Efficacy of Preemptive Embolization of Sac Branches During Endovascular Aneurysm Repair Using N-butyl-2-cyanoacrylate

Kimiaki OKADA[*1], Shinichiro SHIMURA[*1], Jun KOIZUMI[*2], Sohsyu KOTANI [*1], Shigeto ODAGIRI[*1], Tatsuya SEKIGUCHI[*3], Keisuke OZAWA[*1], Akiyoshi YAMAMOTO[*1], Goro KISHINAMI[*1], Takuto NAIKI[*1] and Yasunori CHO[*1]

[*1]*Department of Cardiovascular Surgery, Tokai University School of Medicine*
[*2]*Department of Radiology, Chiba University Hospital*
[*3]*Department of Diagnostic Radiology, Tokai University School of Medicine*

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Objective: A type 2 endoleak (T2EL) is the most frequently occurring endoleak type after endovascular aneurysm repair (EVAR). Residual T2ELs may cause aneurysm rupture; however, the management of a T2EL remains controversial. This study evaluated sac branch preemptive embolization using N-butyl-2-cyanoacrylate, aiming to prevent T2ELs and sac shrinkage.
Methods: Twelve consecutive patients underwent elective preemptive embolization during EVAR at our hospital between August 2018 to March 2019. Their demographic information, operative details, and sac diameters were examined at 6 months after EVAR.
Results: No procedural complications were observed. There were no in-hospital deaths among the 12 patients. Sac shrinkage was observed in this cohort (53.8−52.1 mm, $p = 0.01$). A total of 33 lumbar arteries were occluded with this procedure, and 2 patients had residual T2ELs at 6 months.
Conclusions: A T2EL in preemptive sac branch embolization during EVAR has advantages in terms of safety and reduction. Although no clear evidence is available for the management of T2ELs, this study proposes a new standard to prevent it and improve the long-term outcomes after EVAR. However, embolization remains imperfect and further research is necessary.

Key words: Endovascular aneurysm repair, type 2 endoleak, sac embolization, N-butyl-2-cyanoacrylate

INTRODUCTION

Endovascular aneurysm repair (EVAR) is associated with a significantly lower complication rate, lower in-hospital mortality rate, and shorter hospital stays compared with open surgery [1]. However, long-term observations revealed that approximately 20% of the patients required reintervention for sac enlargement caused by endoleaks after EVAR [2]. A type 2 endoleak (T2EL) is a retrograde inflow from sac branches mainly derived from the inferior mesenteric artery (IMA) and lumbar artery (LA), and is the most frequently occurring endoleak type. According to the Japanese Circulation Society (JCS) 2020 guidelines [3], prompt additional treatment or surgical conversion is required when type 1 or type 3 endoleaks are identified. However, there are no established treatment guidelines for T2ELs due to their low likelihood of rupture and because patients are less likely to respond to additional treatment. Recently, a series of studies have reported on T2ELs with a high level of evidence [4, 5]. One study indicated that the number of cases with aorta-related death after EVAR with residual T2ELs was significantly higher compared with those with no endoleak within 5 years of follow-up (2.6% vs. 0.3%, P = 0.015) [4]. The cumulative incidence rates of abdominal aortic aneurysm-related mortality (1.0% vs. 0.2%), rupture (0.8% vs. 0.1%), sac enlargement (27.4% vs. 2.7%), and reintervention (14.9% vs. 0.7%) were significantly higher in cases with persistent T2EL than in those with non-persistent T2EL (P < 0.001) [5]. Therefore, we can consider that the prognosis of residual T2ELs is no longer benign and the management of T2ELs is closely related to preventing sac enlargement and long-term survival.

Although the optimal management of T2ELs remains controversial, secondary transcatheter intervention is commonly selected for enlarged sacs with residual T2ELs. The success rate of secondary interventions is approximately 45%. Therefore, repeated interventions and careful follow-up may be required [5]. Previously, we considered that patent IMA should be coil embolized and routinely performed during EVAR to prevent T2ELs. More recently, several reports indicate that prophylactic treatment is effective for T2ELs [6−8]. This study investigated the efficacy of preemptive sac branch embolization during EVAR to prevent T2ELs, and the observed shrinkage. We believe that our preemptive embolization (PE) study (including its technical aspects) can help establish prophylactic treatment for T2ELs.

Shinichiro SHIMURA, Department of Cardiovascular Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-93-1121 Fax: +81-463-93-3806 E-mail: shinichiro.shimura@med.toho-u.ac.jp

Table 1 Baseline patient characteristics

Patient Characteristics (n = 12)	Mean [Range], (%)
Age (years)	76.1 [57–89]
Sex	Male 12, Female 0
Use of antiplatelet agents	8 (66.7)
Use of anticoagulant agents	3 (25.0)

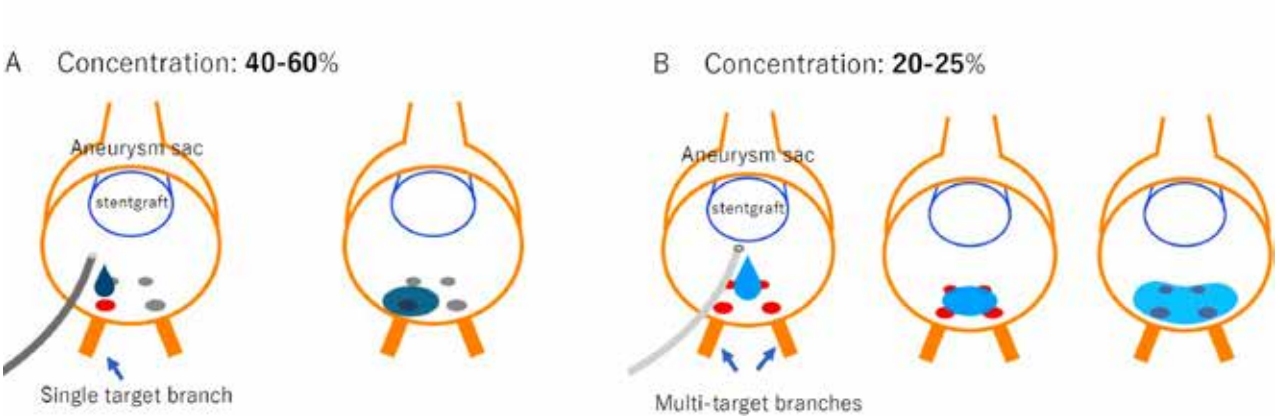

Fig. 1 Mixture of NBCA and Lipiodol Concentration
(A) A blend of NBCA and Lipiodol mixed at a concentration of 40–60% was utilized for the selective occlusion of a single sac branch.
(B) Conversely, a lower concentration of 20–25% was used for widespread occlusion aiming multi-sac branches. NBCA, N-butyl-2-cyanoacrylate

MATERIALS AND METHODS

Patients

Endovascular aneurysm repair employing intraoperative preemptive N-butyl-2-cyanoacrylate (NBCA) (Histoacryl; B. Braun, Aesculap, Germany) injection into the sac was performed on 12 consecutive patients with abdominal aortic aneurysms using the Excluder (W. L. Gore & Associates, Flagstaff, Ariz, USA) between August 2018 to March 2019. The median age was 73 (57–89) years and all patients were male. The patency of the LA was confirmed in all 12 of these cases using preoperative computed tomography (CT). Details regarding patient backgrounds are provided in Table 1. In accordance with the guidelines, our EVAR criteria were as follows: a short axis of aneurysm diameter >50 mm or a more than 10 mm-per-year increase in diameter, and a high risk for open surgery.

Regarding compliance with Instructions for Use, NBCA for medical use, hemostasis of skin wounds, and endoscopic sclerotherapy for esophagogastric varices are covered by insurance in Japan. Transcatheter injection into the arteries was not indicated during the study period.

This study was approved by the Ethics Committee of our institution (approval number: 17R-186). The investigation conforms with the principles outlined in the Declaration of Helsinki. All patients who underwent PE during EVAR provided informed consent.

Technique

For all cases, the procedure was performed under general anesthesia, and the bilateral femoral arteries were exposed. Initially, aortography detected a patent IMA, and coil embolization was routinely performed before deployment. Second, a 4Fr catheter was placed in the sac via the contralateral side of the DrySeal sheath (W. L. Gore & Associates, Flagstaff, Ariz). Subsequently, stent grafts were deployed according to standard protocols. Third, a mixture of NBCA and Lipiodol (Guerbet Japan, Tokyo, Japan) was injected from the catheter just above the target sac branch to confirm the absence of type 1 or 3 endoleaks. The mixture of NBCA and Lipiodol followed the force of gravity and covered the target branch ostia. A mixture of NBCA and Lipiodol concentrations should be used at 40–60% for selective occlusion; conversely, a lower concentration of 20–25% may be used for widespread occlusion (Fig. 1). Since patients undergo EVAR in the supine position, an NBCA laced with Lipiodol with a higher specific gravity of 1.275–1.290 was selectively implanted at the dorsal LA origins. Lipiodol concentrations of 40–60% were administered for single targets and 20–25% for multiple targets. This procedure prevents the spread of NBCA throughout the entire aneurysm. The endpoint of administration was the distribution of mixed NBCA to the target branches. Finally, the catheter was immediately removed, and digital subtraction angiography was performed to confirm that the flow to the sac had ceased.

Evaluation

Six months after EVAR, the demographic information, operative details, and sac diameters measured using CT were examined. Follow-up and imaging studies were routinely scheduled before discharge and 6 months postoperatively. The imaging studies were usually contrast-enhanced CT and ultrasound examinations. Axial CT was used to calculate the sac diameter and residual T2ELs. In cases that were difficult to distinguish from other types of endoleaks, an ultrasound examination was also performed. Sac diameter was calculated as follows: sac diameter = (maximal short axis + maximal long axis)/2.

Table 2 Intraoperative data

Intraoperative data (n = 12)	Mean [Range], (%)
Operative time (min)	170.3 [136–245]
Fluoroscopy time (min)	50.2 [32–104]
Dose of contrast medium (mL)	148.3 [84–200]
Number of occluded lumbar arteries	2.9 [1–6]
Number of occluded IMA	12 (100)

IMA, inferior mesenteric artery

The primary endpoint was the occurrence of T2ELs at 6 months. The secondary endpoint was whether the sac diameter shrunk at 6 months.

Statistical analyses

Data were analyzed using the Mann–Whitney *U*-test and Fisher's exact test for quantitative and categorical variables. A p-value < 0.05 was considered significant. All statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Details of intraoperative data are shown in Table 2. No procedural complications related to NBCA injections were observed. Endovascular aneurysm repair was an initial success in all patients. There were no deaths in the hospital. In this cohort, one patient died from pneumonia 2 months after EVAR. This patient was excluded from follow-up. A total of 33 LAs were occluded using this procedure. Mean operative values were as follows: time, 170.2 min; fluoroscopy time, 50.5 min; contrast use, 148.3 mL; number of occluded lumbar arteries, 2.9; and IMA occlusion rate, 100%.

Preemptive embolization showed a significant reduction in sac diameter: 53.8–52.1 mm ($P = 0.01$), and the reduction rate after 6 months was 3.2%. Two patients had residual T2ELs 6 months postoperatively.

DISCUSSION

Our study demonstrated advantages in terms of safety and reduction of T2ELs in preemptive sac branch embolization during EVAR. However, embolization remains imperfect.

A T2EL is a retrograde inflow from the sac branches and is the most frequently occurring complication of EVAR. T2ELs are generally considered benign. Though T2ELs are recognized intraoperatively, they may disappear over time. The incidence of T2ELs is not rare, varying from 7.8% to 25% [9]. The indications for secondary intervention after EVAR remain controversial. The JCS 2020 guidelines [3] show that further treatment is necessary when sac dilatation is observed. Ajalat *et al.* [10] reported the natural history of T2ELs with a mean follow-up period of 3 years and indicated that T2ELs did not require intervention; instead, T2ELs associated with another type of endoleak require more aggressive management. Kumar *et al.* [11] evaluated the natural history and treatment outcomes associated with type II endoleaks in an Australian cohort with a mean follow-up period of 1.9 years. There were no statistically significant differences in survival between subjects with and without T2ELs. They concluded that T2ELs with sac expansion are not associated with aneurysm rupture. The 2020 JCS guideline was developed based on this evidence. The observation period for T2ELs was slightly shorter in Kumar *et al.*'s study [11] cited in the JCS 2020 guidelines. However, our experience suggested that complications with T2ELs after EVAR often occur over 5 years after EVAR. Some studies suggest that residual T2ELs are not benign. Seike *et al.* [5] reviewed the results of endovascular aneurysm repair in patients from the Japanese Committee for Stentgraft Management registry to determine the significance of persistent T2ELs. Propensity score matching yielded higher estimated incremental risk, including abdominal aortic aneurysm-related mortality, rupture, sac enlargement (≥ 5 mm), and reintervention for persistent T2ELs ($P < 0.001$). They also observed T2EL-related abdominal aortic aneurysm-related mortality, rupture, sac enlargement, and reintervention 2 years after EVAR with increased incidence after 4 years or more. It is suggested that T2ELs affect aneurysm rupture after EVAR. Among 270 patients with aneurysm ruptures after EVAR, the cause was attributed to T2ELs in 23 patients (9.8%) [12]. Another meta-analysis of 32 studies, including 21,744 patients treated with EVAR indicated that there were 1,515 T2ELs and 393 secondary interventions, and 14 patients (0.9%) with an isolated T2EL experienced aneurysm rupture [13]. Moreover, a randomized controlled trial involving 1,252 patients revealed that the survival benefit of EVAR compared with conventional open repair disappeared during long-term observation [14]. This report established that the overall aneurysm-related mortality is a significant early benefit of EVAR during the first 6 months after the procedure. Additionally, it is influenced by an increase in aneurysm-related mortality after 4 years, with a significant difference after 8 years. Eden *et al.* [15] reviewed the effect of T2ELs on sac size changes to determine if sac expansion owing to a T2EL could result in the development of a type 1A endoleak. A total of 389 patients were included, with an average follow-up of 58.8 months. Follow-up imaging diagnosed 124 patients with T2ELs (32%). They had a significantly larger sac size increase compared with patients without T2ELs (9.50 vs. 0.78 mm; $P < 0.0001$). Those with T2ELs were significantly more likely to develop type 1A endoleaks than patients who did not have T2ELs (14% vs. 5%; $P = 0.004$). Thus, a residual T2EL should be recognized as a cause of aneurysm rupture that affects long-term survival. Hence, appropriate management of T2ELs must provide survival benefits after EVAR, and aggressive interventions should be taken for T2ELs. Recently, Samura *et al.* [8] reported on the effective prophylactic treatment for T2ELs. They evaluated the effect of IMA embolization during EVAR in patients at high risk of T2ELs (IMA patency with IMA ≥ 3 mm, lumbar arteries ≥ 2 mm, or an aortoiliac-type aneurysm) in a randomized con-

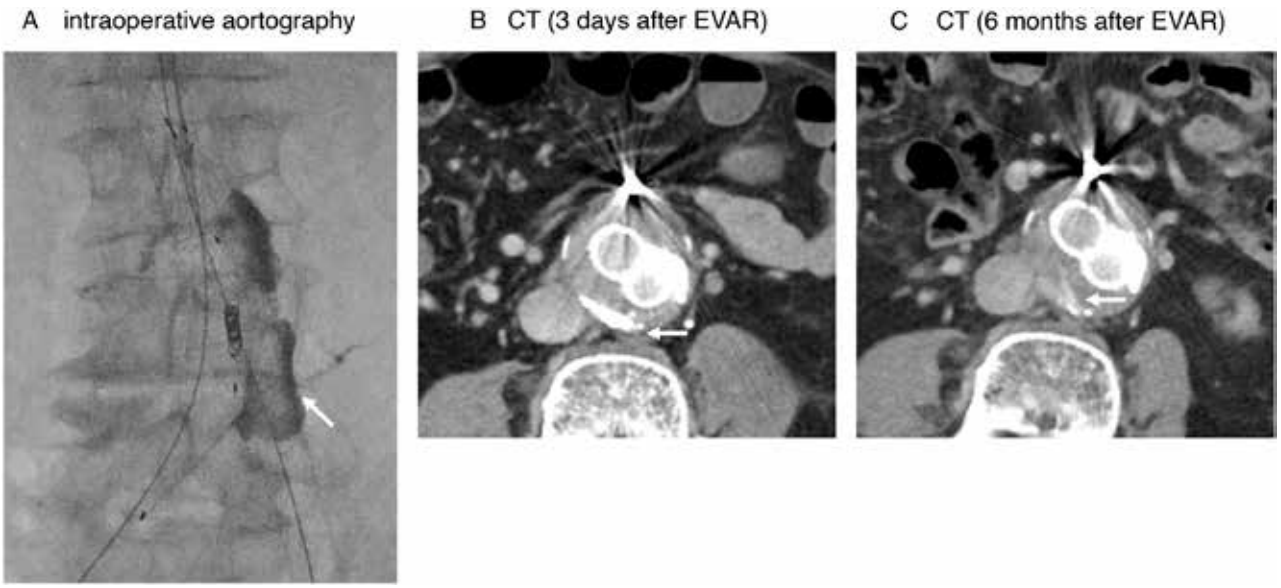

Fig. 2 Images of NBCA
(A) A lower concentration of NBCA was injected to cover multi-sac branches (white arrow).
(B) Computed tomography imaging revealed that NBCA occluded the orifice of the sac branch (white arrow).
(C) Six months after EVAR, the covered NBCA was invisible, and a T2EL was observed (white arrow).
EVAR, endovascular aneurysm repair; NBCA, N-butyl-2-cyanoacrylate; T2EL, type 2 endoleak

trolled trial. There were 133 high-risk patients, with 106 randomized. In the intention-to-treat analysis, the incidence of T2ELs was significantly lower in the embolization group than in the non-embolization group (24.5% vs. 49.1%; P = 0.009). Aneurysmal sac shrinkage was significantly greater in the embolization group (-5.7 ± 7.3 mm vs. -2.8 ± 6.6 mm; P = 0.037), and the incidence of aneurysmal sac growth related to T2ELs was significantly lower in the embolization group (3.8% vs. 17.0%; P = 0.030). They concluded that IMA embolization during EVAR in high-risk patients can effectively prevent aneurysmal sac enlargement associated with T2ELs.

Although the fundamental management of endoleaks involves prosthetic graft replacement (open surgical repair) with removal of the stent graft [16], most residual endoleaks after EVAR were treated with transcatheter intervention as a less invasive therapy considering the risk of open surgery. Several methods aimed at reducing T2ELs are available, including a transarterial approach (TA) and a direct percutaneous approach (DP) that provides sac branch embolization. However, the success rate of secondary transcatheter intervention is approximately 45% [6], is unsatisfactory, and repeated interventions are a concern. Therefore, intensive follow-up is required despite secondary intervention, and the optimal management of T2ELs remains to be elucidated.

Our strategy for preventing T2ELs using PE has some advantages compared with the TA and DP approaches. First, PE is easy and safe to access. Prior to deployment, a slender catheter was placed via the DrySeal sheath into the sac from the contralateral side of the femoral artery. When using the TA approach, the access route runs along the feeding vessels, thereby creating a collateral network with the superior mesenteric, iliolumbar, or internal iliac arteries. This network is evident after EVAR, although it is often narrow and tortuous, making access to the target sac branch challenging. Complications related to long access of TA may include buttock claudication [17] and neuropathy [18]. In contrast, the access route in the DP approach is close and linear according to CT or ultrasound guidance; however, fatal complications such as major vessel or organ injury should be carefully avoided. Operative mortality was higher after secondary DP (12.3%, P = 0.007) compared with TA (2.7%) [19]. Secondly, PE is less invasive than TA and DP. Meanwhile, a clinical case study comparing TA and DP showed that TA and DP required 177 and 85 min of operative time, respectively, and 74.8 and 12.7 mL of contrast medium was used, except for EVAR repair [20]. Hence, PE may be considered less invasive and troublesome.

At present, we described the reduction of T2ELs up to 6 months after EVAR compared to a previous report [21]. However, complete resolution of T2ELs could not be achieved through this procedure. Two patients showed residual T2ELs owing to the possible peeling and loss of the NBCA that covered the orifice of the lumbar arteries, potentially caused by retrograde back flow (Fig. 2). Further embolization deeper into the LA was required. These patients are still in outpatient care and are being followed up in our facilities. Although no clear evidence is available for the management of T2ELs, this novel study suggests a new standard to prevent it. Further investigations to reach NBCA into deeper lumbar arteries or alternative coil embolization should be evaluated in future randomized control studies to assess the efficacy of PE as a new standard treatment.

In conclusion, we discovered advantages in terms of safety and reduction of T2ELs in preemptive sac branch embolization during EVAR. However, embolization remains imperfect, and further research is necessary.

AUTHOR CONTRIBUTIONS

Kimiaki Okada conducted the research and wrote the article. Shinichiro Shimura conducted and managed the research as a corresponding author and an equal contributor. Jun Koizumi constructed the study design, evaluated preoperative imaging, and directed the technical supervision. Tatsuya Sekiguchi contributed to the practical procedures. Sohsyu Kotani, Shigeto Odagiri, Keisuke Ozawa, Akiyoshi Yamamoto, Goro Kishinami, and Takuto Naiki contributed to data analysis and interpretation. Yasunori Cho revised the final version of the article. All authors revised the manuscript and contributed to the final version of the article.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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