Biodegradable Polyglycolide Endovascular Coils Promote Wall Thickening and Drug Delivery in a Rat Aneurysm Model

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OBJECTIVE: We designed biodegradable polyglycolide coils (BPCs) and compared the histopathological response to the coils with that to platinum Guglielmi detachable coils (GDCs), after insertion into ligated common carotid arteries (CCAs) of adult rats. BPCs were also tested for use in local drug delivery.

METHODS: Segments (4-mm) of unmodified BPCs, unmodified GDCs, or BPCs coated with Type I bovine collagen and recombinant human vascular endothelial growth factor-165 (500 μg/ml) were inserted into ligated CCAs of adult rats for 14 days, and specimens were compared with contralateral CCA control specimens.

RESULTS: Arterial segments with BPCs exhibited substantially increased wall thickening, compared with GDCs (0.33 mm versus 0.10 mm, $P < 0.005$), which reduced the luminal diameter by 40%, relative to untreated contralateral control specimens ($P < 0.05$, n = 6). Arterial segments with BPCs also exhibited a marked reduction ($P < 0.05$, n = 6) in luminal area (0.72 ± 0.93 mm^2), with marked cellular proliferation within the coil diameter, indicating coil integration. Arterial segments with collagen/recombinant human vascular endothelial growth factor-coated BPCs also exhibited a marked 2.9-fold increase ($P < 0.005$, n = 5) in wall thickness (0.29 ± 0.11 mm) and a 34% reduction in luminal diameter, compared with contralateral control vessels. There was marked proliferation of cells within the coil lumen of vessels treated with BPCs with collagen/recombinant human vascular endothelial growth factor.

CONCLUSION: In this feasibility study, BPCs enhanced the vascular response of CCA segments, compared with GDCs, and were also suitable for local protein delivery to the vessel lumen, under conditions of stasis and arterial pressurization of vascular cells. (Neurosurgery 49:1187–1195, 2001)

Key words: Aneurysm, Biodegradable, Endovascular, Guglielmi detachable coils, Polyglycolide, Vascular endothelial growth factor

Platinum microcoils have been modified with various proteins, growth factors, and cell types to enhance their long-term effectiveness for the treatment of intracranial aneurysms. Histopathological autopsy evaluations of aneurysms treated with Guglielmi detachable coils (GDCs) have identified some of the shortcomings of GDCs (3, 4, 18, 26, 27, 34, 37). As the aneurysm dome increases in diameter, it becomes increasingly difficult for platinum microcoils to provide the necessary framework for matrix formation and subsequent fibrosis. The addition of biological mediators to the coil surface may enhance the tissue response after coil placement in the aneurysm. The replacement of platinum with a biodegradable material may provide added benefits, in terms of stasis and thrombosis, mechanical stabilization, and coil integration, without the long-term inflammation observed with metallic vascular implants. Considerable work has been performed to improve coronary artery stents, to prevent local inflammation and restenosis, and has included the use of biodegradable materials. Although the goals of coronary artery stenting and aneurysm coiling are entirely different, stents have been altered via both surface modifications and replacement of metal with biodegradable materials such as polyglycolide (PGA) (9, 13, 25, 41–44).

We hypothesized that biodegradable coils would provide advantages, compared with platinum microcoils, in terms of mechanical stability, local vascular inflammation, and local drug delivery of recombinant human vascular endothelial growth factor (rhVEGF) to the aneurysm wall. Vascular endothelial growth factor (VEGF) is a heparin-binding glycoprotein that functions as a vascular permeability factor and is produced by macrophages, endothelial cells, and smooth muscle cells (28, 32). It is currently under intense investigation

because of its therapeutic effectiveness in elevating collateral flow in areas of myocardial ischemia. We hypothesized that it is difficult for larger aneurysms to become completely occluded after GDC therapy because the coils alone do not provide enough mechanical or biological support to promote neck closure. An angiogenesis-promoting factor such as VEGF might enhance fibrosis and subsequent aneurysm obliteration in a similar hemodynamic environment. In this study, we manufactured biodegradable PGA coils (BPCs), to assess their function in vascular embolization and their use as a method of local drug delivery in an in vivo model of arterial stasis and pressurization.

MATERIALS AND METHODS

Coil fabrication

BPCs were constructed from monofilament, synthetic, absorbable suture (Biosyn Glycomer 631; United States Surgical, Norwalk, CT). The actual polymer blend consisted of PGA (60%), dioxanone (14%), and trimethylene carbonate (26%). A size 5-0 suture (diameter, 180 μm) was used as a central core; another 5-0 suture was wound tightly around this core to a length of 4.0 cm (2.13 turns/mm) and an outer diameter of 540 μm, thus forming the primary coil (*Fig. 1A*). The primary coil was further coiled around a 3-mm shaping cylinder, forming a secondary coil (*Fig. 1B*). The secondary coil was heated to 160°C for 20 minutes and allowed to cool for more than 20 minutes before being removed from the shaping cylinder (*Fig. 2*). These heat-treated BPCs displayed mechanical flexibility appropriate for catheter-based delivery (*Fig. 2*). BPCs were sterilized with ultraviolet light for 1 hour and sectioned into 4-mm segments before placement in the common carotid artery (CCA) of adult rats. GDCs (Target Therapeutics, Freemont, CA) were also sectioned into 4-mm segments, under sterile conditions, before use in adult rats.

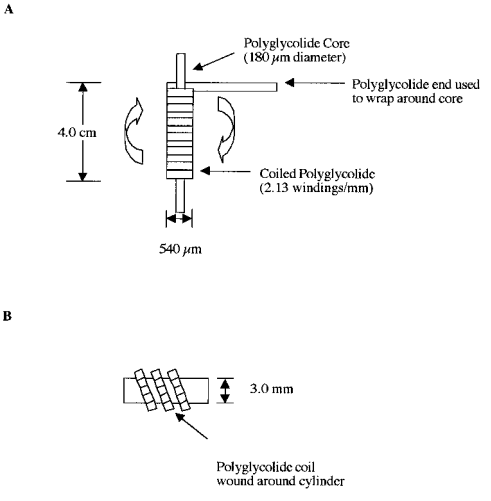

FIGURE 1. Diagram of a BPC. *A*, a 5-0 suture is wound around a core of the same size suture (5-0) to form the primary coil. *B*, the primary coil is then wound around a 3-mm-diameter cylinder to form the secondary coil.

FIGURE 2. Photograph of a BPC.

Coil modification with collagen/rhVEGF

BPC segments were coated with purified, pepsin-solubilized, bovine Type I dermal collagen (3.0 mg/ml) dissolved in 0.012 N HCl (Vitrogen; Cohesion Technologies, Palo Alto, CA). A collagen solution was prepared from 800 μl of the Type I dermal collagen, 100 μl of 0.1 N NaOH, and 100 μl of 10× Dulbecco's phosphate-buffered saline (Gibco BRL, Grand Island, NY) and was thoroughly mixed (pH 6.8). For collagen/rhVEGF coating, a 100-μl aliquot of 5 mg/ml rhVEGF-125 (Genentech, San Francisco, CA) was added to 900 μl of the collagen solution and mixed thoroughly, yielding a final concentration of 500 μg/ml (pH 6.9). BPC segments were immersed in the collagen/rhVEGF solution and incubated at 37°C for 1 hour, to allow polymerization, after which the coils were air-dried in a sterile laminar flow hood for 1 hour. Immediately after drying, the collagen/rhVEGF coils were maintained in a sterile environment and inserted into the CCA of rats.

Animal surgery and coil placement

All procedures were approved by the University of Pennsylvania Regulatory Affairs Committee. A total of 26 arterial segments were collected from 20 adult rats and grouped into normal (n = 6), GDC (n = 9), BPC (n = 6), and BPC plus collagen/rhVEGF (n = 5) groups. The normal group (n = 6) consisted of normal vessels obtained from the contralateral CCA, which underwent no coil placement or surgical disruption. Sprague-Dawley rats (375–425 g) were given access to food and water ad libitum before anesthesia was induced with an intraperitoneal injection of 60 mg/kg sodium pentobarbital. After anesthesia induction, the animals were placed on a heating pad and maintained at a temperature of 37°C for the entire procedure and immediate recovery period. With the animals in the supine position, a right paramedian incision was made with a number 10 scalpel, from the angle of the mandible to the mid-clavicle area. The superficial fascia and muscle layers were separated with blunt dissection until the deep neck muscles could be observed. The investing fascia of the deep neck muscles was incised and, again using blunt dissection, the muscles were separated until the carotid bundle could be observed. With microinstruments, the investing fascia of the CCA was incised and the CCA was skeletonized. A permanent ligature was placed proximal to the CCA bifurcation, and a temporary ligature was placed 1 cm distal to the

origin of the CCA (*Fig. 3A*). After proximal control of the CCA had been obtained, with complete cessation of arterial blood flow, a small arteriotomy was made 2 mm proximal to the distal ligature. The coil segment was then inserted into the CCA, and a new ligature was placed just distal to the arteriotomy, to exclude it from the circulation (*Fig. 3B*). The proximal ligature was released, to reestablish blood flow in the CCA segment. The operative field was inspected, to confirm that the final ligature maintained hemostasis and that the coil was in the newly created sac (*Fig. 3B*). The wound was closed with 4-0 nylon sutures, and the animals were returned to their cages and allowed to recover for 2 weeks. Marked vasodilation proximal to the second permanent ligature was noted upon removal of the temporary ligature.

Vessel and coil collection

The animals were given access to food and water ad libitum for the next 14 days, and then the coils were collected from the CCA. Anesthesia was induced with an intraperitoneal injection of 60 mg/kg sodium pentobarbital, and the animals were killed with an intracardiac injection of 60 mg/kg sodium pentobarbital. The previous incision was opened, and the CCA was exposed. The CCA segment containing the coil was removed. The coil and CCA segments were placed into formalin for preservation. CCA segments from six animals were resected, preserved in formalin for sectioning, and used as CCA control specimens.

Histopathological assessments

Formalin-fixed segments were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. For semiquantitative pathological scoring, a single observer (who was blinded to the coil modification groups) evaluated histopathological sections. Evaluations were based on the grade of intimal proliferation (graded as 0–3) and the percentage of intimal occlusion. Intimal occlusion represents the area of the lumen divided by the total area of the vessel. Histopathological sections of CCA segments were also viewed using a microscope (Axiovert 135; Carl Zeiss, Thornwood, NJ), and images were digitized using a calibrated charge-coupled device camera (Hamamatsu Phototonics, Inc., Bridgewater, NJ). Digitized images were sent to a frame-grabber on a Dell workstation (Dell Computers, Round Rock, TX). At the workstation, digitized images were analyzed using image analysis software (UTHSCSA Image Tool, San Antonio, TX), which allowed quantitative measurements of the lumen perimeter and wall thickness. The effective lumen area and diameter were calculated from the lumen perimeter. Data were expressed as mean ± standard deviation for n vessels analyzed in each set. A two-tailed Student's t test was used to determine the statistical differences between treatment groups, with Bonferroni correction for multiple comparisons with the CCA segments with unmodified coils.

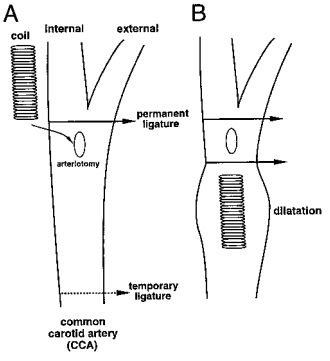

FIGURE 3. Diagram of the coil insertion procedure. *A*, the CCA has been exposed and temporary proximal and permanent distal ligatures placed. *B*, the coil has been inserted into the CCA, a permanent ligature has been placed proximal and distal to the arteriotomy, and the temporary ligature has been released.

RESULTS

The BPC and GDC segments used throughout these experiments were the same length (i.e., 4 mm). There was no evidence of swelling or increases in BPC size at the time of implantation or collection. Collected GDCs were easily removed from the vessel and were observed by gross inspection to exhibit minimal fibrotic encapsulation of the coil after 2 weeks of implantation, which was confirmed by electron microscopy (data not shown). However, CCA sections implanted with BPCs or BPCs plus collagen/rhVEGF demonstrated definitive thrombosis and fibrosis of the vessel wall at the time of collection. In *Figure 4*, representative sections for each group are presented. The CCA segment with a GDC exhibited some vascular dilation and mild intimal proliferation, with minimal changes in lumen patency (*Fig. 4B*). The CCA segment with an untreated BPC demonstrated moderate-to-severe intimal proliferation, with a section of BPC contained within the lumen (*Fig. 4C*). There was also modest intimal ingrowth into the coil. The CCA segment with a BPC plus collagen/rhVEGF exhibited moderate-to-severe intimal hyperplasia (*Fig. 4D*). Also, extensive intimal proliferation into the coil interior was observed in sections with BPCs plus collagen/rhVEGF (*Fig. 4D*).

Pathological scoring

The results of the blinded pathological scoring are summarized in *Table 1* for grading of intimal proliferation (Grades 0–3) and percentage of intimal occlusion. When compared with those for GDCs (1.4 ± 0.73), intimal proliferation grades for BPCs (2.0 ± 0.82, $P = 0.17$) and BPCs plus collagen/rhVEGF (1.8 ± 0.84, $P = 0.42$) were greater, but the differences were not significant. For further assessment of intimal proliferation, lumen patency was characterized on the basis of percent occlusion, compared with normal vessels with 0% occlusion. There were progressive increases in percent occlusion with GDCs (20 ± 14%), BPCs (65 ± 36%), and BPCs plus collagen/rhVEGF (50 ± 36%). Percent occlusion was significantly greater in comparisons of GDCs with BPCs ($P < 0.005$) and GDCs with BPCs plus collagen/rhVEGF ($P < 0.05$).

Quantification of vessel changes

The mean CCA luminal areas were 1.99 ± 0.99 mm^2 with GDCs, 0.72 ± 0.93 mm^2 with BPCs, and 0.75 ± 0.84 mm^2 with BPCs plus collagen/rhVEGF (*Table 2*). The mean CCA luminal areas were significantly smaller in comparisons of GDCs with BPCs ($P < 0.05$) and GDCs with BPCs plus collagen/rhVEGF ($P < 0.05$). The mean CCA luminal diameters were 0.49 ± 0.14

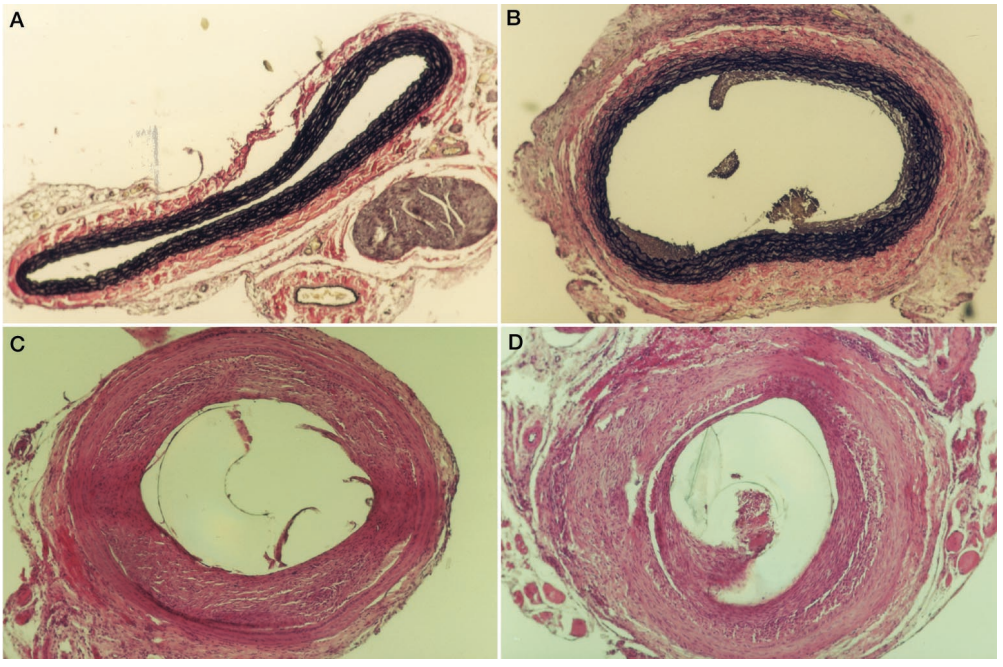

FIGURE 4. Histopathological findings for the CCA segments for each group (hematoxylin and eosin; original magnification, ×20). *A*, normal CCA. *B*, GDCs. *C*, BPCs. *D*, BPCs plus collagen/rhVEGF.

TABLE 1. Intimal Proliferation Grades and Intimal Occlusion[a]

Group	Intimal Proliferation (Grade)	Intimal Occlusion (%)
Normal (n = 6)	0.0	0
GDCs (n = 9)	1.4 ± 0.73	20 ± 14
BPCs (n = 6)	2.0 ± 0.82[b]	65 ± 36[c]
BPCs + collagen/rhVEGF (n = 5)	1.8 ± 0.84[b]	50 ± 36[d]

[a] Values are mean ± standard deviation. GDCs, Guglielmi detachable coils; BPCs, biodegradable polyglycolide coils; rhVEGF, recombinant human vascular endothelial growth factor.
[b] *P* value not significant, compared with GDCs.
[c] *P* value significant, compared with GDCs ($P < 0.005$).
[d] *P* value significant, compared with GDCs ($P < 0.05$).

mm with GDCs, 0.21 ± 0.24 mm with BPCs, and 0.23 ± 0.23 mm with BPCs plus collagen/rhVEGF. The mean CCA luminal diameters were significantly smaller in comparisons of GDCs with BPCs ($P < 0.05$) and GDCs with BPCs plus collagen/rhVEGF ($P < 0.05$). The mean CCA wall thicknesses were 0.10 ± 0.02 mm with GDCs, 0.33 ± 0.19 mm with BPCs, and 0.29 ± 0.11 mm with BPCs plus collagen/rhVEGF. The mean CCA wall thicknesses were significantly smaller in comparisons of GDCs with BPCs ($P < 0.005$) and GDCs with BPCs plus collagen/rhVEGF ($P < 0.005$).

DISCUSSION

PGA was used to develop the first completely synthetic absorbable suture, which was marketed as Dexon (U.S. Surgical, Norwalk, CT) in the 1960s (25). PGA loses approximately 50% of its strength by 2 weeks and 100% of its strength by 4 weeks and is completely absorbed by 90 to 110 days (14). Although PGA is well known as suture material, various forms are used as dental implants, as orthopedic implants, as parts of heart valves, as matrices in tissue engineering, and as a method for local drug delivery (5, 21, 23, 25, 35, 36). The concept of using a biodegradable polymer instead of platinum was adapted from similar efforts to improve coronary artery stents. Biodegradable polymers have been used as stent coatings, as substitutes for metallic stents, and as resorbable endoluminal stents impregnated with recombinant adenovirus (9, 11–13, 16, 17, 30, 33, 41–44). The concept of modifying platinum microcoils was successfully demonstrated in previous studies, and this topic has been reviewed (1). Platinum microcoils have been modified, both in vitro (19, 39) and in vivo (7, 8, 20, 29, 38, 40), with extracellular matrix proteins, polyurethanes, Dacron, implanted ions, and modified cell lines. Overall, the results demonstrated enhanced cellular proliferation on the coils.

VEGF is potent angiogenic growth factor with direct effects on endothelial cells (6, 10). Together, VEGF and basic fibroblastic growth factor exert synergistic effects on endothelial cell differentiation and angiogenesis. Intracoronary injections of recombinant VEGF have been demonstrated to promote the development of collateral vessels within ischemic myocardial tissue (15, 24, 31). We hypothesized that rhVEGF coated onto GDCs might promote a tissue response, under conditions of stasis and pressurization, and could provide the biological activity necessary to induce fibrosis across vascular structures. Using the same rat model as in this study, we evaluated CCA segments with unmodified GDCs, GDCs plus collagen, and GDCs plus collagen/rhVEGF (2). Our results demonstrated that, after 14 days of implantation, CCA segments with GDCs plus collagen/rhVEGF exhibited significantly more occlusive tissue, with an overall enhanced vascular re-

TABLE 2. Area, Diameter, and Wall Thickness[a]

Group	Area (mm^2)	Diameter (mm)	Wall Thickness (mm)
Normal (n = 6)	1.01 ± 0.49	0.35 ± 0.09	0.05 ± 0.01
GDCs (n = 9)	1.99 ± 0.99	0.49 ± 0.14	0.10 ± 0.02
BPCs (n = 6)	0.72 ± 0.93[b]	0.21 ± 0.24[b]	0.33 ± 0.19[c]
BPCs + collagen/rhVEGF (n = 5)	0.75 ± 0.84[b]	0.23 ± 0.23[b]	0.29 ± 0.11[c]

[a] Values are mean ± standard deviation. GDCs, Guglielmi detachable coils; BPCs, biodegradable polyglycolide coils; rhVEGF, recombinant human vascular endothelial growth factor.

[b] *P* value significant, compared with GDCs ($P < 0.05$).

[c] *P* value significant, compared with GDCs ($P < 0.005$).

sponse, compared with segments with GDCs or GDCs plus collagen. In addition, Factor VIII staining was positive for areas of neovascularization within the intravascular tissue surrounding the coils. Although these results were very promising, we further postulated that, for even better responses, platinum should be replaced with a more thrombogenic material such as a biodegradable polymer.

In this study, our results demonstrated significant enhancement of local cellular responses in comparisons of CCA segments with GDCs and those with BPCs. One of the limitations of platinum microcoils is the fact that they do not provide an inherent stimulus for clot organization, cellular proliferation, or coil integration, to strengthen the aneurysm dome. In the initial description of electrolytically detachable coils, it was postulated that the charge density distributed throughout the platinum coils during detachment attracts negatively charged blood cell components. This may be true for the duration of the detachment process (minutes) but does not seem likely after this period. One advantage of using PGA is the enhanced local cellular response from the vascular endothelium in contact with the degrading BPCs. Previous studies demonstrated increased cell growth patterns of smooth muscle cells and extracellular matrix proteins on PGA scaffolds, compared with collagen scaffolds (21–23). In addition, because PGA is hydrolyzed, there is a greater adsorption of serum proteins onto the surface, thus increasing the overall cell seeding density (14).

Biodegradable materials are useful for local drug or gene delivery (30, 36, 42–44). Our data demonstrated no significant difference in vascular proliferation in comparisons of BPCs with BPCs plus collagen/rhVEGF; however, both demonstrated better overall inflammatory responses, compared with GDCs. In comparisons of BPCs with BPCs plus collagen/rhVEGF, the degrees of intimal hyperplasia and vessel narrowing were similar (*Tables 1* and *2*). Although BPCs may serve as a means for drug delivery, there was no significant effect of rhVEGF when it was added to the coils. Previous work by our group demonstrated significant increases in intimal hyperplasia and vessel narrowing when rhVEGF was added to GDCs, in comparison with unmodified GDCs and GDCs plus collagen (2). It may be that PGA itself is thrombogenic enough to mask the effects of rhVEGF and thus the effects are more pronounced with a biologically inert material such as platinum. Another promising aspect of the use of PGA is the possibility of adding adenovirus to the surface for local gene delivery. This may be of clinical significance for patients with vasospasm, for whom treatment would begin with coiling and local release of potent vasodilators from the coil surface, via recombinant protein- or adenovirus-mediated delivery.

The rat "aneurysm" model is a feasibility model that partially recreates aneurysmal conditions of arterial stasis and pressurization. Compared with experimental aneurysm models that use end-to-side venous pouches, this model provides more insight into the alterations in the vascular biological features of the arterial wall. This model exhibits obvious differences from human aneurysms with respect to flow dynamics and arterial histological features. Saccular human aneurysms are devoid of smooth muscle in the medial layer, unlike our model, in which the CCA is competent throughout.

A number of other important considerations remain. We did not perform a sham operation (arteriotomy and ligature alone) because our objective was to compare a known therapy (GDCs) with a new therapy (BPCs). Sham operations would be more useful for validation of the aneurysm model than for evaluation of the vascular biological features of GDCs versus BPCs. The blend of PGA, dioxanone, and trimethylene carbonate in the BPCs could be modified to provide more or less flexibility than the current PGA construct. Also, a fail-safe delivery mechanism is needed, to ensure accurate placement of the devices with the same precision as GDCs. Lastly, we did not perform a spatial analysis of the biological activity along the length of the CCA segments. In gross inspections of the CCA performed at the time of coil collection, vessel involvement was limited to the length of the coil. The next step would be to deploy biodegradable coils in an end-to-side venous pouch aneurysm model in larger animals, which would allow spatial analysis of biological activity around the aneurysm itself and in the parent artery.

CONCLUSIONS

In this preliminary study, we have demonstrated enhanced vascular responses of CCA segments with BPCs or BPCs plus collagen/rhVEGF, compared with GDCs. The BPCs showed promise as a possible alternative to the current platinum

technology and perhaps have greater potential as a method for local drug delivery. Other future considerations for PGA include the potential for local gene therapy, chemotherapy, and radiotherapy delivery. The next step will be to compare the results for BPCs with those for GDCs in a model of experimental venous sidewall aneurysms.

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COMMENTS

The authors present their novel work with an endovascular coiling device constructed of polyglycolide (PGA) suture material. Their study is inspired by similar work with cardiac stents. They discuss the simple construction of these coils and compare these coils' biological effects with those of the widely used platinum Guglielmi detachable coils (GDCs) in an aneurysm model created by ligating the common carotid arteries (CCAs) in rats. The PGA coil was also examined as a local delivery vehicle for recombinant human vascular endothelial growth factor (rhVEGF) in this model.

GDCs are the gold standard for the endovascular treatment of cerebral aneurysms. It is thought that surface charge on the platinum coil during electrolytic release from the microcatheter during deployment encourages deposition of charged blood products, thus promoting thrombosis. These coils generally are not deployable in wide-mouthed aneurysms, undergo coil compaction for longer periods of follow-up, produce artifact on radiographic studies, and remain permanently inside the vascular compartment as a metal foreign body. Biodegradable polyglycolide coils (BPCs) offer several theoretical advantages over GDCs, including relatively rapid degradation; compatibility with imaging studies; and, as the authors demonstrate, the ability to serve as a local delivery vehicle for drugs or proteins (and potentially for virally transduced genes). One potential application that the authors suggest is BPCs deployed in ruptured aneurysms impregnated with drugs or genes designed to combat vasospasm. Another potential use is in the preoperative thrombosis of arterial feeders of malignant tumors in which the delivery of a myriad of drugs, proteins, or genes with antitumor activity might be efficacious.

The next steps in the development of these BPCs should be aimed at understanding the release kinetics and mechanical properties of various formulations of this PGA, dioxanone, and trimethylene carbonate polymer, as well as at developing a suitable microcatheter delivery system comparable in safety to that available with GDCs. The authors have described an insightful and creative idea.

Richard E. Clatterbuck
Henry Brem
Baltimore, Maryland

Abrahams et al. have studied the hypothesis that endovascular BPCs can be used as a drug delivery vehicle in endovascular therapy. They demonstrate that the treated coils seem to reduce lumen area and diameter and to increase wall thickness in a significant way as compared with GDC coils that are not so treated. Because no significant difference was observed between the BPC and the BPC plus collagen/rhVEGF groups, it remains to be seen whether significant drug delivery of bioactive molecules that affect the vascular

wall response are significant. It is conceivable that some aspect of the BBC itself might explain the observed responses. Nonetheless, this provocative article includes straightforward observations regarding the authors' findings.

Ralph G. Dacey, Jr.
St. Louis, Missouri

The authors have tested the hypothesis that BPCs impregnated with rhVEGF increase fibrosis and lead to more effective aneurysm obliteration than that achieved with GDCs. Although intimal proliferation seemed to be greater with the use of the BPC and the BPC with rhVEGF (*Fig. 4*), these results were statistically insignificant. The percentage of occlusion was greater when the BPCs were used. The addition of rhVEGF seems to have had little effect (*Table 2*).

The authors were only partially successful in reaching their stated goal. Most important, the model used has characteristics that are obviously different from those of aneurysms. The study design used a blind pouch model without the complication of keeping the parent artery open and unaffected. This is a crucial part of the experimental evaluation of using new, biologically active coils. There must be some measure of the spatial extent of the biological effect being sought. This unfortunately was not done in this study, a problem that the authors acknowledge. This article provides no information that indicates that the addition of rhVEGF to the BPC adds any value to using these coils.

Clearly, more work needs to be done to evaluate the potential efficacy of using biologically active coils. In the long run, this promising area of investigation is likely to produce clinically involved treatments using coil embolization techniques.

Charles J. Hodge, Jr.
Syracuse, New York

The authors have sought to determine the feasibility of using a BPC to enhance the vascular response as compared with that achieved with platinum GDCs. They performed histological analysis of rodent CCAs after implantation of platinum, PGA, and PGA plus rhVEGF coils into a blind-ended CCA aneurysm model. The investigators found that PGA coils produced significantly greater intimal thickening and reduction in diameter as compared with platinum coils. The addition of rhVEGF did not show a benefit. The authors caution that the differences in histological and flow characteristics in this aneurysm model from those in a human model require further evaluation with different aneurysm models. Nonetheless, these results are encouraging, and we share the authors' enthusiasm for further investigation and evaluation of the use of PGA in aneurysm treatment and drug delivery.

Christopher L. Taylor
Warren R. Selman
Cleveland, Ohio

Abrahams et al. provide a glimpse into the future of endovascular techniques for aneurysm occlusion. This preliminary study in ligated rat CCAs demonstrates significantly increased vascular tissue response with BPCs in comparison with platinum coils.

Although this study does not definitively demonstrate drug delivery, other studies by the authors suggested that drugs can be delivered with a PGA coating. We are encouraged by the increased intimal hyperplasia and vessel narrowing with BPCs. The use of this type of coil may translate to better aneurysm occlusion. Currently, the histopathology of coil embolization is limited to a handful of human case reports and animal experiments (1–3, 6, 7). The limitations of coil embolization have been noted particularly in giant and bifurcation aneurysms, in which reendothelialization across the neck does not occur.

To improve the ability to occlude these aneurysms, the coils need to be packed densely, which increases the risks of parent vessel injuries and thromboembolic complications. An alternative approach is to modify the coil to gain a more robust inflammatory response, with the goal of reendothelialization of the aneurysm neck. The use of PGA coils make intuitive sense, given the response of tissue to absorbable stitches (in comparison to the use of stainless steel). This finding has been replicated in this experiment.

The limitations of this study include direct delivery of the coil under the microscope, so the use of this coil with catheter-based technology and a consistent detachment method needs to be investigated. In addition, the carotid sacs created in this study are not aneurysms and would likely thrombose spontaneously.

Another concern is the ability to control the hyperplastic or inflammatory response so that parent vessel occlusion or stenosis does not occur. Another potential problem is an inflammatory response that increases the mass effect of the aneurysm on surrounding intracranial structures.

The addition of rhVEGF did not improve intimal hyperplasia or vessel narrowing in this study. The hypothesis that the use of rhVEGF improves the ability to occlude aneurysms is unproved. Alternatively, rhVEGF might promote endothelial growth along the coil, resulting in a higher likelihood of recanalization. Indeed, other investigators are examining methods of inhibiting immediate endothelialization of the coils with the hope of improving aneurysm occlusion (unpublished data).

The authors provide their valuable insights with regard to the possible future of endovascular surgery. They, along with Murayama et al. (4, 5), provide a critical first step toward improving the ability to occlude aneurysms. More important, the ability to modify coils and deliver specific drugs may allow neurosurgeons to gain an understanding of the biology of aneurysm formation and, potentially, of the healing process of restoring normal vasculature integrity.

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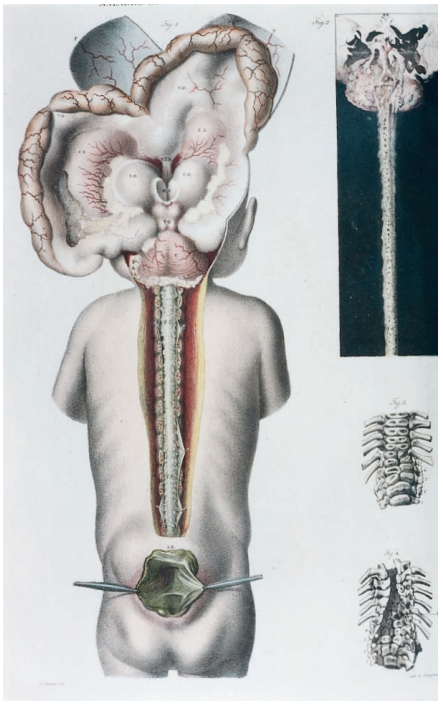

Exploded views of the posterior fossa, medulla, spinal cord, and vertebral malformations of an infant. From, Jean Cruveilhier, *Anatomie pathologique du corps humain, ou Descriptions, avec figures lithographiées et coloriées, des diverses altérations morbides dont le corps humain est susceptible.* Paris, Baillière, 1829–1842, vol. 1. (Courtesy, Rare Book Room, Norris Medical Library, Keck School of Medicine, University of Southern California, Los Angeles, California.)

19th century illustrations of spina bifida, by Jean Cruveilhier, *Anatomie pathologique du corps humain, ou Descriptions, avec figures lithographiées et coloriées, des diverses altérations morbides dont le corps humain est susceptible.* Paris, Baillière, 1829–1842, vol. 1. (Courtesy, Rare Book Room, Norris Medical Library, Keck School of Medicine, University of Southern California, Los Angeles, California.)