Low-Dose Paclitaxel Elution from a Novel Bioerodible Sol-gel Coating on Stents Inhibits Neointima with Less Vascular Toxicity in Porcine Coronary Arteries

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Disclosure Information

- No relationship to disclose

Objective

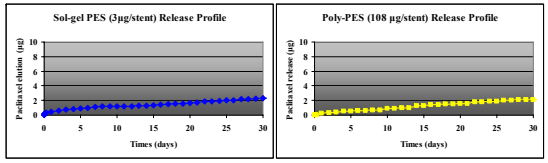
- Although current polymer-based paclitaxel-eluting stents (PESs) decrease restenosis, the permanent polymer and entrapped drug raise concerns about delayed vessel healing and late stent thrombosis. The present study was designed to evaluate a novel PES that releases a very low dose of paclitaxel from a new bioerodible sol-gel film coating, in the porcine coronary model.

Methods

- **Stent Characteristics**
  The sol-gel-PES and sham stents coated with sol-gel matrix, which has both biocompatible and bioerodible properties. The dose density was 0.025 µg/mm2, and total paclitaxel dose was 3 µg per 18 mm stent with slow-release formulation.
- **In Vitro Pharmacokinetics**
  The drug release kinetics were measured from both of the sol-gel-PES (n=5) and poly-PES (n = 3) by high performance liquid chromatography (HPLC).
- **Animal Model:**
  Juvenile domestic Yorkshire hybrid pigs (N=17) body weight 32.3±3.2 Kg
- **Interventional Procedure:**
  Sterilized stents (N=49) of four different types [1] BMS; Driver® (n=14), [2] sol-gel film only stents; sham (n=12), [3] poly-PES; TAXUS® Express® (n=8) and [4] sol-gel with PES (sol-gel-PES, n=15), sized ~15% larger than target site diameter were implanted using standard techniques.
- **Angiographic Restudy and Termination**
  - Animals were terminated at one month post-implant
  - Hearts were excised and fixed *ex vivo* by intravascular perfusion at physiologic pressure
- **Quantitative Coronary Angiography (QCA)**
  - At implant, target vessel diameter and stent-to-artery ratio
  - At follow-up, %diameter stenosis (%DS)
- **Histomorphometry**
  - 1) Luminal area; 2) Internal elastic lamina (IEL) area; 3) External elastic lamina (EEL) area, 4) Neointimal thickness, 5) Area of Tunica Medial (EEL area – IEL area) and 6) Histologic %area stenosis ([1-(luminal area/IEL area)] X 100)
- **Histopathology**
  - 1) inflammation; 2) mural/luminal thrombus; and 3) medial necrosis scored whereby 0=none; 1=mild; 2=moderate; and 3=severe, where 0 represented the least response and 3 represented the greatest response
  - Luminal surface coverage with flattened, confluent cells scored whereby 0=0-25% coverage of circumference; 1=25-50% coverage; 2=50-75% coverage; and 3=75-100% coverage

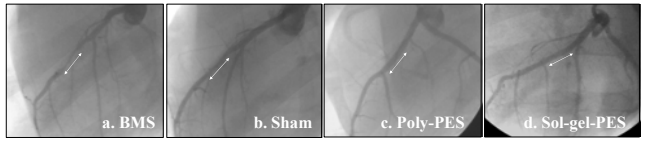
Results

- **Sol-gel PES Release Pharmacokinetics In Vitro**



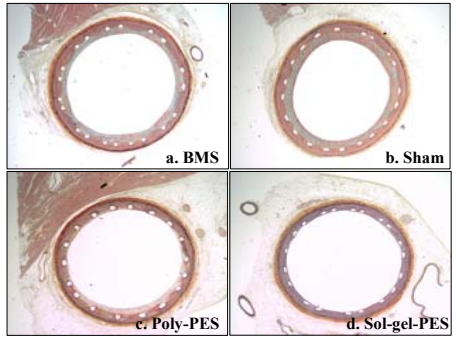
In comparison with the slow-release formulation of poly-PES, Sol-gel-PES elution demonstrated a similar elution curve

- **Angiography 1 Month Post Implant**



% DS; 2.8 ± 21.8% for poly-PES and 0.6 ± 17.0% for sol-gel-PES, vs. 11.7 ± 26.3% for BMS and 27.4 ± 19.3% for sham (p = 0.013 and 0.002 vs. poly-PES and sol-gel-PES, respectively)

- **Low Magnification Images (Movat pentachrome, 20X)**



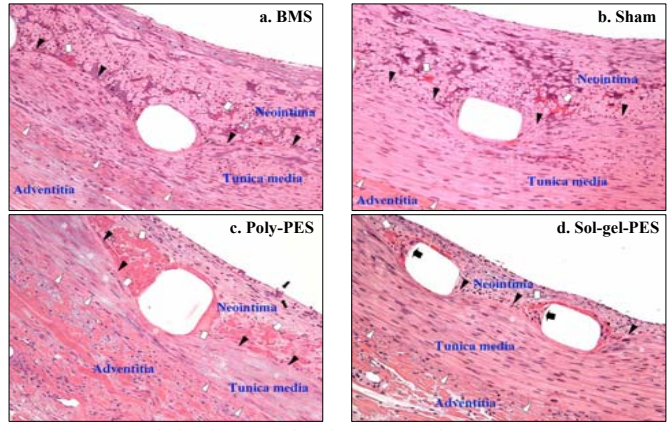
This demonstrates overall vessel morphologies. Suppression of neointimal formation was observed in sol-gel-PES and poly-PES in the absence of significant stent malapposition. Movat, 20X

- **Histomorphometry**

	BMS	Sham	Poly-PES	Sol-gel-PES	*p*
Area of Arterial Lumen	4.68±2.04	3.80±1.07	5.08±1.68	4.88±0.84	NS
Area of Stent/IEL	7.46±2.22	6.66±1.37	6.40±1.48	6.69±1.09	NS
Area of EEL	9.13±2.55	8.29±1.65	7.97±1.55	8.31±1.36	NS
Area of Tunica Media	1.67±0.42	1.63±0.37	1.57±0.18	1.62±0.36	NS
Area of Neointima	2.78±1.57	2.86±1.38	1.32±0.64*†	1.81±1.01¶	0.015
Thickness of Neointima	0.30±0.19	0.35±0.17	0.12±0.14*†	0.18±0.12‡¶	0.006
% Area Stenosis	38.5±18.9	42.2±12.8	21.9±13.6*†	26.3±11.3‡¶	0.005

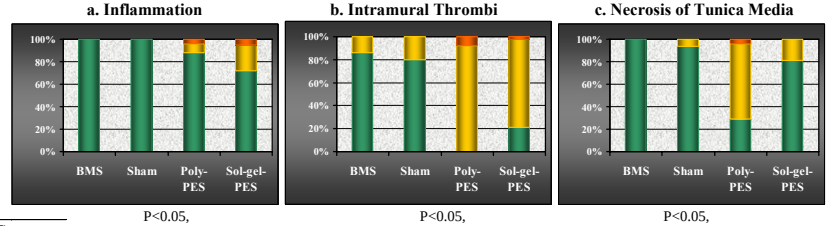
Values are Mean ± SD. *: P < 0.05, Poly-PES vs. BMS, †: P < 0.05, Poly-PES vs. Sham , ‡: P < 0.05, Sol-gel-PES vs. BMS, ¶: P < 0.05, Sol-gel-PES vs. Sham.

- **High Magnification Images (Hematoxylin-Eosin, 200X)**



Black arrowheads indicate internal elastic lamina (IEL) and white arrowheads show outer border of tunica media. (a) BMS group shows compression of fully cellular media, and fibro-cellular neointima with moderate thickness. Intramural thrombus is rarely seen (white arrow), which is indistinguishable from (b) sham group. (c) In the poly-PES group, peri-stent intramural thrombi (white arrows) are seen frequently and in excess. Stent strut is attached to IEL border, while compressed media shows moderate to severe necrosis (asterisk). Luminal surface attachment of inflammatory cells is often seen. (d) In the sol-gel-PES group, compressed tunica media shows almost intact SMC content with focal mild necrosis (asterisk). Intramural thrombi (white arrows) are seen in peri-stent area; multinucleated foreign-body giant cells (black arrows) and luminal surface attachment of inflammatory cells are occasionally seen.

- **Histopathology**



P<0.05, Poly-PES vs. BMS and Sham Sol-gel-PES vs. BMS and Sham

P<0.05, Poly-PES vs. BMS and Sham Sol-gel-PES vs. BMS and Sham

P<0.05, Poly-PES vs sol-gel-PES, BMS and Sham

- Complete coverage of the luminal blood flow tissue interface with a layer of flattened endothelial or endothelial-like cells was present in all samples from all stent implant types.

Summary and Conclusions

- A novel bioerodible sol-gel film coated with low-dose paclitaxel demonstrates less toxicity to the coronary arterial tunica media, while retaining effective inhibition of neointimal formation at 28 days.
- The mechanism of decreasing smooth muscle cell loss in the media may involve the lower sol-gel-PES dose formulation and its unique release kinetics. Further experiments will be required to support long-term safety of this technology.