

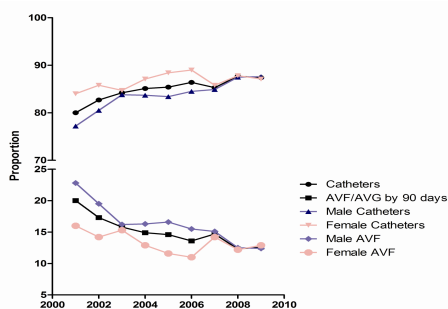
Preventing Catheter Dysfunction: Is Prophylactic rTPA Ready for Prime Time?

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University of Manitoba

Outline

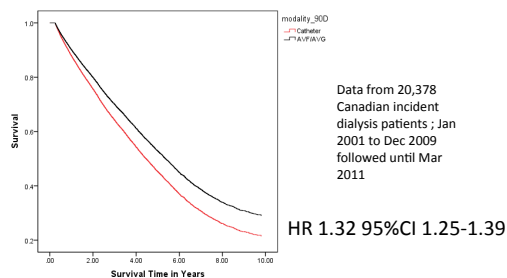
- Catheter usage in Canada
- Catheter complications
- Critical appraisal of a recent Canadian RCT

Trends in Catheter use in Canada



CORR

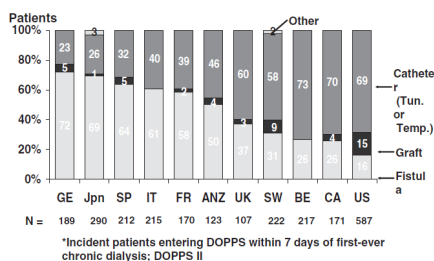
Survival by Access



Adjusted for demographics, co-morbidity, region, pre-HD care, distance, albumin, BMI

CORR

International comparisons – ugh!

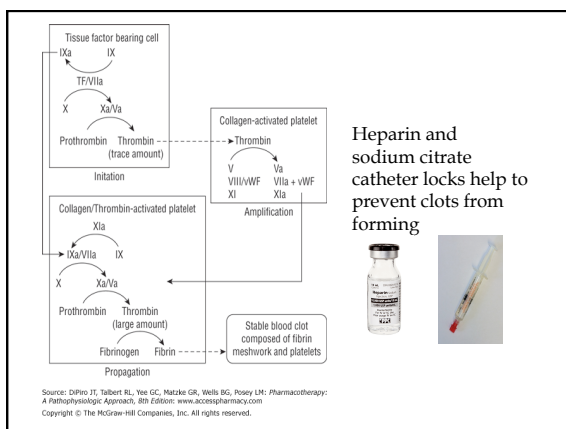


J. Ethier *et al.*

Nephrol Dial Transplant (2008) 23: 3219–3226

Catheter Complications

- Infections 3.8-5.5/1000 days *Infect Control Hosp Epidemiol* 2002;23:538-41.
- Dysfunction: KDOQI definition “inability to attain a sufficient blood flow of 300 ml/min” *Am J Kid Dis* 2006;48:S248-57.
- Due to thrombosis and sheath formation *Kid Int* 2010;78:1218-31.
- Thrombosis rates 4-5.5/1000 days *Kid Int* 2010;78:1218-31.
- CVC loss 1.8-3.6/1000 days
- Citrate or heparin used for thrombosis prevention; rTPA often used for dysfunction



Heparin vs. heparin

Kidney International (2010) **78**, 1218–1231

Agent	First author, year	N	Study design	Treatment groups	Outcome	Effect	P-value	Comment
Heparin	Thomas, 2007 ²⁴	273	P	Heparin (1000 U/ml)	Heparin (10,000 U/ml)	Catheter dysfunction (per 1000 HD sessions)	Low High H 6.7 vs 7.6	NS
					Thrombolytic therapy (per 1000 HD session)	Low High H 26.6 vs 8.2	<0.001	
Heparin	Holley, 2007 ²⁴	64	R	Heparin (1000 U/ml)	Heparin (10,000 U/ml)	Thrombolytic therapy (per 6 months)	Low High H 63 vs 31%	<0.001

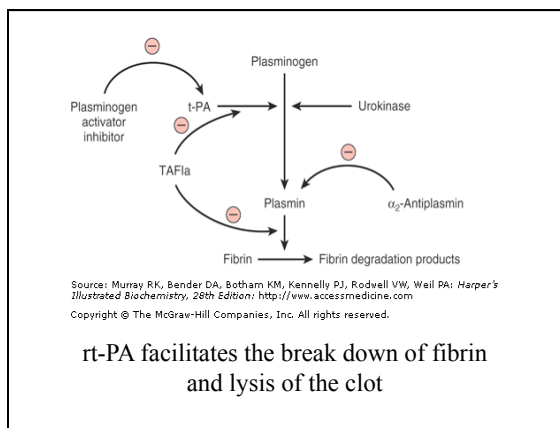
Increasing heparin doses Advantage = less rTPA use
 Disadvantage = bleeding, antibodies

Citrate vs. heparin

Agent	First author, year	N	Study design	Treatment groups	Outcome	Effect	P-value	Comment
Citrate (n)	Chal, 2007 ²⁵	250	P	Citrate 4%	Heparin (2000 U/ml)	Thrombolytic rate (per 1000 blood catheter removal for poor flow (per 1000 days)	3.1 vs 5.3	<0.001
					Catheter removal for poor flow (per 1000 days)	1.65 vs 2.98	0.042	
Citrate (n)	Gradwohl, 2007 ²⁶	307	R	Citrate 4%	Heparin	Thrombolytic rate	0.76	0.07
Citrate (n)	Heudricka, 2007 ²⁷	79	RCT	Citrate 2%	Heparin (2000 U/ml)	Thrombolytic therapy (per HD session)	8 vs 1%	NS
					Accesses of thrombosis	18 vs 7%	<0.001	
Citrate (n)	Sho, 2007 ²⁸	11	P	Citrate 3%	Heparin (2000 U/ml)	Accesses of thrombosis	0 vs 4%	NS
Citrate (n)	Sho, 2007 ²⁸	291	RCT	Citrate 3%	Heparin (2000 U/ml)	Accesses of thrombosis	47 vs 44%	NS
					Catheter removal for poor flow (per 1000 days)	3.2 vs 3.6	NS	
Citrate (n)	Bayes, 1999 ²⁹	93	P	Citrate 4%	Heparin (2000 U/ml)	Accesses of thrombosis	0 vs 4%	NS
Citrate (n)	Flower, 2007 ³⁰	232	HO	Citrate 4%	Heparin (2000 U/ml)	Thrombolytic therapy (per 1000 days)	8.2 vs 4.3	<0.001
					Catheter removal for poor flow (per 1000 days)	1.8 vs 1.3	0.001	

Citrate is equivalent or superior to heparin; reduction in bleeding events

Kidney International (2010) **78**, 1218–1231



Recombinant Tissue Plasminogen Activator Is a Useful Alternative to Heparin in Priming Quinton Permcath

Peter Schenk, MD, Alexander R. Rosenkranz, MD, Gabriele Wolff, MSc, Walter H. Hörl, MD, and Otto Traundl, MD

American Journal of Kidney Diseases, Vol 35, No 1 (January), 2000: pp 130-136

RCT cross over design, 12 pts, 8 mths, heparin 2,000u vs rTPA 2 mg per lumen

Surrogate outcomes improved; too small for hard outcomes

The NEW ENGLAND JOURNAL of MEDICINE

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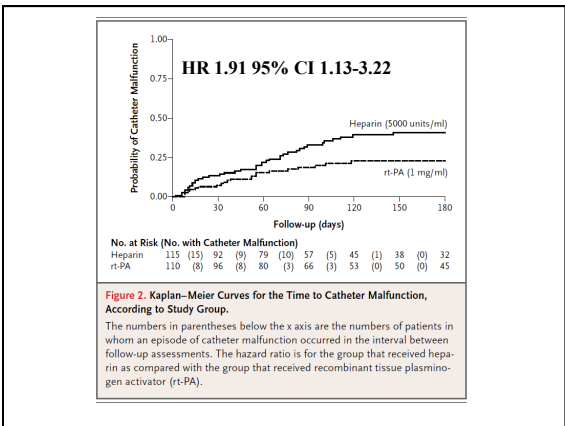
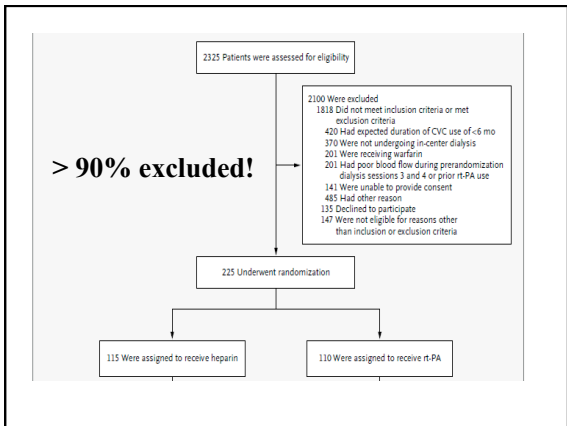
Prevention of Dialysis Catheter Malfunction with Recombinant Tissue Plasminogen Activator

Brenda R. Hemmelgarn, M.D., Ph.D., Louise M. Moist, M.D., Charmaine E. Lok, M.D., Marcello Tonelli, M.D., S.M., Braden J. Manns, M.D., Rachel M. Holden, M.D., Martine LeBlanc, M.D., Peter Farris, Ph.D., Paul Barre, M.D., Jianguo Zhang, M.Sc., and Nairne Scott-Douglas, M.D., Ph.D., for the Prevention of Dialysis Catheter Lumen Occlusion with rt-PA versus Heparin (PreCLOT) Study Group

Study Question: Does prophylactic, once weekly rt-PA as a locking solution (versus heparin thrice weekly) improve catheter dysfunction and bacteremia?

Terrific moment for Canadian Nephrology. Huge advance in vascular access research. NEJM publication. Congrats!

- ### Study design and population
- Randomized, multicentre, blinded
 - Incident catheters
 - In pts with infection-related catheter removals, needed to be treated and Abx free for 3 treatments
 - Comparator was heparin 5,000u
 - Followed for 6 months



Definition of catheter malfunction?

Supplementary Appendix): peak blood flow of 200 ml per minute or less for 30 minutes during treatment, mean blood flow < 200 ml per minute or inability to maintain adequate blood flow. The definition of catheter malfunction was chosen by the study investigators on the basis of published guidelines.¹⁸

Catheter malfunction → **Catheter removal/exchange**

What is this based on?

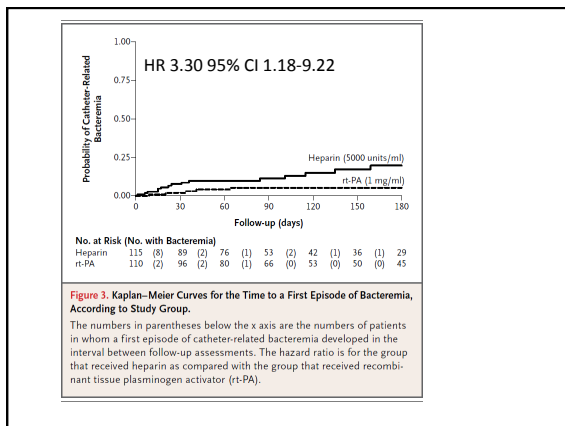
Not much.....

- 1) No RCTs
- 2) Small observational studies
- 3) Workgroup "opinion"
- 4) No other guidelines*

American Journal of Kidney Diseases, Vol 48, No 1, Suppl 1 (July), 2006: pp S248-S257

Surrogate outcomes ≠ Clinical outcomes
Catheter malfunction ≠ Catheter removal

*NAVAC recently suggested opinion-based parameters; Semin Dial 2011



Small numbers

- Small numbers
 - CVC malfunction
 - 40/115 (34.8%) in heparin group and 22/110 (20%) in TPA group
 - CVC removed due to malfunction
 - 3/40 (7.5%) in the heparin group and 1/22 (4.5%) in the rt-PA group
 - Catheter related bacteremia
 - 15 (13%) patients in the heparin group and 5 (4.5%) patients in the rt-PA group; very low rate of infection in both arms; HR 3.30 95% CI 1.18 - 9.22

Did rTPA truly reduce bacteremia?

- Bacteria colonize microthrombi and form biofilms; come out periodically, triggering bacteremia
- A lot of infections (8/15) occurred early! Seems very rapid for microthrombi formation followed by colonization

Hazard ratio, 3.30 (95% CI, 1.18-9.22)

1.37 episodes of bacteremia per 1000 patient-days in the heparin group

0.40 episodes of bacteremia per 1000 patient-days in the rt-PA group

Group	Time (days)	No. at Risk (No. with Bacteremia)
Heparin	0	115 (8)
	30	89 (2)
	60	76 (1)
	90	53 (2)
	120	42 (1)
rt-PA	0	110 (2)
	30	96 (2)
	60	80 (1)
	90	66 (0)
	120	53 (0)

What happened before time 0?

Patient with previous line infection treated with Abx and off for three sessions

heparin 10 (8.7%)

tPA 4 (3.6%)

Hazard ratio, 3.30 (95% CI, 1.18-9.22)

Could the difference in pre-existing bacteremias explain this?

Line infection treatments were centre-specific, recurrent infection information

Comparative effectiveness

- Comparative effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options. The evidence is generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver health care.

RECALL: preCLOT compared tPA vs heparin

The comparator dose.....

- 10 centres in pre-CLOT used heparin
- 4 centres used 4% citrate
- Heparin doses ranged from 1000 u/mL to 10,000 u/mL, 5 centres used Heparin 5,000u/mL

Heparin 5000 u/mls was chosen as the comparator

The comparator choice.....

- Multiple RCTs have shown citrate appears to be equivalent or slightly better than heparin in terms of catheter dysfunction, tPA use and catheter removal
- Appears to cost less (2 Canadian studies)

Bleeding, Bleeding, Bleeding

- HD patients risk of major bleeding = 5% per year (on no blood thinning agents) DOPPS
- Citrate appears to reduce the bleeding events compared to heparin
- In pre-CLOT bleeding 29/225 (12.9%), 8 were major with 1 fatal

If this study was done today would heparin still be used as the comparator?

Kidney International (2010) 78, 1218–1231

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SARP/NARP 4% citrate, UWO 4% citrate, TGH 4% citrate, BC Renal agency 4% citrate

“At the present time, 4% citrate is used in the majority of Canadian HD units”

C Lok KI 2010

Application of study results

- Would need to switch back to heparin (from citrate) to apply study findings
- Heparin 5000u/mL was given in 4 pre-filled syringes to maintain blinding
- How is heparin given in the real world?



Multi-dose vial

Citrate and rt-PA are given in single dose vials


Multi- versus single dose

REVIEW


Hospital-acquired infections related to contaminated substances

R.-P. Vonberg*, P. Gastmeier Journal of Hospital Infection (2007) 65, 15–23

Contaminated substance	No. of outbreaks	No. of patients	Mortality (%)
Blood products			
Red blood cells	14	39	22/39 (56.4%)
Clotting factor concentrates	10	173	2/136 (1.5%)
Citrate-saline products	10	121	4/85 (4.7%)
Heparin/sodium chloride solution	30	451	16/371 (4.3%)
Total parenteral nutrition	9	100	19/39 (48.7%)



WHO best practices for injections and related procedures toolkit



2.2.2 Medication

Types of medication containers and recommendations on their use are given in Table 2.5.

Type of container	Recommendations	Reason
Single-dose vial	Preferred	Low likelihood of contamination
Multiple-dose vial	Only if unavoidable	High likelihood of contamination if aseptic technique is poor
Ampoules	Pop-open preferred	Breaking a glass ampoule may result in particulate matter escaping from the vial; it may also injure the person opening the ampoule
Fluid or solution bags (100–1000 ml) for reconstitution	Not recommended for routine injection	High likelihood of contamination

I could increase bacteremia by administering H2O in a multi-dose vial!

COST-EFFECTIVENESS ANALYSIS

For each patient who received therapy for 6 months, the mean costs (in Canadian dollars) of rt-PA and heparin were \$1,794 and \$195, respectively; the cost of managing complications associated with catheter malfunction and catheter-related bacteremia per patient was \$156 with rt-PA and \$582 with heparin. Thus, the incremental cost of caring for patients with rt-PA as compared with heparin was \$1,173 per patient, or \$13,956 per episode of catheter-related bacteremia prevented.

Cost effectiveness

- Heparin 10,000/5 ml \$1.10 = 0.22\$ per ml
- 4% Citrate 5 ml \$1.07 = 0.21\$ per ml
- R-TPA = \$64 per 2 mg = \$32 per mg
- Roughly 150 X cost increase!

Costing is tricky.....

- What is the costing based on?
- Very few hard endpoints to base the cost effectiveness analysis on
- ? Catheter changes? Bacteremias?
- Costing can be fairly subjective
- What about the cost of bleeding events? (a single hemorrhagic CVA could wipe out ALL cost benefit)

In summary

- Primary outcome catheter malfunction is a Surrogate outcome ≠ clinical outcomes
- Comparison with citrate
- Did it really reduce infection?
- May not be generalizable
- Small number of events – just b/c there is a paucity of RCTs in Nephrology does not mean we should change our standards; needs to be replicated
- Real world application may paradoxically lead to more infection

A single RCT with a short duration of follow up, small numbers of patients and few hard outcomes should not change policy.

rtPA is NOT ready for prime time!

Conclusions

- Catheter usage in Canada is extremely high, increasing and associated with worse outcomes
- Catheter dysfunction can occur due to numerous mechanisms and is common
- Lots of variability in practice; seems citrate 4% is the most widely used
- rtPA is not ready for wide-spread use for prevention of catheter dysfunction