ANNEXES TO CHAPTER 6

Clinical Question XXIX. What influence do the different types of central venous catheter lumen lock have on its dysfunction and infection?

Citrate versus heparin lock solution	
The systematic review with meta-analysis by Zhao (2013) included 13 randomised controlled trials, including 1770 patients and 221,064 catheter-days, comparing citrate (alone or with antimicrobials) and heparin for central venous catheter lock. The results obtained are as follows:	
- catheter removal due to poor circulation: no significant differences between the two. - *citrate only vs heparin*: RR 0.94, 95% CI: 0.59 to 1.49; p=0.78 (three RCT with 21,378 catheter-days). - *citrate + antimicrobial vs heparin*: RR 1.06, 95% CI: 0.41 to 2.69; p=0.91 (three RCT with 143,604 catheter-days).	**Moderate quality**
- mean duration of catheter: difference in means, -32.81 days, 95% CI: -82.91 to 17.29; p=0.2 (three RCT).	**Low quality**

- incidence of bleeding: RR 0.48, 95% CI: 0.30 to 0.76; p=0.002, (two RCT) significantly lower in patients who received citrate lock solution.
 	
 - catheter thrombosis: RR 1.04, 95% CI: 0.46 to 2.34; p=0.9 (two RCT), difference not statistically significant.
 	
 - thrombolytic treatment:
 	
    o *citrate only vs heparin*: RR 1.25, 95% CI: 0.74 to 2.11; p=0.41 (three RCT with 55,851 catheter-days) [I^2: 77%], difference not statistically significant.
 	
    o *citrate + gentamicin vs heparin*: RR 0.62, 95% CI: 0.38 to 1.00; p=0.05 (two RCT with 76,496 catheter-days).
 	
    o *citrate + taurolidine vs heparin*: RR 2.47, 95% CI: 1.68 to 3.63; p<0.00001 (one RCT with 150,118 catheter-days).
 	
 - all-cause mortality: RR 0.81, 95% CI: 0.53 to 1.23; p=0.3 (seven RCT), not statistically significant.
	Moderate quality

- catheter-related readmissions: RR 0.61, 95% CI: 0.13 to 2.74; p=0.5 (two RCT), not statistically significant.
 	
 - catheter-related bacteraemia:
 	
    o The overall combined meta-analysis found that the citrate lock solutions were better than those with heparin: RR 0.39, 95% CI: 0.27 to 0.56; p<0.001 (11 RCT with 217,128 catheter-days).
    o However, subgroup analysis showed that the lock solutions with different antimicrobials were better than heparin, but with the citrate-only lock solution, the difference was not statistically significant.
    o *citrate only vs heparin*: RR 0.54, 95% CI: 0.22 to 1.30; p=0.17 (three RCT with 56,746 catheter-days) [I^2: 67%].
	Low quality

- o *citrate + gentamicin vs heparin:* RR 0.25, 95% CI: 0.13 to 0.47; p=0.0001 (four RCT with 85,343 catheter-days).
- o *citrate + taurolidine vs heparin:* RR 0.45, 95% CI: 0.27 to 0.77; p=0.003 (three RCT with 25,370 catheter-days).
- o *citrate + methylene blue + methylparaben + propylparaben vs heparin*: RR 0.29, 95% CI: 0.12 to 0.72; p=0.008 (one RCT with 49,669 catheter-days).

Broken down by citrate concentration levels, the analysis showed that low (1.04-4%) to moderate (4.6-7%) concentrations of citrate lock solution were associated with a lower incidence of these infections (p<0.001 and p=0.003 respectively), but there were no significant differences between patients who received high concentrations (30-46.7%) of citrate and those with heparin lock solutions (p=0.3).

- - exit site infections: differences not statistically significant.
    - o *citrate only vs heparin:* RR 0.73, 95% CI: 0.35 to 1.53; p=0.41 (four RCT and 59,942 catheter-days) [I^2: 60%].
    - o *citrate + gentamicin vs heparin:* RR 0.57, 95% CI: 0.20 to 1.57; p=0.28 (two RCT and 78,683 catheter-days).
    - o *citrate + taurolidine vs heparin:* RR 1.09, 95% CI: 0.44 to 2.74; p=0.85 (two RCT and 21,175 catheter-days).

Heparin lock solution versus tissue plasminogen activator (TPA)

The reviews published on this subject (Wang 2013; Firwana 2014) found one parallel-design RCT (Hemmelgarn 2011), and two RCT with a cross-over design (Gittins 2007; Schenk 2000). Firwana notes that the two cross-over studies reported the results at the end of the two phases of the study. Consequently, only the findings from the parallel-design RCT are presented below.

The Hemmelgarn RCT (2011) with 125 patients compared heparin three times a week with TPA one day a week and heparin used in the other two sessions, with the following results:

Moderate quality

- - poor functioning of the catheter: HR 1.91, 95% CI: 1.13 to 3.22; p=0.02. Heparin-only group 40/115 = 34.8%; TPA group 22/110 = 20%.

- - catheter-related bacteraemia: HR 3.30, 95% CI: 1.18 to 9.22; p=0.02. Fifteen patients (13.0%) in the heparin-only group, and five (4.5%) in the TPA group (corresponding to 1.37 and 0.40 events per 1000 patient-days respectively; p=0.02).

- - severe adverse events: in 23 patients (20.9%) who received TPA and 34 (29.6%) who received heparin (p=0.14), RR 0.70, 95% CI: 0.44 to 1.12. The analysis broken down by type of event found no statistically significant differences in hospitalisation, bleeding or mortality.

Summary of evidence	
Citrate versus heparin lock solution Meta-analysis of RCT found no statistically significant differences between citrate lock solution and heparin lock solution in relation to mean duration of the catheter, catheter thrombosis, catheter removal, catheter-related readmissions, bacteraemia, exit-site infections, or mortality, with the incidence of bleeding being lower in those treated with citrate.	**Moderate quality**
Citrate plus antimicrobial lock solution versus heparin Meta-analysis of RCT found that adding antimicrobials to the citrate in the lock solution was not associated with differences in the duration of the catheter or catheter removal due to poor circulation. Adding gentamicin to the citrate was associated with less risk of bacteraemia and exit-site infections. Adding taurolidine to the citrate was associated with less risk of bacteraemia, but not of exit-site infections.	**Moderate quality**
Heparin lock solution versus tissue plasminogen activator (TPA) One RCT that compared heparin three days a week to TPA one day a week and heparin the other two days found that the option with TPA was associated with less risk of catheter malfunction and catheter-related bacteraemia.	**Moderate quality**
Patients' values and preferences *No relevant studies related to this aspect have been identified.*	
Use of resources and costs The RCT by Hemmelgarn (2011) estimated the average costs (in Canadian dollars) of tissue plasminogen activator (TPA) and heparin as $1,794 and $195 respectively, and the cost per patient of managing complications associated with malfunction of the catheter and catheter-related bacteraemia was $156 with TPA and $582 with heparin. Therefore, the incremental cost of caring for patients with TPA compared to heparin was $1,173 per patient, or $13,956 per episode of catheter-related bacteraemia prevented.	

Recommendations [Proposal]	
Weak	We recommend locking solutions with heparin, citrate alone or with antimicrobials, or tissue plasminogen activator alternated with heparin in central venous catheters for haemodialysis.

References

Firwana BM, Hasan R, Ferwana M, Varon J, Stern A, Gidwani U. Tissue plasminogen activator versus heparin for locking dialysis catheters: A systematic review. Avicenna J Med. 2011 Oct; 1 (2):29-34.

Gittins NS, Hunter-Blair YL, Matthews JN, Coulthard MG. Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: A randomised controlled trial. Arch Dis Child 2007; 92: 499-501.

Hilleman D, Campbell J. Efficacy, safety, and cost of thrombolytic agents for the management of dysfunctional hemodialysis catheters: a systematic review. Pharmacotherapy. 2011 Oct; 31(10):1031-40.

Hemmelgarn BR, Moist LM, Lok CE, Tonelli M, Manns BJ, Holden RM, LeBlanc M, Faris P, Barre P, Zhang J, Scott-Douglas N; Prevention of Dialysis Catheter Lumen Occlusion with rt-PA versus Heparin Study Group. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. N Engl J Med 2011; 364: 303–312.

Niyyar VD. Catheter dysfunction: the role of lock solutions. Semin Dial. 2012 Nov-Dec; 25(6):693-9.

Schenk P, Rosenkranz AR, Wolfl G, Horl WH, Traindl O. Recombinant tissue plasminogen activator is a useful alternative to heparin in priming quinton permcath. Am J Kidney Dis 2000; 35:130-6.

Wang AY, Ivany JN, Perkovic V, Gallagher MP, Jardine MJ. Anticoagulant therapies for the prevention of intravascular catheters malfunction in patients undergoing haemodialysis: systematic review and meta-analysis of randomized, controlled trials. Nephrol Dial Transplant. 2013 Nov; 28(11):2875-88.

Zhao Y, Li Z, Zhang L, Yang J, Yang Y, Tang Y, Fu P. Citrate Versus Heparin Lock for Hemodialysis Catheters: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Am J Kidney Dis. 2013 Oct 11. pii: S0272-6386(13)01202-X.

Table 1. STUDIES EXCLUDED

Study	Cause for exclusion
Niyyar 2011	Narrative review.
Hilleman 2011	Does not analyse the effect of different types of flushing or locking solutions on central venous catheter dysfunction and infection. Focuses on the management of catheter dysfunction with thrombolytics.

GRADE TABLES

Date: 2014-01-20
Question: Should citrate vs heparin lock be used in patients on haemodialysis with central venous catheter?
Bibliography: Zhao Y, Li Z, Zhang L, Yang J, Yang Y, Tang Y, Fu P. Citrate Versus Heparin Lock for Hemodialysis Catheters: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Am J Kidney Dis. 2013 Oct 11. pii: S0272-6386(13)01202-X.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Citrate lock	Heparin lock	Relative (95% CI)	Absolute		
Mean duration of the catheter per catheter day in days (Better indicated by higher values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0	-	-	MD 32.81 lower (82.91 lower to 17.29 higher)	⊕⊕⊕⊕ LOW	CRITICAL
Removal of the catheter due to bad circulation per catheter day												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/11214 (0.32%)	35/10164 (0.34%)	RR 0.94 (0.59 to 1.49)	207 fewer per 1,000,000 (from 1412 fewer to 1687 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
Catheter-related bacteraemias per catheter day												
3	randomised trials	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	27/29712 (0.09%)	51/27034 (0.19%)	RR 0.54 (0.22 to 1.30)	868 fewer per 1,000,000 (from 1471 fewer to 566 more)	⊕⊕⊕⊕ LOW	CRITICAL

Haemorrhages per catheter day												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	RR 0.48 (0.30 to 0.76)	-	⊕⊕⊕⊝ MODERATE	CRITICAL
								0%		-		
Catheter-related readmissions												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	RR 0.61 (0.13 to 2.74)	-	⊕⊕⊝⊝ LOW	CRITICAL
								0%		-		

[1] Randomisation mechanism inappropriate or not clear in one of the RCTs. Two of them non-blind and with allocation concealment not clear.

[2] Wide confidence interval.

[3] High heterogeneity I2:= 67%.

Date: 2014-01-20

Question: Should citrate + antimicrobials vs heparin lock be used in patients on haemodialysis with central venous catheter?

Bibliography: Zhao Y, Li Z, Zhang L, Yang J, Yang Y, Tang Y, Fu P. Citrate Versus Heparin Lock for Hemodialysis Catheters: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Am J Kidney Dis. 2013 Oct 11. pii: S0272-6386(13)01202-X.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Citrate + antimicrobials	Heparin lock	Relative (95% CI)	Absolute		
Removal of the catheter due to bad circulation per catheter day												
4	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	51/74749 (0.07%)	44/68855 (0.06%)	RR 1.06 (0.41 to 2.69)	38 more per 1,000,000 (from 377 fewer to 1080 more)	⊕⊕⊕⊕ LOW	CRITICAL
								0%		-		

[1] Randomisation mechanism inappropriate or not clear in one of the RCTs. Two of them non-blind and with allocation concealment not clear.

[2] Wide confidence interval

Date: 2014-01-20
Question: Should heparin vs tissue plasminogen activator (TPA) lock be used in patients on haemodialysis with central venous catheter?
Bibliography: ECA: Hemmelgarn BR, Moist LM, Lok CE, Tonelli M, Manns BJ, Holden RM, LeBlanc M, Faris P, Barre P, Zhang J, Scott-Douglas N; Prevention of Dialysis Catheter Lumen Occlusion with rt-PA versus Heparin Study Group. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. N Engl J Med 2011; 364: 303–312.

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Heparin lock	Tissue plasminogen activator (TPA) lock	Relative (95% CI)	Absolute	Quality	Importance
Quality assessment							**No of patients**		**Effect**			
Catheter malfunction												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40/115 (34.8%)	22/110 (20%)	HR 1.91 (1.13 to 3.22)	147 more per 1000 (from 23 more to 313 more)	⊕⊕⊕⊝ MODERATE	CRITICAL
								0%		-		
Catheter-related bacteraemia:												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	15/115 (13%)	5/110 (4.5%)	HR 3.30 (1.18 to 9.22)	97 more per 1000 (from 8 more to 303 more)	⊕⊕⊕⊝ MODERATE	CRITICAL
								0%		-		
Serious adverse events												
1	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[1]	none	34/115 (29.6%)	23/110 (20.9%)	RR 0.70 (0.4 to	63 fewer per 1000 (from 125 fewer to 25	⊕⊕⊕⊝ MODERATE	CRITICAL

		bias							1.12)	more)		
								0%		-		

[1] Wide confidence interval.