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VASCULAR AND INTERVENTIONAL RADIOLOGY

Ethylene–vinyl alcohol copolymer as embolic agent for treatment of type II endoleak: our experience

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Abstract
Aim To evaluate safety, technical and clinical success of embolization of type II endoleak (T2 EL) using ethylene-vinyl alcohol copolymer as embolic agent alone or in combination with others materials.
Materials and Methods From March 2007 to March 2015, 104 patients presented T2 EL during follow-up. A total of 21 patients met the criteria for treatment. T2 EL was treated with TAE ($n = 18$), DPSI ($n = 10$) or laparoscopic ligature of the inferior mesenteric artery ($n = 1$). DPSI was considered in case TAE was unsuccessful (8/18 patients). Ethylene–vinyl alcohol copolymer was used as embolic agent in 12 patients: alone in 5 cases, in association with glue and with glue and thrombin in 3 and 2 cases, respectively, during TAE. Onyx was injected in two cases of embolization performed with DPSI: in one case alone and in the other in combination with thrombin and glue.
Results Technical success rate was 100%. Immediate clinical success was 91.7%; in one patient CEUS revealed persistent T2 EL, decreased if compared with that before the procedure. Secondary clinical success was 91.7%; until today, in one patient T2EL is persistent, nevertheless, the sac diameter remained stable. No major or minor complications were registered.
Conclusions Onyx could be an ideal embolic agent for endovascular and percutaneous embolization of T2 EL.

Keywords Ethylene-vinyl alcohol copolymer · Onyx · Type II endoleak · Embolization

Introduction

Endovascular aneurysm repair (EVAR) is considered the standard therapy for most patients with abdominal aortic aneurysm (AAA) [1]. EVAR has emerged as a treatment of choice for patients with AAA [1]. Endoleak (EL) is a complication that requires long-term follow-up. EL is defined as persistence of blood flow within the excluded aneurysm sac, classified according to the underlying etiology, location, and aortic branch vessel involvement [2]. Endoleak, present in 20–40% of patients after EVAR, is shown to be associated with late sac enlargement. Type I and type III endoleaks require early intervention; however, the treatment strategy for type II endoleak remains controversial because spontaneous resolution is expected [2]. Several recent studies have demonstrated that nearly 20% of immediate type II endoleaks persist and that persistent type II endoleaks are associated with secondary interventions and aneurysm rupture [2, 3]. Persistent type II endoleaks usually have a complex architecture. They have been compared with the arteriovenous malformations with the sac forming the "nidus" of the lesion [4]. There are usually more than one inflow and out flow vessels. These vessels

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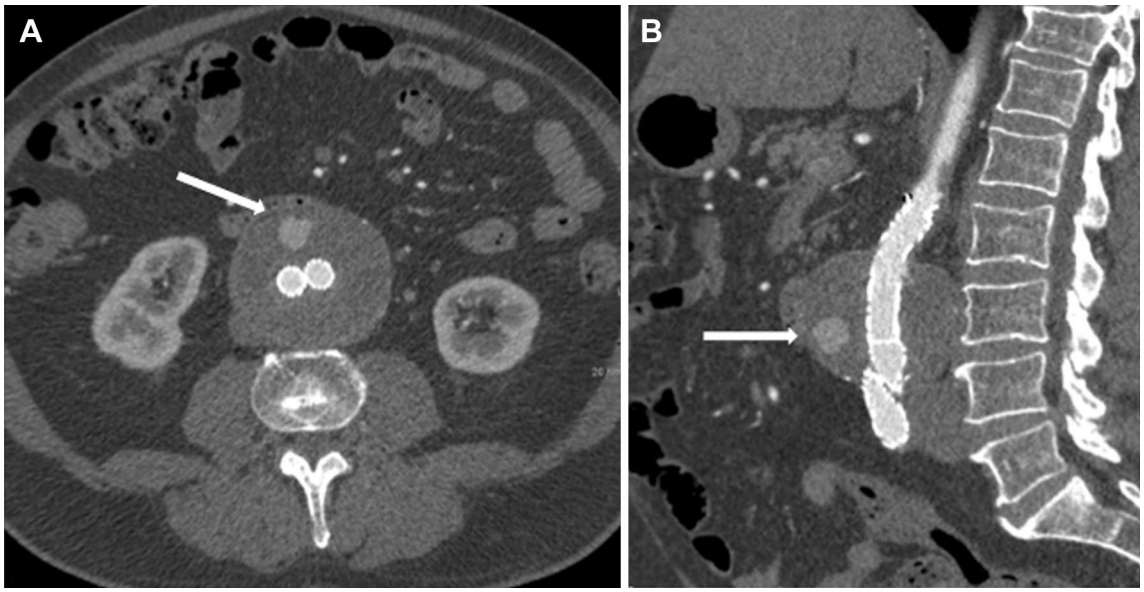

Fig. 1 Axial CT shows aneurysmal sac supplied (type II endoleak) (*arrow*) (**a**); multiplanar reconstruction confirms type II endoleak (*arrow*) (**b**)

communicate through a channel. The channel is different from the endoleak sac that is generally seen during the angiogram and punctured in translumbar embolization. To achieve a successful embolization, the inflow vessels and the channel(s) needs to be embolized. Endovascular embolization is the modality of choice [5]. Direct puncture sac injection (DPSI) is usually performed after unsuccessful transarterial embolization (TAE) or persistent endoleak and enlargement of the aneurismal sac after TAE [5]. A variety of embolic agents have been used either in isolation or in combination for treatment of type II endoleaks. Permanent agents, such as coils, glue [*n*-butyl cyanoacrylate (NBCA)], thrombin and ethylene-vinyl alcohol copolymer are preferred. There are no guidelines for the choice of embolic material to use, and the final decision is often on the basis of the operator experience and confidence. Onyx (ethylene–vinyl alcohol polymer) is a non adhesive liquid embolic agent. Onyx has a lava like flow pattern within blood vessels without any fragmentation during the injection. Due to these properties and because Onyx is not absorbable, it is capable of producing permanent vascular occlusion [6].

We report our experience with the use of ethylene-vinyl alcohol copolymer (Onyx) for the treatment of type II endoleaks after EVAR either with endovascular that percutaneous approach.

Materials and methods

From March 2007 to March 2015, 455 patients with AAA underwent to endovascular exclusion. Patients were routinely monitored at the institution and follow-up included computed tomography angiography (CTA) at 30 days, CTA or contrast enhanced ultrasound (CEUS) at 6 months and CTA at 12 months postoperatively and annually thereafter. One hundred and four ($n = 104$) patients presented type II endoleak during follow-up (6–98 months) (Fig. 1a, b).

Seven patients were excluded from the series for absence of follow-up. In 70 of the remnant 97 patients, T2 EL appeared in the first 12 months; all T2 EL appeared within 48 months. In 25 patients, a spontaneous resolution of the T2 EL was observed during a mean follow-up of 28 months (range 6–98 months). T2 EL treatment was considered if endoleaks were persistent for >12 months and if a sac enlargement of >5 mm between follow-up imaging was observed. A total of 22 patients (30.5%) met the criteria for treatment.

CEUS was performed in all patients before treatment, to confirm T2 EL and its origin (lumbar and/or mesenteric). In one of the 22 patients, CEUS pre-treatment revealed a high flow EL (T1b EL), confirmed by angiography and treated with an iliac endograft. In 21 patients, T2 EL was treated with TAE ($n = 18$), DPSI ($n = 10$) or laparoscopic ligature of the inferior mesenteric artery ($n = 1$). DPSI was considered in case TAE was unsuccessful, which occurred in 8 out of 18 patients.

In this study, we considered all the embolization performed using ethylene–vinyl alcohol copolymer (Onyx, ev3 Neurovascular, Irvine, California) as embolic agent, alone or in combination with other embolic agents. Endovascular embolization was performed using ethylene–vinyl alcohol copolymer as the only embolic agent in five cases (Fig. 2a,

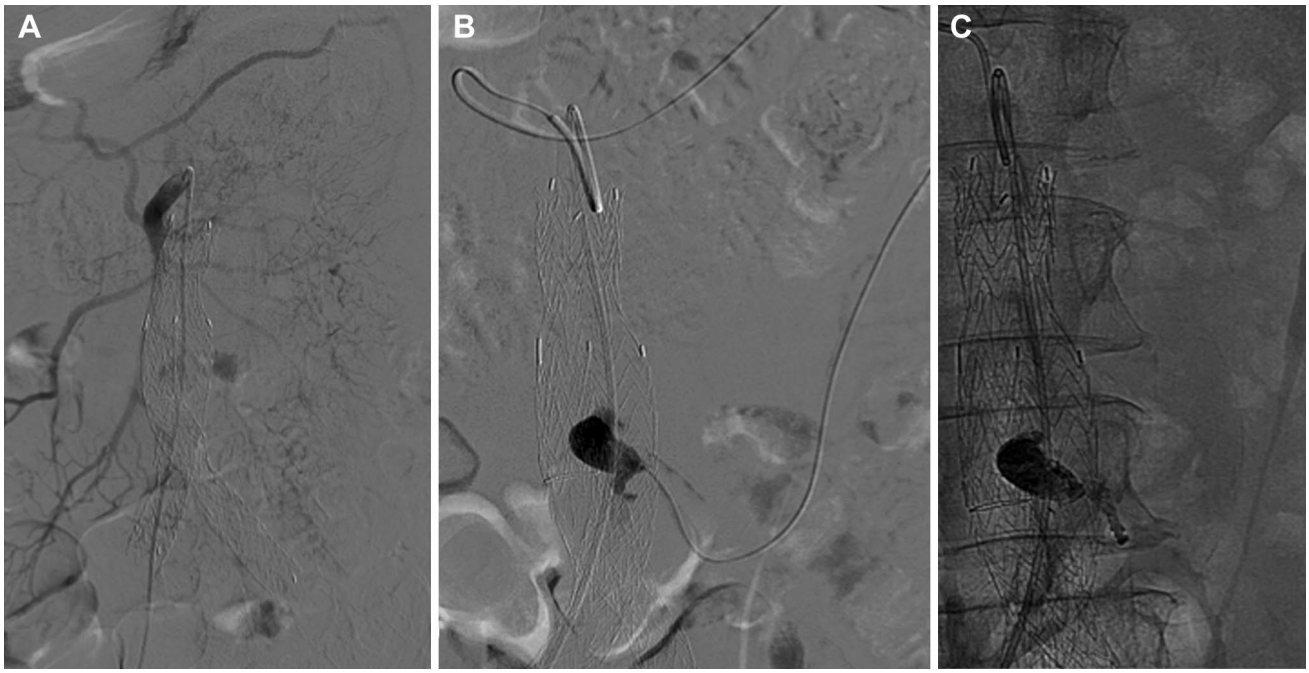

Fig. 2 Selective angiography of the superior mesenteric artery demonstrated sac supplied by inferior mesenteric artery recanalized by Riolan arch (**a**); super-selective navigation of the Riolan arch led to the EL: angiogram performed with the microcatheter in the aneurysmal sac (**b**); post-embolization image shows nidus of the endoleak entirely filled by Onyx (**c**)

b, c); in other three patients Onyx was used in combination with glue (Glubran 2, GEM S.r.l., Viareggio, Italy) and in two cases Onyx was performed in association with thrombin (D-Stat; Vascular Solutions Inc, MN, USA), and glue (Glubran 2, GEM S.r.l., Viareggio, Italy). Onyx was injected in two cases of embolization performed with direct puncture of the sac: in one case alone and in the other in combination with thrombin and glue. The choice of embolic agent was at the discretion of the operator, although glue and Onyx were used primarily when endoleak persisted at the angiography or saccography performed during the procedure.

All procedures performed in this study were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki declaration and its later amendments. Our Internal Review Board approved each procedure. Informed procedural consent was obtained from all individual participants included in the study. Technical success was defined as the ability to perform endovascular or percutaneous embolization using Onyx as embolic agent. Immediate clinical success was defined as the absence or the decrease in size of the endoleak at the CEUS performed after the procedure. Secondary clinical success was defined as the absence of recurrent endoleak during follow-up. Safety was defined as the frequency of intra-, peri- and post-procedural complications [5].

Results

Eleven men and one woman with a mean age of 62.8 years (range 52–83 years old) comprised the study population (Table 1). All of them underwent EVAR for AAAs. The indication for endoleak treatment included persistence of a type II endoleak after 12 months follow-up and enlarging aneurysm sac size.

A direct aneurysm sac access approach was employed in 10 patients and the transarterial access was used in 18 patients. In 8 of 18 cases TAE was unsuccessful so these patients underwent DPSI. Only in one case laparoscopic ligature of the inferior mesenteric artery was employed. Endovascular embolization was performed using Onyx as the only embolic agent in five cases; in other three patients Onyx was used in combination with Glubran and in two cases Onyx was performed in association with thrombin, and glue; Onyx was injected in two cases of embolization performed with percutaneous puncture of the sac: in one case alone and in the other in combination with thrombin and glue (Fig. 3a–e).

Technical success rate was 100%, in particular in all embolizations, either with endovascular that percutaneous approach, ethylene–vinyl alcohol copolymer was used as embolic agent without any technical problem.

Table 1 Patients, age, type of procedure, embolic agent used, follow-up and clinical success

Pt; age (years old)	Procedure: TAE/DPSI	Embolic agent			Follow-up (months)	IMS	SCS
		Thrombin	Glue	Onyx			
1; 70	TAE		+	+	50	Ok	Ok
2; 64	TAE			+	44	Ok	Ok
3; 62	TAE	+	+	+	36	Ok	Ok
4; 68	TAE			+	28	Ok	Ok
5; 52	TAE			+	36	Ok	Ok
6; 60	TAE			+	12	Ok	Ok
7; 82	TAE			+	24	Ok	Ok
8; 70	TAE		+	+	12	Ok	Ok
9; 58	TAE		+	+	30	Ok	Ok
10; 67	TAE	+	+	+	20	Ok	Ok
11; 83	DPSI			+	24	Persistent EL	Persistent EL
12; 72	DPSI	+	+	+	18	Ok	Ok

Pt Patient, *TAE* transarterial embolization, *DPSI* direct puncture sac injection, *IMS* immediate clinical success, *SCS* secondary clinical success

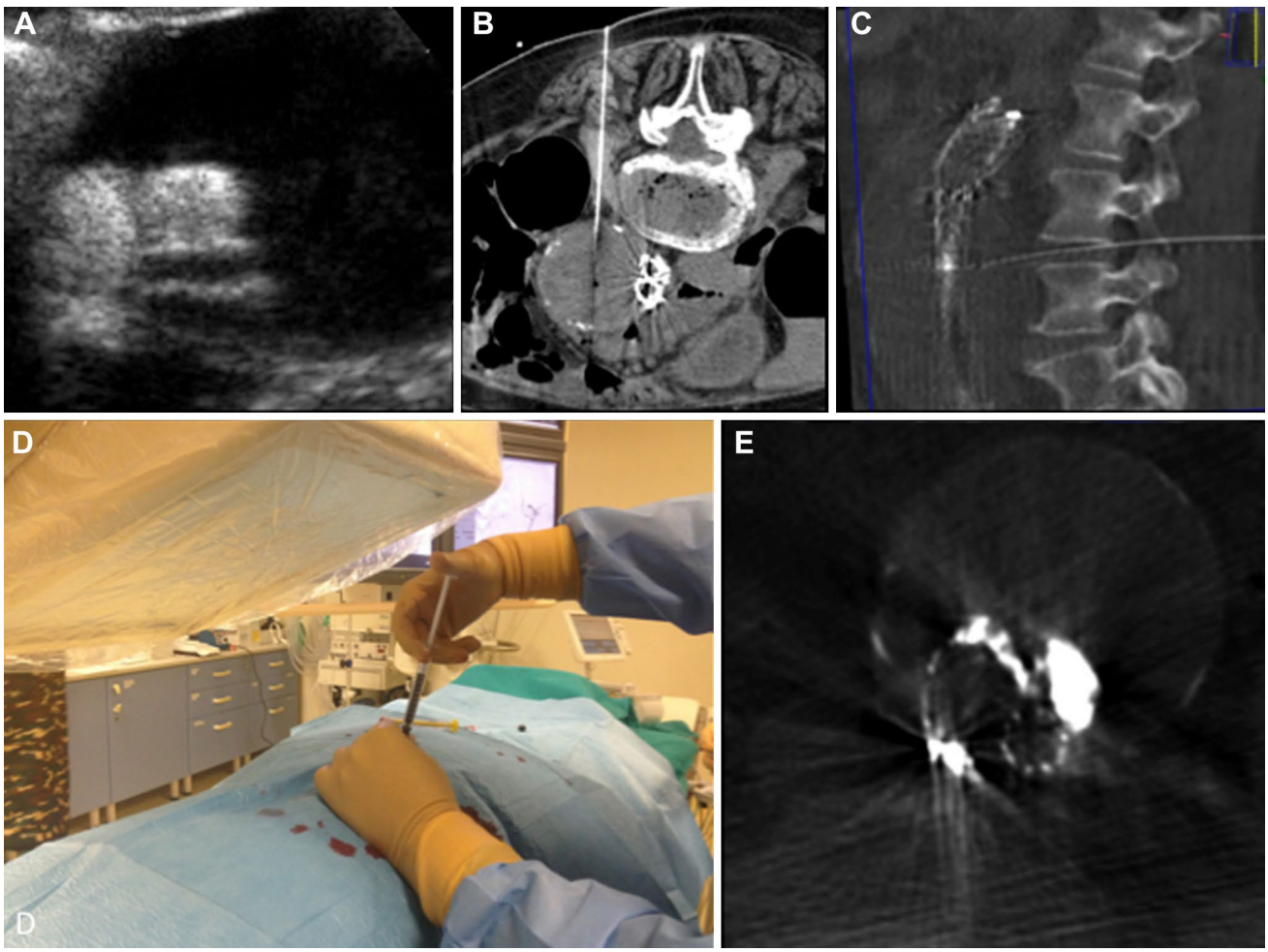

Fig. 3 Contrast enhanced ultrasound (CEUS) confirmed type II endoleak (**a**); direct puncture of the sac was performed using CBCT as imaging guidance (**b**, **c**); Onyx was injected directly by the needle used for the puncture (**d**); final CBCT confirmed distribution of the Onyx in the sac (**e**)

Immediate clinical success was 91.7%, in particular in 11/12 cases CEUS performed at the end of the procedure demonstrated absence of endoleak; in the remaining case (1/12; 8.3%) CEUS revealed persistent T2 EL, decreased if compared with that before the procedure. CTA was performed as protocol of follow-up and confirmed clinical results reported.

Secondary clinical success was 91.7%; until today, in one patient T2 EL is persistent, with suspected inflow from a small patent lumbar artery; nevertheless, at the moment of submission (follow-up of 24 months), the patient remains asymptomatic and the sac diameter is stable (55 mm), therefore, no indication for re-treatment are present.

No major or minor complications were registered during or after the procedure. During the procedure, one patient treated with endovascular approach, complained mild abdominal pain, at the beginning of the embolization (probably related to the arrival of DMSO within the EL), but any analgesic was administered. At the end of the procedure, one of the two patients treated with percutaneous approach, experienced mild back pain, solved with common analgesics within 24 h.

Discussion

Type II endoleak is the most common complication after endovascular aneurysm repair (EVAR) which could lead to a possible risk of aneurysmal sac enlargement and rupture [2, 7, 8]. If the sac is enlarged, surgical intervention might be needed. Many techniques have been described to treat type II endoleak.

In the past, type II endoleaks were usually treated surgically, both with graft explantation and with retroperitoneal ligation of collateral feeding vessels. These invasive methods require hospital admission and carry with them the accompanying morbidity of surgery [3]. For this reason, over the years, new less invasive techniques for the treatment of endoleaks have made their way. Transarterial embolization is usually used to treat type II endoleak. Inferior mesenteric artery, internal iliac artery or lumbar artery is usually selected as the route for transarterial embolization. If there are no arterial routes for transarterial embolization, DPSI is feasible as alternative method to treat type II endoleak [9].

During these years, embolization of endoleaks has been performed with many different embolic agents like glue, coils, thrombin and Onyx. The principal advantage of the use of a liquid embolic agent in the treatment of type II endoleaks relates to the ability of a liquid to fill the endoleak sac completely including all inflow and outflow vessels. The solid cast formed by a liquid embolic agent should result in a non compressible structure through which recanalization does not occur, providing more durable repair than that provided by coils.

The Onyx liquid embolic system consists of an ethylene–vinyl alcohol copolymer dissolved in anhydrous dimethyl sulfoxide (DMSO). Tantalum powder is added to the mixture for radiopacity. Onyx must be previously shaken for at least 20 min before injection to get homogeneous radiopacity of the mixture [10]. Concentration of the copolymer dissolved in DMSO determines the viscosity of the embolic agent. The lower the concentration of the copolymer, the less viscous the agent is and the more distal penetration can be achieved [10, 11]. If the mixture encounters aqueous solutions, precipitation of the polymer is initiated by diffusion of DMSO. This process begins on the surface while the core is still liquid, resulting in a soft, and non adherent mass. Therefore, Onyx has a lavalike flow pattern within blood vessels without any fragmentation during the injection. Due to these properties and because Onyx is not absorbable, it is capable of producing permanent vascular occlusion [10–12]. Using Onyx, the embolized vessels are completely filled by the embolic agent and are less fragile because of the lower inflammatory reaction and the absence of polymerization heat compared with NBCA-embolized. When the inflammatory reaction caused by Onyx was evaluated on histologic specimens on humans, the inflammatory reactions of the vessel wall were less pronounced and were located mainly intravasally, while no reaction of the surrounding interstitium, such as migration of lymphocytes into perivascular areas, was observed [12]. The inflammatory response and vascular toxicity seemed primarily to be associated with the injection rate, as the slow endovascular delivery of DMSO produced no untoward angiographic or pathologic changes but a fast injection of DMSO caused endothelial necrosis and severe inflammatory response in the arterial wall [13, 14].

According to this, Onyx should be the best way to reach embolization. One of the limitations is that it is very expensive. Our results have been excellent when used alone and intravascularly. The association with other embolizing agents, like glue, is to prefer when the sac is large; in this way we can get perfect and safe embolization of the sac. We have started to use it in EL that would need too much Onyx, in particular the last patient of the list with percutaneous approach and in two recent cases of type Ia EL embolization by DPSI was used at the end of the procedure to fill proximal cap with extreme precision.

The major weak point of the manuscript is represented by the small number of patients (12 patients) enrolled in a long time period (9-years). Furthermore, potential procedural bias is present on the basis of technical variables related to different treatments performed, without fixed indications. In addition, Onyx was used alone or combined with other embolic agents, with endovascular or

percutaneous approach on the basis of the operator confidence and/or experience; even this aspect may be considered a technical bias.

No randomized study comparing different embolic agent and its capacity to fill sac is now available; and it is difficult to achieve because even in large centers the number of cases is never so numerous.

On the basis of the characteristics described Onyx could be an ideal embolic agent and our experience demonstrated its safety; to overcome the necessity to use too much Onyx for a single procedure, it could be associated with others embolic agents and in particular its role could be to fill the gap remained in the sac filled by other embolic agents and to create a proximal cap communicating with the feeding vessel. Even this technical tip needs to be confirmed by more clinical practice.

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Compliance with ethical standards

Conflict of interest Authors declare to have no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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