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AJNR Am J Neuroradiol 2009, 30 (1) 85-90
doi: https://doi.org/10.3174/ajnr.A1368
http://www.ajnr.org/content/30/1/85

ORIGINAL RESEARCH

Endovascular Histologic Effects of Ultrathin Gold- or Vitronectin-Coated Platinum Aneurysm Coils in a Rodent Arterial Occlusion Model: A Preliminary Investigation

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BACKGROUND AND PURPOSE: Novel stratagems to improve the efficacy of platinum coils in occluding cerebral aneurysms have primarily involved coating coils with materials thought likely to provoke more desirable histologic reactions. No investigations to date, however, have evaluated the utility of gold or vitronectin coatings, despite known endovascular histologic effects of these agents, which may be favorable for treating cerebral aneurysms. This study was conducted to evaluate the degree of endovascular histologic change associated with ultrathin gold- or vitronectin-coated platinum coils. It was hypothesized that such coatings would increase intra-aneurysmal intimal hyperplasia and the degree of luminal occlusion compared with standard platinum coils.

MATERIALS AND METHODS: The ligated carotid artery rat model was used to study 4 different aneurysm coil conditions: no coil (sham-surgery controls), uncoated platinum coil, and gold- or vitronectin-coated platinum coil. Two weeks postimplantation, the aneurysms were harvested and stained with hematoxylin-eosin. Slides were evaluated for the degree of neointimal response by a pathologist blinded to treatment. Additional quantitative evaluation was performed blindly by using the ratio of intimal-to-luminal cross-sectional area.

RESULTS: A gold- or vitronectin-coated platinum aneurysm coil produced a statistically significant increase in neointimal response compared with a sham (no coil). Arterial segments treated with gold-coated platinum coils also demonstrated a statistically significant 100% increase in neointimal response compared with those treated with bare platinum coils.

CONCLUSIONS: In concordance with our hypothesis, ultrathin coatings of gold provoked a neointimal response and degree of luminal occlusion greater than that of plain platinum aneurysm coils in a rat arterial occlusion model.

Platinum metal is the primary material used in cerebral aneurysm coils due to favorable metallurgical characteristics and excellent fluoroscopic conspicuity compared with alternative materials such as stainless steel.[1-3] Among the potential disadvantages of endovascular coiling of cerebral aneurysms is the possibility of coil compaction and aneurysm regrowth with time, which may be secondary to the relatively inert nature of platinum.[2-13] Novel stratagems to improve the efficacy of platinum coils have consisted chiefly of coating platinum coils with materials thought likely to provoke a more desirable cascade of histologic reaction.[8,12,14-24] Some new-generation bioactive coils presently being used clinically, however, have failed to demonstrate improved efficacy in decreasing the recanalization rate over bare platinum coils, suggesting the need for continued investigation of novel coil-coating materials and technology.[25-27]

Gold has excellent fluoroscopic visibility and has been demonstrated to increase neointimal thickness and vascular restenosis when applied to stainless steel stents.[28-30] Vitronectin, a plasma glycoprotein that plays a role in platelet activation, has been demonstrated to increase the platelet coating of biopolymers.[31-36] Despite these favorable characteristics of gold and vitronectin for the treatment of cerebral aneurysms, no experiments to date have investigated the potential utility of applying these materials to standard platinum aneurysm coils. The purpose of this initial preliminary study, therefore, was to evaluate the degree of neointimal change associated with ultrathin gold- or vitronectin-coated platinum coils in a rodent model of saccular aneurysms. It was hypothesized that such coatings of gold and vitronectin would increase intra-aneurysmal intimal hyperplasia and the degree of luminal occlusion, compared with standard uncoated platinum coils.

Received April 29, 2008; accepted after revision July 2.

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DOI 10.3174/ajnr.A1368

Materials and Methods

Animal Model

The rat arterial occlusion aneurysm model described by Abrahams et al[37] was used because it represents a convenient and cost-effective option for initial preliminary screening evaluation of aneurysm coil nanocoating technology. Adult male Sprague-Daley rats (weight range, 325–395 g) were used. Four groups of rats were studied. Group 1 ($n = 5$) was a control group subjected to sham surgery, in which the carotid artery was ligated, but no coil was placed. Group 2 ($n = 4$) was a control group with a plain uncoated platinum coil implanted in the carotid artery. Group 3 ($n = 3$) had a vitronectin-coated platinum coil implanted, and group 4 ($n = 4$) had a gold-coated platinum coil implanted.

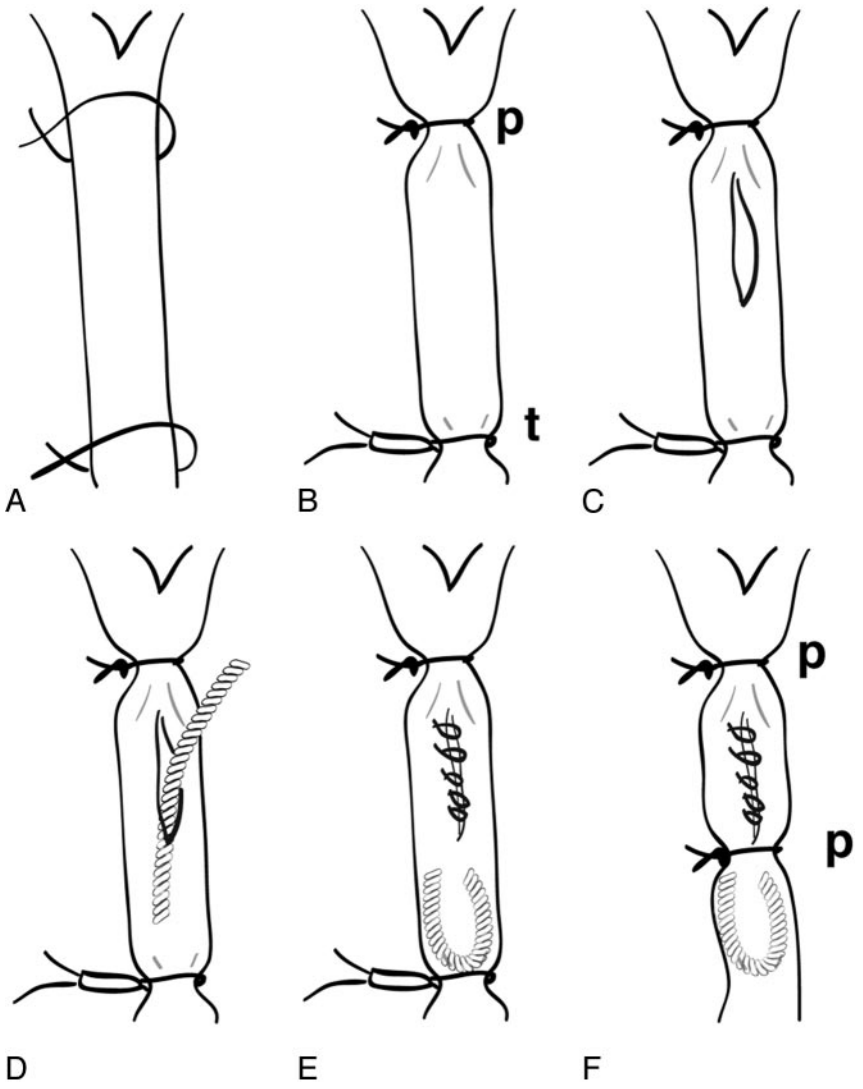

Fig 1. *A—E,* A schematic diagram illustrates the sequential steps in constructing the stump aneurysm model in the right common carotid artery in a rat by using temporary (t) and permanent (p) sutures after Abrahams et al.[37] The artery is small, even in adult rats, and only a short segment of coil, approximately 1 cm, could be fitted retrogradely into the arteriotomy site. *F,* In the final image, a permanent suture separates the coil site from the arteriotomy repair, whereas removal of the temporary ligature below exposes the coil to systemic circulatory conditions.

Animal Care and Surgery

This research study was approved and supervised by the Animal Care and Use Committee at Wake Forest University Medical Center. The protocol followed the one described by Abrahams et al[37] and is summarized succinctly as follows: Adult rats were anesthetized on the day of surgery with an intraperitoneal injection of pentobarbital 60 mg/kg by using a 25-gauge needle. After induction of general anesthesia, a sterile operative field was established and a surgical dissection to the right common carotid artery was performed. An initial ligation of the common carotid artery was performed above (permanent) and below (temporary) the insertion site by using 3.0 sutures (Fig 1). A small arteriotomy was performed to allow retrograde introduction of approximately 1 cm of coil material, and a permanent 3.0 suture was applied to the artery between the coil and the arteriotomy site. The temporary suture was then released, exposing the coil within the arterial stump to systemic circulatory conditions. The neck wound was closed by using 5.0 Ethilon nylon suture (Johnson & Johnson, Langhorne, Pa). The animals were housed for 2 weeks in the animal care facility. Sacrifice was performed by using an intraperitoneal injection of pentobarbital 125 mg, following induction of anesthesia by a similar dose of intracardiac pentobarbital.

Histologic Materials

Extracted carotid arteries were fixed initially in formalin and later embedded in paraffin blocks for sectioning. Histologic sections used for analysis were collected 5 mm distal to the suture material for all groups to control for location. In particular, this method was used to control for the possibility that 1 section closer to the suture material could drive between-group effect size. Slides were stained by using hematoxylin-eosin (HE) and were labeled with a randomized code. The evaluation of neointimal response was performed by a pathologist (V.R.C.), who was blinded to the code. The slides were also evaluated independently by 2 members of our group who were blinded to the code. Histologic measurements of the lumen cross-sectional area of intimal hyperplasia were extracted by using a computer software program, NIH Image (http://rsb.info.nih.gov/nih-image/). A ratio of intimal-to-luminal cross-sectional area was then calculated for each specimen. Values closer to 1 indicated a higher degree of neointimal

response, and, therefore, greater luminal occlusion. Values closer to zero indicated a lower degree of neointimal response and, therefore, less luminal occlusion.

Coils

Plain platinum Guglielmi detachable aneurysm coils (GDC-10; Boston Scientific, Natick, Mass) were coated with elemental gold or vitronectin by using a unique proprietary technique that covalently bonded nanometer-thick layers of gold or vitronectin to platinum via an electrostatic self-assembly process (ESA; NanoSonic, Blacksburg, Va). All coatings were evaluated by NanoSonic for uniformity and thickness with atomic force microscopy measurements. The coils were then repackaged and resterilized before use in rats.

Statistical Analysis

A 1-way analysis of variance (ANOVA) was performed by using the ratio of intimal-to-luminal cross-sectional area as the dependent measure and the group (no coil, platinum coil, gold-coated coil, and vitronectin-coated coil) as the independent variable, followed by post hoc analyses.

Results

Coils

Evaluation of coated platinum coils with atomic force microscopy demonstrated a uniform circumferential 100 ± 10 nm thick layer of gold or vitronectin over the surface of the platinum coil.

Gross Histology

Subjective evaluation of the histologic materials by a pathologist blinded to the labeling codes identified confidently a greater degree of intimal response in the coated coils compared with the plain platinum coils (Fig 2*A-D*). The sham-treatment subjects were readily identifiable by the absence of coil artifact and thus could not be obscured by the blinding process. Discerning with confidence between the groups of coated coils was more difficult. An expansile or distended appearance of the arteries treated with coated coils was evident consistently on the specimens (Fig 2*C*, *D*).

Neointimal Response

The ratio of intimal-to-luminal cross-sectional area (mean ± SD) was 0.22 ± 0.17 for the sham (no coil) control, 0.34 ± 0.09 for bare platinum, 0.52 ± 0.12 for vitronectin-coated platinum, and 0.68 ± 0.20 for gold-coated platinum coil groups (Fig 3). For the calculated ratio of intimal-to-luminal cross-sectional area, ANOVA revealed a main effect of group, such that the ratio was significantly different between groups [$F(3,15) = 7.44$] ($P = .004$). More specifically, post hoc analyses of between-group differences revealed the ratio to be significantly higher in the gold-coated ($P = .001$) and vitronectin-coated ($P = .021$) coil groups, but not in the uncoated platinum group ($P = .271$), as compared with the sham-treated (no coil) controls. The ratio was also significantly higher for the gold-coated coil group ($P = .008$), but not the vitronectin-coated coil group ($P = .152$), compared with the uncoated platinum coil group. There was no statistically significant difference in the calculated ratio between the vitronectin- and gold-coated coil groups ($P = .193$).

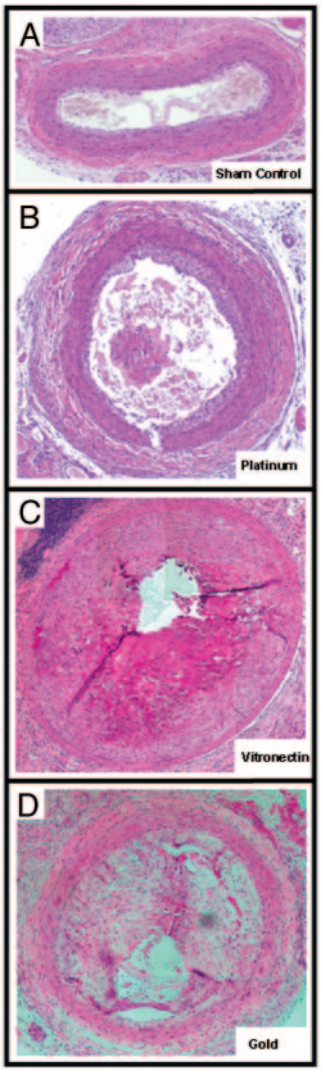

Fig 2. *A,* HE staining of representative slides from 4 subject groups. Sham (no coil) procedure (group 1) demonstrates no evidence of coil or intense neointimal response. *B,* Plain platinum coil (group 2) produces a relatively small degree of luminal distension and neointimal response. *C* and *D,* Vitronectin-coated platinum coil (group 3) and gold-coated platinum coil (group 4) produce increasing neointimal response and luminal distension, respectively (magnification 100×).

Discussion

Several metals have been evaluated in the past for use in biomedical and implantable devices, such as coils or stents, including nitinol, silver, copper, gold, stainless steel, beryllium-copper, and platinum.[3,28] Tanigawa et al[28] evaluated a range of materials in the aortic walls of dogs, including copper and gold. Copper (atomic number 29) was found to provoke an exuberant angionecrotic response in dogs, which defied measurement, and, in some cases, resulted in aortic rupture. Gold (atomic number 79), however, was found to be on the opposite end of the spectrum from copper, producing relatively little effect on the aortic walls of dogs; and the conclusion was that gold reacts only minimally with the vessel wall.

On the basis of these and other studies, gold achieved the reputation of being relatively biologically inert as an implantable intravascular material. For reasons of enhanced fluoroscopic visibility with putative biologic inertness, gold coating was introduced on the NIR Royal coronary stent (Medinol,

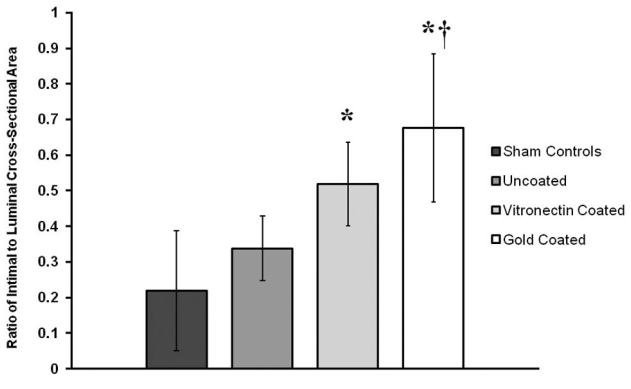

Fig 3. Graph shows the ratio of intimal-to-luminal cross-sectional area, expressed as mean ± SD, for 4 groups: no coil (sham controls), uncoated platinum coil, gold-coated platinum coil, or vitronectin-coated platinum coil. Numbers closer to 1 indicate a greater degree of histologic response. The asterisk (*) indicates a statistically significant difference compared with the sham control group. The dagger (†) indicates a statistically significant difference compared with the uncoated platinum group. Note that the ratio of intimal-to-luminal cross-sectional area is 53% higher for vitronectin-coated and 100% higher for the gold-coated platinum coils, compared with the uncoated platinum coil.

Tel Aviv, Israel) in the 1990s but was quickly found to be correlated with a high rate of in-stent restenosis compared with bare stainless steel stents.[29,30] Kastrati et al[29] identified an angiographic restenosis rate after 1 year with gold-coated stents of 49.7% versus 38.1% ($P < .003$) for stainless steel stents. Using a gold coating of 7 μm on NIR stents, Edelman et al[30] confirmed the angiographic impact of gold versus stainless steel in porcine coronary arteries, with 24%–57% incremental increases in the thickness of neointimal response after 4 weeks. These data and our results in this experiment suggest that gold-coated coils may be capable of provoking a more intense histologic response within a cerebral aneurysm than plain platinum coils.

An alternative agent of interest to our research group is vitronectin, a 75-kDa conformationally labile adhesive glycoprotein normally present in abundant quantities in human plasma at a concentration of 200–400 μg/mL.[31-34] It is capable of forming complexes with plasminogen activator inhibitor, thrombin-antithrombin III, and complement C5b-C9, with consequent conformational changes that expose the heparin-binding site on vitronectin.[38,39] It has complex and incompletely explored roles in the regulation of thrombosis and fibrinolysis,[40,41] pericellular proteolysis, cell attachment, and complement-dependent immune response.[42] High concentrations of vitronectin in atherosclerotic lesions, in which the migration and accumulation of smooth muscle cells are so prominent, have lead to the hypothesis that vitronectin may play an intermediary role in the genesis or propagation of atherosclerotic lesions.[43] Fabrizius-Homan and Cooper[44] studied the effect of wild-type human plasma vitronectin adsorption on polyethylene, silicone rubber, Teflon-FEP (DuPont, Wilmington, Del), and 2 polyurethane derivatives (polytetramethylene oxide-polyurethane [PTMO-PU] and polyethylene oxide-polyurethane [PEO-PU]). The investigators found that vitronectin adsorption increased platelet coating of the biopolymers compared with bare uncoated surfaces during the 60-minute blood contact time.[35,36] Although not statistically significant, the observation in our experiment that vitronectin-coated coils were capable of inducing a cellular intimal response greater than that seen with plain platinum suggests that vitronectin-mediated pathways may have potential utility for application to endovascular devices when thrombosis and smooth muscle cell migration is desired, such as with the treatment of cerebral aneurysms.

The use of animal models for testing of aneurysm coils is a contentious issue, with strong arguments and counterarguments for the use of models involving rats, pigs, rabbits, or other mammals.[10,45,46] In our study, the rat aneurysm model described by Abrahams et al[37] was used because it represents a convenient and cost-effective option for initial preliminary screening evaluation of aneurysm coil nanocoating technology. This model, however, may not duplicate flow characteristics of human aneurysms and other animal aneurysm models. Furthermore, this model is of unknown validity for evaluating neointimal effects of coil-coating technology. Other limitations of this study include the small sample size, technical difficulties related to histologic section sampling, and the short temporal follow-up of the endovascular response.

Few animals were included in this preliminary investigation, which undoubtedly impacts our ability to draw more definitive conclusions. In particular, the small sample size likely explains the lack statistical significance of histologic changes associated with uncoated platinum coils. Increasing the sample size may also help to establish a statistically significant difference between vitronectin-coated coils and plain platinum coils.

The present methods used to evaluate vascular histology are strongly dependent on the location of the section used for analysis. Arterial sections for histologic analysis were collected 5 mm distal to the suture material for all groups to control for the possibility that 1 section closer to the inflammatory changes associated with suture could drive the between-group effect size. Minimal variability in location of the arterial section with respect to the suture, however, could still affect between-group differences.

Relatively short-interval follow-up of endovascular histologic changes post-coil implantation significantly limits the characterization of coil-associated aneurysmal healing, which has been demonstrated to progress in a sequential manner, with the 2-week time point evaluated in our study corresponding with only early changes.[47] It is encouraging, however, that a relatively robust neointimal response was produced despite the very early time point used for follow-up histologic analysis in this study and represents another potential advantage of gold-coated platinum coil.

Finally, some new generation "bioactive" coated coils that are presently being used clinically have failed to show improved efficacy over bare platinum coils,[25,26] despite results demonstrating histologic improvements in aneurysmal healing when applied to animal aneurysm models.[12] Certainly, encouraging results reported in our study could fail to translate into improved efficacy in clinical practice.

Some modified coil designs share the disadvantage that the replacement perforce of platinum with alternative materials invariably alters the mechanical characteristics of the coils. For example, the favorable fluoroscopic conspicuity of platinum is attenuated after partial replacement of the platinum content with radiographically lucent materials such as polygly-

colic/polylactic acid or with hydrophilic acrylic polymer.[10,12,20,21] Additional problems relate to microcatheter friction, ease of coil extraction from a complex nidus in a partially treated aneurysm, and tumbling characteristics within an aneurysm as the coil deploys. An ideal coil modification would improve coil efficacy without altering its mechanical characteristics. In this study, we used new nanocoating technology to apply ultrathin layers of gold or vitronectin to a standard platinum aneurysm coil, which may result in greater coil efficacy, without compromising fluoroscopic conspicuity and other favorable mechanical properties of uncoated platinum coil. The 100-nm coating used in this experiment seems unlikely to impact the overall mechanical properties of the coil. If one assumes that the core wire of the GDC-10 system is approximately 76 μm in diameter, a circumferential layer of 100 nm represents only a 0.26% increase in the diameter of the core-wire and a 0.08% increment to the dimensions of the configured coil as it tracks within the microcatheter or as it tumbles within the aneurysm. These increments are negligible compared with the currently approved coating designs for bioactive coils. Further investigation, however, will be necessary to explore this potentially highly advantageous aspect of nanocoating coil technology.

Conclusion

In concordance with our hypothesis, ultrathin coatings of gold provoked a neointimal response and a degree of luminal occlusion greater than that of plain platinum aneurysm coil in a rat arterial occlusion model. This response is consistent with previous data on this agent, and we opine that our findings are worthy of further investigation.

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