TauroLock™

Clinical Papers Summary - Renal

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FOREWORD

TauroLock™ is the most clinically reviewed catheter locking solution in the market – with over ten years of clinical history, TauroLock meets the requirements set up by the different guidelines in infection prevention as well as uniquely reducing occlusion complications whilst offering a safe alternative to other solutions in the market.

This clinical review booklet collates some of the abstracts of relevant clinical papers published to date as well as a brief summary of the guidelines and recommendations in the prevention of catheter related sepsis in haemodialysis worldwide.

Should you require any copies of these papers, please contact your local representative.

CONTENT

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GUIDELINES

1.1. German Dialysis Standard 2014

German Society in Nephrology in co-operation with the Association of German Kidney Centres and with the Society for Paediatric Nephrology (GPN)

… Between dialysis treatments the central venous access device may be blocked using a diluted heparin solution. Heparin, however, does not have any antibacterial properties. Antibacterial lock solutions should therefore be preferred, which reduce the rate of catheter-related bacteraemia considerably. The use of antibiotics cannot be recommended due to the potential development of resistance. Alternatively, highly concentrated citrate (30% or 45%) or taurolidine-citrate solutions can be used. Due to the risk of severe cardiac arrhythmias highly concentrated citrate must be strictly administered by trained staff according to the instructions of the manufacturer.

1.2. Hygiene Guidelines 2008 Completing 'GERMAN DIALYSIS STANDARD 2006'

German Workgroup for Clinical Nephrology in co-operation with the Verband Deutsche Nierenzentren der DD nÄ e.V. and the Society for Paediatric Nephrology: Hygiene Guidelines 2008 completing the German Dialysis Standard 2014, Chapter 2.5.1 Central Venous Catheters

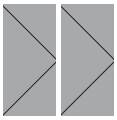
… Between dialysis treatments the central venous access device may be blocked using a diluted heparin solution. Heparin, however, does not have any antibacterial properties. Antibacterial lock solutions should therefore be preferred, which reduce the rate of catheter-related bacteraemia considerably. The use of antibiotics cannot be recommended due to the potential development of resistance. Alternatively, highly concentrated citrate (30% or 45%) or taurolidine-citrate solutions can be used. Due to the risk of severe cardiac arrhythmias highly concentrated citrate must be strictly administered by trained staff according to the instructions of the manufacturer.

1.3. National Kidney Foundation (NKF): KDOQI Guidelines

KDOQI Guideline (2006) Guideline 7

...As shown in table 24, silver impregnation of the catheter was ineffective, whereas a gentamycin/citrate solution and a taurolidine solution used as interdialytic antibiotic locks were effective...

TABLE 24. PROPHYLAXIS FOR DUAL-LUMEN TCC-RELATED INFECTIONS

Author, Year	Study Design	N	Follow-up (Maximum)	Applicability	Intervention 1	Intervention 2	Infection rate			Quality
							Treatment	Control	Result	
Trerotoia 1998 560	RCT	100	730 d		Silver coated catheter	Non-silver coated catheter	1.1	1.4	NS	●
Dogra 2002 561	RCT	83 (112 catheters)	288 d		Genlamicin + citrate CLS (40mg/mL and 3.13% citrate)	Heparin CLS (5000 U/mL)	0.3	4.2	+	●
Allon 2003 562	Prospective with concurrent control	50	90 d		1.35% taurolldine and 4% sodium citrate CLS	Heparin CLS (5000 U/mL)	0.6	5.3	+	○

CLS = catheter lock solution; NS = not significant; RCT = randomized controlled trial; TCC = tunneled cuffed catheter;
+ Statistically significant beneficial effect of treatment compared to control (or intervention 1 vs. intervention 2)
a. Per 1000 catheter days

1.4. Diagnosis, prevention and treatment of haemodialysis catheter-related bloodstream infections (CRBSI): a position statement of European Renal Best Practice (ERBP)

Vanholder, R. et al. (2010) ERBP Recommendation B.3.1. NDT Plus. 3: 234-246

....The preventive use of antimicrobial locks is advocated to reduce the rate of CRBSI....

1.5. Vascular Access for Haemodialysis

Kumwenda M., Mitra, S., Reid, C. (2015) Minimising the risk of catheter related infection. UK Renal Association

...We recommend that an antimicrobial or antibiotic lock solution be used to reduce catheter related bacteraemia and other infections.... (1A)

1.6. Guidelines for the Prevention of Intravascular Catheter-related Infections, 2011

CDC. (2011) Centre of Disease Control, USA.

...Use prophylactic antimicrobial lock solution in patients with long term catheters who have a history of multiple CRBSI despite optimal maximal adherence to aseptic technique...

Anticoagulants: Do not routinely use anticoagulant therapy to reduce the risk of catheter-related infection in general patient populations [139]. Category II

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2.1. A Meta-analysis of Haemodialysis Catheter Locking Solutions in the Prevention of Catheter-Related Infection

Jaffer, Y. et al. (2008) Kidney Disease 51: 233-241.

Background: Catheter-related infection (CRI) is associated with increased all-cause mortality and morbidity in haemodialysis patients and may be reduced by using antimicrobial lock solutions (ALSs).

Study Design: We performed a meta-analysis of studies identified from a search conducted in February 2007 of the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, databases of ongoing trials, major renal journals, and reference lists of relevant reports.

Setting & Population: Patients receiving acute or long-term haemodialysis through a tunneled or non-tunneled central venous catheter. Selection Criteria for Studies: We included all prospective randomised studies that compared ALS with heparin.

Intervention: Administration of antibiotic and/or antimicrobial catheter locking solution.

Outcome Measures: Primary outcome was CRI rate in patients using ALSs compared with those using heparin alone. We also examined effects of ALS use on mortality, adverse events, and catheter thrombosis.

Results: 7 studies were identified with a total of 624 patients and 819 catheters (448 tunneled, 371 non-tunneled). CRI was 7.72 (95% confidence interval, 5.11 to 10.33) times less likely when using ALS. There were no consistent suggestions of adverse outcomes with ALS use; in particular, rates of catheter thrombosis did not increase. There was no evidence of antibiotic resistance developing during a maximum follow-up of 12 months.

Limitations: The major limitation of this review is the relatively short duration of follow-up of the included studies, which does not allow complete reassurance regarding the development of antibiotic resistance. Lack of direct comparison means the determination of the most efficient ALS is not possible.

Conclusions: This review confirms that antibiotic locking solutions reduce the frequency of CRI without significant side effects.

2.2. Taurolidine Lock Solutions for the Prevention of Catheter-Related Bloodstream Infections: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

Yong Liu, Y. et al (2013) PLoS ONE. 8(11): e79417.

Results: Six randomised controlled trials (RCTs) conducted from 2004 through 2013 involving 431 patients and 86078 catheter days were included in the review. TLS were significantly associated with a lower incidence of CRBSIs when compared to heparin lock solutions (Risk Ratio [RR], 0.34; 95% Confidence Interval [CI], 0.21-0.55). Use of TLS significantly decreased the incidence of CRBSIs from gram-negative (G-) bacteria (P=0.004; RR=0.27, CI=0.11-0.65), and was associated with a non-significant decrease in gram-positive (G+) bacterial infections (P=0.07, RR=0.41, CI=0.15-12.09). No significant association was observed with TLS and catheter-associated thrombus (RR=1.99, CI=0.75-5.28).

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2.3. Prevention of dialysis catheter-related sepsis with a citrate–Taurolidine-containing lock solution

Michiel, G, H., Betjes and van Agteren, M. (2004) Nephrology Dialysis Transplant. 19:1546-1551.
Department of Internal Medicine, Division of Nephrology, Erasmus Medical Center, Dijkzigt Rotterdam.

Background: The use of haemodialysis catheters is complicated by catheter-related sepsis. Intraluminal colonisation of the catheter with bacteria is important in the pathogenesis of catheter-related sepsis. The use of a catheter lock solution containing the antimicrobial taurolidine might prevent bacterial colonization, thereby reducing the incidence of catheter-related sepsis.

Methods: In a randomized prospective trial, patients receiving a dialysis catheter were included and catheters were locked with either heparin or a taurolidine-citrate solution. Blood cultures drawn from the catheter lumen were routinely taken every 2 weeks and at time of removal of the catheter to detect bacterial colonisation. Catheter-related sepsis and exit-site infections were registered for both groups.

Results: A total of 76 catheters were inserted in 58 patients. The incidence of catheter colonisation progressed slowly over time with no differences between dialysis catheters filled with heparin or taurolidine-citrate solution. The number of exit-site infections was also similar between both groups. In the heparin group, four cases of catheter-related sepsis occurred as opposed to no sepsis episodes in the patients with catheters locked with the taurolidine-citrate solution ($P<0.5$). No side effects with the use of taurolidine-citrate catheter lock solution were noted.

Conclusions: This study shows that catheter filling with a solution containing the antimicrobial taurolidine may significantly reduce the incidence of catheter-related sepsis. taurolidine appears to be effective and safe and does not carry the risk for side effects that have been reported for other antimicrobial lock solutions containing gentamicin or high concentrations of citrate.

2.4. Observational Study of Need for Thrombolytic Therapy and Incidence of Bacteremia using Taurolidine-Citrate-Heparin (TCH), Taurolidine-Citrate (TC) and Heparin Catheter Locks in Patients Treated with Hemodialysis

Solomon, L, R. et al. (2011) Sem Dialysis 25 (2):233-8

Background: Catheter-related blood stream infections may be reduced by interdialytic locking with taurolidine, a nontoxic antimicrobial agent. A formulation of 1.35% taurolidine in 4% citrate (TC) is associated with a greater need for thrombolysis to maintain catheter patency than 5000 U/ml heparin. Our aim was to determine whether addition of 500 Units/ml of heparin to TC reduces the need for thrombolysis.

Methods: TCH (1.35% taurolidine, 4% citrate and 500 U/ml heparin) was compared to TC and Heparin 5000 U/ml using retrospective data. Hundred and six adult haemodialysis patients with internal jugular tunneled intravascular catheters using TCH were compared with 34 patients using TC and 34 patients using heparin 5000 U/ml respectively.

Results: TCH reduced the need for thrombolysis compared to TC (hazard ratio, 0.2; 95%CI: 0.06, 0.5; $p < 0.001$) and was not significantly different from heparin 5000 U/ml (hazard ratio, 1.4; 95%CI: 0.5, 3.9; $p = 0.5$). The bacteremia rates from all causes were 1.33, 1.22 and 3.25 per 1000 catheter- days ($p < 0.001$) in the TCH, TC and heparin groups respectively.

Conclusions: Addition of 500 U/ml heparin to TC reduces the need for thrombolysis without increasing bacteremia and may achieve patency comparable to heparin 5000 U/ml.

2.5. Prophylaxis against Dialysis Catheter Related Bacteraemia with a Novel Antimicrobial Lock Solution

M. Allon. (2003) , Clin. Infect Dis , 36:1539-1544.

Background: Catheter-related bacteraemia, a frequent complication in patients who are undergoing haemodialysis, may be prevented by eradication of the catheter biofilm. Catheter lock solution (CLS) is an investigational preparation containing taurolidine, a biocompatible antimicrobial agent, and citrate, an anticoagulant agent.

Methods: CLS was instilled into the catheter lumens after each dialysis session for 20 catheter-dependent haemodialysis patients. Catheter outcomes were compared with those observed in 30 concurrent control patients whose catheters were instilled with heparin.

Results: Bacteraemia-free survival at 90 days was higher among patients who received CLS than among control patients who received

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heparin (94% vs. 47%; P < .001). Unassisted catheter patency (without tissue plasminogen activator instillation) was lower among patients who received CLS than among control patients (32% vs. 76%; P < .001).

Conclusions: CLS dramatically reduces the frequency of catheter-related bacteraemia among patients undergoing haemodialysis, although there is an increased requirement for thrombolytic interventions to maintain catheter patency.

2.6. Two Years' Experience with Dialock and CLS™ (A New Antimicrobial Taurolidine-Citrate Lock Solution)

Sodemann, K., Hans, D., Polaschegg, Feldmer, B. (2001) Blood Purification. 19:251-2547

Background: This paper reports about results of a German Dialock/CLS (taurolidine-citrate lock), the first study using an antimicrobial catheter locking solution in a large number of patients.

Results: 42 patients (60% had no infection and this number increases to 45 (64%) when infections occurring within 30 days after implantation are omitted. Excluding these early events, 25 patients experienced a total of 30 infections. The first 7 of these pocket infections caused the loss of the Dialock catheter. After initiation of local treatment with gentamicin no further devices were lost due to pocket infection. No infection events were recorded within the last 3 months although the expectation rate calculated on the previous occurrences would be approximately 4 pocket infections. This may be related to increased nursing care to avoid infection. The study results in a normalised pocket infection rate of 0.8 per 1,000 catheter days and a normalised rate of bloodstream infections of 0.25 per 1,000 days.

2.7. A New Haemodialysis Catheter Locking Agent reduces infections in Haemodialysis Patients

Taylor, C., Cahill, J., Gerrish, M., Little, J. (2008) Journal of Renal Care. 34 (3), 116-120.

Background: Intravenous catheters for haemodialysis increase the risk of sepsis. This study investigates the use of a taurolidine-citrate catheter locking agent for patients receiving hospital-based haemodialysis, auditing the number and cost of infections before and after its introduction.

Methods: The incidence and cost of treatment of catheter sepsis occurring in all patients receiving haemodialysis via a line were investigated over 6-month periods before and after introducing the taurolidine-citrate line-locking agent.

Results: A reduction of 4.62 infections per 1000 catheter days, or 88.5%, was shown after the introduction of the new line-locking agent. The total costs of line infections in the first 6 months were ¤ 52.500 (£ 41.000); after the introduction of the taurolidine-citrate locks, these reduced to ¤ 33.300 (£ 26.000), a reduction of ¤ 19.200
(£ 15.000).

Conclusions: The use of taurolidine-citrate haemodialysis catheter locking agent in our haemodialysis population has significantly reduced the line sepsis rate, with a positive impact on morbidity, mortality and cost.

2.8. Approaches to Prolong the Use of Uncuffed Haemodialysis Catheters: Results of a Randomised Trial

Filiopoulos, V. et al. (2011) Department of Nephrology. Nephrology; 33:260-268.

Background: Use of uncuffed catheters (UCs) in haemodialysis patients is common practice. An antibiotic lock has been recommended to prevent catheter-related bacteremia (CRB), although insufficient data are available about the appropriate antimicrobial agent and dose with prolonged use of UCs.

Methods: This open-label randomised study was conducted to compare gentamicin/heparin (group A) and taurolidine-citrate (group B), as catheter lock solutions, in 119 chronic haemodialysis patients in whom a total of 150 UCs were placed. A well-matched historical control group (heparin) included 67 UCs in 58 patients (group C).

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Results: CRB episodes developed in 6 and 8 patients in groups A and B, respectively, significantly fewer than in group C (20 patients). Cumulative CRB-free catheter survival at 90 days was 82% for A and 78% for B, which is significantly higher than the 26% for C. Similar Gram-positive infection rates were found in all groups. The Gram-negative infection rate was significantly lower in B compared to C. No significant differences in thrombosis rates were observed between the groups.

Conclusions: Gentamicin/heparin and taurolidine-citrate, used for locking UC, were similarly effective at preventing CRB and catheter thrombosis for up to 3 months, until a functional permanent vascular access became available. Both antimicrobial lock solutions were superior to heparin in CRB prevention with similar thrombosis rates.

2.9. Tunneled catheters with Taurolidine-citrate-heparin lock solution significantly improve the inflammatory profile of haemodialysis patients

Fonseré N. et al. (2014) Antimicrobial Agents Chemotherapy. 58(7): 4180-4

Methods: High sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), IL-10 and tumor necrosis factor alpha (TNF-a) were measured in serum, and levels of mRNA gene expression of IL-6, IL-10 and TNF-a were analysed in peripheral blood mononuclear cells (PBMC). Samples were obtained at baseline and again after 3 months' use of taurolidine-citrate-heparin lock solution (TCHLS) in 31 haemodialysis patients.

Results: The rate of catheter-related bloodstream infections (CRBSI) was 1.08 per 1000 catheter days in the heparin period and 0.04 in the TCHLS period ($P<0.023$). Compared with the baseline data, serum levels of hs-CRP and IL-6 showed median percent reductions of 18.1% and 25.2%, respectively ($P<0.01$), without significant changes in TNF-a or IL-10 levels. Regarding cytokine gene expression in PBMC, the median mRNA expression levels of TNF-a and IL-6 decreased by 20% ($P<0.05$) and 19.7% ($P<0.01$) respectively, without changes in IL-10 expression levels.

Conclusions: The use of TCHLS to maintain the catheter lumen sterility significantly reduces the incidence of CRBSI and improves the inflammatory profile in haemodialysis patients with tunneled catheters. Further studies are needed to evaluate the potential beneficial effects on clinical outcomes.

2.10. Taurolidine-citrate-heparin catheter lock solution reduces staphylococcal bacteraemia rates in haemodialysis patients.

Murray, E, C. et al. (2014) QJM. 107(12):995-1000

Methods: Data was collected each calendar quarter through a structured query language interrogation of the renal unit electronic patient record, with staphylococcal bacteraemic events expressed per 1000 vascular access exposed days. Comparison between pre and post-intervention periods were made by student's t-testing.

Results: Two hundred and thirty-nine staphylococcal bacteraemic events occurred over a total of 424 835 HD days in 565 patients; 81 events in 289 389 arterio-venous fistula or graft (AVF/AVG) HD days and 158 events in 135 446 TCVC HD days. Following the introduction of taurolodine-citrate-heparin, bacteraemic events in patients dialysing via a TCVC fell from 1.59/1000 HD days to 0.69/1000 HD days, $P=0.004$. The staphylococcal bacteraemic rate in AVF/AVGs remained unchanged; 0.30 versus 0.26/1000 HD days, $P=0.52$.

Conclusions: Replacing heparin 5000 IU with taurolidine-citrate-heparin as catheter lock solution was associated with a statistically significant 56% reduction in staphylococcal bloodstream infection rates in our TCVC HD population.

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2.11. A Randomised Controlled Trial of Taurolidine Citrate versus Taurolidine Urokinase Lock to Prevent Catheter Related infections in Haemodialysis Patients

Hamad, A.. et al. (2016) Nephrology Dialysis Transplantation 31 (Supplement 1): i259-i273, doi: 10.1093/ndt/gfw173.29

Background: The use of tunneled catheters in haemodialysis is one of the leading causes of morbidity and mortality among dialysis patients. The prevelence of catheter related infections (CRI) range from 2.5 to 5.5 incidence/1000 catheter days, or 0.9 to 2 episodes/patient/year. There is an increased relative risk for infection-related hospitalisation and death by 2-3 folds in dialysis patients using catheters compared with those using fistula or graft. Efforts have been made to prevent and decrease the incidence of CRI. Taurolidine-citrate is a novel antibacterial agent that shows promising results to prevent CRI when used as locking agenct. We carried out a comparative study using taurolidine-citrate with heparin (TauroLock/Hep) as a catheter lock solution versus taurolidine-citrate with urokinase (TauroLock/U) in regard to prevention of CRI.

Methods: This is a prospective randomised controlled trial that included all patients who were undergoing ambulatory regular hemodialysis in Qatar with tunneled catheter. All patients were randomised to receive TauroLock/Hep or TauroLock/U on 1:1 basis using a computer-generated program. Patients were followed for 6 months. Episodes of CRI, catheter removal, time to removal and days of hospital stay were analysed.

Results: 177 patients participated, 30 patients did not complete the study (fistula cannulation, death, transferring to peritoneal dialysis) but were included in the final analysis, 93 patients in TauroLock/Hep and 84 in TauroLock/U group. Age, sex, catheter age, blood flow rates and venous pressure were recorder before the study and use of antiplatelet or Warfrin and co-morbidities did not differ between the two groups. 4 catheters were removed in TauroLock/Hep group due to CRI with mean time to removal of 170 days and mean length of stay (LOS) in hospital of 5 days. CRI rate was 0.3 incidence/1000 catheter days in the TauroLock/Hep group versus 0.08 incidence/1000 catheter days in the TauroLock/U. There were no reported serious adverse events or bleeding reported during study.

Conclusions: In this study to compare Taurolock/Hep to TauroLock/U, both groups showed reduction in CRI well below the current recommendation. There was a further significant decrease in CRI in TauroLock/U group versus the TauroLock/Hep group. This result supports recent studies showing prevention of CRI with recombinant tissue plasminogen activator catheter (rt-PA) lock. The use of urokinase in addition to TauroLock provided a cheaper and practical alternative to rt-PA to decrease CRI. LOS in the hospital for CRI was significantly lower in TauroLock/U versus TauroLock/Hep. Our results were clinically significant but only close to statistically significant because of the low number of events in both categories.

2.12. Antimicrobial Activity of a Novel Catheter Lock Solution

Shah, C, B. et al. (2002) Antimicrobial Agents Chemotherapy. 46; 1674-1679

Background: Intravascular catheter-associated bloodstream infections significantly increase rates of morbidity and hospital costs. Microbial colonisation and development of biofilms, which are known to be recalcitrant to antibiotic therapy, often lead to the loss of otherwise patent vascular access systems.

Methods: We evaluated a new Taurolidine-citrate based catheter lock solution (Neutrolin; Biolink Corporation, Norwell, Mass.) for its activity against planktonic microbes, antimicrobial activity in a catheter model, and biofilm eradication activity. In studies of planktonic microbes, after 24 h of contact, 675 mg of taurolidine-citrate solution per litre caused >99% reductions in the initial counts of Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa, and Entercoccus faecalis. A solution of 13,500 mg/litre was cidal for Candida albicans. Ports and attached catheters inoculated with 50 to 600 CFU of these bloodstream isolates per ml were locked with heparin or the taurolidine-citrate solution. After 72 h, there was no growth in the taurolidine-citrate-treated devices but the heparin-treated devices

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exhibited growth in the range of 6 ¤ 102 to 5 ¤ 106 CFU/ml. Biofilms were developed on silicone disks in modified Robbins devices with broth containing 6% serum (initial counts, 106 to 108 CFU/cm2).

The axenic biofilms were treated for 24 h with taurolidine-citrate or heparin.

Results: Taurolidine-citrate exposure resulted in a median reduction of 4.8 logs, whereas heparin treatment resulted in a median reduction of 1.7 logs ($P < 0.01$). No significant differences in the effects of the two treatments against P. aeruginosa and C. albicans were observed.

Conclusions: These findings suggest that taurolidine-citrate is a promising combination agent for the prevention and treatment of intravascular catheter-related infections.

2.13. Activities of Taurolidine In Vitro and in Experimental Enterococcal Endocarditis

Torres-Viera, C.. et al. (2000) Antimicrobial Agents and Chemotherapy. 44; 1720-1724.

Results: In vitro, the antimicrobial agent taurolidine inhibited virtually all of the bacteria tested, including Vancomycin-resistant enterococci, oxacillin-resistant staphylococci, and Stenotrophomonas maltophilia. At concentrations between 250 and 2,000µg/mL, taurolidine was not effective in experimental endocarditis.

Conclusions: While it appears unlikely that this antimicrobial would be useful for systemic therapy, its bactericidal activity and the resistance rates found (<10-9) are favourable indicators for its possible development for topical use.

3.1. A Randomised Double-Blind Controlled Trial of Taurolidine-Citrate Catheter Locks vs. Heparin (5000 IU/mL) for the Prevention of Bacteremia in Patients Treated With Haemodialysis

Solomon, L, R. et al. (2010) American Journal of Kidney Disease. Vol 55, No 6 (June); pp 1060 -1068.

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Background: Bacteremia is a major cause of morbidity in patients using intravascular catheters. Interdialytic locking with antibiotics decreases the incidence of bacteremia, but risks antibiotic resistance. Taurolidine is a non-toxic broad-spectrum antimicrobial agent that has not been associated with resistance. Preliminary evidence suggests that taurolidine-citrate locks decrease bacteremia, but cause flow problems in established catheters.

Study Design: Double-blind randomised controlled trial.

Intervention: Interdialytic locking with taurolidine and citrate (1.35% taurolidine and 4% citrate) compared with heparin (5,000 U/mL) started at catheter insertion.

Setting & Participants: 110 adult haemodialysis patients with tunneled cuffed intravascular catheters inserted at 3 centres in Northwest England.

Outcomes & Measurements: Primary end points were time to first bacteremia episode from any cause and time to first use of thrombolytic therapy.

Results: There were 11 bacteremic episodes in the taurolidine-citrate group and 23 in the heparin group (1.4 and 2.4 episodes/1,000 patient-days, respectively; p = 0.1). There was no significant benefit of taurolidine-citrate versus heparin for time to first bacteremia (hazard ratio, 0.66; 95% CI, 0.2-1.6: p = 0.4). taurolidine-citrate was associated with fewer infections caused by Gram-negative organisms than heparin (0.2 vs 1.1 infections/1,000 patient-days; p = 0.02); however, there was no difference for Gram-positive organisms (1.1 vs 1.2 infections/1,000 patient-days; p = 0.8). There was a greater need for thrombolytic therapy in the taurolidine-citrate versus heparin group (hazard ratio, 2.5; 95% CI, 1.3-5.2; p = 0.008).

Limitations: Small sample size. The study included bacteremia from all causes and was not specific for catheter-related bacteremia.

Conclusions: Taurolidine-citrate use did not decrease all-cause bacteremia and was associated with a greater need for thrombolytic treatment. There was a decrease in infections caused by Gram-negative organisms and a trend to a lower frequency of bacteremia, which warrants further study.

3.2. Observational Study of Need for Thrombolytic Therapy and Incidence of Bacteremia using Taurolidine-Citrate-Heparin (TCH), Taurolidine-Citrate (TC) and Heparin Catheter Locks in Patients Treated with Haemodialysis

Solomon, L. R. et al (2011) Sem Dial 2011.

Background: Catheter-related blood stream infections may be reduced by interdialytic locking with taurolidine, a non toxic antimicrobial agent. A formulation of 1.35% taurolidine in 4% citrate (TC) is associated with a greater need for thrombolysis to maintain catheter patency than 5000 U/ml heparin. Our aim was to determine whether addition of 500 Units/ml of heparin to TC reduces the need for thrombolysis.

Methods: TCH (1.35% taurolidine, 4% citrate and 500 U/ml heparin) was compared to TC and Heparin 5000 U/ml using retrospective data. 106 adult hemodialysis patients with internal jugular tunneled intravascular catheters using TCH were compared with 34 patients using TC and 34 patients using heparin 5000 U/ml respectively. Outcomes were time to first use of thrombolysis and bacteremia rates. TCH reduced the need for thrombolysis compared to TC (hazard ratio, 0.2; 95%CI: 0.06, 0.5; p < 0.001) and was not significantly different from heparin 5000 U/ml (hazard ratio, 1.4; 95%CI: 0.5, 3.9; p = 0.5).

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Results: The bacteremic rates from all causes were 1.33, 1.22 and 3.25 per 1000 catheter- days ($p < 0.001$) in the TCH, TC and heparin groups respectively.

Conclusions: Addition of 500 U/ml heparin to TC reduces the need for thrombolysis without increasing bacteremia and may achieve patency comparable to heparin 5000 U/ml.

3.3. Sodium Citrate Versus Heparin Catheter Locks for Cuffed Central Venous Catheters: A Single-Centre Randomised Controlled Trial.

Power, A. et al. (2009) American Journal of Kidney Diseases, Vol 53 (6)

Background: Sodium citrate has antibacterial and anticoagulant properties that are confined to the catheter when used as a catheter lock. Studies of its use as a catheter lock have suggested its efficacy in preventing infection and bleeding complications compared with sodium heparin.

Study Design: Open-label randomised controlled trial of 2 catheter locks to examine the hypothesis that sodium citrate catheter locks will reduce catheter-related bacteremia and exit-site infection.

Settings & Participants: 232 consenting long-term haemodialysis patients in 4 satellite dialysis units to a large dialysis program with protocolised treatment and targets. All patients were using twin-catheter single lumen Tesio-Caths (MedComp, Harleysville, PA).

Intervention: 6 months' use of 46.7% sodium citrate (citrate) or 5% heparin (heparin) locked post-dialysis in the dead space of the central venous catheter.

Outcomes & Measurements: Primary end point of catheter-related bacteremia and exit-site infection. Secondary end points of catheter thrombosis defined by the use of urokinase lock and infusion, new catheter insertion, catheter-related admission, blood transfusions, parenteral iron, and erythropoietin requirements.

Results: Catheter-related bacteremia did not differ in the 2 groups, with an incidence of 0.7 events/1,000 catheter-days. There was no significant difference in rates of exit-site infection (0.7 versus 0.5 events/1,000 catheter-days; P _ 0.5).

The secondary end point of catheter thrombosis defined by the use of a urokinase lock was significantly more common in the citrate group, with an incidence of 8 versus 4.3/1,000 catheter-days (P _ 0.001). Other secondary end points did not differ. Citrate treatment was curtailed compared with heparin because of a greater incidence of adverse events, with a mean treatment duration before withdrawal of 4.8 _ 2.0 versus 5.7 _ 1.2 months, respectively (P _ 0.001).

Limitations: Low baseline catheter-related bacteremia and exit-site infection event rates may have underpowered this study. High adverse-event rates may have been related to high-concentration citrate that led to increased overspill and reduction in lock volume. This may also explain the increased rates of thrombosis in this group.

Conclusion: Widespread and long-term use of 46.7% citrate catheter locks with Tesio-Cath access is not justified by this study.

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Comments to Studies 3.1 to 3.3:

A) Prevention of Infection

1. The authors of 3.1 on last page conclude: "Our study may under-estimate the reduction of CRBSI because we included ALL bacteremic episodes. Ideally, a diagnosis of CRBSI would have been based on simultaneous quantitive central and peripheral cultures." Although including ALL Infections the reduction was almost statistically significant (p=0.1).

2. The study includes one infection in the taurolidine-citrate group although the patient has lapsed trial locks for 3 weeks beforehand and and was treated with heparin before the infection (RESULTS, page 1063, left column).

3. The distribution of Gram-negative organisms was skewed. Infections in the taurolidine-Citrate arm were typically from endogenous flora (DISCUSSION, page 1066, left column) whereas in the heparin at least 9 infections were caused by organisms often associated with environmental reservoirs. This result suggests that there was protection against bacterial contamination during connect-disconnect procedures (DISCUSSION, page 1066, left column)

B) Patency of the catheter

1. Regarding occlusion, the study by Soloman et al. (2010) confirms the results of the study by Power et al. (2009), which shows that lock solutions based only on citrate as anticoagulant are increasing the need of thrombolytic interventions in dialysis. This effect is similar at either 4% or 46.7% (see table below):

Author	Lock solution	No. of patient	Use of urokinase in the citrate group	p-value
Solomon et al., 2010	Taurolidine-citrate (4%) (TauroLock)	110	9 per 1000 catheter days (vs. 4 in the heparin group)	P= 0.008
Power et al., 2009	Citrate 46.7%	232	8 per 1000 catheter days (vs. 4 in the heparin group)	P= 0.001

*A. Power et al, American Journal of Kidney Diseases, Vol 53 (6), 2009, 1-34-1041

2. Results with TauroLock Hep500 (3.2. Soloman et al., 2011) confirm the supportive effect of additional 500 IU/mL heparin. Patency is significantly improved versus lock solutions only containing citrate as an anticoagulant (e.g TauroLock) and comparable to undiluted heparin (5000 IU/mL).

PATENCY

3.4. Prophylactic Urokinase in the Management of Long-Term Venous Access Devices in Children: A Children's Oncology Group Study

Dillon, P, D. et al (2004). Clin Oncology (22), 2718-2723.

Purpose: Infection and thrombosis are serious complications of long-term vascular access devices in children undergoing chemotherapy. Since routine fibrinolytic therapy may decrease these complications, the purpose of this study was to compare the efficacy of an every-2-week administration of urokinase with standard heparin flushes in reducing the incidence of device-related infections and occlusions.

Materials and Methods: This study was a prospective, randomised phase III multicenter trial conducted by the Children's Cancer Group, in which patients with implantable ports or tunneled catheters received either urokinase or heparin every 2 weeks for 12 months. Study end points were time to first occlusion or time to first device-related infection.

Results: 577 patients from 29 institutions were enrolled, of whom 51% had external catheters and 49% had ports. Urokinase administration resulted in fewer occlusive events than heparin (23% v 31%; P = .02), a longer time to first occlusive event (log-rank analysis, P = .006), and a 1.6-fold difference in the rate of occlusive events (Poisson regression, P = .003). Similar results were noted when comparing ports and tunneled catheters. The urokinase group also had a difference of 1.4 in the rate of infection (Poisson regression, P = .05) and longer time to first infection (log-rank, P = .07), but the difference was significant only in tunneled catheters.

Conclusion: Urokinase administration every 2 weeks significantly affects the rate of occlusive events inports and tunneled catheters and of infectious events in external catheters compared with heparin administration.

3.5. Review and update of the use of Urokinase in the prevention and management of CVAD-related complications in paediatric oncology patients

Simon, A. et al (2008) American Journal of Infection Control, Vol. 36 (1), 54-58.

Paediatric oncologists from Germany systematically reviewed the literature, considering the use of urokinase in paediatric oncology patients published since 1998 and came to the following conclusions. The use of urokinase to prevent central venous access device (CVAD) related infections in paediatric cancer patients represents an evidence-based approach, at least in external, tunneled catheters (eg, Hickman, Broviac). The effectiveness of urokinase prophylaxis in decreasing infections and thrombotic events is probably related not only to the concentration and timing of the urokinase intervention but also to the type of CVAD, and perhaps to the intensity of the concomitant chemotherapy program. Urokinase can safely and effectively be used on CVADs with malfunctioning or intraluminal occlusion in a dose of 5000 IU/mL or as salvage 3-hour infusion with 1000 IU/kg/hour. Hitherto, adjuvant treatment with urokinase in the management of CVADs with intraluminal infection still relies on case reports and small case series. In this field, a randomised controlled study is necessary.

PATENCY

3.6. A Randomised Controlled Trial of Taurolidine-Citrate versus Taurolidine Urokinase Lock to Prevent Catheter Related infections in Haemodialysis Patients

Alali, F. et al. (2016) Nephrology Dialysis Transplantation 31 (Supplement 1): i259-i273, doi: 10.1093/ndt/gfw173.29

Background: The use of tunneled catheters in haemodialysis is one of the leading causes of morbidity and mortality among dialysis patients. The prevelence of catheter-related infections (CRI) range from 2.5 to 5.5 incidence/1000 catheter days, or 0.9 to 2 episodes/patient/year. There is an increased relative risk for infection-related hospitalisation and death by 2-3 in dialysis patients using catheters compared with those using fistula or graft. Efforts have been made to prevent and decrease the incidence of CRI. Taurolidine-citrate is a novel antibacterial agent that shows promising results to prevent CRI when used as locking agenct. We carried out a comparative study using Taurolidine-citrate with heparin (TauroLock/Hep) as a catheter lock solution versus taurolidine citrate with urokinase (TauroLock/U) in regard to prevention of CRI.

Methods: This is a prospective randomised controlled trial that included all patients who were undergoing ambulatory regular haemodialysis in Qatar with tunneled catheter. All patients were randomised to receive TauroLock/Hep or TauroLock/U on 1:1 basis using a computer-generated program. Patients were followed for 6 months. Episodes of CRI, catheter removal, time to removal and days of hospital stay were analysed.

Results: 177 patients participated, 30 patients did not complete the study (fistula cannulation, death, transferring to peritoneal dialysis) but were included in the final analysis, 93 patients in TauroLock/Hep and 84 in TauroLock/U group. Age, sex, catheter age, blood flow rates and venous pressure were recorder before the study and use of antiplatelet or Warfarin and co-morbidities did not differ between the two groups. 4 catheters were removed in TauroLock/Hep group due to CRI with mean time to removal of 170 days and mean length of stay (LOS) in hospital of 5 days. CRI rate was 0.3 incidence/1000 catheter days in the TauroLock/Hep group versus 0.08 incidence/1000 catheter days in the TauroLock/U. There were no reported serious adverse events or bleeding reported during study.

Conclusions: In this study to compare TauroLock/Hep to TauroLock/U, both groups showed reduction in CRI well below the current recommendation. There was a further significant decrease in CRI in TauroLock/U group versus the TauroLock/Hep group. This result supports recent studies showing prevention of CRI with recombinant tissue plasminogen activator catheter (rt-PA) lock. The use of urokinase in addition to TauroLock provided a cheaper and practical alternative to rt-PA to decrease CRI. LOS in the hospital for CRI was significantly lower in TauroLock/U versus TauroLock/Hep. Our results were clinically significant but only close to statistically significant because of the low number of events in both categories.

4.1. Letter to the Editor

Punt, C.D. and Boer. W.E (2008) Clinical Nephrology, Vol. 69 – No. 4

Trisodium citrate (TSC, 30%) has been successfully used as a catheter locking solution in haemodialysis and because of its antibacterial activity, we initiated the use of TSC (30%) in our intensive care unit. After disconnection, the 2 main ports of the catheter were flushed with normal saline and filled with 30% TSC. The whole 5ml ampoule was used, 2.5ml for each port. Immediatley after the injection, a period of cardiac arrest occurred, which lasted 10 seconds. It was then realized that a similar incident had occurred the day before, though citrate was not thought to have been causative then.

The volumes of the main ports of the catheter we used were 1.6 and 1.5 ml and were indicated on this catheter. Consequently, in our patient the over injection of only 1.9 ml of 30% trisodium citrate had taken place and probably caused a hypocalcemic bolus of blood, leading to a

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period of cardiac arrest.

Strict adherence to the appropriate volumes of the catheter is mandatory.

4.2. Embolic Complications From Central Venous Haemodialysis Catheters Used With Hypertonic Citrate Locking Solution

Willicombe, M. K., Vernon, K., Davenport, A. (2010) American Journal Kidney Disease 55:348-351

Many haemodialysis patients continue to dialyse using central venous access catheters in clinical practice. Catheters are associated with a number of recognised complications, including infection, catheter-associated fibrin sheath and thrombus leading to malfunction, central venous stenosis, and right atrial thrombus. However, symptomatic catheter embolus rarely is reported. We report our experience of catheter-associated emboli in patients dialysing with a twin catheter designed with multiple small side holes in combination with a hypertonic citrate locking solution. 8 patients developed symptomatic emboli from catheter-associated thrombus, typically resulting in sudden hypotension and chest pain shortly after starting haemodialysis, with documented pulmonary and cerebral emboli in 3 cases. Catheters with multiple side holes are susceptible to seepage of the catheter locking solution through the side holes and therefore may be at greater risk of catheter thrombus formation. This may be exacerbated by the use of a hypertonic citrate lock given to just fill the internal catheter lumen because hyperosmolar locks are more likely to leave the catheter tip, resulting in increased risk of catheter associated thrombus.

4.3. Trisodium citrate induced protein precipitation in Haemodialysis catheters might cause pulmonary embolism.

Schilcher et al. (2012) Nephrology Dialysis Transplantation.

Correspondence and offprint requests to: Gernot Schilcher; Email: gernot.schilcher@medinugraz.at

Background: The locking anticoagulant plays a decisive role in the patency of central venous catheters (CVCs) used for haemodialysis. During injection, the hydraulic effects inevitably cause lock solution to spill into the systemic circulation.

Density differences between whole blood (WB) and the lock solution cause further gravity-induced seepage of lock solution. This is followed by an influx of WB into the catheter, also described for trisodium citrate, which is a common agent for serum protein precipitation. Embolic complications from haemodialysis catheters locked with hypertonic trisodium citrate have been reported. We aimed to investigate protein precipitation in trisodium citrate locked catheters as a possible cause of pulmonary embolisms.

Methods: In vitro, WB and trisodium citrate (concentrations ranging from 4.7 to 46.7%) mixtures in a ratio of 1:4 were used to assess protein precipitation. Additionally, WB/trisodium citrate mixture was pumped through a 20- lm mesh filter, simulating pulmonary vessels, and filtrate pressure was measured. In vivo, listed filling volumes of haemodialysis catheters locked with trisodium citrate 4% (n 1⁄4 10), 10% (n 1⁄4 10), 20% (n 1⁄4 10) or 46.7% (n 1⁄4 10) were aspirated and then analysed for protein precipitation.

Results: In vitro, protein precipitation capable of causing filter occlusion was observed in test solutions containing trisodium citrate above a concentration of 12%. In vivo, protein precipitation was detected in all samples from the CVCs filled with trisodium citrate 46.7% (n 10) and 20% (n 1⁄4 10). In contrast, there were no signs of precipitation in samples from the catheters filled with trisodium citrate 4% (n 1⁄4 10) or 10% (n 1⁄4 10).

Conclusions: Our in vitro results demonstrate that protein precipitates inside haemodialysis catheters when trisodium citrate is used above the concentrations of 12%. Precipitated protein may have contributed to the pathophysiology of reported embolisms from haemodialysis

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catheters filled with hypertonic trisodium citrate. Based on our findings, we suggest that trisodium citrate lock solution up to the concentration of 10% can be used safely.

4.4. FDA Warning Letter

The Renal Network, FDA Issues Warning on TRICITRASOL. 2000

The Food & Drug Administration is issuing an urgent warning to all hospital pharmacies and haemodialysis units that triCitrasol, an unnapproved product that has been used to keep bloodlines open, may cause death when infused into patients. TriCitrasol is marketed in individual, sterile, 30 ml glass vials, distributed both individually and in haemodialysis kits.

FDA has learned that a patient died of cardiac arrest shortly after triCitrasol, a 46.7% concentration of sodium citrate anticoagulant, was injected full strength into a haemodialysis permanent blood access catheter that had been implanted. Rapid or excessive infusion of citrate solutions can cause fatal heart rhythm disruption, seizures or bleeding due to loss of blood calcium.

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