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EDITORIAL

Catheter dysfunction and lock solutions: are we there yet?

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INTRODUCTION

Central venous catheter dysfunction continues to be a major source of morbidity and mortality in hemodialysis patients [1], in large part due to infections [2] and/or thrombus formation [3]. There is some evidence that these two processes may be interrelated, as infectious complications increase the risk of catheter-related thrombosis [4] and, once a thrombus is formed, it acts as a nidus for infection [5]. It is essential to understand the underlying pathophysiology, which forms the rationale for the use of lock solutions in the interdialytic period. The endothelial injury that occurs at the time of catheter placement, activation of coagulation and inflammatory pathways and the intraluminal stasis of blood between treatments (Virchow's triad) leads to thrombus and fibrin sheath formation [6]. Catheter-related bacteremia may result from external migration of bacteria from the skin or intraluminal spread, which leads to colonization. Bacterial adherence and resistance are further enhanced by biofilm formation, which protects the bacteria from systemic antibiotics [7].

Interdialytic catheter lock solutions that prevent both thrombosis and infection may help to alleviate some of these complications, as both these processes are primarily localized within the lumen of the catheter. A caveat that universally impacts the utility of lock solutions is spillage into the systemic circulation. *In vitro* studies suggest that a significant amount of the lock solution leaks into the circulation [8], although *in vivo* studies demonstrate that the actual leakage is significantly lower and is more pronounced in nontunneled catheters as compared with tunneled catheters [9]. Moreover, the wide variety of catheter lock solutions, limitations in previous study designs and the diverse patient population in whom these solutions have been studied thus far preclude generalized recommendations for catheter lock use. A multitude of solutions have been used over the years, but each of them has specific limitations [10].

Prophylactic antithrombotic catheter lock solutions

The conventional gold standard, heparin, has fallen out of favor due to concerns of inadvertent systemic anticoagulation [11], adverse events [12] and its tendency to induce biofilm formation [13]. Trisodium citrate 4% is as efficacious in maintaining catheter patency as heparin [14] and has the added advantage of antimicrobial properties [15]. There have been concerns of protein precipitation with higher concentrations, and an *in vitro* study suggests that 10% citrate may be used judiciously with minimal risk of embolic complications [16]. Indeed, 30% citrate when compared with heparin in a randomized double-blind controlled trial was found to have a shorter event-free survival in subclavian catheters, which the authors attributed to the hydraulic aspects of the lock solution [17]. Thrombolytic agents, including tissue plasminogen activator (tPA), have the ability to lyse the clot and can be used for both prophylaxis and treatment, although the costs may be prohibitive for routine prophylactic use, even when the substitution of heparin with recombinant tPA is only once weekly, in the midweek session [18]. Ethylenediaminetetraacetic acid (EDTA) in combination with minocycline, compared with 30% citrate and low-dose heparin in a 1:1:1 randomization, preserved catheter patency better than heparin and equivalent to citrate [19]. However, in another prospective randomized controlled trial comparing EDTA with heparin, although EDTA significantly reduced tunneled hemodialysis catheter colonization, the reduction in catheter-related bloodstream infections was not statistically significant and the EDTA group was associated with more thrombotic complications as compared with those subjects receiving heparin [20]. In an attempt to put this all together, a meta-analysis compared heparin with numerous other lock solutions, including varying concentrations of citrate, tPA, ethanol, cefotaxime–heparin, taurolidine–citrate and hypertonic saline–heparin, in 1883 subjects in both experimental studies and observational designs and found no significant difference in catheter patency between heparin and those treated with other lock solutions [21].

Prophylactic antimicrobial catheter lock solutions

Antimicrobial locks include both antiseptics and antibiotics. Antiseptics penetrate the biofilm without exposing the patient to side effects from systemic antibiotics but may be associated with an increased need for thrombolytics [22]. Antibiotic lock solutions including vancomycin, gentamicin, cefazolin, cefotaxime, minocycline, ciprofloxacin and linezolid are usually combined with an anticoagulant such as heparin, citrate or EDTA. Ideally, antibiotic locks for prophylaxis should be restricted to

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those patients in whom a catheter-related bacteremia would have devastating consequences or those at high risk of infection, due to concerns of systemic side effects and development of resistance [23]. Bactericidal properties of 70% ethanol, which acts by protein denaturation and has the ability to penetrate biofilms, were recently evaluated in a prospective, open-label, randomized controlled trial. The results demonstrated a trend toward increased catheter survival and a decreased rate of catheter-associated bloodstream infection with the use of a once-weekly ethanol lock [24]. A recent meta-analysis evaluated a total of 2575 patients with 3375 catheters from seven eligible randomized controlled trials and found ethanol locks significantly reduced the incidence of catheter-related bloodstream infections in hemodialysis patients with tunneled central venous catheters [25].

Prophylactic dually effective catheter lock solutions

A unique combination of 7% sodium citrate, 0.05% methylene blue and 0.165% parabens showed significantly less catheter-related bacteremia and a trend toward decreased catheter loss secondary to patency failure in a multicenter prospective randomized open-label clinical trial [26]. Researchers compared 4% citrate to taurolidine–citrate with heparin twice a week and taurolidine–citrate with urokinase once a week in another prospective multicenter randomized controlled trial [27]. Their data showed that the combined regular use of two commercially available taurolidine-based catheter lock solutions in a 2:1 protocol reduced the incidence of both catheter-related bacteremia and catheter dysfunction when compared with standard 4% citrate lock solution. Postmarketing experience with another solution containing taurolidine, heparin and calcium citrate showed a reduction in both catheter thrombosis and catheter-related bloodstream infections as compared with recent historical controls [28]. The prophylactic use of solution containing urokinase, taurolidine and 4% citrate once a week is also currently being evaluated in a multicenter randomized double-blind placebo-controlled study [29].

Although these combination protocols have proven to be safe and efficacious, it is difficult to isolate which of the components are responsible for the antithrombotic and antimicrobial effects seen in these studies. Nonetheless, these advances are promising and the development of novel lock solutions that maintain patency and decrease catheter-related bacteremia without serious complications continues to be an area of active and ongoing research.

Sodium bicarbonate: the ‘key’ to the lock?

In this issue of *Nephrology Dialysis and Transplantation,* El-Hennawy *et al.* [30] compare sodium bicarbonate to normal saline as a catheter lock solution in a prospective cohort, clinical open-label trial. Sodium bicarbonate is inexpensive and readily available and currently there is a paucity of data in the hemodialysis population with the use of this lock solution. The underlying premise for the use of sodium bicarbonate as a catheter lock solution is its antimicrobial and antithrombotic properties. The authors cite a plethora of evidence that warrants evaluation of sodium bicarbonate as a prophylactic lock solution. Some of these include bicarbonate-mediated chelation of calcium ions, which leads to decreased conversion of fibrinogen to fibrin, and that alkali solutions, such as those containing sodium bicarbonate, interfere with bacterial adherence and impact biofilm formation.

The researchers compared normal saline catheter lock solution for the first 9 months of the protocol ($n = 226$) with sodium bicarbonate catheter lock solution over the next 9 months ($n = 225$) in all patients requiring hemodialysis with central venous catheters. The study included both internal jugular catheters (tunneled and nontunneled) and femoral catheters (nontunneled). Primary outcomes were catheter loss due to catheter-related thrombus or catheter-related bloodstream infection. The normal saline cohort had higher odds of losing a catheter due to thrombi {odds ratio [OR] 26.6 [95% confidence interval (CI) 3.57–198.52]} and infections [OR 15.9 (95% CI 2.09–121.61)]. Patients who received sodium bicarbonate lock solutions had significantly reduced catheter loss due to thrombi ($P < 0.0001$) or bloodstream infections ($P = 0.0004$). These preliminary results are encouraging, although with the wide CIs, the magnitude of the potential benefit is uncertain and warrants further study.

There are major limitations of the current study, including a sequential study design that does not account for additional external factors that may have contributed to improved outcomes in the second group and the inclusion of both tunneled internal jugular and nontunneled catheters in internal jugular and femoral veins. Although the authors controlled for the type of catheter in a subsequent analysis, other factors unique to each situation may have contributed to the study outcomes. It would indeed be a step forward if sodium bicarbonate as a catheter lock solution is shown to have antimicrobial and antithrombotic properties, in addition to the fact that it is inexpensive and readily available, and the authors should be commended for this study. The significant decrease in both catheter-related thrombus and catheter-related bloodstream infections with the use of sodium bicarbonate locks in this study demonstrates proof of concept. However, the study design needs to be modified significantly in future studies to provide conclusive evidence in this regard. A well-designed randomized controlled trial would assist in further delineating the role of sodium bicarbonate locks in the management of catheter dysfunction. If proven effective and safe, then a catheter lock solution like sodium bicarbonate, that prevents both thrombosis and infection, maintains the structural integrity of the catheter and is not associated with the development of antimicrobial resistance, is highly desirable.

CONCLUSION

The search is on for the perfect ‘solution’, and although there have been remarkable advances in recent years, the field is still wide open for future innovation. The best prophylaxis still remains avoidance of central venous catheter placement in the first place, and if necessity mandates catheter placement, there should be a plan to remove the catheter as soon as feasible. Meticulous infection control and hygienic measures, education of all dialysis staff on proper catheter care and universal

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adoption of strict aseptic techniques may help minimize the morbidity and mortality associated with central venous catheters [31].

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part and the manuscript has been submitted solely to this journal and is not published, in press or submitted elsewhere.

(See related article by El-Hennawy *et al.* Sodium bicarbonate catheter lock solution reduces hemodialysis catheter loss due to catheter-related thrombosis and blood stream infection: an open-label clinical trial. *Nephrol Dial Transplant* 2019; 34: 1739–1745)

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