CerebroFlo™ EVD Catheter with Endexo® Technology

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I. Introduction

Arkis BioSciences® CerebroFlo™ EVD Catheter with Endexo® Technology

Arkis BioSciences 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 510k cleared, Arkis has studied the CerebroFlo EVD Catheter 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 catheters patency.

- Established in clinical use for multiple other medical applications. The anti-thrombogenic 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 56-80% reduction in complications from venous thrombosis [2, 3].

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

- Anti-thrombogenic properties via passive material modification.
- Permanent integration onto all surfaces – enhancements which do not diminish with time.
- Inhibition of biomatter accumulation onto catheter surfaces.

Arkis BioSciences has introduced the Endexo polymer to CSF drainage systems with the CerebroFlo™ EVD Catheter

- Large-gauge (10Fr), 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 makes 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].
- Molecules provide a passive surface that reduces adhesion/activation of blood proteins and components, thereby reducing thrombus formation.
II. 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, 6, 7] resulting in a biologically-passivated surface which reduces protein adsorption [5, 8], 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.

When proteins in CSF 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 anti-thrombotic agent: it does not elute from the catheter and does not alter the coagulative properties of the blood. Rather, Endexo is a non-thrombotic, i.e. non-reactive, compound that passivates the surface properties of the catheter, making protein adhesion less likely.

Figure 1: The Endexo® molecule

Figure 2: Endexo Catheter Surface compared to a Conventional Catheter Surface.
III. 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 Arkis 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)

1. 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.

2. Flow Characterization of In-Vitro Obstruction in Simulated CSF + Blood:

In initial in-vitro studies, the CerebroFlo EVD Catheter’s anti-thrombogenic 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 six 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.

Sectioned catheters from Sample E, see APPENDIX B for further study details.
IV. Clinical Case Reports

1. Ruptured Arteriovenous Malformation (AVM) Treated with Arkis BioSciences CerebroFlo EVD Catheter with Endexo Technology

An 18 year-old male was transferred to a Level I trauma center from an outside institution, intubated and poorly responsive. CT revealed a left parieto-occipital parenchymal hemorrhage with extensive intraventricular hemorrhage and associated hydrocephalus. A right frontal ventriculostomy was placed, using Arkis’ CerebroFlo EVD Catheter with Endexo, 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 Arkis 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.

2. Ruptured Mycotic Aneurysm Treated with Arkis BioSciences 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 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.
V. Endexo® Additive – Future Directions in Neurosurgery

The biological passivation achieved through Endexo technology has great potential in the development of CNS devices beyond EVD catheters. Clinical data suggests that the Endexo polymer may lead to reduced rates of catheter-associated infections. Clinical data from a single center study of 8,314 PICC catheters demonstrated an 86% reduction in catheter-associated blood stream infections for PICC catheters with the Endexo additive [2] compared to historical PICC catheter infection rates [18]. Locked into the polymer matrix, the Endexo molecule does not elute over time. Additionally, because the Endexo additive does not alter the base polymer, bioactive compounds such as antibiotics could be added to produce antimicrobial and anti-thrombogenic devices.

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 in-growth. 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.

VI. Conclusion

The Arkis 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. Arkis BioSciences 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.
References


1 Full hemocompatibility testing results available in Arkis BioSciences CerebroFlo EVD catheter ISO 1099 biocompatibility test reports.
2 Arkis X-ray Photon Spectroscopy (XPS) analysis of CerebroFlo EVD Catheters demonstrated fluorinated end groups present at extruded and cut catheter surfaces.
3 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.
4 See APPENDIX A.
5 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 10Fr diameter). All catheters used in this experiment were new, 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 pre-filled with heparin (e.g. blood was collected from a different animal for each experimental replicate).

Platelets were extracted from 200ml of whole blood via centrifugation. The extracted platelets were suspended in saline solution, and exposed for 30 minutes to radioactive 111Indium 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 200ml/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 non-adhered blood.

Figure 1: The in-vitro test model. Each experiment consisted of two such independent flow systems (each containing one device) circulating blood from the same animal.

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 111Indium Oxine labeled platelets incorporated into the thrombus matrix on each sample emit gamma rays as the 111Indium radioactively decays to 111Cadmium. 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 were counted for 5 minutes.

Results

Figure 2 shows representative post-test photographs and SEM images of the Competitor A and CerebroFlo EVD catheters from one experimental replicate (replicate 11).
Figure 2: Post-test 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 (e.g. 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:

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

After normalizing each replicate by the Competitor A catheter gamma count, the relative percentage difference between the thrombus on Competitor A and 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.

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

<table>
<thead>
<tr>
<th>Replicate</th>
<th>Competitor A</th>
<th>CerebroFlo</th>
<th>% of Competitor A Gamma Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34498</td>
<td>271</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>2795</td>
<td>41</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>8555</td>
<td>145</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>62566</td>
<td>181</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>14220</td>
<td>48</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>128739</td>
<td>2478</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>10190</td>
<td>347</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>28076</td>
<td>37</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>21639</td>
<td>351</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>44710</td>
<td>66</td>
<td>100</td>
</tr>
<tr>
<td>11</td>
<td>11848</td>
<td>21</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>9976</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>37672</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>100</strong></td>
<td><strong>0.96</strong></td>
<td></td>
</tr>
</tbody>
</table>

The Arkis 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: Initial CerebroFlo EVD Catheter In-vitro Obstruction Testing

Overview

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

Experimental Procedure – Test Articles

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

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 93.5 mL anticoagulant citrate dextrose (ACD) solution-A USP to prevent coagulation during transport.

The blood was then mixed in a 50%-50% volume ratio with simulated cerebrospinal fluid (CSF). This was formulated to have the same osmolarity, inorganic salts, and major metabolites as human CSF (see table below). Within each experimental replicate, the Competitor A and CerebroFlo catheters were exposed to identically prepared aliquots of simulated CSF + Blood.

Table 2: Constituents of Simulated CSF.

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Units</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolarity</td>
<td>mOsm/L</td>
<td>295</td>
</tr>
<tr>
<td>Water</td>
<td>%</td>
<td>99%</td>
</tr>
<tr>
<td>Sodium</td>
<td>mEq/L</td>
<td>138</td>
</tr>
<tr>
<td>Potassium</td>
<td>mEq/L</td>
<td>2.8</td>
</tr>
<tr>
<td>Chloride</td>
<td>mEq/L</td>
<td>119</td>
</tr>
<tr>
<td>Calcium</td>
<td>mEq/L</td>
<td>2.1</td>
</tr>
<tr>
<td>Glucose</td>
<td>mg/dl</td>
<td>60</td>
</tr>
<tr>
<td>Lactate</td>
<td>mEq/L</td>
<td>1.6</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>mEq/L</td>
<td>0.08</td>
</tr>
</tbody>
</table>

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 the case in which a clinician prescribes a desired drainage rate, and adjusts the EVD collection bag height (e.g. pressure) to achieve that desired rate. The gravity fed flow model aimed to simulate the case in which a clinician sets the EVD collection bag height (e.g. pressure) and monitors the CSF drainage at that pressure over time. Both systems had drainage rates of 12-15 ml/hour.

Blood was drained from 50 ml centrifuge tubes, through the catheter flow holes, catheter lumens, through PVC tubing, and into collection reservoirs. The centrifuge tubes were placed on an orbital shaker operating at 70 R.P.M. to provide gentle agitation of the simulated-CSF + blood mixture.

Drainage continued until one of the catheters was observed to have significant thrombus combined with a significant drop in flow rate. The time recorded was the time at which the samples were removed from the experiment (e.g. one of the catheters flow was significantly reduced/obstructed). The time to obstruction varies from replicate to replicate because of the natural variability in coagulative response from animal to animal.

At the study endpoint, the downstream small-bore tubing was checked for obstruction to ensure that the flow was indeed reduced or stopped by occlusion of the catheter.

Results

A total of 6 experimental replicates were completed: 3 with peristaltic pump driven flow and 3 with gravity fed flow. In each case, the Competitor A catheter was occluded, while the CerebroFlo EVD Catheter remained patent.
Table 3: Last measured flow rate prior to occlusion and times at the end of study for experimental replicates reaching the study endpoint.

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Flow Type (Pump / Gravity)</th>
<th>Competitor A</th>
<th>CerebroFlo EVD with Endexo enhancement</th>
<th>Time at End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Last Measured Flow Rate as % of Initial Flow</td>
<td>Occluded?</td>
<td>Last Measured Flow Rate as % of Initial Flow</td>
</tr>
<tr>
<td>A</td>
<td>Pump</td>
<td>40%</td>
<td>YES</td>
<td>96%</td>
</tr>
<tr>
<td>B</td>
<td>Pump</td>
<td>0%</td>
<td>YES</td>
<td>100%</td>
</tr>
<tr>
<td>C</td>
<td>Pump</td>
<td>0%</td>
<td>YES</td>
<td>74%</td>
</tr>
<tr>
<td>D</td>
<td>Gravity</td>
<td>&lt;10%</td>
<td>YES</td>
<td>76%</td>
</tr>
<tr>
<td>E</td>
<td>Gravity</td>
<td>0%</td>
<td>YES</td>
<td>82%</td>
</tr>
<tr>
<td>F</td>
<td>Gravity</td>
<td>19%</td>
<td>YES</td>
<td>60%</td>
</tr>
</tbody>
</table>

Summary

In this initial in-vitro flow study, modeling an intraventricular hemorrhage, the data reveals that the Arkis CerebroFlo EVD Catheter with Endexo enhancement remained substantially more patent than an equally-sized competitive EVD catheter. Further study will build statistical significance to these results, which suggest that the Endexo material is significantly less prone to thrombogenic obstruction in-vitro than the equally sized Competitor A.

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