CATHETER LOCKS FOR CENTRAL VEIN CATHETERS FOR DIALYSIS; CURRENT AND FUTURE

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Today's practice of dialysis would not be possible without tunneled central venous catheters for dialysis (CVCD). With the increased efforts of the Fistula First program, numbers of prevalent fistulas have increased and grafts have decreased. However, the percentage of patients dialyzing 90 days after the start of dialysis has remained remarkably constant at about 50%. When we look at CVCD, we see a reasonably effective method for withdrawing blood flow to perform dialysis. What bacteria “see” is a highway to the bloodstream with nice little roadside rest-stops, ideal places to stay and establish biofilm colonies. Luminal contamination causes about 80% of catheter related blood stream infections (CRBSI) and within biofilm bacteria can establish a quiescent metabolism and resistance to antibiotics. The dynamics of catheter colonization are dramatic. By culture of blood removed from the catheter or by brush culture 3-5% of catheters are contaminated with S. Epidermidis by 6 weeks of use (Figure 1). By tip culture a much greater number of catheters are contaminated, indicating that tip cultures probably include organisms collected directly from skin during catheter removal.
Figure 1 Dynamics of colonization with coagulase-negative staphylococci among 27 newly inserted hemodialysis catheters during 9 weeks of follow-up. The percentages represent the proportion of samples that yielded growth of coagulase negative staphylococci in relation to all samples analyzed during the indicated time period.

The standard practice for locking a catheter after use is to infuse a volume of anticoagulant equal to the volume of the catheter. Several studies have demonstrated that patients receiving heparin catheter lock after dialysis are systemically anticoagulated, with PTT values over 200 seconds, even if the volume of lock infused is exactly the same as the catheter volume. When fluid flows through a catheter lumen at a reasonable flow rate, the flow is laminar and the profile of flow is parabolic. The fluid at the edges of the catheter remains stationary and most of the flow is through the center of the lumen. The volume in which most of the fluid flows is therefore less than the catheter volume. Even in catheters without side-holes, 15-20% of the fluid injected into a catheter exits the tip, when the injected volume equals the catheter fill volume. In catheters with side-holes another 10% or so of the lock solution will quickly convect out of the catheter due to blood flowing through the tip. Further catheter lock loss is due to gravitational effects if the density of the lock solution is considerably different from blood. The only way to prevent systemic anticoagulation of the patient during catheter lock with heparin is to under-fill each catheter by 15-20%. This of course means that there is a lower concentration of heparin at the tip of the catheter than expected from the lock solution concentration. A number of studies have shown that the longevity of tunneled CVCD catheters is on average 40 weeks before serious complications prompt their removal. About 3/4 of the catheters are lost to infection, or a rate of approximately 10% per month. When there is clinical suspicion of bacteremia or proven positive blood cultures, it is likely that the catheter is contaminated with bacteria both on the outside and the inside. In order to salvage a catheter in the presence of bacteremia it is necessary to expose all catheter surfaces to antibiotics or antiseptic solutions. If appropriate antibiotic locks are used, then up to 70% of catheters may be salvaged (Figure 2).

Figure 2 Outcome of VanC-Ceftaz lock protocol in catheter-related bacteremia N=47. Poole et al, NDT 2004

Antibiotic or antiseptic catheter locks are also effective in preventing catheter infection. In a timely and complete review of randomized studies, Jaffer et al have demonstrated that in all studies prophylactic use of antibacterial catheter locks reduced the incidence of CRBSI by about 80% locks versus heparin. There were varying definitions of CRBSI by the various authors of these studies, but the conclusions were always consistent. In the following table, the CRBSI results for antibacterial catheter locks are circled:
Table 2 CRI rates provided by each randomized controlled trial and overall effects for gentamicin studies and all studies combined

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Note: CR, catheter-related infection; CRI, catheter-related infection; A5S, antibiotic locking solutions; gentamicin

In an accompanying editorial, Dr. Michael Allon reviewed Dr. Jaffer’s paper and presented these results graphically (Figure 3). The benefit of all of these locks in preventing CRBSI is even more apparently graphically.9

Figure 3 Summary of frequency of catheter-related bacteremia with antimicrobial locks versus heparin locks in published randomized clinical trials. Five trials used an antibiotic lock, one used taurludine, and one used 30% citrate. In each study, the catheter-related bacteremia frequency was 50% to 100% lower in the group with antimicrobial lock, as compared with the heparin controls.

![Figure 3](image)

Dr. Allon points out that of the antibacterial catheter locks that have been tested in randomized clinical trials, all but two have included antibiotics.10, 11, 12, 13, 14 Using antibiotics as prophylaxis for catheter infections is counter to the advice of most infectious disease experts. As Dr. Allon states, “there is a very real concern that longer-term use of prophylactic antibiotics may result in selection for highly antibiotic-resistant microorganisms and infections, since the development of resistant organisms is almost certain. A French dialysis unit routinely using prophylactic gentamicin locks in dialysis catheters obtained monthly cultures of the bacteria colonizing the catheter lumen.15 After 2 years, 100% of the Staph Epidermidis isolates were resistant to gentamicin, methicillin, and quinolones. At that point, prophylactic antibiotic locks were discontinued. After an additional 2 years, only 50% of S epidermidis isolates were resistant to methicillin, 16% were resistant to gentamicin, and 50% were resistant to quinolones.” Figure 4, adapted by Dr. Allon, summarizes the results of the French study for one organism, Staph Epidermidis:

Figure 4

![Figure 4](image)

There are some studies that also show no development of resistance organisms in dialysis units using antibiotic prophylactic locks, as discussed by Dr. Jaffer. However, as Dr. Allon points out, with antibiotic lock solutions there is “potential for systemic toxicity when some of the antibiotic solution leaks from the catheter lumen into the circulation.” Systemic levels of antibiotics can be near to therapeutic levels in patients, when the antibiotic concentration in the lock solution is relatively high. Lower concentrations of antibiotics result in lower, but not zero antibiotic levels in the patients.

Concerns of bacterial resistance are minimized by use of an antiseptic solution as a catheter lock, such as the taurludine-citrate compound studied by Beijes,16 or the 30% citrate compound studied by Weijmer.17 This is due to the intrinsic difference
between antibiotics and antiseptics. Antibiotics work at very low concentrations through specific biochemical mechanisms. Subtherapeutic antibiotic levels generally induce resistant organism strains. Antiseptics work at higher concentrations through physical effects on the bacteria cell walls or cytoplasm. Sub-therapeutic levels have no effect on microorganisms.

However, antiseptic lock solutions can have their own challenges. Studies of taurine have demonstrated an increased tendency towards clotting of catheters, in spite of the presence of 4% sodium citrate. This clotting is probably due to the protein denaturation which occurs from aldehyde generation by taurine. Alcohol in high concentrations such as 70% also denatures proteins, but in lower concentrations of 30% or so any clotting tendency can be offset by citrate, and catheter materials are compatible with this level of ethanol. Isopropyl alcohol was used effectively in the LifeSite device, with some diminution in infection rate.

Citrate in high concentrations such as 30% to 47% is more dense than blood, and therefore will fall from a catheter into the blood stream from an IJ catheter, when the patient is upright. This happens with any lock solution that is different from the density of blood, whether higher or lower. This results in mild symptoms generally as we noted on our original paper on the effects of highly concentrated citrate on CRBSI. However, if injected rapidly and in high concentration, citrate can cause dangerous arrhythmias due to hypocalcemia. There was one case of cardiac arrhythmia and eventual death of a patient who received 10 ml of 47% sodium citrate, as noted in an FDA warning. This prompted recall of all 47% sodium citrate in the US, though it is still available for use with white cell pharessis procedures.

So, what is the safety margin when using citrate as a catheter lock? What is the margin of error or put another way, how many times the locking volume would have to be injected to cause serious symptoms? The following graph from our previous article indicates the citrate content of normal plasma in the patient, of various solutions that are already infused frequently into our patients, and in 2 ml of 23% sodium citrate concentration:

**Figure 5** Citrate content in milligrams of plasma, blood products, catheter lock.

The citrate content of the above 23% solution would be approximately that contained in 11 ml of 4% citrate. This is considerably less than in a unit of FFP. FFP has been infused very rapidly into some patient, and studies have been done to indicate what the limits are for citrate infusion. Figure 6 demonstrates the effects of very large amounts of citrate infusion over periods of 3 minutes to 6 hours. We include for comparison a slow infusion of 2 ml of 23% citrate, performed in a volunteers and also by accidental infusion in some patients (no symptoms occurred).

**Figure 6** Human studies, symptoms vs amount and rate of citrate infusion without calcium reinfusion.
These studies still do not answer the question of what happens with rapid bolus infusion of citrate, but the following graph is a compilation of data from several animal and studies with a comparison of amounts of citrate contained in 2 ml of 23% citrate and 10 ml of 47% citrate (Figure 7).

**Figure 7** Animal study of safety of Bolus IV Citrate vs. Cath lock amount.

![Graph showing animal study results](image)

As is seen, the infusion of 10 ml of 47% sodium citrate rapidly into a patient is an approximate dose of 25-30 mg/pound body weight, and should result in transient EKG abnormalities (but not immediate death). Infusion of 2 ml of 23% citrate should result in no cardiac symptoms, as predicted from animal studies. From a cardiac safety standpoint there is margin of safety of 5-10 fold for highly concentrated sodium citrate locks of 47%.

As noted in our study and that by Dr. Weijner, when catheters are locked with highly concentrated citrate some patients do complain of a “metallic” taste and sometimes tingling, as some of the citrate “falls” from the catheter.

With use of 4% sodium citrate as catheter lock there is a 50-100 fold margin of safety and there are virtually no symptoms when catheters are locked appropriately. Several studies have demonstrated that 4% sodium citrate as a catheter lock maintains catheter patency at least as well as heparin. A study by Lock demonstrated that tunneled CVC exchanges were 2.98/1000 catheter days with heparin versus 1.65/1000 pt-days with citrate (P = 0.01).

Frequency of tPA use was also higher in the heparin group versus the citrate group, 5.49/1000 (HP) vs 3.3/1000 patient-days (P = 0.002). A study by Grudzinski compared dialysis patients in two periods of time, and demonstrated that the rate of flow-related catheter exchange was not different when using citrate versus heparin (1.81 vs 1.88 per 1000 catheter days, P = 0.89). However, falsely elevated INR values were eliminated with citrate. The frequency of use of tPA was similar during for groups using citrate versus heparin (4.1 vs 3.23 per 1000 catheter days respectively, P = 0.07).

In vitro studies have shown that 4% sodium citrate has almost no antibacterial effect. It is only when the concentration is higher, such as 10%, that the antiseptic effect is seen. Not surprisingly there is no data proving that 4% citrate is effective in preventing CRBSI when used as a catheter lock. In the Grudzinski study, the number of bacteraemias was similar during the two periods (0.77 vs 0.94 per 1000 catheter days respectively, P = 0.36) A study by MacRae demonstrated 3.3 CAB/1000 catheter days for heparin vs 2.2/1000 catheter days for 4% citrate patients (NS). There was, as expected, a trend to more systemic bleeds in the heparin patients as compared to the...
citrate 4% pts (11/29, 38% vs 6/32, 19%, P=0.09). The proper concentration of sodium citrate for locking catheters would actually be 7%. This solution has a density of approximately 1.040, which is the same as blood density in a mildly anemic patient. This should be somewhat more effective in preventing catheter clotting than 4% citrate, and therefore be equal to or better than heparin. However in order to obtain a catheter lock that is antibacterial, other components would be needed. In collaboration with other scientists and pharmacists I began thinking of various possibilities some years ago, and had the following requirements for a desired antibacterial lock solution which could be used as a standard locking solution for central venous catheters:

- Anticoagulant properties comparable to heparin.
- Components previously approved for IV administration and generally regarded as safe (GRAS).
- Lack of caustic effects and protein denaturation.
- Safe for use prophylactically, with infusion of both lumen volumes.
- Ability to kill planktonic bacteria and fungal strains within 60 minutes.
- Ability to kill sessile bacteria in biofilm.
- No known bacterial resistance to components.
- Not an antibiotic.
- Relative density of 1.040.
- Preferably has a color, so that it is apparent when catheters are locked.

The practice of dialysis will be greatly aided by an antibacterial catheter lock that can be used routinely in all patients with tunneled dialysis catheters. Though catheter access will still less preferable than use of a fistula, at least catheter access will not create significant dangers of CRBSI and systemic infections.

REFERENCES

7. Poole et al. NDT, 2004, as presented by Dr. Michael Allan, ASDIN 2005.