Codman®

CerebroFlo® EVD Catheter with Endexo® Technology

- Overview
- In Vitro Characterization Studies
- Selected Case Reports

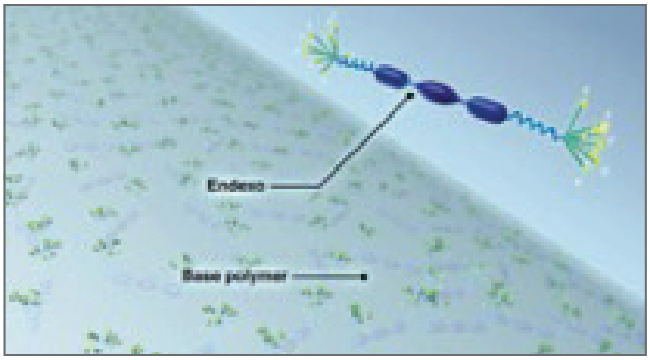
Quentin T. Aten, PhD, Chief Technology Officer
Marvin L. Sussman, PhD, Scientific Advisor

Codman®
SPECIALTY SURGICAL

A DIVISION OF INTEGRA LIFESCIENCES

Codman®

CerebroFlo® EVD Catheter with Endexo® Technology



INTRODUCTION

Codman® CerebroFlo® EVD Catheter with Endexo® Technology

Codman is pleased to introduce the first and only external ventricular drainage (EVD) catheter incorporating Endexo technology.

Endexo polymer is a low-molecular-weight fluoro-oligomeric polymer additive intended to reduce protein adsorption and thrombus formation. Endexo molecules become an integral part of a catheter's lumen by dispersing throughout the base polymer, and by further migrating to the surface's top few nanometers during manufacture. This provides extended efficacy compared to traditional coatings whose effectiveness diminishes with time.

Recently 510(k) cleared, the CerebroFlo EVD Catheter has been studied by Codman with in vitro laboratory testing, following similar or improved testing protocols for previously introduced Endexo-containing medical devices for vascular access. The Endexo additive has been used in vascular devices since 2012, with the introduction of the Navilyst® MNI PICC III (510k 121089) now sold by AngioDynamics.

Within these applications, the Endexo additive has:

- **Demonstrated inhibited platelet activation and thrombus formation.** The fluorinated Endexo polymer surface properties accomplish this by suppressing protein procoagulant conformation, reducing thrombosis, and potentially extending the duration of the catheter's patency.

- **Established in clinical use for multiple other medical applications.** The antithrombogenic Endexo polymer additive has gained clinical acceptance in vascular access catheters offered by AngioDynamics, including BioFlo® PICC catheters, BioFlo® midline catheters, and BioFlo DuraMax® chronic hemodialysis catheters. The literature reports that vascular access catheters with Endexo enhancement have 73% fewer catheter obstructions,[1] as well as a 56-80% reduction in complications from venous thrombosis.[2,3]

What functionality does the Endexo polymer add to CSF drainage systems?

- Antithrombogenic properties via passive material modification
- Permanent integration onto all surfaces–enhancements that do not diminish with time
- Inhibition of biomatter accumulation onto catheter surfaces

Codman has introduced the Endexo polymer to CSF drainage systems with the CerebroFlo EVD Catheter

- Large-gauge (10 Fr), radiopaque catheter with 16 large diameter flow holes, and high-visibility, full-circumference depth markings
- Large flow holes, large diameter lumen, and exclusive Endexo technology that make the CerebroFlo catheter especially useful for patients with intraventricular hemorrhage
- Endexo polymer integrated within the catheter's polyurethane formulation

Endexo Technology – A Permanent Solution

- Endexo polymer, a fluorinated surface-modifying polymer macromolecule integrally mixed with the CerebroFlo polyurethane matrix, modifies all catheter surfaces.
- Unlike superficial coatings, which delaminate, or impregnated agents that elute over time, the Endexo molecule remains locked in the polymer matrix and does not deplete over the catheter's EVD drainage course.
- Unlike anticoagulative drug additives, such as heparin, Endexo technology has been shown in vitro to minimize the accumulation of thrombus on catheter surfaces without the potential for systemic anticoagulation.[4,i]
- Molecules provide a passive surface that reduces adhesion/activation of blood proteins and components, thereby reducing thrombus formation.

HOW DOES THE ENDEXO MOLECULE WORK?

The Endexo molecule's polymer backbone becomes integrated into the base polymer matrix, anchoring Endexo molecules to the structure of the catheter material and modifying the surface properties. The end groups functionalize all extruded and cut catheter surfaces[5-7,ii] resulting in a biologically passivated surface which reduces protein adsorption,[5,8,iii] platelet adhesion,[8] and platelet activation.[9]

Immediately after insertion of a catheter into the body, biological components such as proteins begin to adsorb onto the catheter's surfaces.[10] That absorbed protein layer further mediates the body's biological response to the implanted material, promoting biomatter buildup, which can occlude catheters. Many polymers used in medical devices have surface characteristics that may absorb proteins, activate platelets, and promote conditions leading to thrombosis[11] and foreign body reactions.[12]

The Endexo molecule is a fluorinated polymer, consisting of a polyurethane backbone and fluorinated end groups (Fig. 1). A small amount of Endexo molecules are blended with the CerebroFlo catheter's base material, and these molecules migrate to the catheter's surface. At the surface, the Endexo's polyurethane backbone remains integrated in the base matrix, while the fluorinated end groups are expressed at the catheter's surface.

The Endexo-modified surfaces passivate the CerebroFlo catheter to reduce adhesion of biological components. Because of the weak intermolecular forces between the fluorinated end groups and biomatter [13, 14], proteins and platelets that may adhere have less conformational change or activation, leading to less thrombosis.

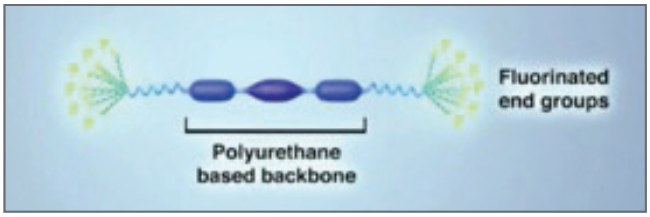


Figure 1: The Endexo molecule.

When proteins in cerebrospinal fluid or blood come into contact with the Endexo fluorinated surface of the CerebroFlo catheter, the low reactivity of the catheter surface significantly reduces protein adsorption and platelet activation and adhesion (Fig 2.).[8,9,15,16] The Endexo molecule is not an antithrombotic agent: it does not elute from the catheter and does not alter the coagulative properties of the blood. Rather, Endexo is a nonthrombotic, ie, nonreactive, compound that passivates the surface properties of the catheter, making protein adhesion less likely.

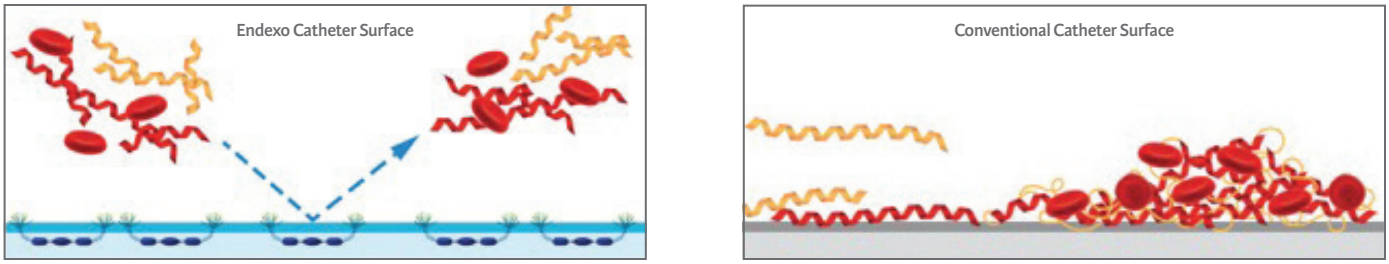


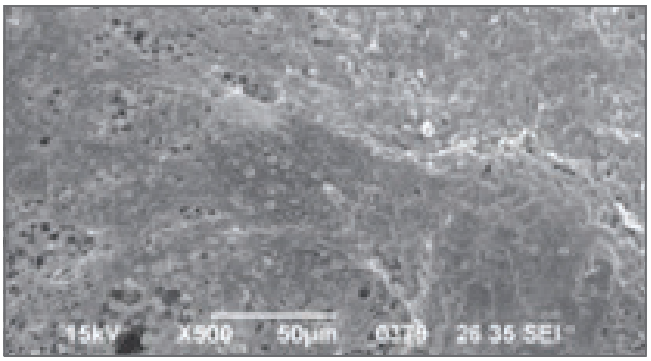
Figure 2: Endexo Catheter Surface compared to a Conventional Catheter Surface.

IN VITRO TESTING

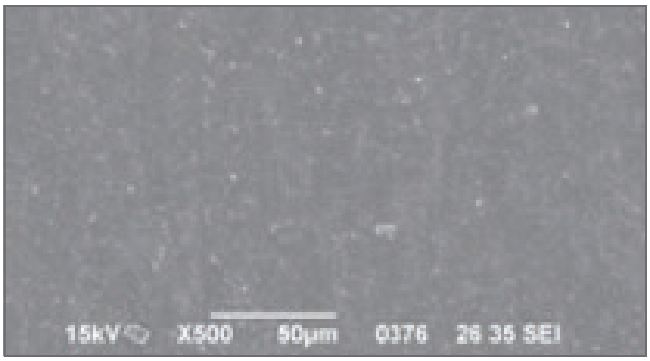
Two in vitro studies were completed to characterize the comparative performance of the CerebroFlo EVD Catheter and a leading EVD catheter. The Codman CerebroFlo EVD Catheter's in vitro test results mimic the in vitro results reported for vascular access catheters incorporating the same Endexo technology.[4,15] (In vitro testing cannot fully predict clinical performance.)

Material Characterization of In Vitro Relative Thrombogenicity

In vitro testing demonstrated that the CerebroFlo EVD Catheter with the Endexo molecule significantly reduced thrombus formation on catheter surfaces compared to a competitive EVD catheter. The relative thrombogenicity of the CerebroFlo catheter was compared to an equally sized EVD catheter (Competitor A) using an established in vitro "blood loop" model.[17] Bovine blood with radiolabeled platelets was circulated in a closed loop system and the resulting thrombus was quantified by measuring radioactive counts per minute (CPM). The CerebroFlo EVD Catheter with Endexo technology demonstrated a 99% reduction in vitro in thrombus formation onto its surfaces. See Appendix A for further study details.



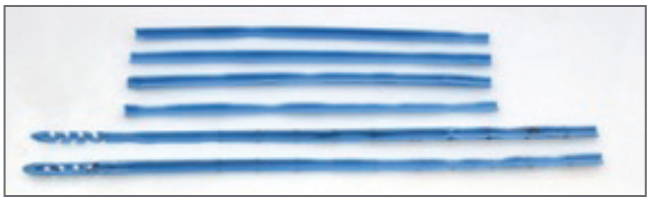
Competitor A
SEM images at 500x magnification revealing thrombus matrix and red blood cell adhesion to catheter.



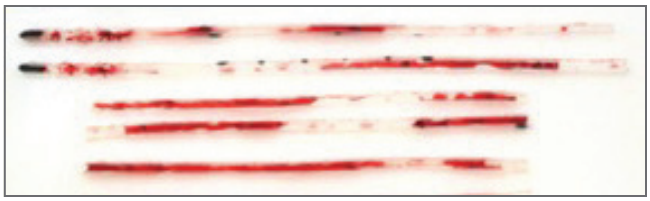
CerebroFlo EVD Catheter with Endexo Technology
SEM images at 500x magnification displaying a substantially clean surface.

Flow Characterization of In Vitro Obstruction in Simulated CSF + Blood

In initial in vitro studies, the CerebroFlo EVD Catheter's antithrombogenic character was shown to reduce catheter obstructions in vitro when compared to an equally sized EVD catheter (Competitor A) without the Endexo enhancement. To simulate drainage associated with an intraventricular hemorrhage, reservoirs of 50% ovine blood and 50% simulated CSF by volume were drained through both catheters at a physiologically relevant flow rate (12-18 ml/hr) until one of the catheters was obstructed. In 6 experimental replicates, the CerebroFlo EVD Catheter with the Endexo enhancement remained patent while the Competitor A catheter's flow holes and/or lumen were occluded by thrombus.



CerebroFlo EVD Catheter with Endexo Technology
showing patent catheter lumen and flow hole



Competitor A
showing obstructions in the catheter flow holes and lumen

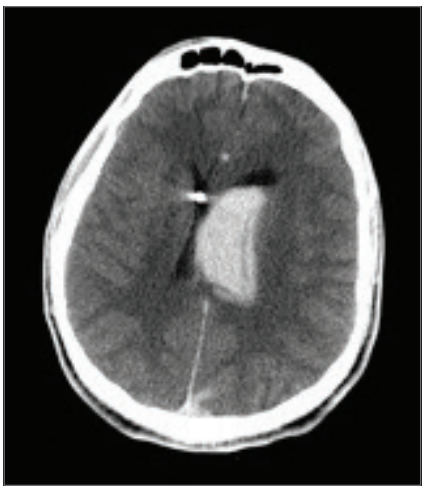
For further study details, see Appendix B.

CLINICAL CASE REPORTS

Ruptured Arteriovenous Malformation (AVM) Treated with Codman CerebroFlo EVD Catheter with Endexo Technology

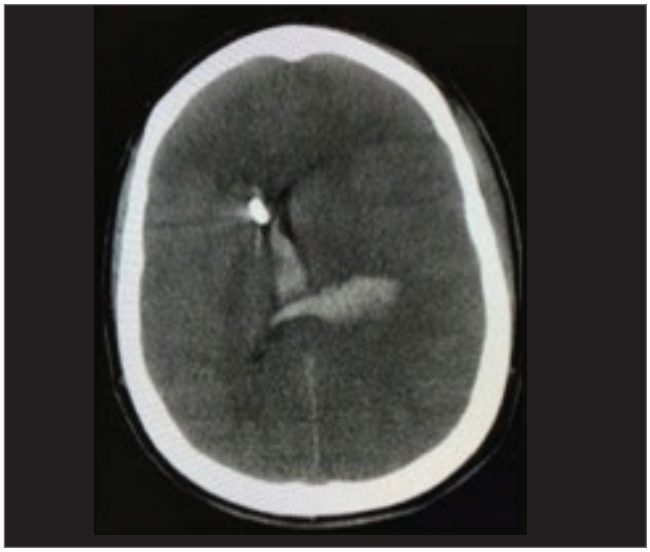
An 18-year-old male was transferred to a Level I trauma center from an outside institution, and intubated with poor response. CT revealed a left parieto-occipital parenchymal hemorrhage with extensive intraventricular hemorrhage and associated hydrocephalus. A right frontal ventriculostomy was placed, using the Codman CerebroFlo EVD Catheter with Endexo Technology, and an arteriogram was performed, demonstrating arteriovenous malformation (AVM). The patient was kept sedated with continuous ventricular drainage at 5-10 cm Hg for 13 days. Intracranial pressure (ICP) was measured periodically by briefly diverting fluid pressure to a strain gauge by closing a stopcock within the system. After 13 days, the drain was gradually raised, clamped, and thereafter removed 2 days later with normal ICP.

The Codman CerebroFlo drainage catheter required no flushing. Immediately after placement, an initial clot was easily aspirated, and the catheter subsequently drained bloody CSF without any flushing, aspiration, replacement, or evidence of occlusion until it was clamped and then removed. Two weeks after removal, there was no evidence of infection, need for further drainage, or complications associated with the Endexo-based catheter.



Ruptured Mycotic Aneurysm Treated with Codman CerebroFlo EVD Catheter with Endexo Technology

A 25-year-old female presented obtunded to a Level I trauma center with massive intraventricular hemorrhage secondary to a ruptured mycotic aneurysm. A CerebroFlo EVD Catheter with Endexo Technology was placed on hospital day one. Patient underwent endovascular coiling of the aneurysm, remaining intubated with minimal neurological improvement. Catheter remained unobstructed without intervention and continuously drained bloody CSF for 11 days. The catheter did not require any irrigations or tPA, and there were no signs of infection.



ENDEXO® ADDITIVE – FUTURE DIRECTIONS IN NEUROSURGERY

Endexo formulations have been developed for a wide range of materials, including implant-grade silicone, possibly signaling a future in the development of subdural drains and silicone hydrocephalus shunts, including component valves and reservoirs. In the future, Endexo-enhanced shunts and components may achieve fewer obstructions due to decreased protein adsorption, reduced thrombus, and/or diminished tissue ingrowth. It is hypothesized that silicone shunt components with the Endexo additive may achieve lower rates of tissue adhesion and colonization due to the Endexo molecule's low bioreactivity.

CONCLUSION

The Codman CerebroFlo EVD Catheter with Endexo Technology is the first-of-its-kind EVD catheter with the potential to inherently reduce EVD catheter obstructions and associated complications.

Codman plans to introduce future device developments incorporating Endexo technology – hydrocephalus shunts, subdural drains, and other CNS catheters to become the new standard of care in CSF management for making a difference in the clinical management of your patients.

CODMAN CEREBROFLO EVD CATHETER WITH ENDEXO TECHNOLOGY

Kit contains the CerebroFlo EVD Catheter, stylet, barbed Luer connector, suture clip, male Luer cap, and trocar.

Indications for Use

The CerebroFlo EVD Catheter is indicated for temporary insertion into a ventricular cavity of the brain for external drainage of cerebrospinal fluid (CSF) in those patients with elevated intracranial pressure (ICP), intraventricular hemorrhage, or hydrocephalic shunt infections.

Caution

Federal law restricts this device to sale by or on the order of a physician.

For complete information on indications, contraindications, etc, see Directions for Use.

Contraindications

- This device is not designed, sold, or intended for use except as indicated.
- The ventricular catheter is contraindicated if scalp infection is present.
- A patient undergoing external drainage and monitoring must be kept under continuous, close supervision. The use of a ventricular drainage catheter is contraindicated where trained personnel are not available to supervise monitoring and drainage on a 24-hour-a-day basis.
- The ventricular catheter is contraindicated for use longer than 21 days.
- Insertion of the ventricular catheter is contraindicated in patients with coagulopathy due to prior administration of anticoagulants or antithrombotic, or who are known to have a bleeding diathesis. Coagulopathy should be corrected according to institutional protocols before insertion of an EVD.

REFERENCES

1. Crites L. Reducing catheter-related complications with new anti-thrombogenic PICC. JAVA. 2015;20(4):256.
2. McDiarmid S, Scrivens N, Carrier M, et al. Outcomes in a nurse-led peripherally inserted central catheter program: a retrospective cohort study. CMAJ Open. 2017;5(3):E535-E539.
3. Sustar L, Kertesz M. Anti-thrombogenic non-eluting polyurethane PICC vs. conventional polyurethane PICC upper extremity DVT rate. The Association for Vascular Access 2013 Annual Scientific Meeting; 2013; Nashville, TN.
4. Lareau R, Facchini F. A new option for short- or long-term peripheral access to the central venous system: a product technology overview of the BioFlo PICC with Endexo Technology, with and without PASV valve technology. AngioDynamics, Inc.; 2014.
5. Tang YW, Santerre JP, Labow RS, Taylor DG. Use of surface-modifying macromolecules to enhance the biostability of segmented polyurethanes. J Biomed Mater Res. 1997;35(3):371-381.
6. McCloskey CB, Yip CM, Santerre JP. Effect of fluorinated surface-modifying macromolecules on the molecular surface structure of a polyether poly(urethane urea). Macromolecules. 2002;35(3):924-933.
7. Ho JY, Matsuura T, Santerre JP. The effect of fluorinated surface modifying macromolecules on the surface morphology of polyethersulfone membranes. J Biomater Sci Polym Ed. 2000;11(10):1085-1104.
8. Jahangir AR, McClung WG, Cornelius RM, McCloskey CB, Brash JL, Santerre JP. Fluorinated surface-modifying macromolecules: modulating adhesive protein and platelet interactions on a polyether-urethane. J Biomed Mater Res. 2002;60(1):135-147.
9. Massa TM, Yang ML, Ho JY, Brash JL, Santerre JP. Fibrinogen surface distribution correlates to platelet adhesion pattern on fluorinated surface-modified polyetherurethane. Biomaterials. 2005;26(35):7367-7376.
10. Schmidt DR, Waldeck H, Kao J. Protein adsorption to biomaterials. In: Biological Interactions on Materials Surfaces. New York: Springer; 2009:1-18.
11. Xu LC, Bauer JW, Siedlecki CA. Proteins, platelets, and blood coagulation at biomaterial interfaces. Colloids Surf B Biointerfaces. 2014;124:49-68.
12. Hu WJ, Eaton JW, Ugarova TP, Tang L. Molecular basis of biomaterial-mediated foreign body reactions. Blood. 2001;98(4):1231-1238.
13. Dalvi VH, Rossky PJ. Molecular origins of fluorocarbon hydrophobicity. PNAS. 2010;107(31):13603-13607.
14. Krafft MP, Riess JG. Perfluorocarbons: Life sciences and biomedical uses dedicated to the memory of Professor Guy Ourisson, a true renaissance man. J Polym Sci. 2007;45(7):1185-1376.
15. Lopez-Donaire ML, Santerre JP. Surface modifying oligomers used to functionalize polymeric surfaces: Consideration of blood contact applications. J Appl Polym Sci. 2014;131(14):40328.
16. Massa TM, McClung WG, Yang ML, Ho JY, Brash JL, Santerre JP. Fibrinogen adsorption and platelet lysis characterization of fluorinated surface-modified polyetherurethanes. J Biomed Mater Res A. 2007;81(1):178-185.
17. Sukavaneshvar S. Device thrombosis and pre-clinical blood flow models for assessing antithrombogenic efficacy of drug-device combinations. Adv Drug Deliv Rev. 2017;112:24-34.
18. Chopra V, O'Horo JC, Rogers MA, Maki DG, Safdar N. The risk of bloodstream infection associated with peripherally inserted central catheters compared with central venous catheters in adults: a systematic review and meta-analysis. Infect Control Hosp Epidemiol. 2013;34(9):908-918.

i. Full hemocompatibility testing results available in Arkis BioSciences CerebroFlo EVD catheter ISO 1099 biocompatibility test reports.

ii. Arkis X-ray Photon Spectroscopy (XPS) analysis of CerebroFlo EVD Catheters demonstrated fluorinated end groups present at extruded and cut catheter surfaces.

iii. Arkis Albumin deposition study, December 2016. The study showed a 58% reduction in the adsorption of albumin onto the CerebroFlo EVD catheter compared to a competitive EVD catheter.

iv. See Appendix A.

v. See Appendix B.

APPENDIX A: CEREBROFLO EVD CATHETER BLOOD LOOP TESTING

Overview

The in vitro thrombogenic characteristics of a market-leading EVD catheter and the CerebroFlo EVD Catheter were compared in a head-to-head in vitro blood loop experiment. Fresh bovine blood was circulated over the catheter surfaces, and the relative thrombus accumulation was quantified by counting the gamma rays emitted by radiolabeled platelets.

Experimental Procedure – Test Articles

A market-leading 10Fr (3.3 mm) diameter silicone EVD, Competitor A, was compared to the CerebroFlo EVD Catheter (also 10 Fr diameter). All catheters used in this experiment were new and sterile packaged (ethylene oxide sterilized by their respective manufacturers), and were within their use-by date at the time of the experiment.

Both catheter types were cut to 15 cm in length to fit within the blood loop experimental setup. The open ends of the catheters were sealed with epoxy to facilitate assessment of thrombosis on the exterior catheter surface. Each catheter was placed in a section of 6.4 mm ID PVC tubing (one catheter type per tubing section), and each tubing section placed into a peristaltic pump.

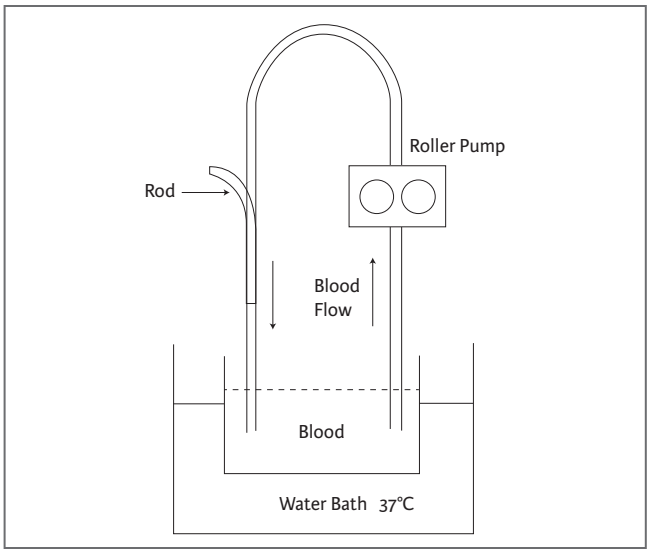
Experimental Procedure – Preparation of Bovine Blood

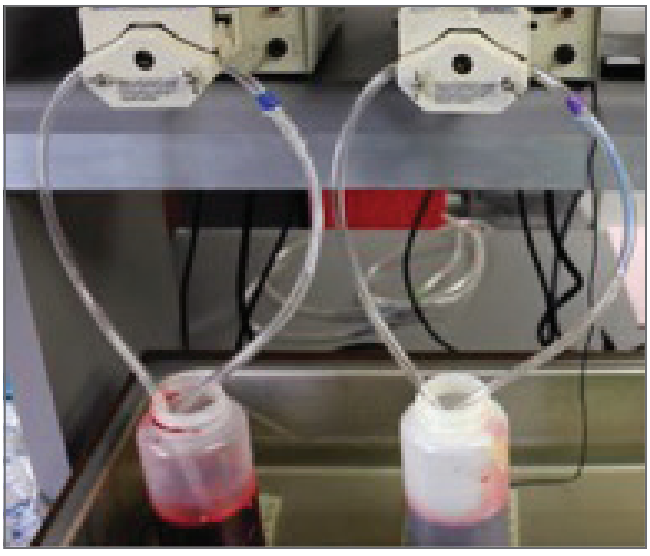
For every experimental replicate, fresh bovine blood was collected from one animal in a bag prefilled with heparin (ie, blood was collected from a different animal for each experimental replicate).

Platelets were extracted from 200 ml of whole blood via centrifugation. The extracted platelets were suspended in saline solution and exposed for 30 minutes to radioactive Indium-111 oxine. The radiolabeled platelets were returned to the blood, and the blood was thoroughly mixed, filtered to remove particulates, and divided into portions for each catheter type tested. Thus, within each replicate, the Competitor A catheter and the CerebroFlo EVD catheter were exposed to identically prepared blood from the same animal.

Experimental Procedure – Blood Circulation

One Competitor A and one CerebroFlo EVD catheter were tested per experimental replicate. Blood was circulated through the PVC tubes around the surface of the catheters at a flow rate of 200 ml/min using two independent peristaltic pumps (see Figure 1 below). Periodically, the flow was stopped, and the catheters were visually inspected for thrombus formation. Flow continued until one of the catheters was observed to have significant thrombus formation. The PVC tubing was then cut to remove the catheters, and the catheters were gently rinsed with normal saline to remove any nonadhered blood.





Kit containing the CerebroFlo EVD Catheter, stylet, barbed Luer connector, suture clip, male Luer cap, and trocar.

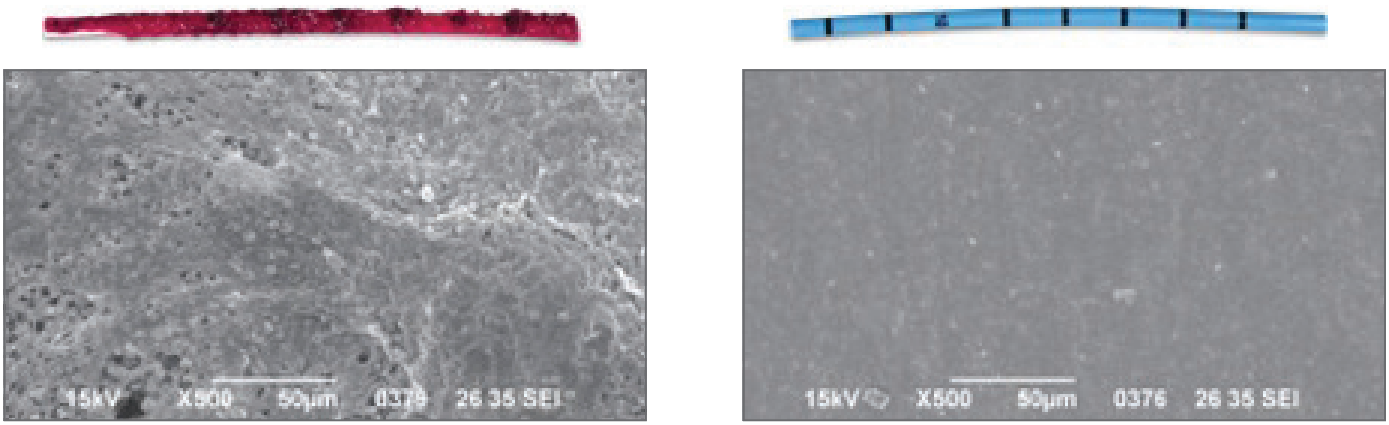
Experimental Procedure – Thrombus Quantification

The catheters were photographed and 2 cm of the catheter at the insertion site and 0.5-1 cm at the tip were cut off to exclude any edge effects during the radiation analysis. The trimmed catheters were then cut into shorter lengths, placed in vials, and placed in a Perkin Elmer gamma counter.

The Indium-111 oxine labeled platelets incorporated into the thrombus matrix on each sample emit gamma rays as the Indium-111 oxine radioactively decays to ^{111}Cadmium. Because each catheter within a replicate was exposed to identical radiolabeled blood, the number of gamma rays emitted by each sample gives a quantitative measure of the amount of thrombus on each sample. The number of gamma rays emitted by each sample was counted for 5 minutes.

Results

Figure 2 shows representative posttest photographs and SEM images of the Competitor A and CerebroFlo EVD catheters from one experimental replicate (Replicate 11).



Competitor A **CerebroFlo EVD with Endexo Technology**

Figure 2: Posttest photographs and 500X magnification scanning electron micrograph (SEM) images of the Competitor A and CerebroFlo EVD Catheter from experimental Replicate 11.

Table 1 lists the gamma ray counts collected over a time period of 5 minutes from each sample. The natural variability of the clotting response from animal to animal influences the thrombus accumulation (eg, the gamma ray count) from replicate to replicate. Some animals have a more (Replicate 6) or less (Replicate 2) aggressive coagulatative response.

However, within a replicate, the same animal's blood is used, the same experimental conditions are used, and the same length of 10 Fr diameter catheter is used in the Competitor A and CerebroFlo samples. Thus, any difference between the Competitor A and CerebroFlo gamma count within a specific replicate is due to differences in the catheter materials' thrombogenic characteristics.

Taking the Competitor A catheter as the reference device, the relative amount of thrombus between the two devices in each replicate is calculated as:

$$\%\ of\ Competitor\ A\ \gamma\ count = 100 \times \left(\frac{\gamma\ count}{Competitor\ A\ \gamma\ count} \right)$$

In this manner, the thrombus accumulation is normalized by the thrombus accumulated (as measured by gamma count) on the Competitor A reference device in each replicate. As shown in Table 1, this normalization gives Competitor A a normalized score of 100% in each replicate, and the CerebroFlo EVD Catheter is given a score that is the relative % of thrombus accumulated as compared to Competitor A.

Table 1: Gamma ray counts collected in 5 minutes from radiolabeled platelets adhered to each sample.

	Gamma Ray Count		% of Competitor A Gamma Count	
Replicate	*Competitor A*	*CerebroFlo*	*Competitor A*	*CerebroFlo*
1	31498	271	100	0.86
2	2795	41	100	1.47
3	8555	145	100	1.69
4	62566	181	100	0.29
5	14220	48	100	0.34
6	128739	2478	100	1.92
7	10190	347	100	3.41
8	28076	37	100	0.13
9	21639	351	100	1.62
10	44710	66	100	0.15
11	11848	21	100	0.18
12	9976	36	100	0.36
13	37672	36	100	0.10
		Average	100	0.96
		Standard Deviation	0	1.00

After normalizing each replicate by the Competitor A catheter gamma count, the relative percentage difference between the thrombus on the Competitor A catheter and the CerebroFlo Catheter is determined by the material's thrombogenic characteristics. As shown in Table 1, the CerebroFlo EVD Catheter accumulated an average of 0.96% of the thrombus accumulated on Competitor A. In other words, the CerebroFlo EVD Catheter had an average 99% reduction in thrombus accumulation when compared to Competitor A.

Summary

The CerebroFlo EVD Catheter demonstrated a 99% reduction in thrombus accumulation compared to an equally sized competitive catheter. While this study does not address in vivo catheter obstruction, it does demonstrate that the CerebroFlo EVD Catheter material with Endexo additive achieved significantly lower thrombus accumulation in vitro when directly compared to the Competitor A catheter.

APPENDIX B: CEREBROFLO EVD CATHETER IN VITRO OBSTRUCTION TESTING

Overview

The in vitro thrombogenic characteristics of a market-leading EVD catheter (Competitor A) and a market-leading EVD catheter with antibiotics (Competitor B) were compared to the CerebroFlo EVD Catheter in a head-to-head in vitro simulation of intraventricular hemorrhage (IVH) drainage. A mixture of 50% simulated cerebrospinal fluid (CSF) and 50% ovine blood was drained from 50 ml reservoirs (representing ventricles) using the CerebroFlo EVD Catheter and one of the Competitor catheters. The drainage continued until one of the catheters became occluded.

Experimental Procedure – Test Articles

Competitor A and Competitor B are market-leading 10 Fr (3.3 mm) outer diameter, 1.9 mm lumen diameter, silicone EVD catheters. Competitor B is additionally impregnated with the antibiotics clindamycin and rifampin. Competitor A and Competitor B were compared to the CerebroFlo EVD Catheter with Endexo Technology (also 10 Fr diameter with 1.9 mm lumen). All catheters used in this experiment were new and sterile-packaged by their respective manufacturers.

Experimental Procedure – Preparation of Ovine Blood + Simulated CSF

Blood was collected from sheep one to three days prior to the execution of each experiment. The blood was collected in 1-L containers and mixed with anticoagulant citrate dextrose (ACD) solution-A USP to prevent coagulation during transport.

The blood was mixed in a 50:50 volume ratio with simulated CSF. This was formulated to have the same osmolarity, inorganic salts, and major metabolites as human CSF (see Table 2). Within each experiment, one Competitor EVD catheter (A or B) and one CerebroFlo EVD Catheter were exposed to identically prepared aliquots of simulated CSF + blood.

Table 2: Constituents of Simulated CSF.

Constituent	Units	Concentration
Osmolarity	mOsm/L	295
Water	%	99%
Sodium	mEq/L	138
Potassium	mEq/L	2.8
Chloride	mEq/L	119
Calcium	mEq/L	2.1
Glucose	mg/dl	60
Lactate	mEq/L	1.6
Pyruvate	mEq/L	0.08

In experiments G–Z, additional $CaCl_2$ was added to each sample to achieve an activated clotting time (ACT) of 132 to 188 seconds. It was found that simulated-CSF + ovine blood with an ACT in this range would be sufficiently recalcified to exhibit a material-mediated thrombotic response while not autocoagulating in the drainage reservoirs or downstream tubing.

Experimental Procedure – Simulated CSF + Blood Drainage

Two fluid flow systems were tested: peristaltic pump-driven flow, and gravity-fed flow. Both models attempted to replicate clinical management of EVDs. The pump-driven flow (volumetric flow rate control) aimed to simulate a clinician prescribing a desired drainage rate and adjusting the EVD collection bag height (e.g. pressure) to achieve that desired rate. The gravity-fed flow model aimed to simulate a clinician setting the EVD collection bag height (e.g. pressure) and monitoring the volume of CSF drained at that pressure over time. Both systems had drainage rates of 12-18 ml/hour.

Blood was drained from 50 ml centrifuge tubes through the catheter flow holes, catheter lumens, PVC tubing, and into collection reservoirs. The centrifuge tubes were placed on an orbital shaker operating at 70 rpm to provide gentle agitation of the simulated-CSF + blood mixture. Additionally, in experiments G – Z the reservoirs and the downstream drainage tubes were maintained at 37°C to provide a more robust material-mediated thrombotic response and to prevent autocoagulation of the blood.

Drainage continued until one of the catheters was observed to have a significant drop in flow rate (>60% decrease in volumetric flow rate). The time recorded was the time at which the samples were removed from the experiment due to one of the catheter's flow being significantly reduced. At the study endpoint, the downstream PVC tubing was checked for obstructions to ensure that the flow was indeed reduced or stopped by occlusion of the catheter.

Results

A total of 26 experimental comparisons were completed: 3 with peristaltic pump-driven flow and 23 with gravity-fed flow.

In the 3 peristaltic pump-driven experiments (experiments A – C), Competitor A was compared to the CerebroFlo EVD Catheter. In all three cases, the Competitor A catheters became occluded, while the CerebroFlo EVD Catheter remained patent (see Table 3). However, it was observed that the pump could generate pressure that significantly exceeded physiological pressures. Consequently, subsequent experiments (D – Z) employed gravity-fed flow.

Table 3: Times at the end of the study for pump-driven experimental experiments comparing Competitor A and the CerebroFlo EVD Catheter. (Note: RT = room temperature.)

Sample ID	*Flow Type (Pump/Gravity)*	*Temperature*	*Competitor A Occluded?*	*CerebroFlo EVD with Endexo Technology Occluded?*	*Time at End of Study*
A	Pump	RT	YES	NO	8 Hours, 38 Minutes
B	Pump	RT	YES	NO	10 Hours, 0 Minutes
C	Pump	RT	YES	NO	5 Hours, 40 Minutes

The remaining 23 experiments were performed using the gravity-fed flow model. The gravity-fed flow model was found to give more clinically relevant drainage pressures of 13.5 +/- 2.6 cm-H20, as well as a clinically relevant flow rate of 12-18ml/hr. Additionally, it was observed that the simulated-CSF + blood mixture's material mediated thrombotic response was slower and more prone to autocoagulation at room temperature (experiments D – F) than at 37°C (experiments G–Z).

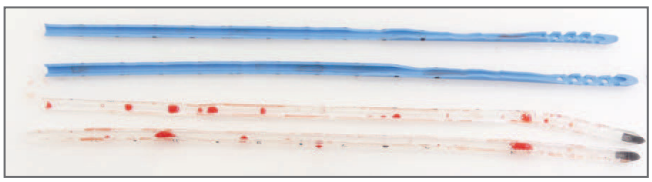
Even with the drainage system maintained at 37°C and the simulated-CSF + blood mixture's ACT controlled (experiments G – Z), the time to obstruction varies from experiment to experiment because of natural variability in coagulative response from animal to animal. In experiments G – Z the occlusion times ranged from 17 minutes in more reactive animals to more than 4 hours in less reactive animals.

Twelve gravity-fed experiments (D – O) compared Competitor A to the CerebroFlo EVD Catheter. In all 12 experiments, the Competitor A catheter occluded first, while the CerebroFlo EVD Catheter remained patent (see Table 4).

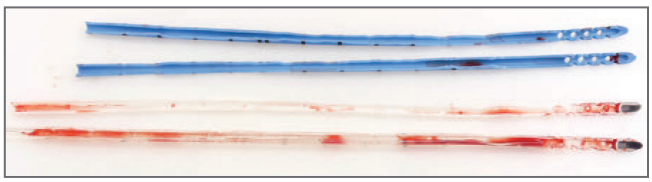
Eleven gravity fed experiments (P through Z) compared the Competitor B EVD catheter to the CerebroFlo EVD Catheter. In 10 out of 11 experiments, the Competitor B catheter occluded first, while the CerebroFlo EVD Catheter remained patent (see Table 5). In one case (experiment X), the CerebroFlo EVD Catheter stopped flowing first, though only a small amount of thrombus could be observed in the CerebroFlo EVD Catheter lumen and on the exterior of the catheter around the flow holes (see Figure 5).

Table 4: Times at the end of the study for gravity-fed experimental experiments comparing Competitor A and the CerebroFlo EVD Catheter. (Note: RT = room temperature.)

Sample ID	*Flow Type (Pump/Gravity)*	*Temperature*	*Competitor A Occluded?*	*CerebroFlo EVD with Endexo Technology Occluded?*	*Time at End of Study*
D	Gravity	RT	YES	NO	6 Hours, 16 Minutes
E	Gravity	RT	YES	NO	3 Hours, 20 Minutes
F	Gravity	RT	YES	NO	15 Hours, 17 Minutes
G	Gravity	37°C	YES	NO	50 Minutes
H	Gravity	37°C	YES	NO	1 Hour, 9 Minutes
I	Gravity	37°C	YES	NO	49 Minutes
J	Gravity	37°C	YES	NO	3 Hours, 40 Minutes
K	Gravity	37°C	YES	NO	4 Hours, 10 Minutes
L	Gravity	37°C	YES	NO	3 Hours, 13 Minutes
M	Gravity	37°C	YES	NO	21 Minutes
N	Gravity	37°C	YES	NO	18 Minutes
O	Gravity	37°C	YES	NO	17 Minutes



Experiment J - 3 Hours, 40 Minutes



Experiment M - 21 Minutes

Figure 3: Representative posttest images of sectioned catheters posttest. CerebroFlo is pictured at top of images, and Competitor A pictured at bottom of images.

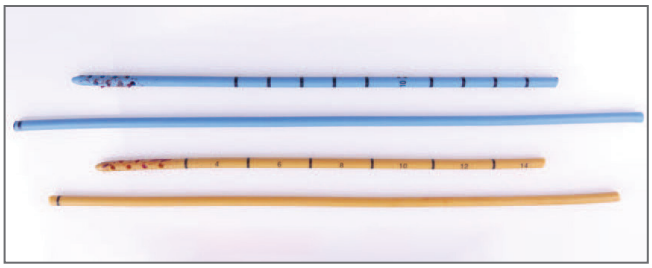
Table 5: Times at the end of the study for gravity-fed experimental experiments comparing Competitor B and the CerebroFlo EVD Catheter.

Sample ID	*Flow Type (Pump/Gravity)*	*Temperature*	*Competitor B Occluded?*	*CerebroFlo EVD with Endexo Technology Occluded?*	*Time at End of Study*
P	Gravity	37°C	YES	NO	53 Minutes
Q	Gravity	37°C	YES	NO	1 Hour, 0 Minutes
R	Gravity	37°C	YES	NO	30 Minutes
S	Gravity	37°C	YES	NO	35 Minutes
T	Gravity	37°C	YES	NO	30 Minutes
U	Gravity	37°C	YES	NO	1 Hour, 36 Minutes
V	Gravity	37°C	YES	NO	1 Hour, 37 Minutes
W	Gravity	37°C	YES	NO	2 Hours, 15 Minutes
X	Gravity	37°C	NO	YES	52 Minutes
Y	Gravity	37°C	YES	NO	55 Minutes
Z	Gravity	37°C	YES	NO	49 Minutes

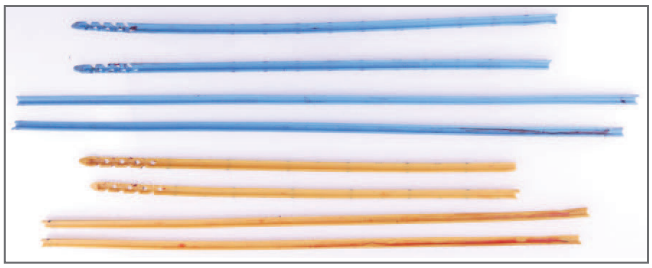
Experiment U–1 Hour, 36 Minutes

Experiment T–30 Minutes

Figure 4: Representative posttest images of sectioned catheters posttest. CerebroFlo is pictured at top of images, and Competitor B pictured at bottom of images.



Experiment X – Prior to Sectioning



Experiment X – After Sectioning

Figure 5: Posttest images of experiment X, in which the CerebroFlo EVD catheter was the first to obstruct. The CerebroFlo EVD catheter is pictured at the top of images, and Competitor B pictured at bottom of images.

Statistical Analysis

For the gravity-fed flow models, binomial confidence intervals were used to estimate the probability that one of the catheters would become obstructed first in this head-to-head comparative in vitro model of IVH drainage. Fisher's exact test was also used to determine if the difference in the observed proportion of obstructed catheters was significant for each group tested.

The statistics were calculated for both head-to-head comparisons performed using the gravity-fed flow model (Competitor A vs the CerebroFlo EVD Catheter, and Competitor B vs the CerebroFlo EVD Catheter). The results of these statistical calculations are reported in Table 6.

Experiments D – F and G – O comparing Competitor A and the CerebroFlo EVD Catheter were collected under the same flow conditions, and consequently were pooled for the statistical analysis in Table 6. Finally, it is recognized that all gravity-fed experiments (D – Z) compared silicone EVDs with similar geometries to the CerebroFlo EVD Catheter. Pooling all of the gravity-fed experiments gives an estimate of the relative probability of obstruction for silicone catheters vs the CerebroFlo EVD Catheter with the Endexo additive (See Table 6) under the reported in vitro test conditions.

In all head-to-head comparisons reported in Table 6, the CerebroFlo EVD Catheters were significantly less likely to obstruct than the Competitor A and B EVD catheters (Fisher's exact test, $P < 0.001$). Considering the pooled data for Competitors A and B vs the CerebroFlo EVD Catheter (experiments D-Z, n=23), a typical obstruction rate of 89.0% for Catheters A and B and 11.0% for the CerebroFlo EVD Catheter can be estimated from the center of the binomial confidence intervals. Thus, the CerebroFlo EVD Catheter is approximately 8x less likely to become obstructed than the Catheters A and B in this in vitro model of IVH drainage.

Table 6: Binomial confidence intervals and Fisher's exact test results for the rate of obstruction in each head-to-head comparison.

Comparison	*Catheter Type*	*Probability of Obstruction*			*Fisher's Exact Test P-value*
		95% CI Lower Limit	*95% CI Center*	*95% CI Upper Limit*	
Competitor A vs CerebroFlo EVD Catheter (experiments D-O, n=12)	Competitor A	0.735	0.868	1.000	< 0.001
	CerebroFlo EVD catheter	0.000	0.132	0.265	
Competitor B vs CerebroFlo EVD Catheter (experiments P-Z, n=11)	Competitor B	0.587	0.792	0.998	< 0.001
	CerebroFlo EVD catheter	0.002	0.208	0.413	
Competitors A and B vs CerebroFlo EVD Catheter (experiments D-Z, n=23)	Competitors A and B	0.781	0.890	0.999	< 0.001
	CerebroFlo EVD catheter	0.001	0.110	0.219	

Summary

In this in vitro flow study, modeling an intraventricular hemorrhage, the data reveal that the CerebroFlo EVD Catheter with Endexo Technology remained substantially more patent than equally sized competitive silicone EVD catheters with and without antibiotic impregnation.

Availability of these products might vary from a given country or region to another, as a result of specific local regulatory approval or clearance requirements for sale in such country or region.
- Non contractual document. The manufacturer reserves the right, without prior notice, to modify the products in order to improve their quality.
- Warning: Applicable laws restrict these products to sale by or on the order of a physician.
- Consult product labels and inserts for any indication, contraindications, hazards, warnings, precautions, and instructions for use.

For more information or to place an order, please contact:

United States, Canada, Asia, Pacific, Latin America
USA 800-654-2873 ▪ 888-980-7742 fax
International +1 609-936-5400 ▪ +1 609-750-4259 fax
integralife.com

INTEGRA®
LIMIT UNCERTAINTY

Printed in USA. 0M 1401368-2-EN