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Mechanical Integrity of Hemodialysis Catheters is Maintained After Exposure to a Novel Catheter Lock Solution

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Abstract

Aim—The objective of this in vitro study was to demonstrate the mechanical integrity of hemodialysis catheters after exposure to the combination of N-acetylcysteine, tigecycline and heparin.

Methods—We used three types of hemodialysis catheters – polyurethane, silicone, and carbothane. Catheter segments were incubated in: (1) a novel catheter lock solution (NCLS) that contained N-acetylcysteine, tigecycline, and heparin, or (2) heparin alone as control for various time intervals up to 2 weeks. At the time of testing, each segment was rinsed and cut longitudinally into 2 sections. All catheter sections were scanned using an optical dissecting microscope to check for surface abnormalities and measurement of wall thickness. We also carried out tensile strength testing of another set of catheters using a universal testing machine. Tested parameters included stress at yield, strain at yield, stress at break, strain at break, modulus of elasticity, and force at break.

Results—The surface of catheters in both groups appeared similar by microscopy. The mean wall thickness was not significantly different in the NCLS- vs. heparin-exposed catheters ($p > 0.05$). Most tested tensile strength parameters were similar in the two groups of catheters at the end of 2 weeks of incubation. In particular, the force at break of all tested catheters remained much greater than that recommended by industry standards.

Conclusions—The use of a novel catheter lock solution, consisting of N-acetylcysteine, tigecycline and heparin, does not impair the mechanical integrity or increase the propensity for fracture of hemodialysis catheters.

Keywords

Hemodialysis catheters; mechanical integrity

Background

Indwelling vascular catheters are a common cause of nosocomial bloodstream infections particularly among hemodialysis-dependent subjects. The incidence of end stage renal disease (ESRD) requiring hemodialysis is approximately 2–3% per year, and in 2007 about 350,000 Americans had ESRD.¹ Review of national surveillance data reveals that 13% of patients with ESRD used central venous catheters (CVCs) for hemodialysis in 1995; this had

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Potential Conflicts of Interest: R.O.D has assigned the rights of a patent describing the use of N-acetylcysteine to combat device-related infections to his employer, Baylor College of Medicine (BCM). There is currently no licensing agreement regarding this patent between BCM and any company and hence no receipt of royalties.

increased to 20% in 2007.¹ Thus, the population at risk for hemodialysis catheter-associated bacteremia has greatly increased in recent years. National data indicate that patients who undergo hemodialysis by means of a CVC have 1.5 catheter infections per patient year.¹ Infection is the second leading cause of death among ESRD patients and use of CVCs as vascular access is a predictor of all-cause mortality and infection-specific mortality.² Another issue contributing to patient morbidity is the increasing prevalence of multi-resistant pathogens. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) species have been isolated from ESRD patients in 72% and 30%, respectively, of hemodialysis units in the United States.³

Salvage of an infected catheter can be attempted in the case of long-term catheters with an intraluminal infection in a hemodynamically stable patient with uncomplicated bacteremia. In most instances of attempted salvage, both systemic antibiotics and antibiotic lock solutions are used. Predicated on the high level of antimicrobial resistance of biofilm-embedded bacteria, the goal of antibiotic lock therapy is to instill antibiotics locally within the catheter lumen at concentrations that are 100–1000 fold higher than those achieved with systemic antibiotics.⁴ We previously conducted a pilot clinical trial investigating the use of a novel catheter lock solution (NCLS) consisting of N-acetylcysteine, tigecycline and heparin in the salvage of infected hemodialysis catheters associated with bacteremia.⁵ In that study population, which included patients with MRSA and VRE infections, we treated the infection successfully in 83% of 18 cases and did not observe any major adverse events. The results of this trial suggest that this NCLS constitutes a feasible, effective, and safe catheter-salvage strategy in patients with bacteremia associated with tunneled hemodialysis catheters.

The use of various catheter lock solutions raises questions about their effect on the mechanical integrity of hemodialysis catheters. Very few studies have examined this issue and this may have limited the wide-spread use of lock solutions for either treatment or prevention of catheter infections. We are aware of only two other studies that investigated the effect of potential lock solutions on the mechanical integrity of hemodialysis catheters.^{6,7} Since we plan to conduct a phase II randomized controlled trial using NCLS as a catheter-salvage strategy, it is important to rigorously assess the effect of this solution on the mechanical properties of hemodialysis catheters. The aim of the current study was to demonstrate the mechanical integrity of hemodialysis catheters after exposure to NCLS vs. heparin alone.

Methods

Catheters

We used the following type of catheters: (1) polyurethane - 11.5 French dual lumen Mahurkar catheters, (2) silicone – 15 French dual lumen Quentin Permucath catheters, and (3) carbothane – 14.5 French dual lumen Tal Palindrome catheters (all manufactured by Covidien, Mansfield, MA).

Experiment 1

1-cm segments of each catheter type were incubated at 37°C in either (1) NCLS that contained NAC 80 mg/ml, tigecycline 1 mg/ml, and heparin 2000 units/ml; or (2) heparin 2000 units/ml alone as control. We elected to use heparin as a control because it constitutes the current standard of care for instillation into hemodialysis catheter lumens when not in use in order to prevent catheter thrombosis. Catheter segments were incubated in the tested solutions for 24 hours, 72 hours, 1 week, and 2 weeks. At the time of testing, a segment was removed from the incubating solution and rinsed with 3 ml of normal saline and then allowed to air dry. Each segment was then cut longitudinally into 2 halves. The inner and

outer lumens of each half of the catheter segment was scanned using an optical dissecting microscope, Nikon SMZ 800 (Nikon Instruments Inc., Melville, NY) with magnification of 60x to look for surface abnormalities such as surface irregularity, fissures and pores. The wall thickness was measured in 2 different areas for each half catheter segment using Motic Images Plus 2.0 imaging software (Ted Pella, Inc., Redding, CA). Each experiment was conducted in triplicate. Thus, there were 12 readings of wall thickness for each time point.

Experiment 2

10-cm segments of the three types of catheters were incubated at 37°C in the NCLS or heparin control as described above. Mechanical testing by means of an Instron 5582 Electromechanical Universal Testing Machine (DatapointLabs, Ithaca, NY) was performed on NCLS- vs. heparin-exposed catheters at baseline, 72 hours and 2 weeks of incubation. Testing was performed by using the International Organization for Standardization specification 10555.⁸ Catheter junction and hubs were not tested. The catheter segments were first cut to a length of 7.5 cm, and then 2.5 cm from each end of the segments were filled with polypropylene to prevent the catheters from being crushed flat during testing. Once plugged, the catheter segments were loaded onto the testing machine such that each end was gripped by the machine and 2.5 cm was left between the grips. Tests were run with a 500 mm/min grip separation rate at room temperature. Segments were pulled at this rate until they ruptured. Force, stress, and strain were recorded from the testing machine every 150 milliseconds. Stress is the measured force divided by the cross-sectional area of the segment. Strain is a ratio of the stretched length of the segment (change in displacement between the grips) to the original length (initial grip separation). Stress-strain curves were accordingly constructed for each catheter segment, as shown in the representative curve in Figure 1. The yield and break-points were calculated from the curve for each segment. The elastic modulus is the slope of the initial linear portion of the stress-strain curve. The experiment was performed in duplicate.

Statistical Analysis

The mean wall thickness of catheter segments at each time point in Experiment 1 and the mean measurements of various mechanical properties in Experiment 2 were compared by two-tailed t-tests. Regarding Experiment 2, we compared the two-week heparin result with baseline, 2-week NCLS result with baseline, and the 2-week heparin with the 2-week NCLS results for each catheter type. A p-value <0.05 was considered statistically significant. Microsoft Excel software was used for data analysis and for graphical representation.

Results

Experiment 1

The microscopic images of the inner and outer surface of most catheters showed occasional shallow fissures or scratches close to or at the cut edge of the catheter (primarily polyurethane), occasional fractures of the catheter at the cut edge (polyurethane), or shavings/fibrils of the catheter material at the cut edge (silicone and carbothane > polyurethane). These observations were similar in the NCLS- vs. heparin-exposed catheters. The main body of the catheters away from the incised edge generally did not have the above mentioned defects and appeared similar in all groups. As seen in Table 1, the mean wall thickness was not significantly different in the NCLS- and heparin-exposed catheters. Additionally, there was no difference in the mean wall thickness of all three types of catheters when the baseline reading was compared to that after 2 weeks of incubation in either NCLS or heparin ($p > 0.05$).

Experiment 2

The mechanical properties of polyurethane, silicone and carbothane catheters incubated for up to 2 weeks in NCLS or heparin are depicted in Figure 2. Since data for 72 hours of incubation were similar, it is not shown.

Polyurethane—Stress at yield significantly decreased from baseline in NCLS-exposed ($p=0.004$) and heparin-exposed ($p=0.003$) catheters, but was similar between the two incubated catheter groups at 2 weeks ($p=0.36$). Strain at yield and strain at break remained similar in the tested groups. Stress at break and force at break decreased from baseline in heparin ($p=0.0497$, $p=0.0497$) and but not NCLS ($p=0.052$, $p=0.052$). Modulus of elasticity decreased significantly from baseline in both NCLS-treated ($p=0.019$) and heparin-treated ($p=0.019$) catheters but remained similar between the two incubation groups ($p=0.32$).

Silicone—Stress and force at break remained similar to baseline in the NCLS treated group ($p=0.14$, $p=0.14$) but were significantly lower from baseline after 2 weeks of incubation in heparin ($p=0.03$, $p=0.03$). Strain at break decreased significantly from baseline in both incubation groups after 2 weeks ($p=0.01$; $p=0.048$, respectively); however, there was no difference between the NCLS- and heparin-exposed silicone catheters at 2 weeks ($p=0.49$). Strain at yield in the heparin group was significantly lower than the NCLS group at 2 weeks ($p=0.02$). Modulus of elasticity remained similar between baseline and incubated catheters.

Carbothane—Stress at yield and stress at break decreased significantly from baseline in catheters exposed to NCLS ($p=0.009$, $p=0.014$) or heparin ($p=0.009$, $p=0.025$) for 2 weeks, but the two incubation groups remained similar to each other ($p=0.7$). Strain at yield and strain at break remained similar in all three groups. Modulus of elasticity decreased significantly from baseline for NCLS-exposed ($p=0.006$) as well as heparin-exposed ($p=0.0095$) catheters, but was significantly less in the NCLS than heparin group ($p=0.004$). Force at break remained the same for the two incubation groups at 2 weeks ($p=0.68$).

Discussion

We have previously demonstrated the efficacy of the combination of NAC and tigecycline against a wide array of clinical biofilm-forming bacterial isolates.⁹ We subsequently conducted a pilot clinical trial which demonstrated a success rate of 83% with the use of NCLS which comprised of NAC, tigecycline, and heparin for treatment of hemodialysis catheter-associated bacteremia.⁵ Prior to performing a large scale randomized clinical trial, we sought to establish the safety profile of NCLS with respect to the mechanical integrity of hemodialysis catheters. Using industry standards, this study rigorously assessed the effects of NCLS exposure on the mechanical integrity of widely used polyurethane, silicone, and carbothane hemodialysis catheters. Since we plan to locally instill NCLS for 2 weeks when treating catheter-associated bacteremia in an upcoming clinical trial, we examined the mechanical integrity of catheters in this in-vitro study after incubation for a maximum of 2 weeks.

Several previous studies evaluating catheter integrity did so by means of imaging the catheter surface for obvious defects such as fissures, fractures or pores.^{7, 10} We examined the surface of the studied catheters using an optical dissecting microscope at a high magnification and did not find any alarming features. The described defects were along the incised surface of the catheter and, thus, likely due to the mechanical disruption of the surface with the incising blade. Accordingly, we believe that use of NCLS in hemodialysis catheters should not cause leakage of fluid from the catheter since fissures, fractures, or pores were absent in the main body of the catheter segments.

The assessments in our study exceeded those described in most previously reported studies as we scrupulously tested the mechanical function of the exposed catheters. From a mechanical point of view, it is appropriate to assess the experimental results in terms of the elastic and plastic behavior of the catheters. The modulus of elasticity (the slope of the initial linear portion of the stress-strain curve) is the definite variable for an elastic behavior analysis. In this region of the curve, the catheter material undergoes no permanent (plastic) deformation, i.e., the catheter recovers its entire length when the load is removed. A higher value means a smaller elastic strain for a given stress. The modulus of elasticity remained similar among NCLS- and heparin-exposed polyurethane and silicone catheters at the end of 2 weeks of incubation; however, there was a slight decrease in the NCLS group for the carbothane catheters. Since the absolute value of the modulus of elasticity of the NCLS-exposed carbothane catheters remained higher than the heparin-exposed silicone catheters, we believe this small decrease will not be clinically significant. The silicone and carbothane catheters were more elastic (as demonstrated by a lower modulus of elasticity) which translates to greater patient comfort during hemodialysis, and this characteristic was minimally or not affected by exposure to NCLS.

We noted a decrease in the modulus of elasticity and the stress at yield of unexposed baseline polyurethane catheters when compared to both the NCLS- and heparin-treated catheters. Per manufacturer information, hemodialysis catheters are made of a “flexible polyurethane material that softens 50% at body temperature to facilitate patient comfort”.¹¹ This softening at 37°C is most likely responsible for the decrease in elasticity of the incubated vs. unincubated catheters, though we did not test this hypothesis. As mentioned earlier, there is no difference in the elastic parameters between NCLS- and heparin-exposed catheters at 2 weeks.

The plastic behavior of materials under tensile loading can be characterized by a number of aspects. Since hemodialysis catheters are subjected to large forces during dialysis, the plastic behavior, such as the force at break, is very important. The force at break in the NCLS-exposed catheters for all three tested materials remained similar to that of heparin-exposed catheters after 2 weeks of incubation. Per the ISO 10555–1 guidelines, which sets the industry standard for intravascular catheters, the force at break is the most reliable predictor of integrity of intravascular catheters and should exceed a minimum of 15 N for large bore catheters such as hemodialysis catheters.⁸ The force at break of all tested catheters, whether treated with NCLS or heparin, exceeded that number by a very large margin (all polyurethane and carbothane catheters >100 N and all silicone catheters >45 N). Thus, the clinical use of NCLS in hemodialysis catheters is anticipated to be safe as it does not increase the propensity for catheter fracture during dialysis.

Another finding of our study is the difference between the physical characteristics of polyurethane catheters (which are usually used for short-term dialysis), vs. silicone and carbothane catheters (which are used for long-term dialysis). In our study, polyurethane catheters were stiffer and, thus, a higher force was needed to produce stretch (hence, a higher modulus of elasticity). The strain at break (which indicates the length of elongation at the break point) is also lower for polyurethane catheters than the other two tested materials, thereby attesting to its stiffness.

Our study has some limitations. First, we assessed only the mechanical integrity of the tubular portion of the catheter. Thus, the effect of NCLS on the catheter hub and junction remains unknown. However, if the catheter hub were to become damaged, the hub and external catheter shaft can be replaced with the catheter in-situ for Quinton and Mahurkar catheters.¹¹ We have also only tested one manufacturer's products though a wide range of

materials were tested. Additionally, we tested for incubation duration of 2 weeks and thus the effect of prolonged incubation of these catheters with the NCLS is unknown.

In conclusion, we have established that the mechanical integrity of various types of hemodialysis catheters is maintained after a 2-week exposure to a novel catheter lock solution consisting of N-acetylcysteine, tigecycline, and heparin. This information is required prior to conducting a large scale placebo-controlled, randomized clinical trial to evaluate the efficacy of this NCLS in patients with hemodialysis catheter-associated bacteremia.

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Figure 1.

Stress vs. strain curves for a silicone catheter segment after incubation for 2 weeks with heparin control or novel catheter lock solution (NCLS) consisting of N-acetylcysteine 80 mg/ml, tigecycline 1 mg/ml and heparin 2000 units/ml. This is a representative curve to demonstrate the elastic modulus, yield point and break point of catheters.

Figure 2.

This figure represents various parameters of tensile strength tested for the three types of catheters at baseline and after 2 weeks of incubation in either heparin 2000 units/ml as control or a novel catheter lock solution (NCLS) consisting of N-acetylcysteine 80 mg/ml, tigecycline 1 mg/ml and heparin 2000 units/ml. MPa is megapascals, N is newtons, % denotes percentage change from baseline measurement. The standard error bars represent standard error of the mean.

Table 1

Mean wall thickness of catheter segments at baseline and after incubation with a novel catheter lock solution (NCLS) consisting of N-acetylcysteine 80 mg/ml, tigecycline 1 mg/ml and heparin 2000 units/ml or with heparin 2000 units/ml alone as control. The p-values are of a t-test between the NCLS and heparin group at each time-point.

Time point	NCLS (mean $\mu\text{m} \pm \text{SD}$)	Heparin (mean $\mu\text{m} \pm \text{SD}$)	p-value
<u>Polyurethane</u>			
Baseline		343.68 $\pm$ 10.52	
24 hours	334.92 $\pm$ 24.23	339.28 $\pm$ 24.37	0.66
72 hours	355.36 $\pm$ 38.45	341.56 $\pm$ 27.97	0.36
1 week	371.76 $\pm$ 47.43	346.67 $\pm$ 11.82	0.09
2 weeks	350.08 $\pm$ 23.3	347.3 $\pm$ 16.17	0.75
<u>Silicone</u>			
Baseline		664.97 $\pm$ 34.06	
24 hours	657.89 $\pm$ 28.33	661.03 $\pm$ 38.37	0.82
72 hours	662.37 $\pm$ 38.68	667.73 $\pm$ 37.86	0.73
1 week	657.79 $\pm$ 35.85	657.68 $\pm$ 26.74	0.99
2 weeks	669.94 $\pm$ 40.42	670.89 $\pm$ 24.27	0.94
<u>Carbothane</u>			
Baseline		674.06 $\pm$ 20.34	
24 hours	683.63 $\pm$ 28.72	675.54 $\pm$ 14.82	0.4
72 hours	685.72 $\pm$ 22.15	681.06 $\pm$ 17.9	0.58
1 week	681.26 $\pm$ 9.59	673.65 $\pm$ 28.44	0.41
2 weeks	670.69 $\pm$ 24.19	678.25 $\pm$ 15.74	0.37