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ORIGINAL RESEARCH

Preliminary Results of the Luna Aneurysm Embolization System in a Rabbit Model: A New Intrasaccular Aneurysm Occlusion Device

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BACKGROUND AND PURPOSE: Recent advances in endovascular devices have been aimed at providing high density, mesh-like metallic materials across the aneurysm neck, in place of coil technology. Therefore our aim was to report the in vivo preclinical performance of a self-expanding intrasaccular embolization device.

MATERIALS AND METHODS: Elastase-induced aneurysms were created in 12 rabbits. Each aneurysm was embolized with a Luna AES. DSA was performed preimplantation; 5, 10, and 30 minutes postimplantation; and at 1 month in 12 rabbits and at 3 months in 8 rabbits. Early postimplantation intra-aneurysmal flow was graded as unchanged, moderately diminished, or completely absent. One- and 3-month DSAs were graded by using a 3-point scale (complete, near-complete, or incomplete occlusion). Aneurysms were harvested for gross and microscopic histologic evaluation at 1 month (n = 4) and at 3 months (n = 8). Tissues within the aneurysm dome and across the aneurysm neck were assessed by using HE staining.

RESULTS: Ten (83%) of 12 aneurysms demonstrated complete cessation of flow within 30 minutes of device implantation. At 1-month follow-up, 10 (83%) of 12 aneurysms were completely occluded. At 3 months, 7 of 8 (88%) aneurysms remained completely occluded. One-month gross examination in 4 rabbits demonstrated that membranous tissue completely covered the device in 3 subjects (75%). Microscopic examination showed that 3 aneurysms had loose connective tissue filling the aneurysm cavity. Three-month gross and microscopic examinations demonstrated membranous tissue completely covering the device, loose connective tissue filling the aneurysm cavity, and neointima formation crossing the aneurysm neck in 8 of 8 (100.0%) subjects.

CONCLUSIONS: The Luna AES achieved high rates of complete angiographic occlusion and showed promising histologic findings in the rabbit aneurysm model.

ABBREVIATIONS: AES = Aneurysm Embolization System; An. = aneurysm; CA = completely absent; CO = complete occlusion; DSA = digital subtraction angiography; HE = hematoxylin-eosin; IVDSA = intravenous digital subtraction angiography; MD = moderately diminished; NO = near-complete occlusion

The goals of endovascular procedures for the treatment of cerebral aneurysms are to exclude the aneurysm sac from the cerebral arterial circulation and preserve parent vessel patency. There are 2 main categories of endovascular aneurysm treatment, intrasaccular and endoluminal procedures.

The safety and efficacy of intrasaccular detachable coil embolization is well documented[1-3] but has limitations. Even with evolving procedural techniques and technology, the rate of aneurysmal total occlusion remains suboptimal.[4,5] The prevalence of coil compaction, which results in posttreatment recanalization and recurrence, is frequent.[4,6,7]

Conceptually, endoluminal flow diverters direct blood flow away from the aneurysm cavity primarily by placing a stent-like device across the aneurysm neck. However, flow diverters have had limited clinical utility, though they have shown excellent occlusion rates, even in large and giant aneurysms.[8-12] These devices may remain problematic in ruptured aneurysms, not only because they require concomitant use of dual antiplatelet therapy but also because immediate aneurysm occlusion usually does not occur. Furthermore, there are drawbacks when placing these devices in bifurcation aneurysms due to the inherent design limitations.

In the present study, we describe the in vivo performance of a new type of embolization device. This new device, the Luna AES (NFocus Neuromedical, Palo Alto, California) is a self-expanding ovoid braided implant that when placed into an aneurysm cavity, provides an attenuated mesh of metal across the neck. The purpose of this study was to evaluate the safety, performance, and efficacy of the Luna AES in the rabbit elastase-induced aneurysm model.

Materials and Methods

The endosaccular embolization device was the Luna AES, a self-expanding ovoid ball-like implant with a delivery system (Fig 1). The implant is made from a double layer of nitinol wire mesh secured at both proximal and distal ends and clearly marked with radiopaque platinum markers. A variety of implant diameters is available, as with coils. The delivery system provides distal navigation through a commercially available microcatheter with detachment controlled by operator activation of the delivery handle. The unexpanded profile for

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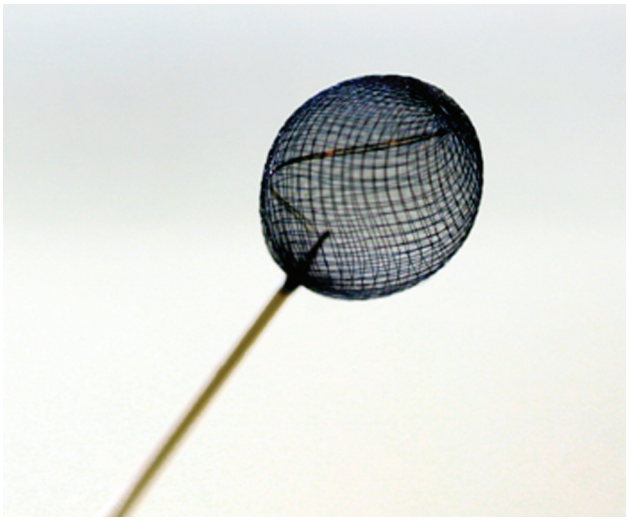

Fig 1. The Luna AES.

each is 1.9F, approximately 0.025 inches—that is, devices can be delivered through a commercially available standard microcatheter with a ≥0.027-inch lumen. In this study, Luna devices were delivered with a 5F guiding catheter.

In Vivo Experiments

Aneurysms ($n = 12$) were created in New Zealand white rabbits as previously described.[13] Aneurysms were allowed to mature for at least 21 days before embolization. Anesthesia was induced by using 74-mg/kg ketamine, 5-mg/kg xylazine, and 1-mg/kg acepromazine and was maintained by using ketamine (10 mg/kg) and xylazine (3 mg/kg). Using a sterile technique, we performed surgical cutdown of the right common femoral artery and a 5F vascular sheath was inserted. Heparin (100 U/kg) was administered intravenously. A 5F guide catheter (Envoy; Cordis Neurovascular, Miami Lakes, Florida) was placed into the aortic arch, and DSA was performed. Following the DSA, the aneurysm size (neck, width, and height) was determined by using sizing markers of a known diameter. The catheter was advanced and gently placed into the aneurysm cavity. The Luna device size was selected to match each aneurysm on the basis of the average of the aneurysm height and width. The Luna device was delivered into the aneurysm cavity via the 5F guide catheter by using the Luna delivery system and was deployed. If the Luna was not the correct size for the aneurysm, it was recaptured and removed, and a different size Luna was placed in the aneurysm. After embolization, DSA of the aortic arch and brachiocephalic vessels was performed at 5, 10, and 30 minutes following device implantation. The catheter and vascular sheath were removed, and the proximal aspect of the femoral artery was ligated with a 4–0 suture. IVDSA for all subjects followed at 1 month. DSA of the aortic arch was performed at the time of sacrifice, either 1 month ($n = 4$), or 3 months ($n = 8$). Animals were then euthanized with a lethal injection of pentobarbital. The harvested embolized aneurysms and aorta were immediately fixed in 10% neutral buffered formalin.

Angiographic Evaluation

DSA was performed at ≤30 minutes after device implantation. Early postimplantation intra-aneurysmal flow was characterized as unchanged, moderately diminished, or completely absent. IVDSA through catheterization of the ear vein for all 12 rabbits was performed at 1 month.[14] Also DSA, followed by sacrifice, was performed at 1 month ($n = 4$) and 3 months ($n = 8$) after implantation. The follow-up sacrifice angiograms were accomplished by a surgical cutdown of the left femoral artery. A 4F catheter was placed in the aortic arch, and DSA was performed. At the 1- and 3-month follow-ups, we graded the degree of aneurysm occlusion by using a 3-point scale (complete, near-complete, or incomplete occlusion), as previously published.[15] All follow-up angiograms were compared with immediate postembolization angiograms. Device migration within the aneurysm (ie, the position of the device relative to the aneurysmal cavity and parent artery) was assessed at all time points.

Histopathology

Each dissected aneurysm and adjacent parent artery specimen were fixed in 10% neutral buffered formalin for at least 24 hours. Gross examination of the sample was performed. Specimens were processed by using previously described histologic techniques.[16] Briefly, samples were embedded in paraffin and subsequently sectioned at 1000-μm intervals in a coronal orientation, permitting long-axis sectioning of the aneurysm neck, with a slow-speed saw (Isomet; Beuhler, Lake Bluff, Illinois). The metallic material of the device was carefully removed under a dissecting microscope (Leica MZ12.5; North Central Instruments, Minneapolis, Minnesota). After metal was removed, the samples were re-embedded in paraffin and sectioned at 5- and 7-μm intervals. Sections were stained with HE. The

Summary of serial cases

No.	Longest Width, Height of An. (mm)	Neck, (mm)	Size of Luna, (mm)	Early Intra-Aneurysmal Flow	Follow-Up (mo)	Findings on Final Angiogram	Gross Findings	Microscopic Findings of Aneurysmal Dome	Microscopic Findings of Neck
1	3.6 × 9.6	2.3	5.5	MD	1	NO	Membranous tissue	Loose connective tissue	Thick neointima
2	3.5 × 11.8	3.0	7.5	CA	1	CO	Small empty cavity	Loose connective tissue	No neointima
3	3.6 × 6.7	1.6	6	CA	1	CO	Membranous tissue	Loose connective tissue	Thin neointima
4	4.3 × 7.6	2.0	6	CA	1	CO	Membranous tissue	Loose connective tissue with unorganized thrombus	Thick neointima
5	3.1 × 8.5	2.5	6	CA	3	CO	Membranous tissue	Loose connective tissue	Thick neointima
6	3.8 × 9.7	2.5	6	CA	3	CO	Membranous tissue	Loose connective tissue	Thin neointima
7	3.2 × 8.4	2.4	6	CA	3	CO	Membranous tissue	Loose connective tissue	Thin neointima
8	3.2 × 12.8	3.6	8	CA	3	CO	Membranous tissue	Loose connective tissue	Thin neointima
9	3.5 × 9.5	3.2	6	CA	3	CO	Membranous tissue	Loose connective tissue	Thick neointima
10	3.2 × 7.2	1.5	6	CA	3	CO	Membranous tissue	Loose connective tissue	Thin neointima
11	4.3 × 12.3	2.5	6.5	MD	3	NO	Membranous tissue	Loose connective tissue	Thin neointima
12	3.6 × 13	2.9	6.5	CA	3	CO	Membranous tissue	Loose connective tissue	Thin neointima

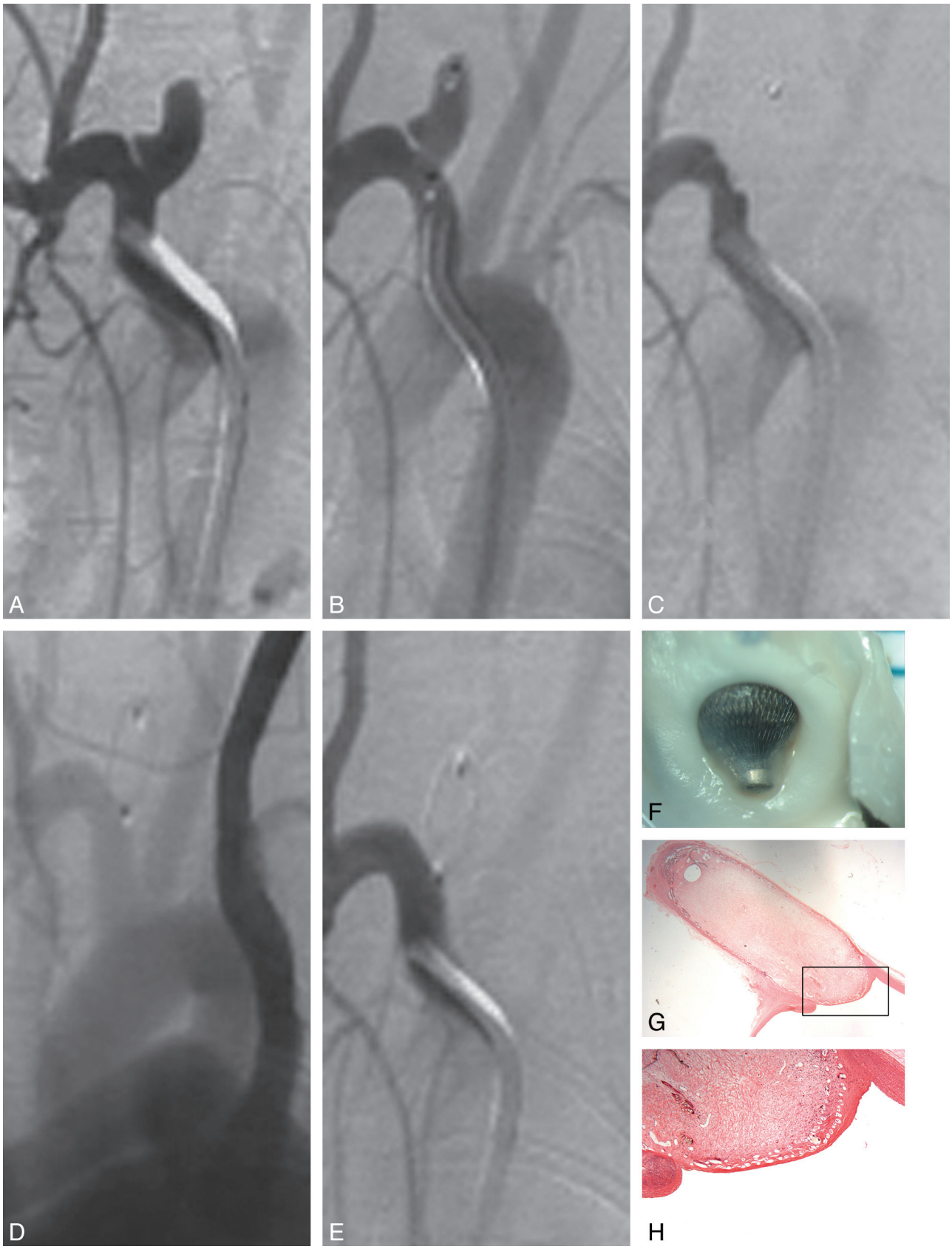

Fig 2. Representative case 5 in the Table. *A*, Pretreatment DSA demonstrates the aneurysm. *B*, DSA immediately after placement of Luna AES shows some cessation of intra-aneurysmal flow. *C*, DSA image at 5 minutes postimplantation shows total occlusion of the aneurysm. *D* and *E*, IVDSA at 1 month (*D*) and DSA at 3 months (*E*) show total occlusion. *F*, Gross examination at the neck orifice shows that the device is covered with a translucent membranous tissue. *G*, Photomicrograph of the aneurysm stained with Hematoxylin and Eosin (H&E; original magnification = 12.5×). This photomicrograph demonstrates that the aneurysmal cavity is filled with loose connective tissue and that a thick layer of neointima crosses the neck interface. *H*, Photomicrograph (enlargement of box in *G*) of the aneurysm's neck stained with H&E (original magnification = 40×). This image shows that the neointima consists of spindle cells, which appear to be smooth muscle cell-like.

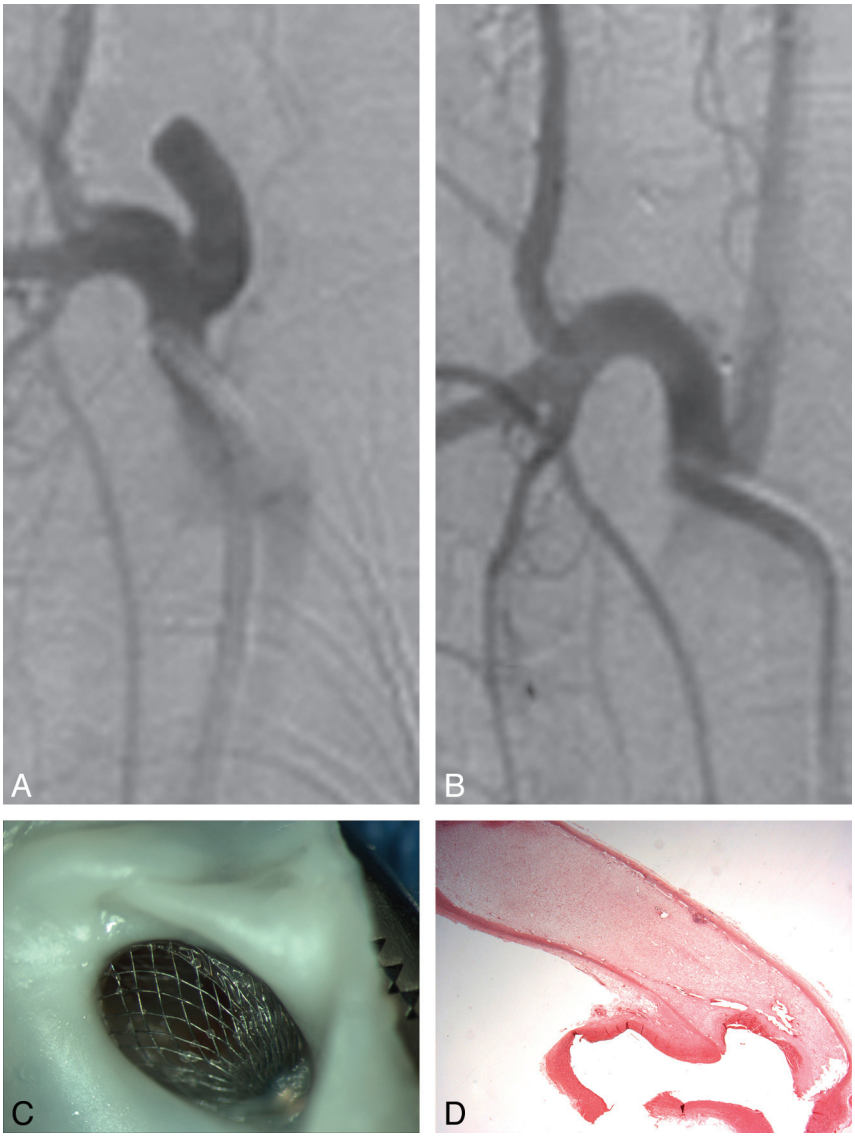

Fig 3. Representative images from case 2 in the Table. *A*, DSA before treatment shows the aneurysm. *B*, Image at sacrifice shows a small remnant at the neck. *C*, Gross examination shows the device is partially covered with membranous tissue, such that the aneurysmal cavity is open to the parent artery through the holes of the device. *D*, Photomicrograph of the aneurysm stained with H&E (original magnification = 12.5×). The photomicrograph reveals thrombus at the neck, with no neointimal layer, and the remnant seen in *B*.

tissues within the aneurysm dome were categorized as unorganized thrombus, loose connective tissues (organized thrombus or organized tissues), and connective tissue. The neointima across the aneurysmal neck was defined as no neointima, thin neointima (tissues on the stent surface at the neck composed of <3 layers of cells, with minimal extracellular matrix deposition), and thick neointima (neointima containing >3 layers of cells, with or without noticeable collagenous matrix deposition).

Results

Dimensions of aneurysms and sizes of deployed devices are summarized in the Table. Luna devices were successfully placed in all 12 aneurysms. There were no perioperative complications. At early postimplantation angiography, we confirmed 3 cases of low-lying devices within the parent artery, but no substantial parent artery compromise was noted at any time point.

Ten (83%) of 12 aneurysms demonstrated complete cessation of flow within 30 minutes following device implantation (Fig 2*C*); 2 others, in which slightly undersized devices were used because of limited inventory for this prototype development project, had moderately diminished intra-aneurysmal flow and small neck remnants. At 1 month, all 10 aneurysms that were completely occluded on the early postimplantation angiogram remained completely occluded; the 2 aneurysms with small neck remnants at early postimplantation were nearly completely occluded. At 3 months, 7 of 8 (88%) aneurysms remained completely occluded. The occlusion of 1 other aneurysm remained near-complete.

One-month gross examination in 4 specimens revealed membranous tissue completely covering the device in 3 subjects (Fig 2*E*); a single subject had an aneurysm cavity that was open to the parent artery through the bare holes of the device (Fig 3*C*). This latter subject had complete angiographic occlusion (Fig 3*B*). One rabbit that had complete tissue membrane covering the device on gross examination was found to have a small neck remnant both pathologically and angiographically. Microscopic examination showed that 3 aneurysms at 1

month had completely organized loose connective tissue filling the entire aneurysmal cavity. Organized loose connective and unorganized thrombus both were present and filled the aneurysm cavity in the remaining subject. The Neointimal formation at the aneurysmal neck could be confirmed in 3 subjects. Three-month gross and microscopic examination in 8 rabbits showed a membranous tissue completely covering the device, organized loose connective tissue filling the entire aneurysm cavity, and neointima crossing the neck in all 8 specimens (Fig 2*F*).

Discussion

In this study, we described the in vivo preclinical performance of the Luna AES device, designed to be placed in the aneurysmal cavity and to provide flow disruption across the metallic struts from the parent artery to the aneurysm. Using the Luna AES, we noted complete or near-complete cessation of intraaneurysmal flow within minutes after placement in most cases. High rates of complete aneurysm occlusion were noted at 1 and 3 months. The histologic findings showed excellent healing within the aneurysm cavity and along the aneurysm neck in most cases. These data suggest that the Luna AES might be used for occlusion of intracranial saccular aneurysms, both ruptured and unruptured.

With the advent of intraluminal flow-diversion devices, the endovascular community has refocused attention away from devices aimed at filling the aneurysm cavity and toward devices that can achieve disruption of flow along the aneurysm neck.[8-12] Unlike current endoluminal flow-diversion devices, the Luna AES does not require the use of dual antiplatelet therapy. Furthermore, at least on the basis of the preclinical work described here, the Luna AES might also achieve immediate or nearly immediate cessation of flow within the aneurysm cavity due to a high degree of neck coverage compared with coiling, allowing its use in ruptured aneurysms.

Notwithstanding the promising results from the current study, there remain substantial uncertainties about the use of the Luna AES. The device is not suitable for complex irregular, wide-neck, and fusiform aneurysms. The aneurysms treated in this preclinical study almost certainly were more regular in shape than many human aneurysms; as such, the high rates of complete occlusion may be overstated here in comparison with what may be expected clinically. Precise device sizing and positioning are the most important factors for good results but will require refinement as the device is applied clinically, because the geometry of an aneurysm is a 3D sphere and the morphology and delivery are markedly different from that of coils. Furthermore, strategies for addressing incomplete aneurysm occlusion, either immediate or delayed, may be problematic because coil placement into the lumen of the indwelling Luna AES device will not be feasible.

Because this was the initial feasibility trial, it was powered for practical and not statistical considerations; therefore, the number of aneurysms treated was small for drawing a conclusion concerning aneurysm obliteration or parent artery patency rates. In addition, the devices were placed through 5F guiding catheters rather than microcatheters. Further study regarding trackability in a tortuous vasculature through the microcatheter will be needed. Finally, the aneurysm dimensions were relatively small, and the aneurysm necks were relatively narrow, so the use of the Luna AES in large and wide-neck aneurysms remains unexplored.

Conclusions

The Luna AES, an intrasaccular flow-diverting device, provided excellent acute and short- and midterm continuous angiographic and histopathologic aneurysmal occlusion in the rabbit model. Furthermore, no antiplatelet therapy is required.

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