Next Generation Antibacterial Vascular Closure Device

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Statement of Purpose: From a clinical perspective, a systemic antibiotic or antibacterial agent is generally recommended when a vascular closure device is used in high risk patients (e.g., prior myocardial infarction, stroke, and diabetes). Most infections associated with medical devices are caused by bacteria. The primary mode of infection associated with medical devices is attachment of microorganisms to the device followed by growth and formation of a biofilm on the device. Once a biofilm is formed, it is practically impossible to treat the infection without actually removing the device. ExoSeal®, an investigational product, is a novel extravascular closure device with a unique visually guided deployment mechanism that delivers a poly (glycolic acid) [PGA] plug to close the femoral artery anchored by the neuro-vascular bundle sheath. This study summarizes the preparation and characterization of a vascular closure device that incorporates an antibacterial agent coated or dispersed within the porous structure.

Methods: A porous vascular closure device or plug was prepared from the bioabsorbable material, poly (glycolic acid) [PGA]. A typical process to prepare the plug was to melt extrude PGA into multifilaments which were then crimped, cut, carded and needle punched to prepare a non-woven mat with the desired density and integrity. The mat was then cut into cylindrical plugs. Molecular weight of the plugs was measured by using a tetradetection gel permeation chromatography (GPC-T, Model 302) by Viscotek using hexafluroisopropanol (HFIP) as the mobile phase. Inherent viscosity (IV) of the plugs was determined by using Ubbelohde viscometer in HFIP. Thermal properties of the plug were measured by Perkin Elmer Differential Scanning Calorimeter (DSC-7) at 15°C/min under nitrogen. Coating experiments were conducted using the plugs to evaluate the effect of triclosan as an antibacterial agent. Plugs were coated with the antibacterial agent using either dip coating or vapor deposition methods. Table I summarizes different coating compositions that were used to prepare antibacterial plugs. The coating solutions for the dip coating process consisted of triclosan, and triclosan with poly (lactide-co-glycolide) 65/35 and poly (caprolactone-co-glycolide) 90/10 in ethyl acetate. Each plug was dipped in a coating solution for 10 seconds and then air dried at ambient temperature for 2 h. Samples 1 to 6 were packaged in universal folders containing vapor hole without tyvek patches, and samples 7 and 8 were packaged in universal folders containing the vapor hole and dosed tyvek patches. All the coated plugs were sterilized using ethylene oxide. The sterilized plug samples were then cut into two pieces and tested against two strains of bacteria (Staphylococcus aureus and Escherichia coli) to determine zone of inhibition (ZOI). The evaluation of the tissue reaction and absorption of the plug was determined in a rat gluteal flap model and porcine vessels.

Results:

Material Characterization: IV of pre-sterile PGA plugs ranged from about 0.8 to 1.0 dL/g and the weight average molecular weight (M_w) was determined to be 24,000 to 27,000 g/mole. The melting point of the plug was about 235°C with the heat of fusion value of 86 J/g. The percent crystallinity of PGA was determined to be about 62% based on heat of fusion value of 139 J/g for pure PGA (1). An optical and a scanning electron micrograph of a typical PGA plug are shown in Figures 1 and 2. The plug structure can have different porosity and absorbent capacity based on the density of the non-woven structure.

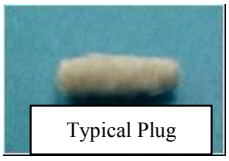
Antibacterial Properties: The triclosan coated plug samples were tested against two strains of bacteria (Staphylococcus aureus and Escherichia coli) to determine zone of inhibition (ZOI). Table I summarizes the results from this test. The ZOI results showed that all the plug samples provided maximal antibacterial effects for S. aureus bacteria; and different levels of inhibition (from 7.7 mm to greater than 40 mm) for E. coli.

Pre-Clinical and Clinical Studies: Several pre-clinical studies were conducted to determine the biocompatibility and absorption of the ExoSeal® plugs in different animal models. Significant mass loss was observed of the plug after 90 days with minimum tissue reaction in a rat gluteal flap model. Several clinical studies have been conducted outside and in the U.S. (2). Time to hemostasis and time to ambulation were significantly reduced in ExoSeal® patients compared with manual compression.

Conclusions: A novel bioabsorbable vascular closure device has been developed from PGA. The treatment of a vascular closure device with triclosan provided antibacterial activity which may be clinically relevant. The results suggest that this approach could be a promising next generation treatment option for high risk patients that will combine the efficacy of the ExoSeal® plug and the antibacterial effect of triclosan.

References:

1. Barrows TH. Clin Mater. 1986; 1:233.
2. Wong SC. American College of Cardiology Abstracts, March 2008.



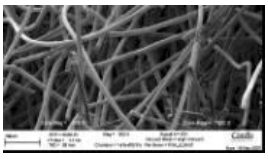


Figure 1. OM of Plug Figure 2. SEM of Plug

Table I. Summary of antibacterial coating compositions

Sample ID	Substrate	Sample Type	Coating Composition	Zone of Inhibition (mm)	
				S. aureus	E. Coli
1	PGA plug	Control	No Coating	0	0
2	PGA plug	Coated	2% w/w triclosan/ethyl acetate (no polymer)	>40	7.7
3	PGA plug	Coated	2% w/w triclosan /5% w/w PLGA 65/35/ethyl acetate	>40	14.5
4	PGA plug	Coated	2% w/w triclosan/1% w/w PLGA 65/35/ethyl acetate	>40	14.5
5	PGA plug	Coated	2% w/w triclosan/ 5% w/w PCL/PGA 90/10/ethyl acetate	>40	>40
6	PGA plug	Coated	2% w/w triclosan/1% w/w PCL/PGA 90/10/ethyl acetate	>40	>40
7	PGA plug	Vapor	8 mg triclosan/tyvek patch by vapor deposition (no polymer)	>40	14.5
8	PGA plug	Vapor	4 mg triclosan/tyvek patch by vapor deposition (no polymer)	>40	14.5