$), again suggesting better performance of the catheter in group 1. On assessing the change in the blood flow rate on weekly basis all through the study period, group 1 patients had near constant blood flow rate with no significant decline ($p = 0.715$), unlike group 2 patients who showed a significant decline in the blood flow rate ($p = 0.006$) suggesting poorer performance of their catheters. These results may be explained by better antithrombotic effect of taurolidine + citrate + heparin lock than classic lock with heparin only (Figures 1 and 2). However, these results were against the results published by Chapla et al., in their meta-analysis in which they concluded that there was no significant difference in catheter patency in those receiving heparin only versus those treated with other lock solutions. Catheter patency did not differ between treatments in experimental studies or observational design.[17] Also, our results disagreed with the results by Allon,[18] in which they used taurolidine in conjunction with citrate as a lock solution, and they stated that it was found to be inferior to heparin for prevention of catheter dysfunction. During the study period, a total of nine patients in group 2 (three in third week and six in fourth week) versus only one patient in group 1 (in fourth week) developed symptoms and signs of CRBSI that was proved by cultures results (Figure 3). Rate of infection was 1.1 per 1000 catheter days in group 1 versus 10.3 per 1000 catheter days in group 2. This difference in the infection rate between both groups was apparently in favor of the group 1. These results were consistent with the results by Handrup et al.,[19] who showed that taurolidine significantly reduced the incidence of CRBSI compared with heparin only lock solution. Moreover, our results agreed with the results by Fontseré et al.,[14] who stated that in adult HD patients with cuffed tunneled catheters, the use of (Taurolock-hep500™) after each hemodialysis session was associated with a significant reduction in the rate of CRBSI. As regards blood cultures, the most common isolated organism was pseudomonas (27.7%) followed by Coagulase- negative staph (25.9%) then Klebsiella (22.2%), Acinetobacter (11.1), MRSA (9.4%), and E. coli (3.7%). This was unlike the results reported by Altaee et al.,[20] which showed that all the isolated organisms were Staphylococcus species, (S. aureus in six, methicillin resistant S. aureus in four, and coagulase negative Staphylococcus in seven). While Knežević et al., recorded that the most common pathogen was Coagulase negative staphylococci (42.8%), then Staphylococcus aureus 31.7%, Enterococcus faecalis 7.9%, Enterococcus spp. 3.2% and Enterococcus faecium 1.6%. Gram negative (Proteus mirabilis and Klebsiela pneumonia) 2% and polymicrobic microorganisms were isolated in 6.3% patients.[21] In conclusion, our study showed that the use of taurolidine + citrate + heparin combination was superior

to unfractionated heparin as a lock solution for temporary non-tunneled hemodialysis catheters in many aspects. Incidence of CRBSI was lower with TCHLS, supporting the beneficial antimicrobial effect of taurolidine, in addition on comparing blood flow rates and URR between both groups, results were in favor of TCHLS group (group 1) that may indicate better catheter performance and better anti-thrombotic effect of TCHLs. The limitations of the study were the small number of patients included and the short duration of follow up period.

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