Safety and efficacy of embolization using Onyx® of persistent type II endoleaks after abdominal endovascular aneurysm repair

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KEYWORDS
Endoleak; Abdominal aneurysm; Abdominal endovascular aneurysm repair (EVAR); Embolization; Interventional radiology

Abstract
Purpose: To retrospectively evaluate the safety and efficacy of embolization of persistent type II endoleaks occurring after abdominal endovascular aneurysm repair (EVAR) using ethylene vinyl alcohol copolymer (Onyx®).

Material and methods: Between 2008 and 2016, 28 consecutive patients (25 men, 3 women) with a mean age of 75.3 years ± 9 (SD) (range: 59–90 years) were treated for 29 persistent type II endoleaks with increasing aneurysm size > 5 mm occurring after EVAR. A total of 35 embolization procedures were performed using Onyx®, via a transarterial route (n = 25) or direct puncture (n = 10), with or without additional metallic coils. The endpoints were to evaluate the clinical efficacy, corresponding to the stabilization or decrease of aneurysm size, and the technical efficacy, corresponding to the ability to complete the embolization.

Results: No severe complications were observed during and after embolization. The primary and secondary clinical efficacies were 75% (21/28) and 96.4% (27/28), respectively. Overall primary technical efficacy rate was 58.6% (17/29), greater for transarterial technique (72.8%) than for direct puncture (14.3%) (P = 0.01). Secondary technical efficacy was 72.4% (21/29), with no differences between transarterial (81.8%) and direct puncture (42.8%) (P = 0.06).

Conclusion: Embolization with Onyx® of type II endoleaks after EVAR appears a safe and effective procedure.

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Over the last decade, endovascular aneurysm repair (EVAR) has become a widely used minimally invasive technique of care of abdominal aortic aneurysm (AAA) [1–4]. However, the rate of repeat intervention after EVAR remains higher than after open surgery due to the type II endoleaks frequently observed within the aneurysm sac [5–7].

A type II endoleak corresponds to a retrograde filling of an aneurysm from one or more arterial branches. While more than 50% of initially identified type II endoleaks seal spontaneously, a non-negligible risk of rupture remains when endoleaks persist, or when occur lately (i.e. after 6 months) [8]. This risk is estimated to 0.5–0.9% [6]. Therefore, a consensus was reached to treat only type II endoleaks persistent after 6 months that show an increasing size of the aneurysm greater than 5 mm [1].

In order to avoid an open surgery, transarterial and direct puncture embolization techniques have been developed due to their minimally invasive nature [1,8,9]. However, literature remains scarce in particular for procedures using liquid embolic agents [10].

The aim of our study was to retrospectively evaluate the safety and efficacy of embolization with Onyx® of persistent type II endoleaks occurring after abdominal EVAR.

Materials and methods

Patients

Between 2008 and 2016, 28 consecutives patients were treated with transarterial or direct puncture embolization. All patient data was obtained through review of medical records and imaging reports. The Institutional Review Board approved the waiver of obtaining informed consent for this retrospective review of prospectively recorded patient data.

There were 25 men and 3 women with a mean age of 75.3 years ± 9 (SD) (range: 59–90 years). Patients were initially treated by EVAR for AAA (1 emergency procedure for ruptured aneurysm: 25 EVAR (23 aorto-bi-iliac and 2 aorto-uni-iliac), 2 fenestrated EVAR (for the 2 renal arteries), and 1 chimney EVAR (for 2 renal arteries and for superior mesenteric artery [SMA]).

Embolization was proposed after discussion during multidisciplinary meetings comprising vascular surgeons and interventional radiologists. All patients had a persistent endoleak with an increasing aneurysm sac ≥ 5 mm on 2 successive computed tomography (CT) examinations at 6 months apart. One patient had successively 2 different endoleaks. Transarterial embolization was attempted in first intention. However, for patients with impaired renal function, those with small and tortuous lumbar arteries identified on CT and angiography or those with failed endovascular embolization, direct puncture embolization was proposed as an alternative. Patient characteristics are summarized in Table 1.

Procedure details

Transarterial embolization

All transarterial procedures were performed on the same angiographic unit (Philips, Best, Netherlands), under conscious sedation using midazolam and fentanyl and local anesthesia after a preprocedural evaluation by an anesthesiologist. The anesthesiologists performed continuous monitoring.

After percutaneous introduction of a 4-Fr sheath in the right or left femoral artery, the endoleak was selectively catheterized through a collateral filling branch using a 4F cobra-type catheter and a 0.035-In hydrophilic guidewire (Terumo, Tokyo, Japan). Catheterism involved the lumbar artery via the internal iliac artery (n = 16) (Fig. 1) or the inferior mesenteric artery (IMA) (Fig. 2) through Riolan arcade from the SMA (n = 8). In case of complex endoleak from IMA and lumbar artery, IMA was firstly catheterized selectively. Special attention was given to the location of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of 28 patients with 29 type II endoleaks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td>Mean [range] or n (%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>75.35 [59–90]</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (89%)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Mean aneurysm size before treatment (mm)</td>
<td>58.8 [45–75]</td>
</tr>
<tr>
<td>Type of prosthesis</td>
<td></td>
</tr>
<tr>
<td>Excluder (Gore®)</td>
<td>11 (39%)</td>
</tr>
<tr>
<td>Anaconda (Vaskutek®)</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>Endurant (Medtronic®)</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Powerlink AFX (Endologix®)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Zenith (Cook®)</td>
<td>4 (14%) (1 EVAR; 2 with fenestrated grafts; 1 with chimney graft)</td>
</tr>
<tr>
<td>Endoleaks characteristics</td>
<td></td>
</tr>
<tr>
<td>Mean time of occurrence after EVAR (months)</td>
<td>26 [1–6]</td>
</tr>
<tr>
<td>Time category</td>
<td></td>
</tr>
<tr>
<td>Early (&lt; 6 months)</td>
<td>9 (32%)</td>
</tr>
<tr>
<td>Delayed (&gt; 6 months)</td>
<td>20 (68%)</td>
</tr>
<tr>
<td>Type of endoleak (n = 29)</td>
<td></td>
</tr>
<tr>
<td>Ila</td>
<td>18 (13 LA, 5 IMA) (62%)</td>
</tr>
<tr>
<td>Ilb</td>
<td>11 (8 LA, 3 LA + IMA) (38%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>18 (62%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Previously treatment</td>
<td></td>
</tr>
<tr>
<td>Second intervention before embolization</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>LA ligature open surgery</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Extension cuff for type I endoleak</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Chimney graft for type I endoleak</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

LA: lumbar artery; IMA: inferior mesenteric artery; EVAR: endovascular aneurysm repair.
Adamkiewicz artery during opacification of lumbar artery. Next micro-catheterization was performed using a coaxial technique with a 2.7-Fr microcatheter (Progreat®, Terumo, Tokyo, Japan; or Marathon®, Ev3 Inc., Irvine, CA, USA) as near as possible to the endoleak cavity (nidus). The embolic agent was ethylene vinyl alcohol copolymer (Onyx 18®, Ev3 Inc.) with or without coils (Ruby®, Penumbra Inc, Alameda, California, USA or Azur®, Terumo). Onyx® was slowly injected under fluoroscopic control when the microcatheter tip was as close as possible to the aneurysm sac. A digital subtraction was used to have full control and visualization during Onyx® delivery. Onyx® and coils had to embolize the collateral vessels and the endoleak completely. If the nidus could not be catheterized, Onyx® was injected through the network of collateral afferent arteries.

Direct puncture embolization

All direct puncture embolizations were performed under local anesthesia and ultrasound, fluoroscopy and CT guidance. The fluoroscopy system was positioned in front of the CT scanner, for a combined approach. When the aneurysm sac was visible on ultrasound and could be safely punctured, direct ultrasound-guided puncture in the endoleak was initially attempted through a transabdominal or translumbar approach. Otherwise, puncture of the endoleak using real-time CT monitoring was done using a translumbar approach. An 18-G needle-catheter was used. A free and pulsatile blood reflux defined the optimal position of the catheter. For all patients, placement of a 4-Fr sheath was performed under fluoroscopy monitoring on an exchange guidewire. Embolization was directly performed with Onyx® and coils under fluoroscopic control through the needle-catheter or after selective catheterization of the endoleak with a microcatheter (Fig. 3).

Post-procedure management

Procedure duration (min), fluoroscopy time, dose area product (DAP, in mG.cm²) and renal function (ml/min) were recorded for each patient. After embolization, patients were admitted to the vascular surgery department for 24 hours, to monitor pain, femoral access and renal function. Patients were discharged when no complications were observed during this time.

Clinical and imaging follow-up

All patients underwent clinical and imaging follow-up using CT examination following a standardized protocol that
Figure 2. Transarterial embolization of type II endoleak via the inferior mesenteric artery (IMA). A. CT image in the transverse plane obtained during the arterial phase shows type II endoleak from IMA (arrow). B. Three-dimensional CT image during the arterial phase shows Riolan arcade (arrowheads). C. selective catheterization of SMA shows Riolan arcade (arrowhead) and confirmation of type II endoleak (arrow). D. Angiogram during opacification of IMA shows endoleak (arrow). E. Angiogram shows embolization of endoleak and ostium of IMA (arrowhead) with Onyx®. F. CT image in the transverse plane 9 months after embolization reveals no residual endoleak remains from IMA (arrow).

Figure 3. Embolization of type II endoleak using direct puncture. A. Angiogram during injection through a microcatheter shows endoleak (arrow) and lumbar arteries (arrowheads). B. Angiogram shows injection of Onyx® (arrow) through the microcatheter. C. Final control angiogram shows no residual endoleak.

included a pre-contrast acquisition, an arterial phase and a delayed phase. The maximum diameter of the aneurysm was measured in a plane perpendicular to the center line of the vessel on multiplanar reformatted images, and compared with the dimensions recorded on prior CT examination. On each CT scan, the largest diameter of the aneurysm was noted.

Early endoleak was defined as an endoleak occurring less than 6 month after EVAR. Delayed endoleak was defined as an endoleak occurring more than 6 months after EVAR.
A contrast-enhanced ultrasound or an MR angiography using intravenous administration of a gadolinium chelate was proposed for patients with impaired renal function and who have received nitinol-based stents. Technical failures were considered as the presence of a residual endoleak. If there was a growth of aneurysm size more than 5 mm at 6 months, a new embolization session was planned, if not, the follow-up was continued.

**Study endpoints**

The primary endpoint was to evaluate the clinical efficacy of embolization. The primary and secondary clinical efficacy were defined respectively by decrease of at least 5 mm or an increase <5 mm (considered as stabilization) of the aneurysm on the first CT examination after embolization and the last CT examination irrespective of the number of embolizations and endovascular procedures.

Secondary endpoints were the primary and secondary technical efficiencies and safety procedure. The primary and secondary technical efficiencies were defined respectively as the absence of the endoleak on the first CT examination after embolization and the last CT examination irrespective of the number of embolizations and endovascular procedures. Safety was defined as the absence of complications classified according to the Clavien-Dindo grading system [21] and to the Society of Interventional Radiology (SIR) classification [22].

**Statistical analysis**

Statistical analysis was performed using software (STATA®, College Station, TX, USA). Mean, range and standard deviation (SD) were evaluated for the distribution of quantitative continuous variables. Qualitative variables were compared using Fisher exact test or χ² test for. Wilcoxon signed-rank test was used to compare quantitative variables. A P value ≤ 0.05 was considered significant.

**Results**

**Patients**

A total of 29 type II endoleaks were embolized in 28 patients. One patient had two different type II endoleaks treated with 2 embolizations at 25 months apart. Mean follow-up time of endoleaks with CT was 20 months ± 12 (SD) (range: 6—49 months).

Nine early type II endoleaks and 20 delayed type II endoleaks were embolized. According to the SIR guidelines for EVAR [1], the grade of branch vessels were Grade 1 (n = 18), Grade 2 (n = 6) and Grade 3 (n = 5). Mean time interval between EVAR and embolization was 26 months ± 17 (SD) (range: 8—62 months).

**Clinical and technical efficacy**

A total of 35 image-guided procedures were performed to embolize 29 endoleaks in 28 patients. In addition to the patient who underwent 2 embolizations for 2 different type II endoleaks, 6/28 patients (21.4%) had multiple procedures to achieve the treatment of the same endoleak. Five of 28 patients (17%) had 2 procedures, and 1/28 patient (3.5%) had 3 procedures. Twenty-five embolizations were performed using a transarterial embolization and 10 using a direct puncture embolization. The mean volume of Onyx® injected was 2.2 mL ± 1.8 (SD) (range: 0.5—9 mL).

The primary clinical efficacy rate on a patient basis was 75% (21/28). A clinical failure was observed in 7/28 patients (25%) at the time of the first evaluation after embolization. The reasons detected were 6 persistent type II endoleaks and one new type II endoleak. Additional embolization procedures were performed in 6/28 patients (21.4%) with persistent endoleaks, successfully in 5 patients after one (n = 4) or two sessions (n = 1). At the date of last follow-up, aneurysm diameter decreased in 5/28 patients (17.8%) with a mean decrease of 13.7 mm (range: 6—22 mm). Aneurysm diameter remained stable in 22/28 patients (78%) and increased of 11 mm in 1/28 patient (3.5%). Secondary clinical efficacy was 96.4% (27/28).

After embolization of the 29 type II endoleaks, the overall primary and secondary technical efficacy rates were 58.6% (17/29), and 72.4% (21/29), respectively. Primary technical efficacy was greater with transarterial technique (72.8%) than with direct puncture (14.3%) (P = 0.01) and when the embolization was complete (100%) than incomplete (29.4%) (P = 0.001) or when its origin was the IMA (P = 0.05) (Table 2). Secondary technical efficacy was greater when the embolization was complete (100%) than incomplete (52.9%) (P = 0.009) (Table 2).

During the follow-up, three type I endoleaks were treated (2 using endovascular treatments and 1 with a combined treatment with endovascular and embolization) 10 months after embolization (range: 9—12 months), and one type III endoleak (36 months after the embolization) was treated by extension of EVAR. Patients with type I and type III endoleaks had a stable aneurysm size after a mean follow-up of 11.5 months (range: 4—19 months).

**Safety**

The average fluoroscopy procedure duration was 45.9 min (range: 16—97 min) and total dose area product (DAP) was 419 mgG/cm² (range: 30—1266 mgG/cm²). No differences were observed between the mean creatinine clearance before (72.4 mL/min ± 23 [SD]; range: 24—123 mL/min) and after (74.6 mL/min ± 22 [SD]; range: 45—125 mL/min) embolization (P = 0.999). No severe adverse effects were reported. During the follow-up, four patients (14.28%) died due to comorbidities (mean delay, 15 months; range: 4—24 months). Extravasation of Onyx® occurred in 1 patient in the retroperitoneal space after translumbar embolization, and a symptomatic reflux in muscular branches of lumbar artery occurred after transarterial embolization in another patient. The mean time of hospitalization stay was 2 days.

**Discussion**

As demonstrated in our study, embolization appears safe and effective to treat type II endoleaks. Embolization of endoleaks tends to normalize the sac pressure through a
minimally-invasive approach, and may be safely proposed as a standard of care for persistent type II endoleaks after 6 months associated with an increase in the aneurysm diameter greater than 5 mm [11].

In our study, the primary and secondary clinical efficacy were respectively 75 and 96.4%, similar to those of other studies that reported an efficacy ranging from 74 to 100% [10,12–15]. In addition, the primary and secondary technical efficacies were respectively 58.4 and 71.4%, similar to those of other studies that have reported efficacies ranging from 95 to 88% [12,13].

Embolization procedures of endoleaks with Onyx® appear feasible for an interventional radiologist with an experience in arteriovenous malformation embolization [14,15]. However our results suggest that embolization is more effective when total occlusions of the nidus and the feeding branches are obtained as reported by Muller-Whille et al. [13]. As this objective may remain challenging using direct puncture, it may be recommended to perform transarterial embolization as a first option. Direct puncture, even feasible, may be attempted only if the nidus cannot be easily and safely catheterized through the feeding artery.

In order to limit the risks of complications but also to achieve embolization, we used Onyx® with either a transarterial or translumbar approach [15,16]. No severe adverse effects were observed in our study. This rate appears low compared to another study with a rate of 32% for severe adverse effects [17]. As ischemia remains often the most frequent complication due to more extensive embolization than required, the use of Onyx® may have overcome this [16]. Moreover, only asymptomatic complications were reported in both techniques of embolization, which contrast with the conclusion of Sidloff et al. who reported a rate of complications significantly greater with transarterial embolization than with direct puncture [6].

The use of Onyx® appears not limited by the injection of dimethyl-sulfoxide (DMSO), which is a solvent and part of the final Onyx® formulation. It has been previously demonstrated that short-term exposure of endograft material to DMSO and Onyx® is not associated with structural compromise of four commonly used aortic endografts (i.e., Gore® Excluder® AAA endoprosthesis, Gore Medical; Zenith® Flex AAA endovascular graft, Cook Medical; AneuRx® Stent Graft System, Medtronic AVE; Talent® LPS stent graft, Medtronic AVE) [18]. However the effect of peri-graft embolization with Onyx® on pressure transmission into the sac has not been studied yet and further study should be done. Alternatively, N-butyl-2-cyanoacrylate may be used [17,19].

While 17.1% of patients in our study had additional embolization with metallic coils, no embolizations were performed with coils alone because of the high rate of recanalization reported so far [20]. Coils were used as an adjunct to reduce the blood flow velocity, and then to diminish the risk of non-targeted embolization [7]. This technique was used to reduce the volume of Onyx® when endoleak was too large.

The main limitations of our study are its retrospective nature, the limited population size, and the absence of control of aneurysm volume. In addition, we did not measure the volume of aneurysm sac, although researchers showed that a change in volume is detected sooner that a change in diameter [21]. Moreover, embolization procedures in our study were performed by the same operator in a single center, using predominantly an intravascular approach, thus limiting comparison between the two different approaches.

In conclusion, the results of our study suggest that embolization with Onyx® of type II endoleaks after EVAR appears safe and effective. Our results need now to be confirmed in the long term and on larger cohort. Studies about procedure cost are in progress.

### Table 2

<table>
<thead>
<tr>
<th>Origin of feeding artery</th>
<th>n</th>
<th>Primary technical efficacy (%)</th>
<th>P</th>
<th>Secondary technical efficacy (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMA</td>
<td>5</td>
<td>100</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>13</td>
<td>83.3</td>
<td>&lt;0.05</td>
<td>84.6</td>
<td>0.4</td>
</tr>
<tr>
<td>IMA BLA</td>
<td>3</td>
<td>33.3</td>
<td></td>
<td>66.7</td>
<td>1</td>
</tr>
<tr>
<td>Multiple LA</td>
<td>8</td>
<td>0</td>
<td>&lt;0.001</td>
<td>37.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Results are given on an endoleak basis. IMA: inferior mesenteric artery; LA: lumbar artery.
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Disclosure of interest

The authors declare that they have no competing interest.

References