INTRODUCTION

Cerebral aneurysms are found in 45 million individuals worldwide, and approximately 30,000 patients in the United States suffer from subarachnoid hemorrhage annually. Following several clinical trials demonstrating the benefits of coil embolization, endovascular techniques
for aneurysm treatment have been increasingly applied to a wide array of both ruptured and unruptured aneurysms. For larger aneurysms and particularly those with wide-neck dome-to-neck \(d:n\) ratios, coil embolization still poses significant challenges. Thus, a number of adjunctive devices and novel treatment strategies have been introduced.\(^{29,31}\)

A new generation of liquid embolics, including PPODA-QT, may be particularly useful for difficult-to-treat aneurysms. In lieu of a porous network of coils or a metal mesh that only partially blocks flow in an aneurysm, PPODA-QT can completely fill the aneurysm volume with a mass that is both solid and stable.\(^6\) PPODA-QT may confer improved delivery control, vessel protection, and reduced recanalization rates in larger aneurysms with medium- to wide-necks [Figure 1].\(^{6,7,25}\)

Several parameters, including aneurysm dome height and \(d:n\) ratio, are widely used to classify difficult-to-treat aneurysms. For this study, dome height is categorized as small (<5 mm height), medium (5–10 mm height), large (10–25 mm height), and giant (>25 mm height).\(^{30}\) The \(d:n\) ratio is defined by the midline diameter of the aneurysm dome (d) divided by the major diameter of the aneurysm neck (n). For this study, these ratios are classified as small-neck (>2:1 \(d:n\) ratio – Figure 1a), medium-neck (2:1 to 1.33:1 \(d:n\) ratio – Figure 1b), wide-neck (1:1 to 1.33:1 \(d:n\) ratio – Figure 1c), and beyond wide-neck (< 1:1 \(d:n\) ratio – Figure 1d) aneurysms.\(^{4,6,9}\)

PPODA-QT is a water-based (no organic solvents), self-gelling, and non-adhesive device that exhibits superior mechanical properties and biocompatibility when compared to both metal devices and Onyx. A volume of PPODA-QT, equivalent to the volume of the aneurysm dome, is delivered and solidified in a short time-frame, without exposure to blood flow, under a single balloon inflation cycle. The result is a complete and cohesive occlusion without distal embolization, cytotoxic effects, or delivery catheter adherence to the vessel wall or to the device.\(^{6-8}\)

PPODA-QT is composed of liquid monomer precursors (polypropylene glycol and pentaerythritol tetrakis [3-mercapto-propionate]) delivered in a pH-titrated, injectable contrast media. When mixed, the components undergo rapid, self-contained cross-linking into a stable gel. This material exhibits a safer and faster polymerization than Onyx – which is reliant on elution of cytotoxic organic solvents into the blood stream as it slowly precipitates into a semi-solid mass while in contact with blood flow (resulting in a high risk of migration).\(^{6,7,15,19,21,23,28}\) Conversely, PPODA-QT gelation occurs in a predictable and controllable manner over a pre-set length of time.\(^{6,7,25}\) Under balloon protection, the viscous liquid can be delivered with the same microcatheters used for coil, stent, and flow diverter placement. Under angiography, the radiopaque gel coalesces to completely fill and conform to the aneurysm sac while blood is displaced between the delivery catheter and the inflated balloon. The liquid embolic properties of PPODA-QT and Onyx, referenced in this manuscript, are summarized for comparison in [Table 1].

Table 1: Comparison of liquid embolic properties referenced for PPODA-QT and Onyx-HD 500.

| Liquid embolic property | PPODA-QT | Onyx (HD 500) | Ref. |
|-------------------------|----------|----------------|-----|
| Solidification Mechanism | Self-contained, pH driven | Precipitation from blood exposure | [6,7,15,19] |
| Exothermic characteristics | Mild (below body temp.) | None | [6-8,19,21,27] |
| Delivery pH | Neutral (ph 7) | Neutral (pH 7) | [6-8,21,27] |
| Delivery Rate | Adjustable, up to 2 ml/min | Limited, 0.1 ml/min | [6,7,15,19] |
| Solidification Time | <10 min with balloon protection | ~10 min after balloon deflation | [6-8,19,27] |
| Migration Risk | None after solidification | High, during solidification | [6-8,15,21,27] |
| Adhesive (tissue or catheter) | Non-adhesive | Non-adhesive | [6,7,15,19] |
| Solvent Used | None | DMSO | [6,8,15,19,21] |
| Toxicity | None | Cytotoxic (DMSO) | [6-8,15,21] |
| % sac fill | >90% Typical | >80% Typical | [6-8,19] |

DMSO: Dimethyl sulfoxide

Figure 1: (a-d) Dimensional classification for small, medium, wide, and beyond-wide neck aneurysms.

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(<10 min) without unstable material migration, particulation, or balloon-induced ischemia.\(^{[6,8]}\)

The goal of this study was to further assess the efficacy of PPODA-QT by evaluating the tissue response following embolization of cerebral aneurysms using a well-characterized in vivo rabbit-elastase aneurysm model in preparation for a future FDA investigational device exemption (IDE) submission. In addition, the rabbit elastase aneurysm model was assessed for applicability with balloon-assisted endovascular device delivery.

MATERIALS AND METHODS

All animal study methods followed guidelines of, and were approved by, the Institutional Animal Care and Use Committees of Northern Arizona University (NAU – Flagstaff, AZ) and the Barrow Neurological Institute (BNI – Phoenix, AZ). A total of 14 New Zealand white rabbits (4-5 kg) were elastase-incubated and survived for at least 3 weeks to allow for aneurysm maturation. Eight initial rabbits were used to develop the model and assess final aneurysm dimensions through fluoroscopic imaging prior to animal terms. Six additional rabbits were enrolled to acquire aneurysm embolization survival and control data. All six rabbits underwent histological assessment. The well-established endovascular elastase incubation technique was employed to create the aneurysm models.\(^{[1,3,5,11]}\)

**Endovascular elastase incubation**

The right common carotid artery (RCCA) was exposed through a one-inch incision along the jugular groove, lateral to the thymus. A 5F introducer sheath was inserted in the artery with a 6-0 suture used to ligate the artery around the sheath. A 3F Fogarty balloon catheter was introduced through the sheath and inflated at the carotid’s origin. A 0.017” ID microcatheter, (SL-10\(^{6}\) - Stryker Neurovascular, Fremont, CA) cut to 12” long to reduce dead volume and fitted with a lure hub attachment (Nordson Medical, Minneapolis, MN), was also introduced through the sheath to deliver the elastase solution. For the endovascular technique, the elastase solution was mixed 3:1 with Isovue\(^{®}\) 370 liquid contrast to improve fluoroscopic visualization during injection. 0.3 mL of elastase solution, containing 50 U elastase (0.15 ml of lyophilized porcine elastase dissolved in sterile PBS, titrated to a pH of 9 with 1 M NaOH, and mixed with 0.15 ml of 0.5 M CaCl\(_2\)) was injected through the microcatheter.\(^{[9]}\) The elastase solution was left to incubate for 20 min. After the balloon and sheath were removed post-incubation, the carotid was ligated with the 6-0 suture at 30 mm distal to the carotid origin. Aneurysms were allowed to mature for a minimum of 3 weeks after elastase incubation.\(^{[1]}\)

The effects of elastase on the vessel wall after a 3-week maturation (acute control) and the effect of PPODA-QT (survival) on the elastase aneurysms were assessed by histological examination. Histology from acute, 1-month, and 3-month rabbit models was evaluated to assess the vessel integrity and tissue response following elastase incubation and PPODA-QT embolization (\(n = 6\)).

**PPODA-QT delivery technique**

PPODA-QT was delivered through a dual catheter delivery technique: microcatheter delivery (Velocity\(^{®}\) - Penumbra Inc., Alameda, CA) under balloon protection (Scepter-XC\(^{®}\) - Microvention Inc., Aliso Viejo, CA). A 5F introducer sheath was placed in the right femoral artery of the rabbit. When inserted directly into the 5F sheath, the introducer accommodated both the 2.6F Velocity microcatheter and the 3F Scepter balloon. This technique was used because it proved difficult to consistently place 5F or larger introducer sheaths in the small rabbit femoral or Iliac arteries without risking surgical-based complications for the survival studies. Dual femoral access with 4F or smaller introducers was avoided due to the risk of post-operative blood flow disruption to both legs of a survival rabbit.

The embolization procedure began with a 1–2 min mixing step by adding liquid contrast (Conray\(^{®}\)) at a pH of 10–11. The increase in pH initiates a mildly-exothermic reaction lasting 10 min (±30 s). The pH is self-contained in the gel, and benchtop pH testing of the PPODA-QT in a PBS solution (pH 6.5–7) showed a pH variation <2%. The resulting temperature increase is <10°C during the 10-min gelation (initiated at room temperature and remains below body temperature). Under balloon protection a PPODA-QT volume, equivalent to the aneurysm volume (determined by fluoroscopy and calculated with AngioCalc.com), was injected by hand in less than 2 min (max flow rate of 2 ml/min).\(^{[6,7]}\) Under angiography, the radiographically-visible gel coalesced to completely fill and conform to the aneurysm sac while blood was displaced between the delivery catheter and the inflated balloon. Self-contained, non-adhesive solidification was complete within 3 min after delivery. Subsequently, the microcatheter was removed (gel does not adhere to the catheter) under balloon protection. The balloon was then deflated and removed leaving a stable and uniform gel mass.\(^{[6-8,17,25]}\) Angiographic images were recorded post-embolization and at term.

**Histology preparation**

The rabbit RCCA elastase aneurysm tissues and left common carotid artery control tissues were harvested and fixed in a standard formalin solution. The samples were then placed in a tissue processor and paraffin-embedded. Tissues were sliced into 10 μm sections to provide a frontal view of the aneurysm and parent vessel. Serial sections of tissue were
stained with alternating hematoxylin and eosin (H & E) and Van Gieson stains.

The H & E staining procedure followed a standard protocol. For the Van Gieson stain, slide-mounted samples were saturated with Verhoeff’s hematoxylin, which contributed to a black appearance of elastin fibers and cell nuclei. Subsequently, the tissue was differentiated with ferric chloride, placed in the Van-Gieson counterstain to distinguish the collagen and muscle layers with red coloring, and dehydrated. All stained samples were viewed using a Zeiss Axio A1 light microscope and digitized with a Zeiss AxioCam MRc5 camera.

RESULTS

All aneurysms were created by incubating 30 mm of carotid vessel segment with elastase. However, all the aneurysms matured into small (<10 mm dome height) domes with beyond wide-necks (<1:1 d: n ratio) [Figure 1d and 2].

Although the aneurysms developed using this model did not match the desired larger sized (>10 mm dome height) aneurysms with medium- to wide-necks (>1.1:1 d: n ratios) intended for PPODA-QT injection [Figure 1a and b, Figure 2], PPODA-QT embolizations were nonetheless performed to validate the delivery technique and acquire biocompatibility data at 1-month and 3-month survival timepoints. Examples of radiographic delivery of PPODA-QT and post-embolization of an acute and a 3-month survival rabbit aneurysm model are provided [Figure 3a-d]. The resulting aneurysm dimensional data and the rabbit survival timepoints for the six treated aneurysms are displayed in [Table 2].

Histology results

Histological data from the control tissue displayed a unicellular layer of undisrupted tunica intima, evenly distributed elastin fibers throughout the tunica media, and a loosely-organized tunica adventitia [Figure 4a].

The cross-section of an H & E-stained acute control aneurysm, which matured for 3 weeks post-elastase incubation, exhibited no apparent tissue damage or immune response [Figure 4b]. Similarly, there was no evidence of cell lysis, injury, nor acute inflammation from the elastase incubation.

The 1- and 3-month aneurysm histology [Figure 4c and d, respectively] revealed areas of direct device contact with the aneurysm wall and neck. 1- and 3-month survivals also showed evidence of smooth muscle remodeling at the aneurysm wall. Tissue reorganization in response to the PPODA-QT was demonstrated by the condensed and linear grouping of cells adjacent to the material, likely improving stability of the embolized aneurysm lumen. There was no evidence of a chronic inflammatory response to PPODA-QT, indicated by the absence of Foreign Body Giant cells (FBGC). Further, there was no evidence of fibrosis or injury to the tunica media, which would present with architectural distortion and a patchy appearance of the tissue.
**Table 2: Rabbit aneurysm model dimensions with PPODA-QT treatment survival timepoints.**

| Survival timepoint | Figure reference | Aneurysm sizes (mm) | Dome:neck (d:n) ratio |
|--------------------|------------------|---------------------|---------------------|
|                    |                  | Dome height         | Midline diameter    | Neck                |
| Acute Control      | Figure 2a        | 5                   | 3.5                 | 3.8                 | 0.92               |
| Acute Control      | Figure 2b        | 9.6                 | 5.4                 | 7.8                 | 0.69               |
| 1 month            | Figure 2c        | 3.5                 | 1                   | 1.5                 | 0.67               |
| 1 month            | Figure 2d        | 7.5                 | 3                   | 3.5                 | 0.86               |
| 3 months           | Figure 2e        | 4.5                 | 2.5                 | 2.7                 | 0.93               |
| 3 months           | Figure 2f        | 3                   | 1.4                 | 1.5                 | 0.93               |

**Figure 4:** Rabbit arterial tissue for control, acute, 1-, and 3-month timepoints. (a) Arterial cross section from control rabbit, hematoxylin and eosin (H&E) at ×100. (b) Acute aneurysm wall after elastase injection, H&E (×300). (c) Rabbit aneurysm 1 month after embolization with arterial-PPODA-QT interface, H&E (×100). (d) Aneurysm wall 3 months after embolization with arterial-PPODA-QT interface (×100). (e) Aneurysm wall 3 months after embolization with arterial-PPODA-QT interface, Van Gieson (×100). (f) Neo-intimal aneurysm neck with displaced PPODA-QT artifact, H&E (×300).

The Van Gieson stain from the same 3-month tissue demonstrated a reorganization of the vessel wall. The more distal layer showed an organized, dense, and linear pattern of elastin while the proximal layer (at the aneurysm lumen) was less uniform and replaced by the reorganized smooth muscle layer [Figure 4e]. At the aneurysm neck a homogenous neo-intimal layer, measuring approximately 200–300 µm, formed at the PPODA-QT interface sealing off the parent vessel from the aneurysm dome [Figure 4f]. Similar to the response at the aneurysm wall, there was no evidence of FBGCs, fibrosis, or injury to the new tunica media at the neck region. It should also be noted that neo-intimal growth was not evident in either the control tissue or the acute aneurysms [Figure 3a and 3b, respectively].

**DISCUSSION**

Aneurysm size is a direct correlation to the risk of aneurysm rupture, and therefore large aneurysms are likely candidates for treatment. However, these larger aneurysms with medium- and wide-necks also suffer from an increased frequency of incomplete occlusion in the short-term and high recanalization rates in the long-term following endovascular treatment.[26,29,31] Embolization of aneurysms using PPODA-QT targets the treatment of these larger (>10 mm dome height) aneurysms with medium- to wide-neck d:n ratios [Figure 1b and c].

In recent years, rabbit elastase models have grown in popularity due to physiological similarities to humans, availability, and economic feasibility as an animal model. Although rabbit vessels do not scale to the human vasculature to the extent of canines and swine, they have a similar clotting cascade and healing process when compared to humans. The elastase aneurysm creation procedure has also been touted as less surgically invasive, potentially resulting in a more effective differentiation of the immune responses from the aneurysm surgery and the subsequent device implantation.[1,4,6,14] However, a major limitation of the rabbit-elastase model, as seen in this study, is the inability to consistently create medium, large, or giant aneurysm models (per size definitions in Figure 1). In addition, introduction and insertion of human-gauged guide wires and guide catheters are difficult into the small arteries of the rabbit, for example, the femoral artery. This situation is made even more difficult if embolization requires more than one endovascular device deployment, such as a microcatheter in the aneurysmal sac to deliver the device and a balloon catheter or stent to protect the aneurysm orifice. Moreover, endovascular introduction procedures often injure the small rabbit femoral artery, making follow-up access procedures inconvenient. In short, the rabbit vascular system, while useful for pilot studies, does not allow for uncomplicated or unmitigated success in procedure replication or translation of more involved endovascular procedures to the human condition. To better simulate more complex aneurysms and endovascular procedures, a larger vascular animal model with a similar healing response to humans is needed.[4,6,28]

In general, the response of arterial tissue to foreign bodies such as biomaterial devices is regulated by the device’s surface properties. The reaction occurs within the first 2–4 weeks after implantation and continues for the entire duration of the tissue-device interface.[10] Histological data of the rabbit aneurysms post-PPODA-QT embolization were therefore evaluated at 1- and 3-months. The initial histological data acquired, although not statistically robust,
suggests that PPODA-QT exhibits excellent biocompatibility, tissue reorganization, and promotes neck healing. This result has not been consistently reported for metal coils delivered to both animal models and human patients.\textsuperscript{6,7,9}

Although metal coils remain the “gold standard” for treatment of medium aneurysms with small and medium $d: n$ ratios and neck diameters $< 4$ mm, these coils (including the newer curtain mesh design, i.e., Medina\textsuperscript{®}, Medtronic) fill $< 30\%$ of the aneurysm volume.\textsuperscript{4,6,30} Although many coils are classified as “soft” and “flexible,” the metal core is still over 100,000 times stiffer than surrounding tissue. Coils also tend to compact inside the aneurysm, causing stress shielding, stress transmission and aneurysm regrowth (recanalization), seen in roughly $15–35\%$ of smaller aneurysms.\textsuperscript{4,6,24} Coiling effectiveness decreases dramatically with increased aneurysm size and wide-neck morphologies.\textsuperscript{11,12} Medium to large aneurysms exhibit recanalization rates of $25–50\%$, while large and giant aneurysm recanalization rates are $35–70\%$.\textsuperscript{4,6,13,26,29,31}

Flow Diverters, such as the Pipeline\textsuperscript{®} embolization device, redirect blood flow away from the aneurysm. However, these devices can be difficult to navigate, deploy, and properly expand in tortuous vessels and can increase complication rates ($30–40\%$ in some series).\textsuperscript{10} Of note, device placement has only been FDA-approved for aneurysms along the internal carotid artery.\textsuperscript{10,12,18} In some cases, flow diverters do not result in complete occlusion of the aneurysm.\textsuperscript{10,12} Furthermore, the strict requirement for dual-antiplatelet medication limits their use for ruptured intracranial aneurysms.

Flow disrupters consist of an intrasaccular metal frame that expands in the aneurysm, thereby reducing the metal surface exposure at the parent vessel in an attempt to reduce thrombogenic effects.\textsuperscript{11} This is exemplified by the WEB\textsuperscript{®} System (Microvention-Terumo).\textsuperscript{11,12} However, the sizes and shapes of the WEB that are currently available are limited ($< 10$ mm dome diameter, per device IFU). Placement often results in flow remnants at the neck that may ultimately lead to recanalization.

Coils, WEB devices, and flow diverters are all composed of metal alloys, which have limited compatibility with blood and can promote local or downstream thrombus. These devices also exhibit inconsistent healing responses, especially in larger aneurysms with medium-to-wide-neck $d: n$ ratios, resulting in high aneurysm recanalization rates.\textsuperscript{10-12,18} These limitations suggest that continued research on novel embolic treatment devices is necessary to expand treatment options to further improve patient outcomes.

**Limitations of previous liquid embolics**

Polymer-based devices, such as liquid embolics, have mechanical properties that closely approximate natural tissue, can completely fill varied aneurysm morphologies, and exhibit high biocompatibility compared to their metal counterparts. However, liquid embolics for cerebral aneurysm embolization have not been widely accepted, due in large part to the limitations observed in the only available aneurysm treatment material: Onyx HD-500\textsuperscript{®} [Table 1]. Onyx is a precipitating co-polymer system composed of ethylene-co-vinyl alcohol (EVOH). Onyx is dissolved in the organic solvent dimethyl sulfoxide (DMSO), allowing delivery through a microcatheter. Rapid delivery of Onyx and DMSO solvent into the bloodstream has been linked to cytotoxicity and vasospasm.\textsuperscript{6,13,20,21} Slow delivery of Onyx allows the DMSO to diffuse more safely; however, this requires prolonged procedures with multiple balloon deflations (to avoid ischemia). Onyx slowly precipitates as DMSO is flushed away by the blood, leaving Onyx susceptible to migration and particulation.\textsuperscript{22,27} These issues have resulted in clinical complications that have stifled interest in Onyx-HD-500 and liquid embolics in general for the treatment of cerebral aneurysms.

**CONCLUSION**

The results of the present study suggest that PPODA-QT can be successfully delivered to wider-neck aneurysms, leading to aneurysm tissue reorganization and stabilization that facilitates continuous healing at the aneurysm neck. Ultimately, such a result may reduce recanalization and rupture of larger aneurysms. Because PPODA-QT treatment currently targets larger aneurysms than those created by the rabbit elastase model, further evaluation of more complex aneurysm models with a statistically significant number of subjects is the next step. Surgical anastomosis canine models provide more flexibility for creating larger aneurysms with consistent $d: n$ ratios while also exhibiting a healing response similar to the human condition. Such an alternative aneurysm model will be investigated to further verify the biocompatibility results of PPODA-QT reported in this study.

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**Declaration of patient consent**

Patient’s consent not required as there are no patients in this study.

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Conflicts of interest
Mark C. Preul MD, Andrew F. Ducruet MD, and Timothy A. Becker PhD have financial interest in Aneuvas Technologies, Inc. (ATI) which now manufactures a version of PPODA-QT as NeuroCURE®. Dr. Ducruet also has formal consulting roles with Stryker, Penumbra, Cerenovus, Medtronic, and Koswire. The Barrow Neurological Institute and Northern Arizona University have no commercial collaboration with ATI in the production, distribution, or marketing of NeuroCURE®.

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