Central Venous Catheters for Hemodialysis: How to Overcome the Problems

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The use of central venous dialysis catheters is increasing in clinical practice. These devices, although relatively easy to insert, do have problems. Catheter size limits the amount of dialysis that can be delivered. Central venous hemodialysis catheters minimize cardiopulmonary recirculation, but have increased potential for access recirculation compared to native or artificial arteriovenous (AV) fistulas and grafts. Developments in catheter design and optimal positioning have improved the amount of dialysis that can be delivered. Similarly, infection rates are improving with careful attention to peri-insertion care and the use of topical antiseptics and antibiotics. Although catheter thrombus remains a problem, the introduction of recombinant tissue plasminogen activator and mechanical dislodgement with an endoluminal brush have improved patency rates, but some patients may require long-term warfarin therapy.

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Key words

Central venous catheter, thrombosis, sepsis

Introduction

Central venous dialysis catheters have been used for access in patients with acute and end-stage renal failure (ESRF) for more than two decades. Not only are they the primary access in nearly all patients with acute renal failure treated by conventional intermittent hemodialysis and/or continuous renal replacement therapy, but they are also used more frequently in patients with ESRF. In part, this is due to the late presentation of some patients with ESRF or acute or chronic renal failure. In these cases, venous access dialysis catheters can be used as a temporary bridge until more permanent access, such as a native arteriovenous (AV) fistula, can be fashioned and allowed to mature. However, as more and more elderly patients with increasing comorbidity are taken onto hemodialysis programs, native fistulas, or the increased cardiac shunt from artificial AV grafts, may not be appropriate; central venous catheters become the preferred permanent option for vascular access.

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Adequacy of hemodialysis

Central venous hemodialysis catheters minimize cardiopulmonary recirculation, but have increased potential for access recirculation compared to native or artificial AV fistulas and grafts. In an audit — using a single-pool variable-volume model (Fresenius AG, Bad Homburg, Germany) — of approximately 100 patients in our own hospital dialysis program, adequacy of dialysis was highest in patients with AV fistulas, lower in those where an AV fistula was used for connection to one line and a central venous catheter was used for the other line, and least in those dialyzing solely through venous catheters (Fig. 1). Indeed, if there is a technical problem with one of the catheter lumens and the blood flow through the arterial and venous lumens is reversed, the result will be increased recirculation and even less adequate dialysis achieved. We now have an array of commercially available venous dialysis catheters, differing in design, varying from two single lumens to a single catheter with two lumens, which may have D-shaped or O-shaped cross sections of lumens, with no, single, or multiple side holes.

These differences in catheter design and internal diameter result in the generation of different flows and pressures [1], as laminar blood flow is related to the fourth power of the radius (Poiseuille's law), and even greater pressure is required to maintain blood flow when turbulence occurs. Thus, in clinical practice the use of different catheter designs results in differences in adjusted Kt/V, with greater Kt/V achieved

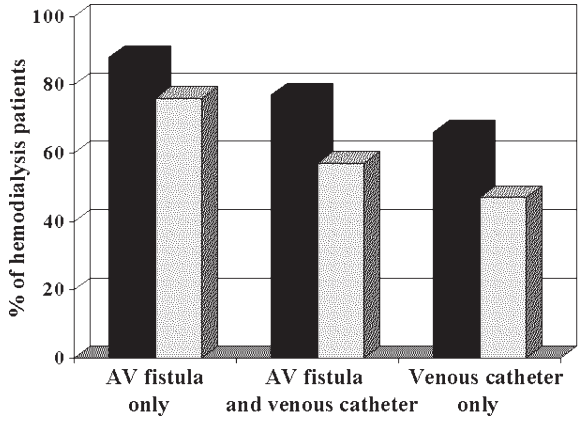

FIGURE 1 Percentage of hospital dialysis unit patients achieving an average Kt/V of > 1.2 (dark bars) or > 1.4 (light bars). A single-pool variable-volume model was used.

with twin catheter designs compared to dual lumen catheters with a double-D shape [2]. In addition, catheter position can also affect dialysis adequacy. Mechanical kinking of the catheter will result in increased resistance to flow and increased turbulence, thus reducing Kt/V. Thus, right-sided internal jugular catheters often provide more adequate dialysis than left-sided catheters due to the anatomical differences in venous shape. Similarly, the distance between the tips of the dialysis catheter will affect the degree of recirculation, with greater recirculation when the distance is short [3]. For twin catheters, a separation distance of 4 cm has been recommended to minimize recirculation [4].

Many studies have shown that the positioning of the venous dialysis catheter is important in determining catheter survival. Thus, right-sided internal jugular catheters have a greater reported survival than left-sided, and similarly, those with the catheter tip located in the right atrium compared to those with the tip in the superior vena cava [5]. Once there has been a problem and the original catheter removed, then second and subsequent catheters do not survive, on average, as long as the original [5].

Catheter-related problems

Although many catheters are removed electively, more are removed due to catheter-related problems [6]. The most common catheter-related problems causing removal are infections — whether it is of the exit site or a proven or suspected catheter-related bacteremia — and catheter thrombosis [7].

In theory, the dialysis catheter could become colonized by periluminal spread from migrating skin organisms. Once the integrity of the epidermis has been breached, an electrical gradient is set up that encourages bacterial migration along the catheter [8]. More recently, attention has been focused on bacterial contamination of the catheter hub. Rarely, catheter colonization follows hematogenous spread from a distant site, and exceptionally, after an infusion of a contaminated infusate. In many cases of bacterial colonization of the catheter, the number of micro-organisms is relatively small and does not cause systemic upset. At the time of connecting the patient to the extracorporeal circuit, small numbers are dislodged due to vigorous mechanical syringing of the catheter. Even so, blood cultures taken through the catheter are often negative. To try to overcome this, some studies have concentrated on the positive and negative predictive values of the results of nasal, catheter-hub, and exit-site cultures. Nielsen and colleagues reported similar predictive values for exit-site and catheter-hub cultures and subsequent episodes of catheter-related sepsis [9].

A single positive blood culture taken through the dialysis catheter may be due to intraluminal catheter colonization, hub contamination, or systemic bacteremia. To differentiate between catheter colonization and systemic bacteremia, most microbiology departments would report catheter colonization when the number of colony forming units was five times or greater from the catheter specimen compared to a comparable peripheral blood culture [10].

To improve the detection rate of catheter-related bacteremia, it is important to try and suck back the terminal clot in the catheter and send this for culture, rather than merely dislodging the clot. In addition, if the bacteria count is low, then detection rates can be improved by increasing the amount of blood taken for culture, from a minimal 5 mL to 20 mL. More recently an endoluminal catheter brush has been developed. These brushes are available in a variety of sizes and it is important to choose the correct brush size for the particular venous dialysis catheter. Studies utilizing the endoluminal brush have reported a much improved detection rate of catheter bacterial colonization [10]. The best results come from the tip of the brush, which should be processed using the acradine-orange Cytospin method (Cytospin centrifuge, Shandon, Runcorn, U.K.). Also, blood cultures taken through the catheter after brushing are more likely to be positive than cultures taken without prior brushing [10]. In controlled trials, endoluminal brushing was superior to all other conventional bacteriological methods, including catheter tip roll and tip flush [11]. The main advantage of the endoluminal brush is that the catheter does not have to be removed. In a small number of cases, catheter brushing will result in a transient bacteremia [10].

Because infection is one of the major causes of catheter loss, several strategies have been adopted to try to prevent colonization and contamination. Peri-insertion care is important. Many centers advocate prophylactic antibiotics and the use of nasal creams, such as the antiseptic chlorhexidine and naseptin, or antibacterial mupirocin for those with methicillin-resistant *Staphylococcus aureus* [12]. Topical mupirocin has been reported to reduce catheter colonization by up to fivefold [10]. The importance of taking optimum care with catheter insertion is emphasized by our own data, which showed that, following the same peri-insertion protocol, there was a greater infection rate in catheters inserted in the interventional radiological suite compared to the surgical theater (Fig. 2).

Following catheter insertion, a nonocclusive gauze dressing is preferred to prevent moisture at the exit site [12]. Although chlorhexidine has been shown to be superior to povidone iodine ointment for exit-site care [10], chlorhexidine is alcohol based and regular application may adversely affect some of the dialysis catheter materials. To be effective, povidone-iodine ointment has to be applied for several minutes. More recently, topical mupirocin applied to the catheter exit site after each dialysis session has been reported to increase catheter survival and reduce *S. aureus* exit-site infections [13].

Work on catheter composition has shown that hydrophobic staphylococci have increased adherence to polyvinyl chloride, silicone, and polyethylene, whereas adherence is reduced when other polymers such as tetrafluoroethylene and polyurethane are used [10]. The importance of catheter polymer composition

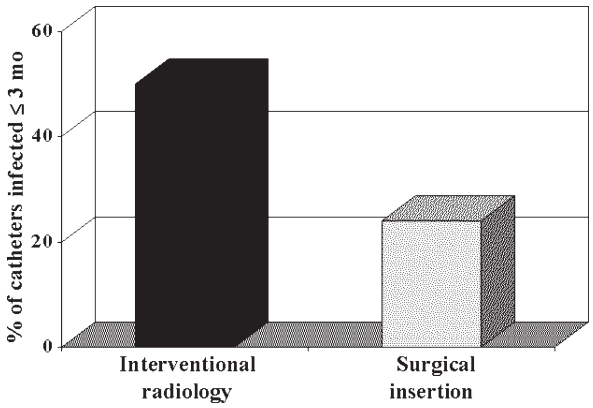

FIGURE 2 Percentage of Tesio catheters (Medcomp, Harleysville, PA, U.S.A.) that developed exit-site infection and/or catheter-related bacteremia within 3 months of insertion. Catheters were inserted in either the interventional radiology suite or in the operating theater suite. The same peri-insertion protocol was followed in all cases.

has been shown to be relevant in clinical studies, which have shown increased bacterial colonization with polypropylene catheters compared to tetrafluoroethylene or polyurethane catheters [14]. A further development has been the introduction of silver-coated catheters. *In vitro*, silver has antibacterial properties. Some studies have reported a reduction in bacterial colonization [15], whereas others have not shown any advantage [16]. These differences may reflect the difficulty in coating the catheter and that some coatings may be more effective than others [14]. However, up to 5% of patients develop an allergic reaction to the silver, requiring catheter removal. Antibiotic-coated catheters have been introduced for short-term use in the intensive care unit, with a reduction in the incidence of catheter-associated bacteremia and colonization reported with combinations of minocycline and rifampicin, and chlorhexidine and sulfadiazine. These catheters may not be effective as chronic catheters in ESRF patients, as the antibiotics leech out with time. Further development will be required for chronic use [17].

Other strategies to reduce catheter colonization have included intraluminal antibiotics with an antibiotic flush at the end of each dialysis session, and the use of antibiotics or antiseptics for the catheter hub. Whereas intraluminal antibiotics have not been shown to be effective [10], both gentamicin catheter locks [18] and the use of the antiseptic taurolidine (personal communication, B. Canaud) have been recently reported to be effective.

To overcome the increased risk of infection, two implantable devices have been developed. One (Dialock,™ Biolink Corp., Middlesboro, MA, U.S.A.) has a single implantable device with two chambers, each linked to a separate catheter; the other (LifeSite, Vasca, Inc., Tewksbury, MA, U.S.A.) has one catheter per chamber and thus requires two chambers to be implanted for dual catheter dialysis. At the current time, each system requires special needles to be used to enter the implantable chamber. Until standard dialysis needles can be utilized, this will add substantial costs to implantable catheters. Initial trials reported 21 infective episodes in 23 patients [19]. More recently, the introduction of an antiseptic lock has resulted in a marked reduction in infective episodes (personal communication, B. Canaud).

Catheter-related thrombosis

After infection, thrombosis is the next most important complication of venous catheters [7]. The catheter is a bioincompatible device lying within the major veins. Whereas AV fistulas and artificial grafts primarily result in endothelial and platelet activation, dialysis catheters predominantly result in thrombin generation, due to activation of the contact coagulation cascade, resulting in a fibrin sheath being deposited around the catheter. Once again, catheter polymer composition and design affect bioincompatibility and the risk of thrombin generation.

Catheter position is also an important factor in determining the likelihood of thrombosis. Left-sided catheters and those with the tips in the superior vena cava are more prone to thrombosis [5]. This may be due to the effects of volume changes during dialysis and contact between the catheter tip and the superior vena cava wall. Thrombus may also develop due to inadequate anticoagulation during hemodialysis [20].

In addition, patient factors are important, as a hypercoagulable state may develop secondary to catheter infection or due to a primary deficiency of one or more of the natural anticoagulants, anti thrombin III, heparin cofactor II, or phenotypic mutations in factors II or X, and either a deficiency or relative inactivity of proteins S and C, due to anticardiolipin antibodies or factor V Leiden.

Typically, catheter thrombosis is divided into intraluminal thrombus, with thrombus within the catheter lumen; catheter tip thrombus, with an occlusive thrombus that acts as a ball valve, preventing effective blood flow; pericatheter thrombus, with adherent clot between the venous wall and the catheter; and, finally, mural thrombus. Intraluminal thrombus can develop due to an inadequate volume of heparin inserted at the end of the dialysis session, or heparin escaping from the catheter between sessions, allowing the entry of blood into the catheter. Similarly, heparin loss may result in the development of a catheter-tip thrombus, but mechanical factors may also be important. Differences in catheter design — some having no side holes, others with multiple side holes — may affect heparin escape during the interdialytic period (Fig. 3). Historically, patients with intraluminal and tip thrombi were treated with urokinase [20], but with the withdrawal of urokinase other treatments are required.

Recombinant tissue plasminogen activator (rtPA) is another fibrinolytic, but it differs from urokinase in that it has a shorter half-life and is more effective, causing fibrinolysis not only on the surface of a thrombus but also within the thrombus, so being more potent than urokinase. Typically,

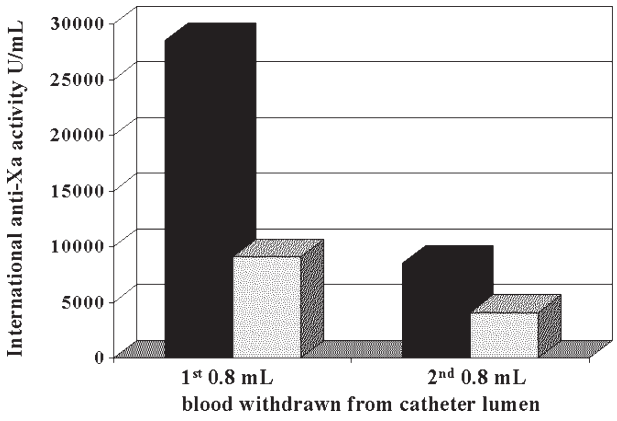

FIGURE 3 Median amount of heparin remaining in a dialysis catheter prior to commencing hemodialysis, in a catheter with multiple side holes (Tesio, Medcomp, Harleysville, PA, U.S.A.; light bars) and a catheter with a single side hole (Gamcath, Gambro AB, Lund, Sweden; dark bars). Heparin remaining measured as international anti factor Xa activity (U/mL).

2 mg of rtPA is instilled into the catheter lumen, and the catheter aspirated after 20 minutes. If not effective, then a second dose can be given. One study using rtPA on a regular basis as a capping-off solution reported that those treated with rtPA had better catheter blood flow rates than the control heparin group, and no patient required further thrombolytic treatment, whereas some 20% of the heparin group required thrombolysis [21]. As with urokinase, rtPA should not be administered to patients with recent intracranial hemorrhage, AV malformation or aneurysm, recent surgery, uncontrolled proliferative retinopathy, or systemic hypertension. Other treatments for intraluminal and catheter-tip thrombus include mechanical methods, such as the endoluminal brush or external catheter stripping [7].

Once the thrombus has been dislodged, many centers then use warfarin to try to prevent recurrence. Earlier studies in patients treated for hematological malignancy or parenteral nutrition claimed improved central venous catheter patency rates when patients were given 1 mg of warfarin, a dose that had no discernable effect on the International Normalized Ratio (INR). In our own patients, this approach using low-dose warfarin was not effective in preventing further thrombus formation. Similar studies using warfarin prophylactically from the time of catheter insertion did not show any significant benefit [22]. Some centers have found that once catheter thrombosis has occurred then patients require systemic anti-coagulation with warfarin, the dose being titrated upwards in a stepwise manner until the thrombotic episodes resolve [23]. Similarly, we have systemically anticoagulated those patients unfortunate enough to develop pulmonary emboli or intra-atrial thrombus, aiming for an INR of 3 – 4.5.

Ash recently reported that the use of high concentration citrate as a catheter lock resulted in improved catheter patency rates [24]. This may have been due to the anticoagulant effects of citrate, although citrate usually only works as an effective extracorporeal anticoagulant when ionized calcium is depressed, but the observed effect may have been due to a bactericidal effect of the high citrate concentrate. Synthetic hirudin analogs would be the most effective agents to use for catheter locks because they are the most potent inhibitors of thrombin. Unfortunately their cost is prohibitively high for clinical trials. Low molecular weight heparins (LMWHs) are more effective than standard unfractionated heparin in preventing thrombus formation on dialyzer membrane surfaces, but there is little information as to whether the use of LMWHs reduces dialysis catheter thrombus formation. In the future, the arrival of oral LMWHs may replace warfarin for the treatment of recurrent catheter thrombus formation.

Late complications of central venous dialysis catheters include venous stenosis. This typically occurs in the large elastic veins and is due to intimal damage at the time of insertion, or intimal activation due to either mechanical irritation or abnormal flow, either from the terminal tip or the catheter side holes, resulting in platelet activation and vascular smooth muscle activation and growth. Despite changing from subclavian vein to internal jugular catheterization, we have seen 10 patients with superior vena cava occlusion in the past 5 years. This is a much higher rate than previously reported [3,25] and may reflect the trend to insert twin catheters with much larger lumens than historically used. Our data are supported by a recent abstract suggesting that increasing catheter diameter is associated with increased superior vena cava stenosis [26]. Although these stenoses often respond to venoplasty, as they occur in elastic veins, the stenosis usually recurs and often requires stenting and life-long anticoagulation with warfarin [27].

Summary

The amount of dialysis that can be delivered by central venous catheters is limited by their internal diameter and length. The larger the catheter, the greater the trauma at catheter insertion; this may then lead to increased risk of infection and catheter thrombosis, which may later lead to central venous stenosis. To overcome these problems, we need further development to produce less bioincompatible catheters, which may result in reduced thrombogenicity and bacteriological adherence. Catheter coating with antibiotics and/or silver may prove beneficial in preventing infection. Similarly, the development of implantable devices may lead to a reduction in bacteriological contamination. For traditional catheters, topical mupirocin has had a significant impact in reducing local infection, but the question arises as to whether widespread use will eventually result in microbiological resistance. Other centers report similar benefits from topical antiseptics.

Although catheter thrombus formation still occurs, the incidence may decrease with a reduction in catheter colonization and infection. The withdrawal of urokinase has led to the introduction of rtPA, a more potent antithrombolytic. Similarly, the development of the endoluminal brush allows

improved diagnosis of catheter colonization and mechanical dislodgement of catheter thrombus. Until oral LMWHs are established in clinical practice, long-term warfarin remains the mainstay of treatment for recurrent catheter thrombus.

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