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Large, Wide-Neck, Side-Wall Aneurysm Treatment in Canines Using NeuroCURE: A Novel Liquid Embolic

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Abstract

BACKGROUND: Untreated intracranial aneurysms can rupture and result in high rates of morbidity and mortality. Although there are numerous approved endovascular aneurysm treatment devices, most require dual anti-platelet therapy, are minimally biocompatible, or are prone to recanalization. Neurovascular Controlled Uniform Rapid Embolic (NeuroCURE) is an innovative polymer gel material with long-term stability, biocompatibility, and hemocompatibility developed for the treatment of large, wide-neck aneurysms.

METHODS: Sidewall aneurysms were surgically created in 10 canines and NeuroCURE was injected through a 0.025 microcatheter under a single balloon inflation period. Aneurysm treatment was angiographically assessed post-embolization and pre-term with Raymond–Roy occlusion classification and a qualitative flow grade scale. Aneurysm neck stability and biocompatibility was histologically assessed to grade platelet/fibrin thrombus, percent

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endothelialization, and neointimal formation. Aneurysm sac stability was assessed by NeuroCURE sac content, inflammation, and neo-angiogenesis scales.

RESULTS: Explanted aneurysms exhibited a smooth surface at the aneurysm neck with nearly complete neointimal coverage at 3-months. By 6-months, neck endothelialization was 100% in all animals (average Raymond–Roy occlusion classification of 1.2), with no instances of aneurysm recanalization or parent vessel flow compromise. Biocompatibility assessments verified a lack of inflammatory response, neo-angiogenesis, and platelet/fibrin thrombus formation.

CONCLUSION: The NeuroCURE material promotes progressive occlusion of wide-necked side wall aneurysms over time without the need for dual antiplatelet agents. NeuroCURE also promotes neointimal tissue infill without dependence on thrombus formation and thus resists aneurysm recanalization. NeuroCURE remains a compelling investigational device for the treatment of intracranial aneurysms.

Keywords

aneurysm; canine; endovascular device; hemorrhagic stroke; liquid embolic; NeuroCURE

Cerebral aneurysms are present in 45 million individuals worldwide, and approximately 30 000 patients in the United States suffer from subarachnoid hemorrhage annually.[1–7] Aneurysm treatment is associated with complications and recanalization, leading to retreatment, rupture, or even permanent morbidities and mortality, particularly for larger, wide-neck aneurysms.[8–10] We have developed a new generation liquid embolic (Neurovascular Controlled Uniform Rapid Embolic [NeuroCURE]) that may improve treatment outcomes for large, wide-neck aneurysms relative to current options, including coils, flow diversion, and flow disruption devices.

Metal coils, the current gold standard for intracranial aneurysm treatment, do not provide complete aneurysm occlusion, are prone to compaction, and exhibit high rates (15%–35%) of recanalization, even in small aneurysms.[1–3,6,11–13] Coiling suffers from even higher rates of recanalization (50%–70%) in large, wide-neck aneurysms.[1,3,9,14–20] Flow diverters are often used in lieu of or in conjunction with coils for larger aneurysms; however, they are associated with gradual progression of aneurysm occlusion that is often incomplete (studies have shown 32% occlusion at 0–1 month, and high variability ranging from 50% to 93% occlusion at 6 months and 69%–100% occlusion at 12 months) and can require long-term (>6 months) dual antiplatelet therapydual-antiplatelet therapy.[8,10,15,21,22] Flow disrupters (e.g., the WEB System [MicroVention, Inc. – Aliso Viejo, CA]) can be used for a subset of small to medium sized aneurysms of specific shapes and provide less surface area of metal exposure at the parent vessel.[9,15] However, WEB placement often results in flow remnants at the neck that typically do not resolve and can lead to recanalization, promote local or downstream thrombus formation, and exhibit inconsistent neointimal healing responses, especially in larger and wide-neck aneurysms.[8,9,10,15,21]

Liquid embolic agents, such as Onyx, are approved for use in embolization of brain arteriovenous malformations, but the dimethyl sulfoxide solvent release into the bloodstream has been linked to cytotoxicity and vasospasm.[1,5,23–28] A more viscous version (Onyx

HD-500) was developed to treat brain aneurysms and was evaluated previously under an Humanitarian Device Exemption. Slow delivery of Onyx allows the dimethyl sulfoxide to diffuse; however, lengthy injection and filling procedures with multiple balloon deflations (to avoid ischemia) are the result. In addition, Onyx slowly precipitates as dimethyl sulfoxide is flushed away by the blood, leaving Onyx susceptible to downstream migration.[29–33] These issues have resulted in clinical complications that have stifled interest in Onyx-HD-500 for treating cerebral aneurysms.

NeuroCURE is an innovative polymer gel material that was developed after extensive research and testing of non-metal biomaterials with the goal of fulfilling a list of necessary material characteristics: little or no thrombus effects, high viscosity in liquid form, conformability for maximum aneurysm volume filling (near 100%), minimal migration and particulation (0%), non-adhesive gelling effects, relatively high mechanical gel strength, relatively low stiffness (highly elastic), and biocompatibility in gel form.[15,16,23,26,27,34–37] NeuroCURE is formed from poly-propylene glycol diacrylate and pentaerythritol tetrakis 3-mercaptopropionate polymer precursors. NeuroCURE is water-based (no organic solvents), nonadhesive, and exhibits superior biocompatibility over metal devices and Onyx. NeuroCURE can consistently form a cohesive and stable gel within large aneurysms within 1 balloon inflation cycle (<5 minutes) with no migration, particulation, nor balloon-induced ischemia.[32,38] A large volume of NeuroCURE is focally delivered in a short timeframe, under 1 balloon inflation cycle with no material exposure to blood flow, resulting in a more complete occlusion without distal embolization, cytotoxic effects, or the device or delivery catheter adhering to the vessel wall.[1,39,40] The hydrophobicity of the NeuroCURE components allows it to reliably and predictably gel in aqueous and physiological environments with or without the presence of anticoagulant medications.

The NeuroCURE device can be delivered into any larger aneurysm accessible by microcatheter and temporary balloon occlusion and does not require that the patient be placed on dual-antiplatelet medication. Administration of NeuroCURE into smaller aneurysms may be possible, but for the purposes of this study larger aneurysms were targeted as they suffer from higher post-treatment aneurysm sac instability and elevated recanalization rates. Importantly, the NeuroCURE surface exposed to the parent vessel blood flow serves as a scaffold for rapid and complete endothelial growth across the aneurysm neck. Long-term stability, biocompatibility, and hemocompatibility of NeuroCURE were verified in the following long-term canine study.

METHODS

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

The canine animal procedures were conducted at American Preclinical Services (APS – Minneapolis, MN) and Barrow Neurological Institute (Phoenix, AZ) and approved by their respective institutional animal care and use committees. Ten male canines (n= 10) underwent aneurysm creation and subsequent NeuroCURE embolization. Males canines were used to mitigate potential confounding effects of hormonal cycles. Six of 10 (n=6)

canine aneurysm models were created and embolized at Barrow Neurological Institute, with 4 animals surviving for 3 months (n=4) and 2 animals surviving for 12-months (n=2). The remaining 4 (n=4) canine aneurysm models were created and embolized at APS following Good Laboratory Practice conditions and these survived for 6-months. Explanted tissues/materials from all 10 animals were fixed and processed by APS for histopathological evaluation, also following Good Laboratory Practice guidelines. Under Federal Food and Drug Administration guidance, the animal sample size represented the minimum number of models while statistically demonstrating a data trend and accounting for variability among animals and surgically created aneurysm morphology. No animals were excluded.

Large, wide-neck aneurysms were surgically created in all 10 canines. An incision was made on the left side of each animal's neck to access the left external jugular vein (EJV). The EJV was ligated proximally and distally, and a 15–30 mm segment of the EJV was excised, cleaned of excess tissue, and immersed in isotonic saline. The left side of the neck was sutured closed and an incision was made on the right side of the animal's neck to expose the right common carotid artery (RCCA). The RCCA was clamped proximally and distally to prevent blood loss, and a 6–8 mm beveled arteriotomy was made on the RCCA to prepare for aneurysm creation. The excised section of the EJV was sewn (end-to-side) to the defect created on the RCCA. Next, the vessel was rinsed and purged of air. Then, the distal lumen of the EJV section was sewn closed to create the aneurysm fundus.

In the 4 canines treated at APS, a second aneurysm pouch was also created from the excised EJV segment and sewn on the left common carotid artery to serve as an untreated control aneurysm. All aneurysms had an initial dome height >9 mm and a wide dome:neck ratio < 2:1. No randomization was performed and confounders were not controlled.

All 10 canines were housed for at least 2 weeks to allow for healing of the aneurysm and surgical sites. Aspirin was given post-aneurysm creation and up to day 0 of NeuroCURE embolization procedure to ensure aneurysm patency for implant; however, the animals were not placed on anticoagulants or antiplatelet therapy after embolization or during their survival period. Angiograms were performed immediately before the embolization procedure to determine aneurysm shape (spherical, ellipsoid, cylindrical, or "barrel" shaped). Aneurysm dimensions were measured with a calibrated fluoroscopy system (OEC 9900, GE). For spherical and ellipsoid aneurysms, volume (V1) was calculated with Equation (1):

$$\mathrm{V1\ (mL)} = \frac{\pi\ (\mathrm{D} * \mathrm{W} * \mathrm{H})}{6000} \quad ((1))$$

For cylindrical and "barrel"-shaped aneurysms, volume (V2) was calculated with Equation (2):

$$\mathrm{V2\ (mL)} = \frac{\pi\ (\mathrm{D} * \mathrm{W} * \mathrm{H2})}{4000} + \frac{\pi\ (\mathrm{D} * \mathrm{W} * (\mathrm{H} - \mathrm{H2})}{6000} \quad (2)$$

All aneurysm dimensions were measured in millimeters (mm): D is the depth of the aneurysm dome perpendicular to the parent vessel direction. W is the width of the aneurysm dome parallel to the parent vessel direction. H is the maximum height to the top of the dome of the aneurysm. H2, used for cylindrical or "barrel" aneurysms only, is the average height of the left and right straight sides of the aneurysm. In all 10 animals, the RCCA aneurysm was embolized. In addition, the left common carotid artery aneurysms in the 6-month survival animals were left untreated (controls). Since each animal had both a treated and a control aneurysm, randomization of animals into treatment/control groups was not necessary.

NeuroCURE was delivered through a dual catheter delivery technique employing a 2.6F microcatheter delivery (0.025″ ID, 0.64 mL dead space, Penumbra PX Slim) under balloon protection (5×20 mm, Medtronic Hyperglide). An 8F introducer sheath was placed in the right femoral artery of the canine and the microcatheter and balloon were introduced via an 8F guide catheter (Guider Softip XF, Boston Scientific). Under fluoroscopic guidance, the balloon catheter was advanced to the site of the aneurysm neck (RCCA) and the microcatheter was advanced into the aneurysm sac. The embolization procedure began with a 1-minute mixing step of the components of NeuroCURE: poly-propylene glycol diacrylate, pentaerythritol tetrakis 3-mercaptopropionate, and liquid contrast (Conray) titrated to a pH of 11. The increase in pH initiates a molecularly efficient "click chemistry" reaction lasting 10 minutes (±30 seconds). Under balloon protection and fluoroscopic guidance, a volume of NeuroCURE (based on 90%–100% of the measured aneurysm volume – Table 1) was injected by hand in less than 2 minutes (max flow rate of 2 mL/min).[1,38]

The radiopaque NeuroCURE polymer gel coalesced to fill and conform to the aneurysm sac's shape, while blood was displaced out of the aneurysm between the delivery catheter and the inflated balloon. Once solidification was complete, the microcatheter was removed and the balloon was deflated. No adhesions of the microcatheter or balloon to the NeuroCURE were observed. The single balloon inflation time in all cases was less than 10 minutes. Angiographic images were recorded at both post-embolization and at study termination. Aneurysm occlusion (using the Raymond scale) and qualitative carotid artery flow were assessed in all treated aneurysms post-embolization and at study termination. Assessment of all canine aneurysms followed the same grading system. Raymond scores and the qualitative flow grades were assessed for each aneurysm model according to the definitions in Table 2.

All canines were humanely euthanized at their respective survival time points (3-, 6-, or 12-month). A complete necroscopy was performed before the aneurysms were excised for histological preparation. The RCCA aneurysms and their parent arteries were excised in each of the 3- and 12-month canines, and both left common carotid artery and RCCA aneurysms and their parent arteries were excised in the 6-month canines.

Before parent vessel and aneurysm excision, the carotid artery was cannulated upstream of the aneurysm site and rinsed with an isotonic solution to clear any blood remnants. The vessels were then perfusion-fixed with 10% neutral buffered formalin for a minimum of 5

minutes. Next, the treated vessels were excised with a minimum of 5 mm of vasculature proximal and distal to the treatment site, anatomy permitting, and immersed in 10% neutral buffered formalin. Gross inspections were performed of the brain, aneurysm neck, and treatment site for mass effects, tissue compression, and other abnormalities. The aneurysm and brain were grossly photographed and immersed in 10% neutral buffered formalin before being shipped to APS for histopathologic analysis. Brain tissue from the canines was evaluated via histopathology for treatment-related infarct and/or micro-emboli.

Each excised aneurysm was sectioned at 3 positions (proximal neck, mid-neck, and distal neck) to create cross-sections of the aneurysm and parent vessel. Sections were mounted on viewing slides and stained alternating between a hematoxylin and eosin stain and a Pentachrome stain per APS standard operating procedures. All slides were examined using light microscopy. The parent vessel/neck surface was scored based for platelet/fibrin thrombus presence, percent endothelialization, and neointima formation (Table 3), while the aneurysm sacs were scored for percent occlusion, inflammation, and neoangiogenesis (Table 4). All parameters were scored on a semi-quantitative scale (0–4). For NeuroCURE, the goal was 90+% fill of the aneurysm sac with test article; therefore, the presence of thrombus in the sac, immune response, and thrombus reorganization into vessel channels (neoangiogenesis) is not expected (scores 0–1). What is expected is continuous neointimal growth and endothelialization of the aneurysm neck (scores 3–4)

RESULTS

The consistent large and wide-neck aneurysm size, morphology, and accessibility via a femoral puncture attained in the canine model proved to be much more relevant to the human condition than the rabbit aneurysm models treated with an early version of NeuroCURE in a previous study.[41] The canine aneurysms were all considered large on average when measured via angiography pre-embolization (11.27±1.77 mm maximal dome height). NeuroCURE fill volumes were also within 94.9%±2.3% of calculated aneurysm volumes (Table 1).

Raymond–Roy occlusion classification (RROC) and qualitative flow for the NeuroCURE treated aneurysms were evaluated immediately post-embolization and immediately pre-termination (Figure 1). Considering the nature of the balloon occlusion (the balloon creates a slight dimple into the neck of the aneurysm when inflated, confirming aneurysm neck protection), the average Raymond score of all aneurysms after treatment was 2.2±0.4 due to the NeuroCURE conforming to the aneurysm and the balloon dimple shape at the neck. After 3 months, the endothelization of the aneurysm neck had begun but was not complete, resulting in a slight reduction of the average Raymond score (2.0±0.8). The change in the Raymond score was not statistically significant after 3 months (P value=0.62). However, pre-term angiography showed the aneurysm neck and dimple healed in the survival animals and the average Raymond score was 1.2±0.4 at term, a statistically significant resolution of the Raymond score (P value<0.01) (Table 5). The control aneurysms that were not implanted with NeuroCURE were found to be fully patent with no signs of angiogenesis in all cases.

Gross evaluation of the explanted aneurysms showed a smooth NeuroCURE surface (pearl white color) at the neck with nearly complete neointimal coverage at 3-months (yellow layer). Complete neointimal neck coverage is seen at both 6 months (continuous yellow layer) and 12 months (yellow/pink layer – Figure 2).

Histopathologic evaluation of the explanted NeuroCURE treated aneurysms showed no evidence of inflammation, recanalization/neoangiogenesis, or fibrotic encapsulation, while supporting complete neointimal growth and reendothelialization across the neck of the aneurysm (Figure 3). The average NeuroCURE fill in all aneurysms was greater than 90% in all survival animals. There was also no thrombus found at the blood interface in all cases. In some slides, the angle of the cut may have excluded a section of the neck with respect to the aneurysm sac. In these instances, the slides were scored “n/a.” Gross and histological assessment of the aneurysms verified that the neointimal growth and % endothelialization was high in all animals (average score 3.6) and complete by the 6-month survival time point (average score 4.0), with the anticipated low average scores for sac content (0.1), inflammation (0.8), neo-angiogenesis (0.0), and platelet/fibrin thrombus (0.0) (Table 6). Histopathological evaluation of brain tissues showed no signs of infarct or emboli from thrombus or the NeuroCURE device.

DISCUSSION

NeuroCURE performed well as an aneurysm occlusion device in all 10 canines tested in this study. Even in the 12-month survival canine (#9) that had an initial RROC score of 3, the aneurysm was nearly 90% filled with the device and the residual aneurysm was contained within the NeuroCURE device. Despite the poor initial RROC score for this particular aneurysm, there was no recanalization, fibrosis, or inflammation, and it was deemed to present a very low risk for recanalization. The RROC for canine #9 resolved to a “1” at term. In all animals, NeuroCURE was not observed to degrade or initiate angiogenesis at the 3-, 6-, or 12-month implantation timeframes used in this study.

Limitations of this study include a focus on large and wide-neck aneurysms with traditionally higher recanalization rates post-treatment. Further studies would be needed to compare NeuroCURE performance in small- and medium-sized aneurysms. Also, the device is intended to eliminate thrombus formation in the aneurysm sac, which necessitates refinement of the traditional fluoroscopic and histological scoring systems used to define initial and long-term aneurysm sac stability.

Further clinical evaluation of NeuroCURE may necessitate a modified RROC classification system due to the temporary balloon protection during NeuroCURE delivery that requires conformation around the balloon dimpling into the aneurysm sac. In the current RROC classification, this is considered a residual “neck.” Since the dimpling of the balloon ensures a complete seal at the neck during treatment, this residual neck is unavoidable, resulting in all NeuroCURE initial RROC scores being an average of 2.2. Unlike typical thrombus formation in the aneurysm sac, NeuroCURE with a residual neck is mechanically stable and provides a smooth surface scaffold for neointimal growth, which fills in the dimple – resolving to an average RROC of 1.2. The data from this study, as well as previous in

vivo and in vitro studies on NeuroCURE, suggests that the residual neck in NeuroCURE-treated intracranial aneurysms does not result in thrombogenesis/thromboembolism nor recanalization of the aneurysm. Balloon occlusion proved ideal to achieve a good seal at the aneurysm neck. Additionally, early proof-of-concept studies show that the viscosity and hydrophobicity of NeuroCURE may allow it to successfully be injected and cured behind a temporary flow diverting stent or braided mesh device. The flow diverter or mesh device would allow for perfusion of the artery while still providing a barrier to prevent NeuroCURE from migrating downstream during injection. Flow diverter-assisted injection of NeuroCURE would also potentially reduce or eliminate the residual neck left in NeuroCURE by balloon occlusion.

None of the canines in this study were placed on dual-antiplatelet therapy. NeuroCURE was observed to be extraordinarily biocompatible and hemocompatible with minimal inflammation and without thrombosis at the blood interface of the device. Hemocompatibility was further confirmed with concurrent ISO 10993 biocompatibility testing. NeuroCURE was found to have less partial thromboplastin time activation than the negative control used in the study. NeuroCURE was also classified as a nonactivator of the SCB5-9 blood complement system and as nonhemolytic (within 1% of the negative control).

The hemocompatibility results and the animal management without the administration of dual-antiplatelet therapy suggest that the use of NeuroCURE in the clinical setting will likely not require this drug regimen, which is currently required with standard metal-based neurovascular implant devices. A fundamental difference in these devices is that the delivery of the mechanically stable and biocompatible NeuroCURE would stabilize the aneurysm without the need for mechanically unstable thrombus formation. The NeuroCURE material promotes neointimal tissue infill from the device surface outward rather than depending on thrombus formation to resist residual flow and recanalization effects, both of which are exacerbated by thrombus mechanical compression and thrombus neoangiogenesis. The lack of thrombus formation with NeuroCURE treatment may also reduce the potential for downstream thromboembolic events compared with coils, flow diverters, and flow disruptors.

CONCLUSION

In vivo implantation of NeuroCURE in canine aneurysm models has further established the proof-of-concept of the material for use in the treatment of intracranial aneurysms and has exhibited crucial biocompatibility and mechanical stability for up to 1 year postimplantation. NeuroCURE remains a compelling investigational device for the endovascular treatment of intracranial aneurysms and verifies the need to potentially augment, coat, or replace some standard metal-based devices used in neurovascular treatments.

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Nonstandard Abbreviations and Acronyms

APS	American Preclinical Services
EJV	external jugular vein
RCCA	right common carotid artery
RROC	Raymond–Roy occlusion scale

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CLINICAL PERSPECTIVE

- Neurovascular Controlled Uniform Rapid Embolic (NeuroCURE) is an exciting new liquid embolic under investigation for the treatment of large, wide-neck intracranial aneurysms.
- This study exhibits NeuroCURE's ability to be quickly delivered, fill and occlude the entire aneurysmal volume, and provide a highly biocompatible surface at the aneurysm neck to promote rapid neointimal growth and a permanent, stable occlusion.
- This study shows that NeuroCURE can successfully treat in vivo models of large, wide-neck intracranial aneurysms and has strong potential as an investigational device for the treatment of these intracranial aneurysms that can often be challenging to treat with current standard practices of care.

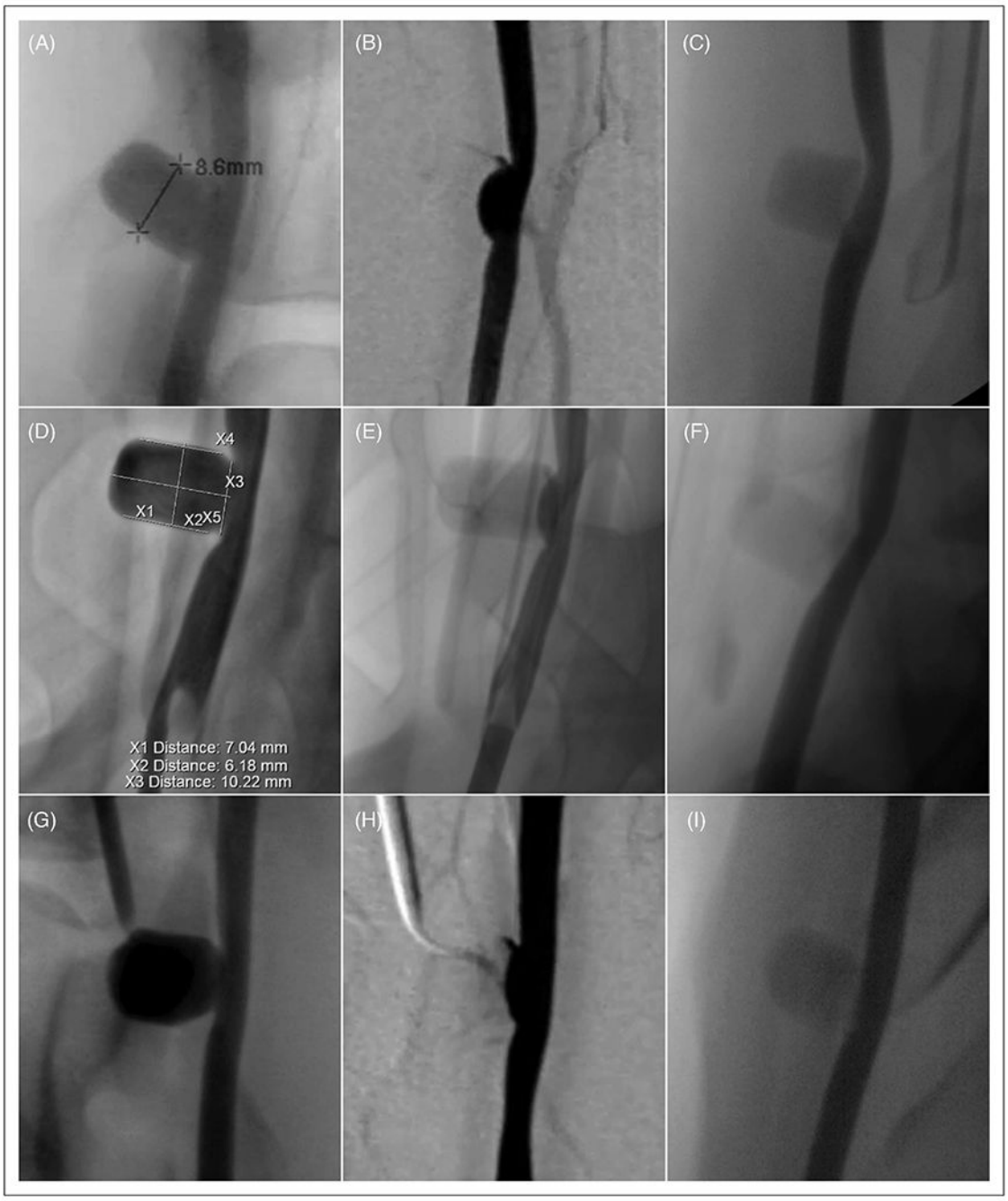

Figure 1. Angiographic image of the aneurysm pre-treatment (left column), post-treatment (middle column), and pre-term (right column).

Dimple from the balloon is apparent post-treatment (middle column) but resolves pre-term (right column). **A–C**, 3-month survival, (**D–F**) 6-month survival, and (**G–I**) 12-month survival.

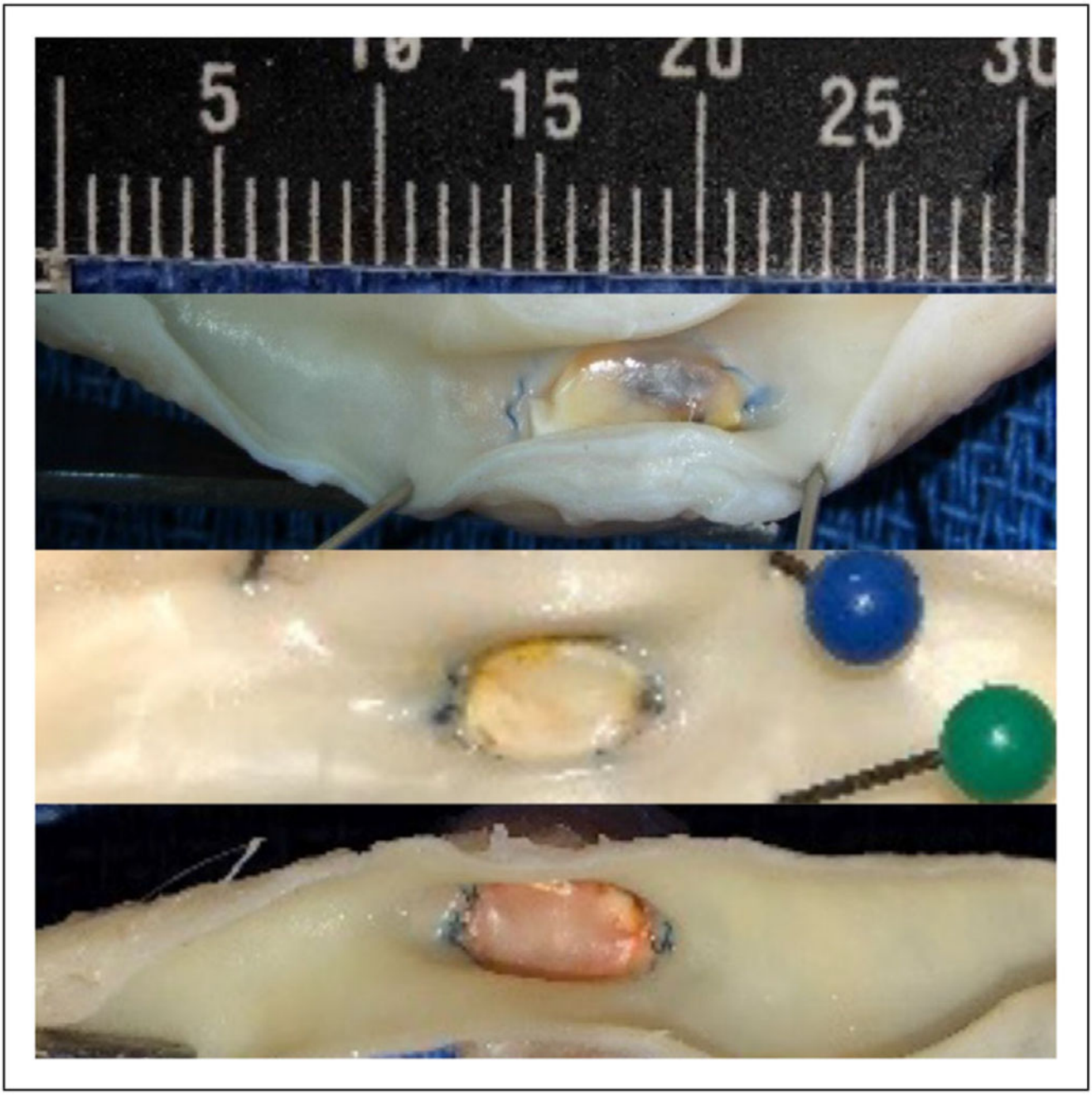

Figure 2. Representative gross evaluations of the neck of the Neurovascular Controlled Uniform Rapid Embolic (NeuroCURE) treated aneurysms.

Top image left side of neck is exposed NeuroCURE (white) with the majority of the neck covered with neointimal growth (translucent yellow) at 3 months. Middle image is complete neointimal growth at the neck at 6 months (translucent yellow). Bottom is a stable, mature neointimal layer at the neck at 12 months (translucent yellow/pink).

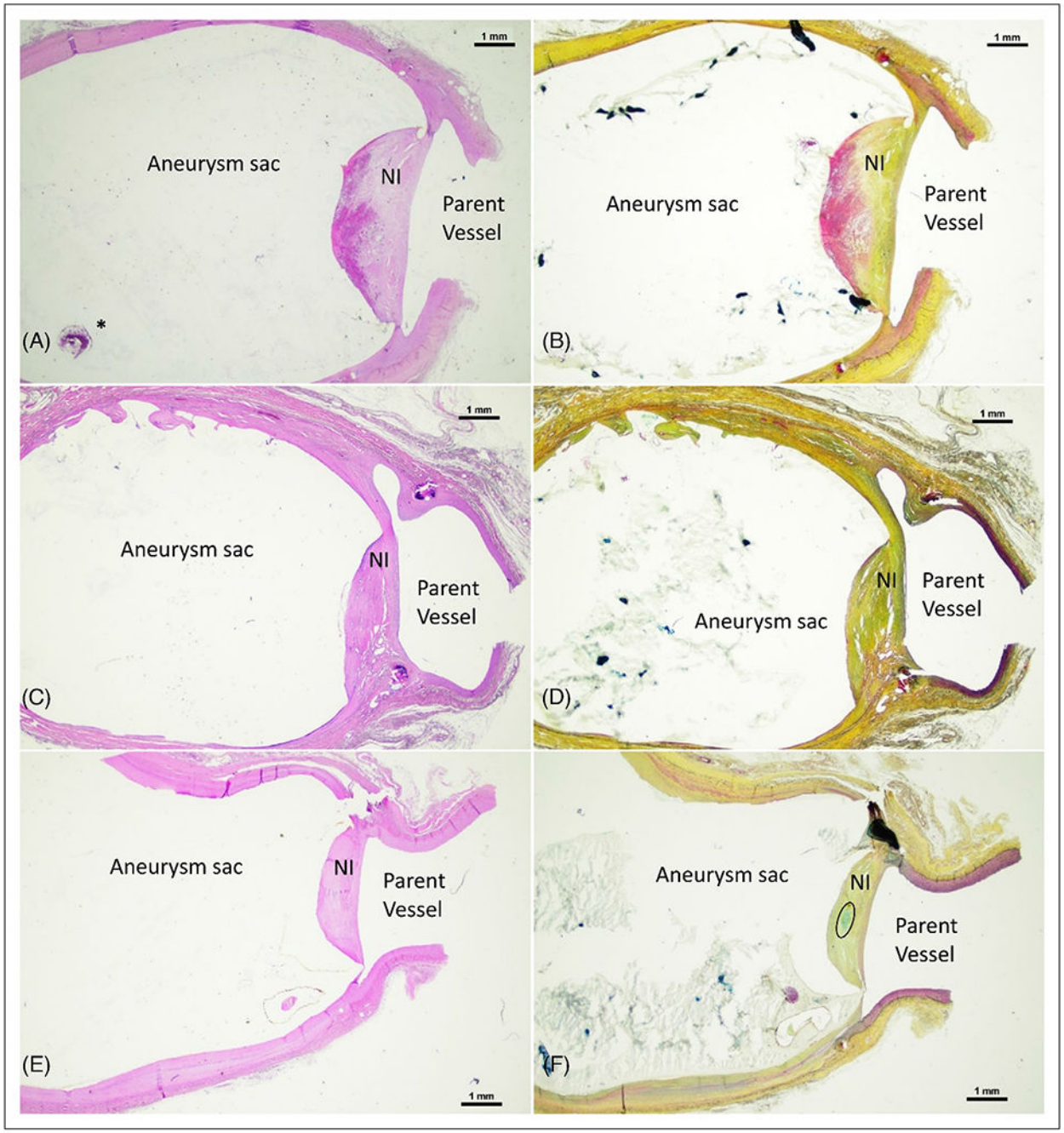

Figure 3. Representative histopathologic images of Neurovascular Controlled Uniform Rapid Embolic (NeuroCURE) treated canine aneurysms where left images are stained with hematoxylin and eosin (H&E) and right images are stained with Movat Pentachrome.

A and **B**, 3-month survivals, (**C, D**) 6-month survivals, and (**E, F**) 12-month survivals. All histologic images show the NeuroCURE filled aneurysm sac fully, with a dimple at the aneurysm neck where a band of continuous neointimal tissue (NI) grew at the dimple, separating the sac from the parent vessel. The arrows indicate the presence of fibrin in the neointima. * indicates a single focus of mature fibrous stroma within the aneurysm sac

from the original delivery catheter placement. Oval indicates a small focus of chondroid metaplasia.

Table 1.

Canine Aneurysm Model Dimensions and Neurovascular Controlled Uniform Rapid Embolic (NeuroCURE) Treatment Information

Canine	Aneurysm size (mm)					Dome/neck	Aneurysm	NeuroCURE	NeuroCURE	Survival
#	Dome	H2	Width	Depth	Neck	Ratio (DNR)	Vol (mL)	Vol (mL)	% Fill	Time (mo)
1	11.2	–	12.1	9.0	6.6	1.83	0.64+	0.60	94	3
2	12.7	–	8.6	13.2	7.5	1.15	0.75+	0.72	95	3
3	14.4	12.0	9.6	11.1	7.5	1.28	1.14*	1.10	97	3
4	13.5	10.5	9.4	8.0	7.0	1.34	0.74*	0.70	95	3
5	9.4	–	8.7	7.4	6.6	1.31	0.31+	0.31	99	6
6	9.8	–	7.7	7.1	5.6	1.38	0.28+	0.26	93	6
7	10.5	–	8.0	7.5	6.2	1.29	0.33+	0.31	94	6
8	10.3	–	8.7	7.1	6.1	1.43	0.33+	0.31	93	6
9	11.7	–	7.6	9.0	7.3	1.04	0.42+	0.41	98	12
10	9.3	–	7.5	7.5	5.0	1.50	0.27+	0.25	91	12

Aneurysm volumes labeled “+” were spherical/ellipsoid aneurysms (Equation 1), aneurysm volumes labeled “*” were barrel/cylindrical aneurysms (Equation 2).

Table 2.

Angiographic Aneurysm Assessment Criteria for Aneurysm Occlusion and Parent Artery Patency

Raymond score (aneurysm occlusion assessment)	
1	Complete (100%) obliteration of aneurysm, including the neck
2	Near complete occlusion (90%–99%), contrast filling the neck of the aneurysm without opacification of aneurysm sac
3	Incomplete occlusion (less than 90%), contrast filling the sac of the aneurysm
Qualitative flow grade	
0	Absence of any antegrade flow beyond a vascular obstruction
1	Faint antegrade flow beyond a vascular obstruction, with incomplete filling of the distal vessel
2	Delayed or sluggish, antegrade flow beyond a vascular obstruction with complete filling of the distal vessel
3	No vascular obstruction with normal antegrade flow that fills the distal vessel completely

Table 3.

Histopathological Evaluation Criteria for the Parent Vessel and the Neck of the Aneurysm

Platelet/fibrin thrombus	
0 (Absent)	Not present
1 (Minimal)	Focal or <25% of the surface
2 (Mild)	Multi-focal 25%–50% of the surface
3 (Moderate)	Regional, diffuse 51%–75% of the surface
4 (Marked)	Diffuse; >75% of the surface
Percent (%) endothelization	
0 (Absent)	Not present
1 (Minimal)	<25% of the surface
2 (Mild)	25%–50% of the surface
3 (Moderate)	51%–75% of the surface
4 (Marked)	>75% of the surface
Neointima formation	
0 (Absent)	Not present
1 (Minimal)	<25% of the area at the neck interface
2 (Mild)	25%–50% of the area at the neck interface
3 (Moderate)	51%–75% of the area at the neck interface
4 (Marked)	>75% of the area at the neck interface

Table 4.

Histopathological Evaluation Criteria for the Aneurysm Sac and Its Contents

Sac Content (percent of sac occupied by test article and/or void/empty space)	
0 (Complete)	>90% of the sac contained test article (void)
1 (Marked)	68%–90% of sac filled with test article (void)
2 (Moderate)	46%–67% of sac filled with test article (void)
3 (Mild)	24%–45% of sac filled with test article (void)
4 (Minimal)	0%–23% of sac filled with test article (void)
Inflammation	
0 (Absent)	Not present
1 (Minimal)	Minimal inflammatory response forming sparse infiltrates or small solid aggregates a few cells thick (~2–3 layers or less)
2 (Mild)	Mild inflammation forming denser infiltrates or larger aggregates (more than 3 cell thick) but no widespread aggregates
3 (Moderate)	Moderate inflammation forming dense infiltrates or widespread aggregates of inflammatory cells that do not efface or replace pre-existing tissue and/or test article components
4 (Marked)	Severe inflammation or overwhelming change forming dense infiltrates or widespread aggregates of inflammatory cells that efface or replace pre- existing tissue and/or test article components
Neoangiogenesis	
0 (Absent)	Not present
1 (Minimal)	Focal 1–3 vessel (40x HPF)
2 (Mild)	3–5 vessels (40x HPF)
3 (Moderate)	6–10 vessels (40x HPF)
4 (Marked)	≥11 vessels (40x HPF)

Table 5.

Angiographic Evaluation of Aneurysms for Occlusion (Raymond Score) and Parent Artery Patency (Qualitative Flow Grade)

Canine information		Scores after embolization		Scores at term	
Canine number	**Survival timepoint (mo)**	**Raymond score**	**Qualitative flow grade**	**Raymond score**	**Qualitative flow grade**
1	3	2	3	2	3
2	3	2	3	1	3
3	3	3	3	3	3
4	3	2	3	2	3
5	6	2	3	1	3
6	6	2	3	1	3
7	6	2	3	1	3
8	6	2	3	2	3
9	12	3	3	1	3
10	12	2	3	1	3

Table 6.

Semiqualitative Histopathologic Scoring of the Neurovascular Controlled Uniform Rapid Embolic (NeuroCURE) Treated Aneurysms

Canine information			Neck surface assessment			Aneurysm sac assessment		
Canine number	**Survival timepoint (mo)**	**Tissue section**	**Platelet/fibrin thrombus**	**% Endothelization**	**Neointimal formation**	**Sac content (%NeuroCURE)**	**Inflammation**	**Neoangiogenesis**
1	3	Proximal	0	4	4	0	1	0
		Middle	0	3	3	0	1	0
		Distal	0	4	4	0	1	0
2	3	Proximal	0	4	4	0	1	0
		Middle	0	4	4	0	1	0
		Distal	0	n/a	4	0	1	0
3	3	Proximal	0	3	3	0	1	0
		Middle	0	2	2	0	1	0
		Distal	0	n/a	n/a	0	1	0
4	3	Proximal	0	3	3	1	1	0
		Middle	0	2	2	0	1	0
		Distal	0	2	2	0	1	0
5	6	Proximal	0	4	4	0	1	0
		Middle	0	4	4	0	1	0
		Distal	n/a	n/a	n/a	0	0	0
6	6	Proximal	0	4	4	0	0	0
		Middle	0	4	4	0	1	0
		Distal	n/a	n/a	n/a	n/a	n/a	n/a
7	6	Proximal	0	4	4	n/a	n/a	n/a
		Middle	0	4	4	0	1	0
		Distal	0	4	4	0	0	0
8	6	Proximal	0	4	4	0	1	0
		Middle	0	4	4	0	1	0
		Distal	0	4	4	0	1	0
9	12	Proximal	0	4	4	1	0	0

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Canine information			Neck surface assessment			Aneurysm sac assessment		
Canine number	**Survival timepoint (mo)**	**Tissue section**	**Platelet/fibrin thrombus**	**% Endothelization**	**Neointimal formation**	**Sac content (%NeuroCURE)**	**Inflammation**	**Neoangiogenesis**
		Middle	0	4	4	0	1	0
		Distal	0	n/a	n/a	0	0	0
10	12	Proximal	0	4	4	0	1	0
		Middle	0	4	4	0	1	0
		Distal	0	4	4	0	1	0
Average scores	0.0	3.6	3.6	0.1	0.8	0.0		