Nitric Oxide Releasing Catheters for Newborns

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Statement of Purpose: The small diameter of pediatric catheters leads to rapid occlusion resulting in loss of function of monitoring and of infusion of medication. Systemic prophylactic anticoagulation can be used, but this puts newborns at a higher risk of bleeding. A better alternative is local inhibition of clot formation. One such approach is the use of nitric oxide (NO) releasing surfaces. In this work NO, known to be a potent anti-platelet agent, was incorporated into extruded catheters for biocompatibility testing in a short-term animal model.

Methods: NO-releasing catheters (L= 6 cm, ID = 21-guage (0.0723 cm), OD = 12-gauge (0.2052 cm), active layer thickness ≈ 200 µm) were extruded to incorporate DACA-6: N-(6-aminohexyl) aminopropyl-trimethoxysiloxane and Potassium tetrakis(4-chlorophenyl) borate (Sigma Aldrich, St Louis MO), during extrusion of silicone (nuSil Silicone Tech, Carpinteria CA) rubber catheters. The extruded catheter and it's cross section are shown in Figure 1. In this figure, the catheter was partly filled with a mixture of water and blue food dye for visualization. The extruded NO releasing part of the catheter, left of the demarcation, was connected to a commercial catheter to allow infusion and drawing of fluids. In addition, the active (middle) layer of the cross section shown in Figure 1B served as the NO-releasing layer. After extruding all three layers of the catheters and curing for 24hrs in ambient temperature, they were charged with NO at 80 psi for 72 hrs to form diazeniumdiolates in the active layer [1]. Catheter samples (L=1cm) were bathed in a chelex-treated phosphate buffer saline (pH 7.34, 37ºC) medium to measure their NO release with a Sievers Nitric Oxide Analyzer 280i (GE instruments, Boulder CO). They were then implanted in the carotid arteries and jugular veins of rabbits (avg. weight = 3kg) for 4 hrs. Platelet counts and function, methemoglobin (metHb), hemoglobin (Hb), white cell counts and functional time (defined as patency time of catheter) of implanted catheter were monitored.

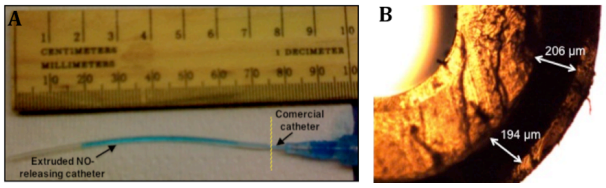


Figure 1: Representative structure A) and cross section B) of extruded silicone-rubber nitric-oxide-releasing catheters

Results: The catheters (N=4) maintained fluxes above 2 X 10^{-10} mol/min/cm^2 for over 24 hours in vitro (See representative flux profile in Figure 3). MetHb, Hb, white cell and platelet counts and platelet function at 4hrs were not significantly different from baseline ($\alpha = 0.05$). However clots on controls were visibly larger and 3 out of 4 prevented blood draws 2 hours into experiment whereas all 4 NO-releasing catheters lasted the entire period (See Figure 4). This level of NO release from extruded catheters prevented thrombosis in a short-term animal model.

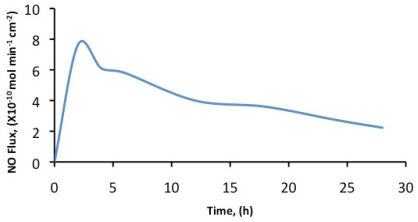
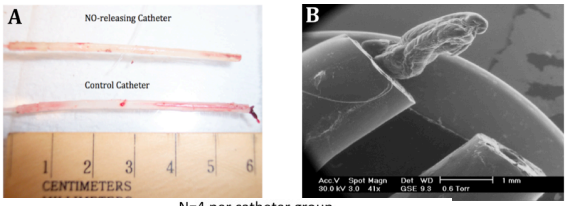


Figure 2:Nitric oxide release duration as measured by cchemiluminescence.



N=4 per catheter group

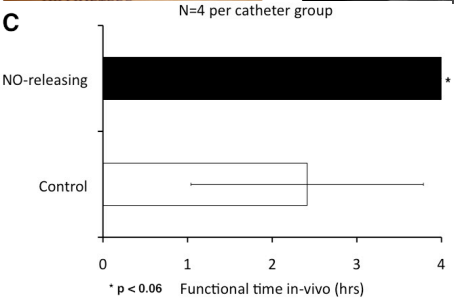


Figure 3: A) Explanted catheters showing clots on the tip of control (bottom) and clean NO-releasing catheter, B) SEM of control (top) and NO-releasing catheter, and C) Functional time of implanted catheters.

Conclusion: NO releasing catheters were fabricated by incorporating DACA-6 and borate during extrusion of silicone rubber catheters. The amount of NO released from catheters prevented thrombosis in a short-term animal model.

Future direction: Fabrication and long-term testing of 21 gauge OD catheters using different polymers.

Reference: Zhang H et al. Biomaterials. 2002; **23**(6): p 1485-1494.