Matrix and Bioabsorbable Polymeric Coils Accelerate Healing of Intracranial Aneurysms

Long-Term Experimental Study

Yuichi Murayama, MD; Satoshi Tateshima, MD; Nestor R. Gonzalez, MD; Fernando Vinuela, MD

Background and Purpose—Acceleration of intra-aneurysmal clot organization and fibrosis may be a solution to preventing aneurysm recanalization after endovascular treatment. The purpose of this study was to evaluate the short-term efficacy and long-term safety of the new Matrix coil system.

Methods—Matrix coils consist of thin platinum coils covered with a bioabsorbable, polymeric material (polyglycolic acid/lactide). Fifty-two experimental aneurysms were created in 26 swine. All of the aneurysms were tightly packed with Matrix or Guglielmi detachable coils (GDC). Comparative angiographic and histopathologic data were analyzed at 2 weeks (n=14), 3 months (n=6), and 6 months (n=6) after embolization.

Results—Three aneurysms treated with GDC ruptured despite tight packing. No recanalization or rupturing was observed in the aneurysms embolized with Matrix coils. At 14 days after embolization, the aneurysms treated with Matrix coils exhibited a more extensive area of organized thrombus when compared with the aneurysms treated with GDC (87% versus 75%, P=0.008, n=11). At 3 months, both Matrix and GDC-treated aneurysms demonstrated complete clot organization. Neck tissue thickness was higher in Matrix-treated aneurysms at 14 days and 3 months, but not at 6 months. No untoward parent artery stenosis was observed in aneurysms treated with Matrix during follow-up. The angiographic cross-sectional area of the Matrix-treated aneurysms was smaller than those treated with GDC at the 3 months.

Conclusion—Matrix accelerated aneurysm fibrosis and neointima formation without parent artery stenosis. The Matrix system might prevent aneurysmal recanalization after endovascular treatment of cerebral aneurysms. (Stroke. 2003;34: 2031-2037.)

Key Words: animal models ■ endovascular therapy ■ intracranial aneurysm ■ polymers ■ swine

In the past decade, endovascular therapy using Guglielmi detachable coils (GDC) has proven to be a successful alternative for the treatment of intracranial aneurysms.1–11 The most important limitation of the GDC system is the possibility of aneurysm recanalization, particularly in wide-necked or large or giant aneurysms.3,6

Platinum coils are biologically inert and produce a limited and delayed inflammatory response.12 The utilization of “bioactive” material as an embolic agent may be a promising approach to overcome the current limitations of the GDC system.12–24

Recently we applied the concept of tissue engineering to aneurysm therapy using bioabsorbable polymeric material (BPM).25,26 BPMs have been used in biocompatible devices such as sutures and implants and, more recently, as drug delivery vehicles or scaffolds for tissue engineering. BPMs can stimulate cells to regenerate tissue and act as scaffolds for cell transplantation both in vitro and in vivo.

This cellular reaction is necessary to promote scar formation in the aneurysm and can be controlled by the composition of the copolymers. Brain aneurysms can be considered a defect of the normal arterial wall and they can be repaired by applying the concept of tissue engineering. This experimental study was designed to evaluate the acute phase of tissue reaction and long-term safety of Matrix detachable coils in experimental aneurysms.

Materials and Methods

The study was conducted according to the standard operating procedures of our animal research committee. Twenty-six Yorkshire swine of both sexes were acclimated to laboratory conditions for at least 7 days before aneurysm creation and embolization. The swine were approximately 3 to 4 months old and weighed 25 to 40 kg.

Coil Preparation

Matrix detachable coils are platinum coils covered with a bioabsorbable polymer (90% polyglycolide, 10% polylactide) and attached to a stainless steel delivery wire. The details of the coil characteristics...
were previously described and the detachment system was the same as the one used with GDC.\textsuperscript{26} Coil diameters ranged from 2 to 12 mm and coil lengths ranged from 4 to 30 cm with both GDC and Matrix detachable coils. Both coil groups were sterilized twice with ethylene oxide prior to use.

Anesthesia
Ketamine 150 mg and xylazine 150 mg were administered intramuscularly. The animals were then intubated and maintained on halothane, 1% to 4% inhaled, administered to effect, in 100% oxygen at 4 to 5 L/min. Monitoring during anesthesia included heart rate, respiratory rate, and temperature.

Aneurysm Construction
Fifty-two lateral wall experimental aneurysms were constructed microsurgically in both common carotid arteries of 26 swine. The details of aneurysm construction have been previously reported.\textsuperscript{18} Aneurysm sacs (8 to 12 mm) and necks (7 mm) were created of equal size, bilaterally. Aneurysm dimensions were recorded (height, width, length) at the time of creation and used in aneurysm volume and packing density estimation.

Aneurysm volumes were estimated using the formula $V_a = \frac{4}{3}\pi (a/2) (b/2)(c/2)$ mm$^3$, where $V_a$ equals aneurysm volume, equals height, $b$ equals width, and $c$ equals length; dimensions were obtained at time of aneurysm creation.

The volume of coils was estimated using the formula $V_c = \pi (OD/2)^2 L$, where $V_c$ equals coil volume, $OD$ equals the average outer coil diameter (GDC-18, 0.381 mm; GDC-10, 0.254 mm; Matrix, 0.32 mm), and $L$ equals the total length of coils deployed in the aneurysm. The packing density (PD) for each aneurysm was calculated using the formula $PD = (V_c/V_a) \times 100\%$.

Aneurysm Embolization
All endovascular procedures were performed immediately after aneurysm creation (Figure 1). A total of 52 experimental aneurysms were embolized with standard platinum GDC ($n=26$) or Matrix coils ($n=26$). For each swine, the type of coil used to occlude the first aneurysm was randomly chosen.

A 6-F sheath was placed in the right femoral artery and selective angiography was performed using a 6-F Fasguide guiding catheter. An intravenous bolus of 3000 U of heparin was injected to prevent thromboembolic complications.

Both GDC and Matrix coils were immersed in sterile saline before embolization. Prior to the embolization procedure, a 2-tipped microcatheter was positioned in the carotid artery to measure the angiographic size of the aneurysm and the parent artery (distance between 2 markers is 3 cm). An Excel 14-microcatheter/Mizzen 10 microguide wire system (Boston Scientific/Target) was advanced through the guiding catheter and the tip of the microcatheter was positioned in the center of the aneurysm. All aneurysms were densely packed using either GDC or Matrix coils.

Postembolization angiograms were performed with the 2-marker microcatheter positioned in the parent artery adjacent to the aneurysm.

Follow-Up Angiogram
At 14 days, follow-up angiograms were performed in all cases, and 14 of 28 animals were then euthanized using standard approved procedures. The remaining 12 animals were kept alive for 3 months ($n=6$) and 6 months ($n=6$).

The thickness of the radiolucent tissue gap between the flowing contrast media in the parent artery and the coil mass in the aneurysm (angiographic evidence of neointima) was measured. The measurements were made in 3 points along the neck of the aneurysm corresponding to the center of the coil mass and ±2 mm beyond the center.

Histopathological Analysis
The parent arteries were cut longitudinally, rinsed with saline and photographed (Figure 2). The specimen was placed in 10% buffered formaldehyde. The harvested specimens were sent to an independent pathology laboratory (Wasatch Histology Consultants, Inc, Winnipeg, Nev, and Pathology Associates International, Frederick, Md), and pathology reports were prepared by an independent pathologist. Aneurysms were embedded in methylmethacrylate (MMA). MMA blocks were cut using a diamond band saw blade (EXAKT). At least 3 serial cross-sections (proximal, middle, and distal portions of the aneurysm) were taken across the neck of the aneurysm and aneurysms perpendicular to the parent artery. Sections were grounded to a thickness of approximately 100 μm. The percentage of nonorganized clot versus organized thrombus and the tissue thickness across the neck of the aneurysm were evaluated from digital images using NIH Image Software. The neck tissue thickness was determined by...
drawing a line between the sutures used to create the aneurysm. They were located at the base of the artery and evident on both sides of the aneurysm neck. The distance between the lumen of the artery and this demarcation line was measured as an average between maximum and minimum measurements. If coils were crossed by this line, the demarcation line was moved parallel to its original position, toward the lumen, and redrawn so as to exclude the coil.

**Statistical Evaluations**

Statistical significance of the differences between control and test groups was evaluated using Excel (Microsoft Corp, Inc), or JMP (SAS Statistical Software, Piscataway, NJ). Both the paired t test and the fixed factor analysis of variance (ANOVA) were used primarily as control for different sources of variation. The paired t test was used as control in animal-to-animal variation. The ANOVA, in this case, was a 3-factor nonreplicated analysis.

**Results**

**Packing Densities**

The packing densities were similar between GDC and Matrix-treated aneurysms (Table 1).

**Clinical Outcome and Complications**

A total of 23 swine survived the surgical and endovascular procedures. Three deaths occurred due to rupturing of aneurysms embolized with GDC (2 at 5 days and 1 at 12 days postimplantation). In these 3 cases, the aneurysms embolized with Matrix were completely occluded. One aneurysm embolized with Matrix developed a parent artery occlusion due to initial damage of the parent artery (first case). The Matrix coil broke before it had been completely deposited in the aneurysm. The coil was retrieved using a coil retriever. The procedure of coil retrieval damaged the parent artery with concomitant arterial occlusion. This manufacturing failure was technically fixed and it was not observed in subsequent embolizations with Matrix.

**Neck Tissue Thickness Measured on Angiography**

At day 14, the angiographic measurement of neointimal thickness at aneurysmal neck level showed significant differences between Matrix- and GDC-treated aneurysms (average 0.41±0.2 mm for Matrix versus 0.25±0.2 mm for GDC; P=0.009, n=11).

At 3 months, the neck tissue thickness for Matrix was 0.15±0.22 mm and 0 mm for GDC (P=0.0036, n=5). The

<table>
<thead>
<tr>
<th>TABLE 1. Aneurysm Coil Packing Densities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Group</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>14-day group n=14</td>
</tr>
<tr>
<td>3-month group n=6</td>
</tr>
<tr>
<td>6-month group n=6</td>
</tr>
</tbody>
</table>
apparent loss in neck tissue thickness could be related to the increased size of the parent artery due to normal growth of the animal. At 6 months postembolization, the tissue thickness at aneurysmal neck level could not be obtained due to poor radiographic documentation related to the increased thickness of skull bones. No progressive parent artery stenosis was observed in either GDC- or Matrix-treated aneurysms at 3 and 6 months.

**Macroscopic Findings**

The 2 animals that died 5 days after implantation exhibited unorganized clot in the sac of the aneurysm treated with GDC. The animal that died 12 days after implantation showed almost complete neointimal coverage of the neck of the aneurysm embolized with Matrix, whereas the aneurysm embolized with GDC showed rupturing and a large neck hematoma.

At day 14, the necks of all Matrix-treated aneurysms were completely covered with a fibrous membrane (n=11). The necks of 7 out of 11 GDC-treated aneurysms were completely covered with fibrous tissue. In 4 aneurysms the necks were partially covered with neointima.

All 3- and 6-month aneurysm specimens exhibited fibrous tissue covering the neck of the aneurysms except for 1 GDC-treated aneurysm that had a hole in the orifice. No excessive tissue reaction at the neck was observed with Matrix- and GDC-treated aneurysms. These observations were confirmed by microscopy.

**Histological Findings**

**Thrombus Organization in the Aneurysmal Sac**

At day 14, Matrix-treated aneurysms exhibited a more extensive area of organized thrombus when compared with aneurysms embolized with GDC (Figure 3). Matrix-treated aneurysms showed an average of 87% of their area as organized thrombus. GDC-treated aneurysms averaged 75% (P=0.008, n=11). In specimens recovered after 3 and 6 months, both GDC- and Matrix-treated aneurysms were completely occluded with fibrous connective tissue.

**Tissue Thickness of the Neck of the Aneurysm**

At day 14, Matrix-treated aneurysms had a thick and mature neointimal tissue covering the neck of the aneurysm. Cells with morphology consistent with endothelium were present at the luminal surface.

It was found that the average neck tissue thickness was 0.29 mm±0.30 for Matrix versus 0.13 mm±0.17 for GDC (P<0.0001, n=11) at 14 days postimplantation. In month 3, Matrix specimens showed a 71% increase in neck tissue width with a thickness of 0.24 mm±0.20 versus 0.14 mm±0.18 for GDC observed in GDC specimens (P=0.0027; ANOVA; n=5). In aneurysm specimens at month 6, the difference was not significant; 0.19 mm±0.29 for Matrix versus 0.15 mm±0.20 for GDC (P=0.09; n=6).

**Tissue Reaction to the Coils**

At 14 days, the coils of both GDC and Matrix were observed to be surrounded by either leukocytes or well-organized granulation tissue, depending on the location of the coils (Figure 4). The latter surrounded coils in the neck region whereas the former characterized coils in the aneurysm center. The leukocytic infiltrate around the extracellular matrix was subjectively greater for the Matrix coils. The difference in the leukocyte infiltrate was apparent at 14 days, but not at 3 or 6 months postimplantation. At 3 and 6 months
postimplantation, for both Matrix and GDC, thrombus was no longer present in the aneurysms. No chronic inflammatory reaction was seen with Matrix and GDC.

The absorbable polymer on the Matrix coils was visible at the 14-day stage and was essentially gone at the 3-month stage. Detachment or migration of absorbable polymer away from the coils was not seen and no voids were left by its disappearance.

**Angiographic Aneurysm Cross-Sectional Area**

The cross sectional area of aneurysms was measured from angiographic images at time zero, and directly from sections for the various end point times. Consistent with baseline aneurysm volume measurements, baseline aneurysm area measurements (measured from angiograms) were equivalent between GDC and Matrix (Table 2).

Area measurements taken from 14-day angiograms revealed that both Matrix and GDC groups grew in area over this time period. Three-month angiograms revealed that aneurysms treated with Matrix were 18% smaller than baseline ($P=0.03$). In contrast, GDC-treated aneurysms remained essentially unchanged (4% increase in area, $P=0.55$). It was not possible to collect end point data on aneurysm cross-sectional area for the 6-month group because of poor radiographic quality due to growth of skull bone.

**Discussion**

The original concept of the GDC system was that the electric current produced thrombus formation in the aneurysm (electrothrombosis). However, it was noted that the most important mechanism of acute aneurysm occlusion was the mechanical disruption of intra-aneurysmal flow and thrombosis. From histopathologic reports on human aneurysms embolized with GDC, it appears that the intra-aneurysmal clot undergoes a slow organization. It may therefore be advantageous to modify the biological behavior of the coils to accelerate the biological mechanisms that induce clot maturation and fibrosis.

**Bioactive Embolic Agents**

It is known that platinum coils elicit a mild biological response when deployed into an aneurysm. Tamatani et al reported no endothelial proliferation on the bare-platinum coil surface in an in vitro study.

Some investigators have modified the surface of GDC by coating them with extracellular matrix proteins such as collagen. However, protein coatings on a platinum surface are usually weak, and they may be easily removed during standard microcatheter coil delivery. Ion implantation technology in combination with a protein coating has been used to modify the surface of GDC. Several investigators evaluated a modified GDC using growth factors or genetically modified cells.

**Tissue Engineering and Bioabsorbable Polymeric Materials for Aneurysm Embolization**

Tissue engineering is a new scientific field that studies tissue repair and replacement using bioactive materials. Bioabsorbable polymeric materials (BPM) are being used in 3-dimensional scaffolds to which cells attach and grow to reconstitute tissues. Synthetic polymers such as polylactic (PLA), polyglycolic acid (PGA), and polyglycolic/poly-L-lactic acid copolymer (PLGA) are widely used in the field of tissue engineering.

| TABLE 2. Baseline Aneurysm Areas Measured From Angiograms at the Time of Embolization (mm²) |
|----------------------------------|------------------|------------------|------------------|
|                                  | 14-Day Group     | 3-Month Group    | 6-Month Group    |
| GDC                              | Baseline         | 86.46±12.95      | 81.46±7.31       | 85.64±19.79      |
|                                  | 14 days          | 101.06±24.11     | 85.55±18.82*     | NA               |
| Matrix                           | Baseline         | 87.83±18.45      | 77.97±12.37      | 86.39±12.93      |
|                                  | 14 days          | 107.51±38.33     | 64.30±9.83†      | NA               |

Values are in millimeters squared.

* $P=0.55$; † $P=0.03$.
We recently reported that aneurysm healing could be controlled by the composition of the polymer ratio. PGLA 50/50 (50% PGA/50% PLA) is a fast, absorbable copolymer and it demonstrated strongest tissue reaction. PGLA 85/15 demonstrated the weakest reaction. There was a linear relationship between polymer absorption time and collagen expression in the aneurysm.27

Based on these findings, we developed a newly designed hybrid platinum/BPM coil (Matrix). Polyglycolic/poly-L-lactic acid copolymers were used for the coating of Matrix. PGLA 90/10 polymer degrades and is absorbed relatively slowly, producing a mild inflammatory reaction.

Histologic results in animal models show that the molecular and histologic responses elicited by these materials accelerate clot maturation. Thicker neointima and neoneothelial coverage of the neck of experimental aneurysms in swine was also noted within 14 days. Another important finding with Matrix is the progressive reduction of aneurysm size within the Matrix test aneurysms. No GDC-treated aneurysms showed such size reduction in long-term angiographic follow-up. Because Matrix consists of 70% BPM and only 30% platinum, the bioabsorbed polymer seemed to be replaced by mature connective tissue. Mature scar tissue also retracts by the process of wound healing. This size reduction may be clinically important, especially in unruptured aneurysm presenting with mass effect.

One major question elicited from the preliminary study was the potential risk of untoward parent artery stenosis or occlusion related to the intra-aneurysmal clot organization and fibrosis. We observed no aggressive parent artery stenosis with the exception of 1 case that required intense arterial manipulation with a clot retrieval system to retrieve a Matrix coil from the parent artery.

There were 3 aneurysm ruptures; all of them had been embolized with GDC coils. Autopsy findings revealed that the rupture point was at the dome of the venous pouch. Although the reason of these ruptures is unknown, we believe that they are related to the high flow created in the wide-neck aneurysms. Some potential limitations of this study should be considered. The samples were not completely interpreted in a blinded manner. Although all specimens were evaluated by an independent pathologist, 14-day specimens clearly identified polymer material under the microscope. Biomechanical properties other than polymer coating (such as coil stiffness) might contribute to therapeutic differences between Matrix and conventional coils. The swine model variables of increased thickness of tissue at aneurysm neck, increased clot organization at 2 weeks, and decreased size of aneurysm at 3 months have not yet been validated as predictors of decreased rate of aneurysm recurrence in humans.

Conclusions
Treatment with Matrix exhibits an improved tissue-filling behavior of the aneurysmal space when compared with the standard GDC treatment. Matrix also demonstrated a greater inflammatory cell reaction around the coils at 14 days, but inflammatory reaction was similar to that of GDC at the 3- and 6-month end points. Long-term evaluation indicated that the Matrix was histologically similar to GDC, that the absorbable polymer was no longer visible microscopically, and that the aneurysms packed with Matrix had decreased in size. If the latter observation is confirmed in humans, this may be a beneficial outcome given that reduction in mass effect is held to be a desired result.

Acknowledgments
This project was supported by Boston Scientific/Target Therapeutics. This study was conducted in accordance with the GLP regulations as described in Food and Drug Administration 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies. We gratefully acknowledge the assistance of Yih-Lin Nien, MD, John Robert, Shawn McGill, and Fernando Vinuela, Jr, of the Leo G. Rigler Radiological Research Center, and Janlee Jansen, DVM, and Jerry Werk, Laboratory Animal Medicine at the University of California, Los Angeles. We thank Serge Rousselle, DVM, for histopathologic evaluation. We also thank Paul Siefert, Mike Wallace, Joe Eder, Gulie Grinde, Like Que, Tom Witzel, and Dave Barry from Boston Scientific/Target Therapeutics.

References
15. Kallmes DF, Borland MK, Ciofi HJ, Altes TA, Dion JE, Jensen ME, Hankins GR, Helm GA. In vitro proliferation and adhesion of basic


Matrix and Bioabsorbable Polymeric Coils Accelerate Healing of Intracranial Aneurysms: Long-Term Experimental Study
Yuichi Murayama, Satoshi Tateshima, Nestor R. Gonzalez and Fernando Vinuela

Stroke. 2003;34:2031-2037; originally published online July 17, 2003;
doi: 10.1161/01.STR.0000083394.33633.C2

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/34/8/2031

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/