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Prevention of Hemodialysis Catheter-Related Bloodstream Infection Using an Antimicrobial Lock

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Key Words

Hemodialysis · Subcutaneous port · Tunneled catheters · Bloodstream infection · Catheter-related infection · Taurolidine

Abstract

Among currently available vascular access options for hemodialysis, central venous catheters show the poorest reliability, with frequent complications of thrombosis and stenosis impairing patency. The most serious problem, however, is catheter-related bloodstream infection (CRBI), which is typically a cause for removal of the catheter and protracted systemic antibiotic therapy. In our experience, a totally implanted device (Dialock®, Biolink Corp.) seems to confer a better global protection against catheter-related infections than standard tunneled catheters, accounting for 0.97 vs. 4.75 infection episodes/1,000 catheter-days, respectively ($p < 0.001$). Bloodstream infection rates, however, are not statistically different in the two groups (0.85 vs. 0.81 per 1,000 catheter-days; p = n.s.), indicating that the improvement is mainly related to local cutaneous infections. On the other hand, in the Sodemann experience, a new taurolidine-based lock solution (Neutrolin®, Biolink Corp.) greatly reduced CRBI rates with both subcutaneous ports and tunneled catheters to 0.29 and 0.20 episodes/1,000 catheter-days, respectively. These promising results await further confirmation from ongoing clinical trials.

Introduction

Effective hemodialysis (HD) therapy requires recurring access to the central blood supply three times a week over the patient's lifetime reliably without incurring medical complications. Few patients have been able to achieve this goal and most require several access sites and repair procedures over the years [1–3]. The situation is particularly distressing for those patients using catheters for their primary access. Although catheters provide an important benefit by allowing an immediate blood access, easy installation and removal as well as low cost of material and implantation, in the long term they carry high costs. Catheters have the poorest reliability with frequent complications of thrombosis and stenosis impairing patency. Schwab and Beathard [1] in their recent review paper point out the dilemma of relying on catheters. The most serious problem of HD tunneled catheters is catheter-related bloodstream infection (CRBI). Bloodstream infection is typically a cause for removal of the catheter and

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Table 1. Various catheter infection rates from the literature

Author	Date	Infections/ 1,000 days	Notes
Canaud review	1999	4.3	Range 0.5–20
Schwab review	1999	4	Only bacteremia
Kairaitis study	1999	6.5	Temporary catheters
Dittmer study	1999	14.1	68% colonized
Churchill study	1997	15.5	Temporary catheters
ASN Meeting posters	1999	4	7 study results averaged

Table 2. Catheter usage

	1996		2000	
	USA	Europe	USA	Europe
Incident patients	19%[a]	–	60%[b]	21%[b]
Prevalent patients	13%[a]	–	35%[b]	15%[c]

Catheter usage reported in: [a] USRDS reports; [b] DOPPS study data; [c] EDTNA/ERCA European Survey.

protracted systemic antibiotic therapy prescribed for several weeks. Blood infection is often the reason for hospitalization and is the second highest cause of mortality in the USA HD population. The latest results of catheter-related infections from published works are quite variable from clinic to clinic, as shown in table 1. A recent report in *Kidney International* emphasizes the possible severe complications of bloodstream infection related to access, like endocarditis, septic arthritis, epidural abscess, septic pulmonary emboli and osteomyelitis [4]. The authors reported on several recent studies having between 21% and more than 50% of the catheters becoming infected and this results in most of them being lost to use.

In spite of known problems, catheter use has been increasing in Europe and the USA, both as temporary access and as permanent access (table 2). The number of patients using catheters 1 month into their ESRD treatment was reported to have increased from 15% of HD patients to over 40% from 1991 to 1994 [3]. The 2001 Atlas of ESRD in the USA reported a 71% increase in the insertion rate of permanent catheters per 1,000 patient-years at risk from 1996 to 1999, with a rate of catheter insertions (temporary and permanent) in 1999 of 590 catheter insertions per 1,000 patient-years. The increasing use of catheters and associated complications and risks warrant effective preventive strategies.

Several studies support the notion that implanted devices predispose to infection by providing surfaces for bacteria to adhere to and form biofilm on the lumenal surface of the catheter [5]. This pattern is typical of vascular catheters and ports, and virtually all of them have biofilm developed and adhered to their lumenal surface [6].

Prevention of Catheter-Related Infections (CRI)

Jurewitsch described in a case report [7] his results using 2% taurolidine as a catheter lock for prevention of sepsis in parenteral nutrition patients. The lock was left indwelling for 12 h before removal. He reported a reduction in infection rate from 8.5 infection events per 1,000 days to 0.5 per 1,000 days.

In 1993, Sodemann evaluated a group of 35 HD catheter patients who started using an antibiotic lock consisting of high-concentration gentamycin and 1.3% sodium citrate. The results demonstrated 100% success in preventing bacterial infections over approximately 30 patient-years of experience, including some patients who were treated for over 4 years [8]. The technique consisted of instilling gentamycin/citrate into the catheter lumen after each HD session and to withdraw it before the subsequent HD session, in place of the customary heparin lock. Although this approach was successful and cost-effective, it was subsequently considered risky from the viewpoint of inducing bacterial resistance and was later dropped in favor of a non-antibiotic lock method.

In another attempt to prevent CRBI, Ash reported a technique of using a high-concentration citrate (47%) as a lock and he showed reduced infections in his clinic (1999 ASAIO Meeting presentation). However, citrate in high concentration (i.e., >10%) may not be safe as even small amounts of citrate entering the right atrium of the heart can cause a local reduction in Ca ions in heart muscle. Reduced ions can impair the pacemaker function and interfere with muscle contraction. In vivo experiments suggest that a citrate lock concentration even at 10% could degrade heart function if it is spilled [9]. Subsequently, high-concentration citrate was implicated in patient death(s) and the FDA issued a warning against the use of citrate in concentrations above 4%.

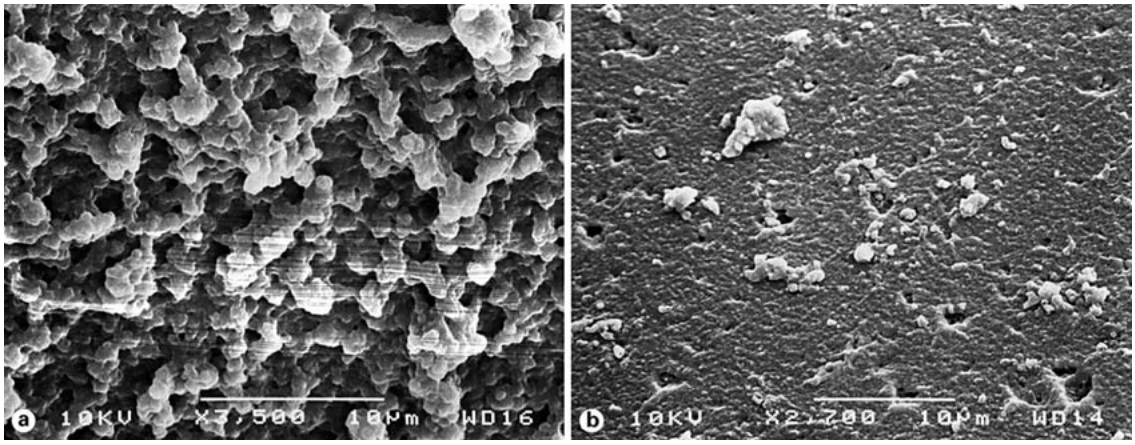

Fig. 1. SEM photographs of the inner surface of two catheters which were used for HD access and then removed. **a** Heparin lock, 7 months implanted, *S. epidermidis* biofilm. **b** Neutrolin lock, 5 months implanted, no microbial colonization [with permission from 5].

A New Antimicrobial Lock

Neutrolin® is a proprietary catheter lock solution invented by Sodemann [10] and developed by Biolink Corporation. The two active ingredients are taurolidine (an antimicrobial agent) and citrate, which is a well-established anticoagulant. Both of these agents have no measurable effects on the systemic system or cardiac function, even if the entire lumenal volume of the catheters is spilled into the bloodstream. However, Neutrolin has a powerful local effect inside the catheter [11–13]. It prevents intraluminal clotting and the colonization of both bacteria and fungi within the catheter, thus eliminating the formation of biofilm. Figure 1 shows two scanning electron microscope (SEM) photos of the lumenal surfaces of two different catheters. The left catheter was removed from a HD patient who had been using a conventional heparin lock for 7 months. Its surface was completely covered with biofilm. The photo on the right of an HD patient using a Neutrolin locked catheter has no evidence of any biofilm after 5 months in vivo. These photos show the typical effects on biofilm formation in vivo with and without using an antimicrobial lock.

Taurolidine is a unique nontoxic substance that eliminates binding of bacteria and some fungi to surfaces. Taurolidine is not an antibiotic and it has never demonstrated emergence of bacterial resistance. Taurolidine is a broad-spectrum antimicrobial active against virulent bacteria and fungi, responsible for most HD infections. This solution has been tested extensively to determine its biological safety. It has proven effective in preventing catheter colonization at the planktonic level and eradication of a developed biofilm in several types of in vitro tests. Table 3 summarizes the major relevant attributes of taurolidine.

Table 3. Attributes of Neutrolin which improve lock effectiveness

Broad-spectrum antimicrobial effect against bacteria and fungi
Safe and compatible with tissue and blood
No evidence of bacterial resistance
No systemic pharmacological effect
Avoidance of complications of heparin (i.e., bleeding and allergic reaction)
Inactivation of endotoxins
Reduced adherence of bacteria and blood to surfaces
Inhibition of coagulation induced by *Staphylococcus*

Clinical Results

Non-Antimicrobial Lock Solution

Subcutaneous Ports. According to preliminary USA and European studies that reported a reduced incidence of CRI with implantable ports with respect to standard tunneled catheters, in February 2000 we started at the Dialysis Unit of the Giovanni Bosco Hospital in Turin the first Italian experience with the Dialock®, a new implant-

Table 4. Infection rate: Quarello's Dialock/citrate 3.8% results; 35 patients at an average use of 7.5 months and a total experience of 22.3 patient years

	Patients %	Infections/ 1,000 days	Hospital admissions, %	Port lost %	Deaths %
None	80	–	–	–	–
Bloodstream	17	0.85	5.7	2.8	0
Exit site	0	0	0	0	0
Pocket	2.8	0.12	2.8	0	0
Results	–	0.97	8.5	2.8	0

Table 5. Infection rate: Quarello's catheter/heparin results; 37 patients at an average use of 12 months and a total experience of 40.2 patient-years (last implantations and still in use)

	Patients %	Infections/ 1,000 days	Hospital admissions, %	Catheter lost, %	Deaths %
None	31	–	–	–	–
Bloodstream	23	0.81	7.8	7.9	2.6 (1 pt)
Exit site	63	3.6	0	0	0
Tunnel	10.5	0.34	2.6	0	0
Results	–	4.75	10.4	7.9	2.6

able subcutaneous port produced by Biolink. In agreement with previous studies, we utilized a citrate 3.8% lock solution between each dialysis session to maintain the catheter patency [14].

Up to August 15, 2001, we implanted 35 devices in 17 men and 18 women (mean age 61.2 years, median dialysis duration 12.8 months). Mean follow-up was 232 days (13–559), accounting for a total observation time of 267.1 patient-months. During this 18-month period, 7 episodes of CRBI were recorded in 6 patients (0.85/1,000 catheter-days) and only 1 episode of pocket infection (0.12/1,000 catheter-days) (table 4). One patient developed severe endocarditis and spondylodiscitis, but recovered completely after catheter replacement and prolonged antibiotic therapy, with salvaging of the port. In another patient the sudden occurrence of a severe sepsis required the removal of the device.

Slightly better preliminary results (0.73 episodes of CRBI per 1,000 catheter-days) were observed in the Dialock Italian Multicenter Study (interim analysis).

Tunneled Catheters. Since 1993, in our dialysis unit more than 300 chronic HD patients were submitted to long-term indwelling tunneled catheters (Tesio, Medcomp). A prospective survey for major adverse effects in 250 of these pairs of catheters, excluding the patients lost to follow-up, indicated that an infectious event was the cause of catheter loss in 8.4% (21/250) of the cases. Heparin was utilized as lock solution in all Tesio catheters.

With the aim of gathering information in environmental conditions analogous to Dialock patients, avoiding the bias of high nurse turnover and changing protocols over time, we limited our infectious complications survey to the tunneled catheters implanted in the last 2 years or still functioning at that time. Data about 38 catheters in 37 patients (14M/23F), mean age 65.5 (41–87), mean follow-up 386 days, and cumulative follow-up of 482 patient-months were available for analysis (table 5). Twelve episodes of CRBI occurred (0.81/1,000 catheter-days), causing catheter loss in 3 cases. One patient died as a consequence of endocarditis and cerebral metastatic colonization. No catheter removal was due to exit site infection (3.6/1,000 catheter-days) or tunnel infection (0.34/1,000 catheter-days).

Although several methodological biases emerge from the comparison of two heterogeneous groups (i.e. patient selection, access indication, comorbidity, duration of follow-up), our results deserve a few comments. The quite unusual low incidence of CRBIs achieved with either tunneled catheters and ports probably reflects the strict sterile measures for catheter care in our unit. On the other hand, the high exit site infection rate with tunneled catheters, resulting in recurring antibiotic therapy delivery, though not a cause of major complications and higher hospitalization incidence, may predispose to antibiotic resistance and affect possible future CRI treatments. Moreover, the rate of catheter removal is higher in the Tesio group and a sepsis-related death should also be taken into account (though only one since 1993). The unsatisfactory situation with tunneled catheters is opposed by the almost nonexistent pocket infection rate with the subcutaneous port. This comparison demonstrates the validity of the new device in avoiding local skin infections.

Antimicrobial Lock Solution (Neutrolin®)

Subcutaneous Port. A clinical trial was conducted by Sodemann to evaluate the utility of combining the new implantable device Dialock® (Biolink Corp.) and a new antimicrobial and anticlotting lock (Neutrolin, formerly called CLS) made up of taurolidine and low-concentration citrate [15]. Starting in June 1998, patients were implanted with Dialock, produced by Biolink Corporation. After each dialysis session the catheters were locked

with Neutrolin allowing it to dwell in the catheter between cycles. The study included 71 patients treated for an average time of 16 months with several patients exceeding 3 years [9]. The bloodstream infection rate was less than 0.3 episodes/1,000 days of treatment (table 6). This is substantially less than published reports with HD catheters. In 64% of these long-term patients no infections were registered and 77% of the infections were resolved with a conventional course of systemic antibiotics.

Tunneled Catheters. Concurrent with the Dialock study, Sodemann's catheter patients were also evaluated using a Neutrolin lock solution. During more than 3 years, 76 patients with an average experience of 6.5 months were observed. They also experienced a very low infection rate. The bloodstream infections were 0.20 episodes/1,000 days. In 41 patient-years of treatment, only 1 patient was hospitalized for infection complications, no catheters were lost due to infection and no deaths occurred due to infection. No infectious complications were experienced by 84% of the patients (table 7).

Current Studies. Two major randomized, controlled studies have been planned. In the USA, the first phase of a study using taurolidine in HD patients has started patient enrollment. The trial will compare infection and patency measurements of patients with taurolidine against a cohort of heparin lock patients. Similar studies are underway in Italy and will measure the infection and patency rates of catheters and Dialock using Neutrolin and compare the results to the citrate alone cohort.

Table 6. Infection rates: Sodemann's Dialock/Neutrolin Study; 71 patients at an average time of over 16 months

	Patients %	Infections/ 1,000 days	Resolved %
None	64	–	–
Bloodstream	11	0.29	100
Pocket	28	0.8	68
Result		1.09	77

Table 7. Infection rates: Sodemann's catheter/Neutrolin results; 76 patients at an average usage of 6.5 months and total experience of 41 patient-years

	Patients %	Infections/ 1,000 days	Hospital admissions, %	Catheter lost, %	Deaths %
None	84	–	0	0	0
Bloodstream	4	0.20	1.3	0	0
Exit site	14	0.74	0	0	0
Tunnel	6.6	0.33	0	1.3	0
Result	–	0.80	1.3	1.3	0

Conclusive Remarks

Our 18-month experience with a totally implanted device as HD vascular access demonstrated a better protection against CRI than standard tunneled catheters, accounting for 0.97 vs. 4.7 infections/1,000 catheter-days, respectively ($p < 0.001$). Bloodstream infections rates, however, are not statistically different in the two groups (0.85 vs. 0.81 per 1,000 catheter-days), indicating that the improvement is mainly related to local cutaneous infections. On the other hand, in the Sodemann clinical study, a new taurolidine-based lock solution (Neutrolin®, Biolink Corp.) greatly reduced the CRBI rate in both subcutaneous ports and tunneled catheters to 0.29 and 0.20 episodes/1,000 catheter-days, respectively.

In conclusion, although the use of a totally implanted device already confers a better protection against CRI than standard tunneled catheters, the possible occurrence of rare but life-threatening complications remains an unsolved problem. Based on the currently available data, the Sodemann clinical results with taurolidine-based lock solution appear to be a crucial advance in this direction. These promising results await further confirmation from ongoing clinical trials.

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