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Infusion of Iodine-Based Contrast Agents into Poly(p-dioxanone) as a Radiopaque Resorbable IVC Filter

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Abstract

Purpose: To determine the feasibility of infusing resorbable inferior vena cava (IVC) filter with iodine-based contrast agents to produce a radiopaque, computed tomography (CT)-visible IVC filter.

Materials and Methods: Infused poly(p-dioxanone) (PPDO) was obtained by incubating PPDO in different concentrations of 4-iodobenzoyl chloride (IBC) and 2,3,5-triiodobenzoic acid (TIBA). Characterizations of infused and nascent PPDO were done using elemental analysis, micro-CT, tensile strength analysis, scanning electron microscopy, and differential scanning calorimetry.

Results: Elemental analysis showed percentage loading of 1.07 ± 0.08 for IBC and 0.73 ± 0.01 for TIBA. Micro-CT images showed increased attenuation of the infused PPDO compared with the nascent PPDO. The Hounsfield unit values for infused and nascent sutures were 110 ± 40 and 153 ± 53 for PPDO infused with 2mg/mL IBC and TIBA, respectively, but only 11.35 ± 2 for nascent PPDO. In contrast the HU for bone was 116 ± 37 . Tensile strength analysis showed maximum loads of 1.01 ± 0.43 kg and 10.02 ± 0.54 kg for IBC and TIBA, respectively, and 10.10 ± 0.64 kg for nascent PPDO. Scanning electron microscopy showed that the morphology of the PPDO surface did not change after coating.

Conclusion: PPDO infused with a contrast agent is significantly more radiopaque than nascent PPDO on micro-CT imaging. This radiopacity could allow the position and integrity of infused resorbable IVC filter to be monitored while it is in place, increasing its safety and efficacy as a medical device.

Keywords

iodine contrast agent; radiopaque; computed tomography; x-ray; resorbable filter

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INTRODUCTION

Inferior vena cava (IVC) filter, which is inserted inside a large abdominal vein to trap large clot fragments and prevent them from traveling to the heart and lungs, can prevent life-threatening venous thromboembolism, including deep vein thrombosis and pulmonary embolism (PE) [1,2]. Approximately 350,000 to 600,000 people each year in the United States (US) are affected by blood clots, and between 100,000 and 180,000 people die of PE each year [3]. Even though most patients with blood clots are treated with parenteral anticoagulants, an IVC filter is indicated in cases with contraindications to anticoagulants, bleeding complications, or recurrent venous thromboembolism despite optimal anticoagulation [1,2].

IVC filters are implanted percutaneously and can be permanent or non-permanent. However, permanent IVC filters increase the incidence of certain complications [4]. Significant long-term risks of permanent IVC filter include IVC perforation, filter dislocation, filter migration, IVC filter fracture, recurrent venous thromboembolism, thrombophlebitis, and venous stasis disease [4]. To decrease the risk of long-term complications related to permanent filters, non-permanent IVC filters have been developed and were approved by the US Food and Drug Administration in 2003 [5,6]. These non-permanent IVC filters can be either removed once the risk of thromboembolic disease is reduced (retrievable filters) or altered to cease functioning as a filter while remaining in the IVC (convertible filters) [7]. However, retrievable filters, too, have several of identified problems noted previously including filter fracture and perforation due to prolonged use well beyond the risk of venous thromboembolism. For instance, in 446 trauma patients who had retrievable IVC filters implanted, only 22% of those filters were retrieved [8]. The primary reason for non-retrieval was that patients did not follow up after discharge [9,10]. Most recently, the FDA published a communication, advising physicians to remove retrievable filters within 29 to 54 days based on a comprehensive risk/benefit analysis [11].

A resorbable filter would provide critical protection against pulmonary embolism through the period of highest risk immediately after major surgery or trauma (when a patient is contraindicated to anticoagulants), while avoiding the long-term disadvantages of currently available filtration devices [9]. Resorbable polymers, such as poly(p-dioxanone) (PPDO), polyglactin, polyglycolic acid, poly(L-lactide), and others have been used in other implantable medical devices. These implants can function safely and effectively during their required duration and then simply be absorbed into the body through hydrolysis, thereby avoiding costly removal procedures and downstream complications [1].

Poly(p-dioxanone) (PPDO), a synthetic, absorbable, biodegradable polymer, was recently suggested to be a strong candidate for a novel absorbable vascular filter. However, although the resorbable IVC filter shows promise in PE prevention, an important limitation is its significant clot burden [9] and inability to visualize during deployment under fluoroscopy. Monitoring the absorption and any significant clot burden of these filters using imaging techniques may improve the efficacy and also reduce the risks of resorbable IVC filters. Therefore, there is an urgent need to develop new imaging enhancers to readily determine

the positioning and integrity of these absorbable devices using conventional imaging modalities.

The purpose of this study was to determine the feasibility of infusing a resorbable inferior vena cava (IVC) filter with iodine-based contrast agents to produce a radiopaque, computed tomography (CT)-visible IVC filter. Two organic solvent-soluble, radiopaque, iodine-based contrast agents were used: 4-iodobenzoyl chloride (IBC) and 2,3,5-triiodobenzoic acid (TIBA). These contrast agents were dissolved in various organic solvents to optimize their solubility and then loaded into PPDO filters through direct diffusion with the iodine-based contrast agent in the organic solvent. The infused PPDO filters were characterized in terms of morphological texture and radiopacity.

MATERIALS AND METHODS

Chemicals and Materials

PDS II sutures (violet monofilament, Z880G) (PPDO sutures) were purchased from Ethicon (Johnson & Johnson). IBC (97%), TIBA (98%), DCM (meeting American Chemical Society specifications [ACS reagent], 99.5%), dimethyl sulfoxide (DMSO, ACS reagent, 99.9%), and ethyl acetate (ACS reagent, 99.5%) were obtained from Sigma-Aldrich (St. Louis, Missouri). All chemicals were used without further purification unless otherwise noted.

PPDO Infusion with Iodine-Based Agents

Two organic solvent-soluble, radiopaque, iodine-based contrast agents, IBC and TIBA, were used in this study. IBC and TIBA were each dissolved in 100% DCM, or in 5% DMSO in DCM for 2 mg/mL concentration or 10% DMSO in DCM for 15 mg/mL. The difference in the amount of DMSO used in the mixed solvent is due to the poor solubility of the iodinated compounds in DCM. Increasing the amount of DMSO ensures complete dissolution of IBC and TIBA. Infusion of PPDO with IBC and TIBA was done by measuring approximately 60 cm of PPDO monofilament, incubating in 2 mg/mL IBC or in 15 mg/mL TIBA for 24 hours, and air dried at room temperature. After 24 hours of air-drying, the infused PPDO was gently washed with ethyl acetate and then air dried at room temperature for another 24 hours.

Elemental Analysis

The total iodine loading was determined using inductively coupled optical emission spectrometry (ICP-OES). Briefly, approximately 98 mg of iodine-infused sutures were digested in concentrated nitric acid at room temperature to completely dissolve the sutures, and then the suture solution in nitric acid was diluted with DMSO (2% nitric acid in DMSO) and aliquoted. Control, such as nascent PPDO, was used. The amount of iodine in the suture solution in parts per million (ppm) was analyzed using a Varian 720-ES spectrometer (Varian, Santa Clara, CA). The experiments were conducted in triplicate with a single suture in each container. The elemental analysis data were analyzed using the regression results obtained from calibration curves ($R^2 = 0.998$) plotted between the concentration and absorption of iodine at 179.85 nm.

Micro-Computed Tomography (CT) Imaging

The radiopacity of solutions of iodine-based contrast agents, filters infused with contrast agents, and a bone standard was determined using a CT-Explore Locus RS pre-clinical in vivo scanner (GE Medical Systems, London, Ontario). The scanner uses a tungsten-source x-ray tube operating at 80 kV and 450 μ A. The x-ray source and charge-coupled device-based detector gantry are rotated around the subject at approximately 1.0° increments. The MedRes-Mimic10min-Mimic protocol was used, operating at 80 kVp and 450 mA, and ran for approximately 10 minutes. Controls including a nascent filter and solvent (without contrast agent) embedded sutures were used. The radiopacity of the materials in Hounsfield units (HU) was quantified by an in-house software application. HU values are reported as mean $\pm$ standard deviation.

Thermal Properties

The thermal history of the iodine-loaded suture was determined using differential scanning calorimetry (DSC) with a Thermal Analysis SDT Q600 (TA Instruments, New Castle, Delaware) at a scanning speed of 10°C/min under an argon atmosphere. All samples weighed at approximately 10 mg and were placed in platinum pans.

Scanning Electron Microscopy (SEM)

SEM model LEO1525 with GEMINI column (Carl Zeiss Inc., Thornwood, New York) operating at 15 kV was used to examine the texture of the infused absorbable filters. All samples were deposited on a conductive tape.

Tensile Strength

The tensile strength of the suture samples was assessed using the eXpert 7601 tensile testing machine with MTEST Quattro software (ADMET, Norwood, Massachusetts) after 24 hours of immersion with the iodine-based solutions. The tensile strengths of the suture samples were assessed at a cross-head speed of 3 cm/min using a high resolution 100-lb load cell and 2KN pneumatic grippers to prevent slippage during testing. Each sample was stretched until failure, and the maximum loads were recorded in kg and tabulated for analysis.

Statistical analysis

Results were analyzed using a two-tailed unpaired Student t-test or one-way ANOVA. A p-value < 0.05 was considered statistically significant.

RESULTS

PPDO Infusion with Iodine-Based Agents and Assessment of Solubility

Table 1 shows a comparison of the solubility of the different concentrations of iodine-based agents in the different solvent systems in terms of CT signal intensities (Hounsfield unit). Solvents were selected to optimize the solubility of the iodine-based contrast agents and maximize the loading of these agents into the PPDO. At first, DCM was our preferred solvent to dissolve IBC and TIBA for infusing into PPDO sutures because DCM is less toxic than chloroform and PPDO sutures can swell in DCM [12]. However, IBC and TIBA are

almost completely insoluble in 100% DCM. This is due to the difference in polarity of DCM compared to IBC and TIBA (polarity order: TIBA > IBC > DCM). Figure 1 shows the structures of IBC and TIBA. Therefore, a mixed solvent system, 5 or 10% (vol/vol) DMSO in DCM, was used to dissolve IBC and TIBA (Table 1). Five percent DMSO-DCM completely dissolved IBC and TIBA at 2 mg/mL, but only slightly dissolve the 15 mg/mL. Increasing the amount of DMSO at 10% completely dissolved the 15 mg/mL. Also, a lower HU values was observed with 100% DCM solvent system as compared with 5 or 10% DMSO-DCM (Table 1). Specifically, the HU value for PPDO infused with 15 mg/mL IBC was 290 ± 4 in 10% DMSO-DCM compared with 258 ± 13 at 100% DCM. Similar increase in HU values was seen with 2 mg/mL IBC and both concentrations of TIBA. Therefore, 5% DMSO-DCM was used to infuse 2 mg/mL, and 10% DMSO-DCM was used for 15 mg/mL.

Quantification of the Amount of Iodine Embedded in the PPDO (Elemental Analysis)

After the PPDO was infused with IBC and TIBA, the amount of iodine embedded in the PPDO was quantified using elemental analysis. Results presented in Table 2 confirm the presence of iodine in the PPDO and quantification of the percentage of iodine embedded in the PPDO showed greater infusion as the concentration of the iodine-based dipping solution is increased.

Micro-CT Imaging

The HU values of the iodine-based solutions in organic solvent were determined using micro-CT imaging. The concentrations, micro-CT images, and corresponding HU values of each solution are presented in Table 3. DCM alone was included as a control. The radiopacity of the solutions with iodine-based agents was much higher than that of DCM alone. Also, the radiopacity of the iodine-based solutions had higher HU values than bone (116 ± 37). The HU value for IBC at 2 mg/mL was lower than that of TIBA at the same concentration. As expected, the higher the concentration of the IBC solution, the more intense the CT signal.

Figure 2 shows the micro-CT images of the PPDO sutures infused with iodine-based agents and of the bone standard. The iodine-infused PPDO showed increased attenuation, whereas the nascent PPDO showed none, validating the radiopacity of infused PPDO.

Thermal Properties

Changes in the crystallinity of the PPDO with the concentration of loaded iodine-based agents and the solvents used were investigated using DSC. DSC thermograms for the heating scans of the infused and nascent sutures, as well as sutures embedded with solvents alone are shown in Figure 3A. PPDO samples with different infusing agents and solvents had different melting temperatures (T_m) (Figure 3B). Sutures infused with 15 mg/mL IBC showed the lowest T_m (108.2°C), indicating that this sample had the lowest crystallinity among the modified sutures. Also, PPDO infused with 2 mg/mL IBC had a lower T_m than nascent and TIBA-infused PPDO.

Surface Morphologies and Tensile Strengths

The surface morphologies of the infused and nascent suture materials were determined using SEM. Electron micrographs (Figure 4) did not show any noticeable morphological changes between the infused PPDO, the nascent PPDO, and the PPDO in 100% DCM.

Aside from thermal property and surface morphology, the mechanical strength of the infused and nascent PPDO samples was also evaluated. To test the tensile strength, each of the samples was stretched to failure. The maximum load at break in kg for each of the samples is shown in Table 4. The tensile strength of the PPDO samples infused with TIBA at concentrations of 2 mg/mL and 15 mg/mL did not significantly differ from that of the nascent PPDO ($p < 0.01$). However, PPDO infused with IBC was weaker than the other samples, with maximum loads of 6.06 ± 0.25 kg for 2 mg/mL IBC and 1.01 ± 0.43 kg for 15 mg/mL IBC.

DISCUSSION

Our results show that infusing PPDO with iodine-based contrast agent significantly increases its radiopacity compared to nascent PPDO on micro-CT imaging. This ability to be imaged could allow improved deployment and monitoring of the position and integrity of the resorbable IVC filter and thus increasing its safety and efficacy as a medical device.

PPDO slightly swells in some organic solvents, such as dichloromethane (DCM) and chloroform [12,13]. Thus, low molecular weight compounds that are soluble in organic solvents could be loaded into the polymer by diffusion through exposure to a DCM solution of such a compound. This approach has previously been studied to incorporate ibuprofen and triclosan into PPDO monofilaments [12,13]. In addition, the kinetics and release of triclosan incorporation into absorbable polymer monofilaments were also evaluated [14,15]. Promisingly, the filaments with triclosan through exposure to DCM solution did not significantly affect the mechanical properties of the monofilaments [12].

In our study, PPDO was infused with IBC and TIBA to investigate their ability to enhance the radiopacity of polymeric IVC filters depending on the type and content of the incorporated iodine-based compounds. Our results show that attenuation was greater than bone and the higher the concentration of the contrast agent, the higher the HU values. The attenuation at the same concentration was also observed to be higher with TIBA as compared to IBC. Although the percentage of IBC in the PPDO was higher than that of TIBA per elemental analysis, it could be argued that the IBC molecule is smaller and less bulky than the TIBA molecule since the TIBA molecule has two more iodine atoms, and therefore IBC can be more easily infused in PPDO than TIBA can be (Figure 1). However, IBC and TIBA showed lower percentages of loading into PPDO than triclosan does [12]. It may be due to the fact that triclosan dissolves very well in DCM and 100% DCM can swell or open the surface of PPDO for encapsulation better than the 5–10% DMSO-DCM mixture can.

The thermal properties of the infused and nascent PPDO sutures were studied using DSC. Generally, a decrease in melting temperature, T_m , indicates a decrease in the degree of

crystallinity [16] and changes in T_m is a fundamental consequence of the chain scission of the hydrolytically unstable ester bonds located in the amorphous region [17]. Therefore, we can determine the physical properties of infused and nascent PPDO by monitoring changes in their T_m . Nascent PPDO sutures had a T_m of 113.6°C, whereas PPDO sutures infused with 15 mg/mL IBC demonstrated the lowest T_m at 108.2°C, and thus have the lowest crystallinity of all the sutures. However, elemental analysis showed IBC having the highest percentage of infusion of iodine in PPDO (Table 2). It might be reasoned that high-concentration IBC within the PPDO disrupts the hydrolytically unstable ester bonds of PPDO, increasing the disorder of its molecules, and significantly decreasing the T_m of PPDO infused with 15 mg/mL IBC. On the other hand, sutures infused with TIBA at 2 and 15 mg/mL did not significantly differ from nascent sutures in terms of T_m , indicating that the incorporation of TIBA does not change the crystallinity of PPDO.

Aside from thermal property, the mechanical requirements of absorbable scaffolds, such as durability, flexibility, and radial strength, are crucial factors in biomedical applications [18]. Therefore, the influence of contrast agent incorporation on the mechanical properties of the infused PPDO was determined (Table 4). The mean load at break of PPDO infused with TIBA (2 mg/mL and 15 mg/mL) did not significantly differ from that of nascent PPDO ($p < 0.01$). Additionally, the surface morphology of the TIBA-infused PPDO does not show any significant change as compared to nascent PPDO. These tensile strength values agree with those found in a previous tensile strength study of PPDO [10]. However, the IBC infusion weakened the PPDO. Therefore, TIBA appears to be more suitable than IBC for infusing PPDO for IVC filter use in the clinic.

Although TIBA showed the highest micro-CT attenuation and does not alter the surface morphology, thermal, and mechanical properties of the PPDO, the physiological and the long-term stabilities of TIBA-infused PPDO are also questionable. Also, further studies on the release of TIBA in biologically relevant media and its effect over time, is needed. Large animal imaging of these implants is also necessary for translation into the clinic. In addition to organic CT contrast agents, inorganic nanoparticles (e.g., gold, silver, and magnetic nanoparticles) have been incorporated into a biodegradable polymer (polymeric poly[L-lactide]) and effectively enhanced its radiopacity [18]. These nanoparticles capable of increasing attenuation is also currently being incorporated into the PPDO as an alternative radiopaque material.

CONCLUSIONS

PPDO infused with a contrast agent is significantly more radiopaque than nascent PPDO. This radiopacity could allow monitoring of the resorbable IVC filter, thus increasing its safety and efficacy as a medical device. IBC provides the highest percentage of coating, however, may not be suitable for biomedical use due to decrease in crystallinity and poor tensile strength. Therefore, TIBA-coated PPDO shows promising potential as a new material for absorbable IVC filter. However, the long-term physiological stability and toxicity of TIBA-coated PPDO needs to be investigated.

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4-Iodobenzoyl chloride (IBC)

2,3,5-Triiodobenzoic acid (TIBA)

FIGURE 1.
Molecular structures of IBC and TIBA.

FIGURE 2.

The micro-CT images of the infused and nascent PPDO sutures. (A) Illustrations of infused and nascent PPDO sutures generated from different concentrations of iodine contrast agents. (B) Micro-CT images of the sutures represented in (A). HU = Hounsfield units.

Figure 3. DSC thermograms of the heating scans (A) and melting temperatures (T_m) (B) obtained from the infused and nascent samples.

Figure 4. SEM micrographs of the nascent PPDO, PPDO in 100% DCM, and iodine contrast agent–infused PPDO (IBC-2, IBC-15, TIBA-2, and TIBA-15). IBC-2: 2 mg/mL IBC; IBC-15: 15 mg/mL IBC; TIBA-2: 2 mg/mL TIBA; TIBA-15: 15 mg/mL TIBA

Table 1.

Solubility Levels and HU Values of Different Iodine Contrast Agents, Contrast Agent Concentrations, and Solvent Systems

Contrast Agent	Concentration (mg/mL)	Solvent System	Solubility	HU (mean $\pm$ sd)
Blank	-	DCM	-	-
IBC	2	DCM	Good	66 $\pm$ 2
IBC	2	5% DMSO-DCM	Very good	74 $\pm$ 8
TIBA	2	DCM	Fair	195 $\pm$ 65
TIBA	2	5% DMSO-DCM	Very good	239 $\pm$ 20
IBC	15	DCM	Poor	258 $\pm$ 13
IBC	15	10% DMSO-DCM	Very good	290 $\pm$ 4
TIBA	15	DCM	Very poor	308 $\pm$ 6
TIBA	15	10% DMSO-DCM	Very good	313 $\pm$ 3

Each row represents samples done in triplicate.

Table 2.

Percentage of Infusion of Sutures with Iodine Contrast Agents

Embedded Contrast Agent	Concentration* (mg/mL)	Percentage of Infusion (mean $\pm$ sd)
IBC	2	0.60 $\pm$ 0.10
IBC	15	1.07 $\pm$ 0.08
TIBA	2	0.17 $\pm$ 0.01
TIBA	15	0.73 $\pm$ 0.01
Control (nascent)	0	0

* Solvent is 5% DMSO-DCM for concentrations of 2 mg/mL and 10% DMSO-DCM for concentrations of 15 mg/mL.

Table 3.

Concentrations, Micro-CT Images, and Corresponding HU Values of Iodine Contrast Solutions

Contrast Solution	CT Image	HU Value (mean $\pm$ sd)
DCM		270 $\pm$ 81
2 mg/mL IBC		2695 $\pm$ 47
15 mg/mL IBC		3143 $\pm$ 59
2 mg/mL TIBA		3301 $\pm$ 129
Bone	-	116 $\pm$ 37

Table 4.

Tensile Strengths of Infused and Nascent PPDO

Sample	Load at Break (kg)	
	Mean	SD
2 mg/mL IBC	6.06	0.25
15 mg/mL IBC	1.01	0.43
2 mg/mL TIBA	9.78	0.17
15 mg/mL TIBA	10.02	0.54
Nascent	10.10	0.64

SD: standard deviation