

Two Years' Experience with Dialock[®] and CLS[™] (A New Antimicrobial Lock Solution)

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Introduction

Central venous catheters are reluctantly used as blood access for hemodialysis because of safety concerns and frequent complications, e.g., sepsis, thrombosis and vessel stenosis. Nevertheless, 20% or more of all patients are relying on atrial catheters for chronic dialysis because of lack of any other blood access. Two recent developments tackle the most critical problems of the catheter: safety and sepsis. An implantable access port ameliorates or eliminates safety problems as air embolism and blood loss to the environment and the antimicrobial locking solution eliminates sepsis related to biofilms in catheters. This paper reports about results of a German Dialock[®]/CLS study, the first study using an antimicrobial catheter locking solution in a large number of patients. Dialock and CLS have been developed by Biolink Corp., USA.

The study was approved in May 1998 by the ethics committee of the 'Landesärztekammer Baden-Württemberg'. Eligible patients were at least 18 years of age requiring hemodialysis. Inclusion criteria were vessel exhaustion and/or congestive heart failure. Pregnancy and inability to provide informed consent were exclusion criteria. The purpose of this pilot trial was to demonstrate the safety and efficacy of the Dialock in combination with a new heparin-free antimicrobial lock solution.

Materials

The original Dialock system has been described elsewhere [1].

Dialock is a subcutaneous device consisting of a titanium housing with two passages with integrated valves connected to two silicone catheters. The system is implanted subcutaneously below the clavicle. The tips of the catheters are placed in the right atrium. The port is accessed percutaneously with needle-cannulas.

Half of the patients originally received the first version of Dialock. The current version of Dialock has a modified body allowing for easier needle access and improved wire reinforced catheters without side holes. This version was implanted beginning in the middle of 1999.

Between dialysis sessions the housing and catheters are filled with the catheter locking solution (CLS). CLS is a mixture of taurolidine – an antimicrobial substance –, citric acid and citrate for anticoagulation. Taurolidine is a unique nontoxic substance with antimicrobial [2], antimycotic [3], antiadherent [4] and antiendotoxic [5] properties. It is effective against multiresistant bacteria [6] and also inhibits staphylococcus coagulase [7], a clotting activator not inhibited by heparin, hirudin or antithrombin.

Systemically, the infusion of even large volumes of taurolidine solution showed no measurable effect in a large randomized study [8]. Taurolidine has no systemic activi-

ty on the coagulation system or on laboratory samples. For this reason citrate was added to CLS. The pH of CLS is titrated with citric acid to increase the biocidal activity of taurolidine [9].

Risk Analysis

No adverse effects related to the CLS have been surfaced so far. Taurolidine dissociates into taurultam and this decays with a half-time of $t_{1/2}(\alpha) = 0.14$ h and $t_{1/2}(\beta) = 2.22$ h respectively. The final products are taurine (an amino acid), water and carbon dioxide [10].

The CLS is injected at the end of the treatment into the catheter and aspirated again before the next treatment. During this procedure it is possible that a small part of the CLS bolus leaves the catheter. Furthermore, taking user error into account, larger amounts of the CLS may be injected. As for any device, risk analysis must show that the combination of likelihood and severity of such an event is below an acceptable threshold.

The likelihood of double injection into the same lumen must be assumed as probable. The pre-filled syringe contains 6 ml. Under worst case fault condition the full syringe is injected into one passage. This means that approximately 3.5 ml of the CLS are injected as bolus.

Effect of Taurolidine. Blenkarn [11] mentions studies where up to 20 g of taurolidine per day have been applied. 3.5 ml of CLS contains only 0.2% of this amount. As total dose this amount is clearly negligible. Assuming a short term distribution in the plasma volume of 3 liters only, the concentration is ~ 16 mg/l compared to 50 mg/l plasma concentration mentioned as typical by Blenkarn [11]. In the same paper, bolus application of 1 g of taurolidine is mentioned. It is therefore concluded that taurolidine in CLS poses no risk in case of unintended bolus injection.

Effect of Citrate. Again, short-term distribution in plasma space is assumed. Citrate complexes ionized calcium and the related hazard is hypocalcemia. Two molecules of citrate bind three molecules of calcium. 3.5 ml of CLS contain 0.47 mmol of citrate able to bind ~ 0.7 mmol of ionized calcium. For comparison: 250 ml of ACD(A) blood for transfusion purposes contain ~ 5.6 mmol of citrate, which is a tenfold higher amount but cannot be infused within 2 s.

The normal value of Ca^{2+} is 1.26 mmol/l under physiological conditions and the total amount in 3 liters of plasma is 3.78 mmol. This amount is reduced by citrate to 3.08 mmol and the resulting plasma concentration is ~ 1.03 mmol/l that can be regarded as safe under the worst-case assumptions made for the distribution of ci-

trate. The citrate will rapidly distribute in the extracellular space and will be metabolized within a few minutes by the liver. Biolink has confirmed the safety of CLS with large animal acute studies.

However, the same calculation with 3.5 ml done for a 1,600 mmol/l citrate concentrate (467 g/l or 46.7% solution, triCitrasol®) would result in a complete depletion of Ca^{2+} . This complete depletion of ionized calcium even for a short period is life-threatening [12].

Patient Demographics

The study began in Ettenheim and Lahr where most of the study patients are dialyzed. After the initial success, patients from all parts of Germany were accepted. Between June 1998 and September 2000, 70 patients (29 male, 41 female) were enrolled into the study. The mean age at implantation was 63 years (range 30–88). The distribution is shown in figure 1. Thirty-one patients were diabetics and 13 had implanted pacemakers. Other comorbidities were short-bowel syndrome with colostomy bag, previous cardiac surgery, existing infection at the time of implantation, hypercoagulability, liver cirrhosis with low platelet count, anomaly of the vena cava and venous vessel stenosis. Twenty-four patients died from causes not related to Dialock. Six patients were transferred to other treatments during 76 patient-years.

Catheter Placement

The right internal jugular vein was the preferred vessel for catheter placement. In more than 50% of cases, however, another vein had to be used and in 12 cases the femoral vein was the only remaining choice. Table 1 shows the veins used for the first catheter implantation. Six patients required a catheter replacement and 1 patient required two catheter replacements because of flow problems. The femoral route was used as a last resort. Intended placement of catheter tips was the right atrium. This was achieved in each patient at least on half of the time in all upper torso placements. For femoral placement, the catheters only reached the kidney level in the IVC. Now using longer catheters, the atrial position is achieved.

Access Procedure

Accessing the Dialock has previously been described [1]. The puncture site is first cleaned with alcohol and then disinfected with an alcohol pad for 3 min. The needles are placed and the trocars are withdrawn. The clamps are closed and the needle caps removed. The locking solution is aspirated and the remaining procedure is identical to the common access technique. Neither patients nor

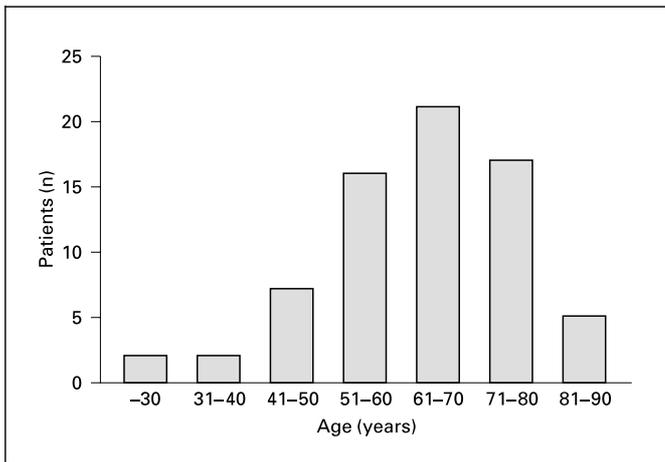


Fig. 1. Distribution of patients at implantation.

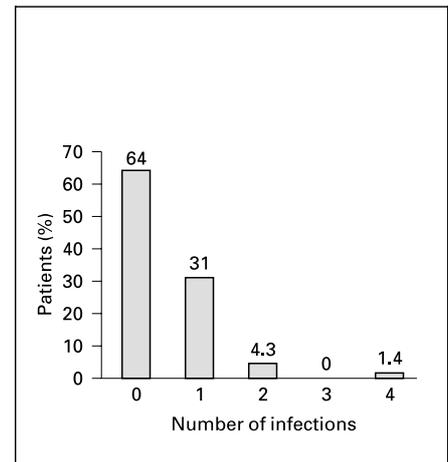


Fig. 2. Distribution of infection episodes among patients (13 months average patient experience using Dialock/CLS).

medical staff wear masks during the procedure. The use of gloves is optional. The whole procedure from the start until the beginning of dialysis takes less than 10 min. At the end of the treatment, the port and the catheters are rinsed with saline and each side is filled with 3 ml of CLS from a pre-filled syringe.

Treatment of Sepsis

Fever and shivering were indicators for sepsis that was confirmed by elevated white blood cell counts, increase of C-reactive protein (CRP) and positive blood culture. Pocket infection was identified by redness, pain or swelling around the port. Treatment was initiated immediately after taking blood samples by systemic antibiotic treatment through the Dialock (vancomycin, cefotiam). For pocket infections this treatment alone was insufficient and seven devices were explanted between May and November 1999. Subsequently, losses of implants were avoided by injection of 160 mg gentamicin into the pocket in addition to the systemic antibiotic treatment. Blood samples following this application revealed a slow release of gentamicin into the blood stream. The highest concentration observed was 4.2 µg/ml.

Data Evaluation

Death and/or explantation of the Dialock as of October 2, 2000 were the endpoint for data evaluation. The number of catheter days for each patient on the study was calculated from the difference between the endpoint and the implantation date. Data from treatment protocols were put into a relational database and all adverse events

Table 1. Veins used for the first catheter implantation

Jugular internal right	33
Jugular internal left	12
Jugular external left	2
Subclavian right	5
Subclavian left	6
Femoral right	10
Femoral left	2
Total	70

were transferred to a spread sheet program for further evaluation. Infection events occurring during the first 30 days after implantation (surgery-related) or following a previous infection within 30 days were not counted as independent infection events.

Results

Forty-two patients (60%) had no infection and this number increases to 45 (64%) when infections occurring within 30 days after implantation are omitted. Excluding these early events, 25 patients experienced a total of 30 infections (fig. 2). The majority (22 events in 20 patients) were pocket infections. The first 7 of these pocket infections caused the loss of the Dialock. After initiation of local treatment with gentamicin no further devices were lost due to pocket infection. No infection events were recorded within the last 3 months although the expecta-

tion rate calculated on the previous occurrences would be approximately 4 pocket infections. This may be related to increased nursing care to avoid infection.

The study results in a normalized pocket infection rate of 0.8 per 1,000 catheter days and a normalized rate of bloodstream infections of 0.29 per 1,000 days.

Discussion

Safety concerns and high complication rates have caused catheters to be regarded as temporary or last resort blood access. Potentially fatal risks related to central venous catheters include air embolism [13], severe blood loss [14] and electric shock [15]. These specific risks have been substantially eliminated by the inherent design and implantation of Dialock.

The complications of infection have been quite low in this study. Catheter-related infection or bacteremia was less than 0.3 episodes per 1,000 catheter days of use, which is considerably below recent reviews of catheter

studies. Schwab and Beathard [16] reported rates of 4 episodes per 1,000 days and Canaud [17] reported 3.5 episodes per 1,000 days with permanent catheters.

Pocket infection in this study were 0.8 episodes per 1,000 days. This rate is lower than analogous catheter exit site infections reported as 1.8 episodes per 1,000 days when the site is protected with mupirocin in the treatment group and 14.3 in the control group [18].

We have observed that the incidence of pocket infection has been reduced in the last 10 months of the study following greater attention to accessing technique. Currently, we strive to treat all infections to avoid removal of Dialock and now have a 77% eradication of infection over the full study. In addition, we have instituted an infection prevention strategy that has eliminated pocket infections in all of the currently enrolled patients (40) over the last 4 months.

Our experience with the Dialock/CLS has been gratifying. We believe the Dialock system is ready for widespread evaluation by clinicians to further elucidate its role in hemodialysis access.

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