A Randomized Controlled Trial of Wire-Exchange versus Catheter Removal in Patients with Tunneled Dialysis Catheter-related Bacteremia

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ABSTRACT
Study Purpose

Catheter-related bacteremia (CRB) is a serious and frequent complication of tunneled-dialysis catheter (TDC) use with the potential for real harm, including endocarditis, septic arthritis, epidural abscesses, osteomyelitis, and even death. It is widely accepted that treatment of such infections with antibiotics is insufficient with only 20-30% cure rates most likely secondary to an inability to clear the catheter itself of bacteria. However, how to manage the catheter remains controversial. Given the potential risks of removing the catheter and later replacing it at a different site, investigators have looked at catheter exchange over a wire as an alternative. In observational studies and in one retrospective study wire exchange appears to have equivalent cure rates to catheter removal with delayed replacement. However, the patients who received catheter exchange in each of these studies were measurably less sick at presentation than those who had their catheters removed. We therefore propose a randomized, prospective clinical trial investigating the efficacy of wire-exchange versus catheter removal and delayed replacement in the treatment of less severe CRB, hypothesizing that removal and delayed replacement will be superior to wire-exchange given the potential for cross-contamination during wire exchange and the documented efficacy of catheter removal in the sickest patients.

Study Subjects and method of recruitment

Four hundred and forty patients with documented CRB secondary to a TDC requiring hospitalization at CPMC will be included in the study with 220 patients randomized to either wire-exchange or catheter removal. All study participants will be adults over 18 year of age. Any patient with signs of hemodynamic instability or shock will be excluded, as will all patients with evidence of exit site and/or tunnel site infection and all immunocompromised patients. Subjects will be recruited from the pool of patients with TDCs receiving care at CPMC clinics and/or medical offices, the emergency department, or any of our affiliated dialysis centers. Physicians practicing at all of these sites will be asked to notify study investigators of any potential study participants.

Study procedures

Patients will by definition require hospitalization for their infection. The number of blood draws and blood cultures should be equivalent to standard of care. Patients will undergo either wire-exchange or catheter removal with replacement 5 days later, both at 4 days after presentation. Patients randomized to catheter removal will require 1-2 temporary femoral line placements for dialysis before the TDC is reinserted. Patients may also require PICC line placement for the 3-week course of antibiotics at the discretion of the treating physician. Patients will need to be seen once in person at one week after the completion of antibiotics for surveillance blood cultures and will be contacted by phone at 2 week intervals during the 3-month follow-up to evaluate for signs and/or symptoms of potential recurrence of infection. In the event of such signs and symptoms, patients will be asked to return to either the medical office or the emergency department at CPMC for further evaluation and treatment.

Issues

Given that both interventions are included in the standard of care of CRB and neither has been proven to be more effective, we don't foresee any practical or ethical problems with the study. However, it could be argued that catheter removal and delayed replacement has the potential for more risk with regards to pain, bleeding, infection, and/or pneumothorax given the need for both new catheter insertion and intermittent femoral line placement for continued dialysis.

A. Study Proposal and Rationale

There are currently over 250,000 Americans receiving hemodiaylsis (1), and anywhere from 15-30% of these patients are receiving dialysis through a tunneled dialysis catheter (TDC) (2). One of the most important complications of TDCs is catheter-related bacteremia (CRB), occurring at rates of 2.0-5.5 episodes per 1000 catheter days, which is equivalent to 22,000-100,000 cases annually in the United States (3-5). Furthermore, CRB often results in serious systemic infections including endocarditis, osteomyelitis, epidural abcesses, septic arthritis, and even death (6). While antibiotic therapy is agreed to be crucial in the treatment of CRBs, what to do with the catheter is unclear. It is generally accepted that treatment with antibiotics alone without any manipulation of the catheter (ie catheter salvage) is insufficient, with only 22-32% of infections being cleared without recurrence (6); however, what to do with the catheter itself (removal with delayed replacement, guide-wire exchange, antibiotic lock therapy) is less clear.

Given the potential morbidity of removing the catheter with delayed replacement, investigators have studied less-invasive alternative approaches including guide-wire catheter exchange. Several observational studies of guide-wire exchange have documented comparable cure rates to those of removal and subsequent replacement (80-88%) but many of these studies have been criticized for inequality between groups, with the catheter removal group being more ill at the time of intervention. Robinson et al and Saad report 82% and 81% cure rates by guide-wire exchange in 23 and 43 patients respectively but did not evaluate catheter removal with delayed replacement amongst a similar patient populations (7,4). Beathead investigated the effect of guide-wire exchange alone versus guide-wire exchange with a new tunnel and exit site versus catheter removal and delayed replacement in 114 patients with cure rates of 88%, 75%, and 87% in each group. However, the groups were not randomized but instead the sickest patients received catheter removal, and those with potential exit site infection had a new tunnel and exit site created (8).

One retrospective study examined the outcomes of all cases of CRB at an institution during a 2 year time period amongst less systemically ill patients and found equivalent infection-free survival time between those patients who underwent guide-wire replacement and those who had their catheter removed with delayed replacement (9). However, in this study the decision as to how the catheter was managed was left to the clinical discretion of the physician, and although they argue that the patients were equivalently ill based on the incidence of severe systemic illnesses (including endocarditis, septic arthritis, and epidural abscess), they do not account for differences in the degree of illness at the time of presentation.

In light of these studies, it has become generally accepted that in patients with evidence of septic shock or hemodynamic instability, exit-site or tunnel-site infections, or recurrent CRB the catheter must be removed. However, in patients with less severe CRB the most effective treatment strategy has yet to be proven. Given the potential for contamination during wire-exchange and the very real potential for serious systemic illnesses as a result of continued or ineffectively treated CRB, in addition to the lack of generalizable evidence supporting equivalent cure rates between wire-exchange and catheter removal, we propose a randomized clinical trial among a less severely ill population of hemodialysis patients with CRB. Our hypothesis is that amongst a similarly ill patient population with CRB, catheter removal will be superior when compared with guide-wire exchange.

B. Study Design and Statistical Analysis

Any patient with chronic renal failure and end stage renal disease on hemodialysis via a TDC presenting to Columbia Presbyterian Medical Center (CPMC) with a CRB will be eligible for this study. Chronic renal failure is defined as renal failure requiring dialysis without a reversible cause or treatment other than dialysis or transplantation, to differentiate this from acute renal failure requiring temporary dialysis until renal function recovers. CRB will be defined as fever and bacteremia in patients with no other obvious source of infection, ie clear chest radiograph and urine studies and no other localizing

source of infection. Hemodynamically unstable patients will be excluded, as defined by a systolic blood pressure of less than 100mmHg, as will all patients with evidence of an exit site and/or tunnel site infection. All patients with persistent fever or bacteremia at 24 hours post-antibiotic initiation will be excluded. Additionally, any patient with HIV, underlying hematologic malignancy, chronic use of immunosuppressive medications, or any functional immunodeficiency will be excluded from the study.

Patients with documented CRB and clearance of their fever and bacteremia at 24 hours who have not been excluded for the above reasons will then be enrolled and subsequently randomized into one of two arms: guide-wire exchange versus catheter removal with replacement 5 days later. Interventions will be done 4 days after presentation as this will be the necessary amount of time to document both the original bacteremia and its clearance within 24 hours of antibiotic administration.

In all patients, specific antimicrobial therapy will be dictated by the treating physician, based on culture sensitivities and continued for a total of 3 weeks. Any patient with a Staphylococcus aureus bacteremia will require a trans-esophageal echocardiogram before enrollment in order to document the presence or absence of endocarditis, with all patients with endocarditis being excluded from the study. Blood cultures will again be drawn at one week after completion of antibiotics. The primary endpoint will be presence or absence of recurrent bacteremia within a 3-month follow-up period. Any bacteremia involving the original organism within a 3-month follow-up period will be considered a treatment failure. All data will be analyzed on an intention to treat analysis and if a patient dies, is lost to follow-up, or the catheter is removed for another reason, these patients will be considered to be treatment successes assuming there has been no documented bacteremia. Bacteremia with a different organism will likewise be considered as a treatment success assuming there is no evidence of recurrent bacteremia with the original organism within the 3-month follow-up period. Cures will be defined as a negative blood culture at one-week post-antibiotic completion and the lack of symptoms or positive blood cultures within the 3-month follow-up period.

Assuming a success rate of 80% with guide-wire exchange in this patient population, we will need a total of 440 patients (220 in each arm) to demonstrate a 12.5% improvement in treatment success (or 90% success rate) with catheter removal with 80% power and an alpha value of 0.05. Statistical comparisons will be made using the Chi-Squared test. A multi-variate regression analysis will be done at the completion of the study to investigate the effect of age, duration of TDC use before study enrollment, and bacteria type on treatment success. We will also document all adverse events incurred in each group as a result of the intervention (ie bleeding, infection, pneumothorax), comparing their frequency between the two groups using the Chi-Squared test.

C. Study Procedure

Patients with documented CRB currently require some manipulation of the TDC as part of their treatment so randomizing patients to guide-wire exchange and catheter removal will not subject participants to an unnecessary procedure; however, more patients may have their catheter removed and replaced than would typically. Additionally, because the catheter will be removed and replaced 5 days after removal, these patients will require 1-2 additional temporary femoral line placements to receive dialysis than if they had the line exchanged over a wire. Patients may require a PICC line in order to receive 3 weeks of antibiotics, but again, both the duration of antibiotics and necessity of a PICC line are standard of care. The number of blood cultures and blood draws would be equivalent to standard of care with a CRB. Finally, a trans-esophageal echocardiogram should be done on all patients with Staph aureus bacteremia because the duration of antibiotic treatment and perhaps the choice of antibiotics are different for endocarditis versus CRB. Therefore, this would not be an additional procedure. We anticipate the study to take approximately 1-2 years in order to achieve our enrollment goal.

D. Study Drugs

The only medications needed for this study will be IV antibiotics to be prescribed at the discretion of the treating physician, in accordance with the standard of care of CRBs.

E. Medical Device

There are no medical devices being studied. All catheters used will be standardized based on the catheters used at CPMC. If, during the 1-2 years of the study, CPMC changes the catheters they use, all patients in this study will continue to receive the catheters used at the study outset.

F. Study Questionnaires

There will be no questionnaires administered during this study.

G. Study Subjects

All patients over age 18 years of age presenting within the Columbia Presbyterian Medical Center with a documented CRB secondary to a TDC will be potential study participants. A CRB will be defined as the presence of documented fever and bacteremia in patients with a TDC without any other localizing source of infection (ie clear chest radiograph, negative urine studies, no evidence septic arthritis, osteomyelitis, cellulitis, or a wound infection other than at the TDC site). Amongst these patients, all who defervesce and clear their blood cultures within 24 hours of initiation of broad-spectrum antibiotics will be enrolled. Any patient with evidence of hemodynamic instability as defined by a systolic blood pressure of less than 100 mmHg at presentation or during the first 24h of antibiotics and any patient with evidence of an exit site and/or tunnel site infection will be excluded. Additionally, any patient with Staph aureus bacteremia with a trans-esophageal echocardiogram positive for endocarditis, and any immunocompromised patient as defined by HIV positivity, underlying hematologic malignancy, use of immunosuppressant drugs, and/or functional immunocompromise will be excluded. Additionally, all patients must be able to give consent. No potential participant will be excluded on the basis of race and/or gender.

H. Recruitment of Subjects

All study participants will be recruited from the pool of patients that present within the Columbia Presbyterian Medical Center (including outpatient clinics, the emergency department, and all affiliated hemodyalsis units) with a CRB secondary to a TDC requiring admission to the hospital (a decision which is up to the discretion of the initial physician). Physicians that practice in any of these places will be advised to contact a study physician with any potential cases of CRB secondary to a TDC that they believe would be well-suited for the study. Once eligible, patients will be asked to enroll in person by a study physician.

I. Confidentiality of Study Data

All participants will be coded by a random number system in order to ensure confidentiality. Data will be stored in a secure location, only accessible to the study investigators.

J. Potential Conflict of Interest

There is no apparent potential conflict of interest.

K. Location of the Study

The study will occur at Columbia Presbyterian Medical Center. Patients with a CRB secondary to a TDC requiring hospitalization will be potential study candidates and will be hospitalized within the Medical Center. Patients will have their interventions done during the hospitalization in appropriate areas and will be discharged to continue their IV antibiotics at the discretion of their dedicated physicians. Follow-up will require a visit to a medical office in order to repeat blood cultures within one-week of completion of antibiotics but will otherwise occur at 2-week intervals by phone during the 3-month follow-up period. If any patients endorse signs or symptoms suggestive of recurrent bacteremia, they will be asked to return to either the above-mentioned medical office or to the Columbia Presbyterian Medical Center Emergency Department for further evaluation and treatment.

L. Potential Risks

There is risk inherent to both the exchange of a catheter over a wire and catheter removal. The potential risk of catheter removal with subsequent replacement, however, is likely to be greater given the necessity of a new puncture and the need for intermittent femoral catheter placement for dialysis before the TDC is replaced. These risks include pain, bleeding, new infection, and pneumothorax. Additionally, any patient with a Staph aureus infection will incur the risks inherent to a trans-esphogeal echocardiogram, such as aspiration, respiratory distress, esophageal rupture, bleeding and infection.

M. Potential Benefits

The benefit to both groups would be treatment of their infection with appropriate catheter manipulation. There may or may not be any additional benefit offered by the specific manipulation they are randomized to receive.

N. Alternative Therapies

As the standard of care in treatment of CRB involves antibiotics and catheter manipulation, there is no real alternative therapy. However, the patient could elect to attempt treatment with catheter salvage, either through systemic antibiotic treatment alone or with antibiotic lock therapy. This is, however, obviously dangerous given the need for continued dialysis through the catheter, potentially spreading bacteria into the blood and perhaps fostering systemic infections such as endocarditis, septic arthritis, epidural abscesses and/or osteomyelitis. The obvious alternative to participating in the study, however, is to elect for one's own method of catheter manipulation under the guidance of one's principle physician.

O. Compensation to Subjects

There will be no compensation made to study participants.

P. Cost to Subjects

The subjects will not incur any additional costs as a result of participating in the study.

Q. Minors as Research Subjects

All subjects will be required to be over 18 years of age.

R. Radiation or Radioactive Substances

The only radiation exposure will be for chest radiographs and radiography used at the time of the catheter-related intervention. There will be no radioactive substance used.

S. References

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