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Phase II Trial of Transarterial Embolization Using an *n*-Butyl-2-Cyanoacrylate/Lipiodol Mixture (JIVROSG-0802)

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Abstract

Purpose To evaluate the embolic effect and the safety of transarterial embolization (TAE) using *n*-butyl-2-cyanoacrylate (NBCA) in a prospective multicenter trial.

Materials and Methods This study was an open-label, multicenter, phase II trial. The inclusion criteria were (1) active bleeding or pseudoaneurysm, (2) true aneurysm, (3) arteriovenous malformation (except cerebral lesion), (4) arteriovenous fistula, or (5) need for arterial distribution before transarterial treatment. Selective TAE with NBCA diluted 2–10 times was performed. The primary endpoint was the success rate of embolization with a per-patient analysis based on the angiographic findings. Secondary endpoints were safety, evaluated based on Common Terminology Criteria for Adverse Events (CTCAE) version 4, and the success rate of embolization with a per-vessel calculation.

Results Sixty-five patients were initially enrolled, but due to protocol violation in two patients, efficacy was ultimately analyzed in 63 patients (103 vessels) and safety was analyzed in 64 patients. The success rate per patient was 98.4% (62/63; 95% confidence interval (CI), 91.5–100.00), and the success rate per vessel was 99.0% (102/103; 95% CI, 94.7–100.0). Adverse events of grade 3 or above based on CTCAE version 4 occurred in 22/64 patients (34.4%). Twelve intraoperative or postoperative adverse events grade 3 or above, which may have been related to embolization using NBCA, occurred in 11/64 patients (17.2%). Three patients died after embolization using NBCA, but their deaths were unrelated to TAE.

Conclusion In this prospective multicenter clinical trial, the efficacy of TAE using NBCA was 98.4% and adverse events were clinically acceptable.

Level of Evidence Level 3b.

Keywords Transarterial embolization · NBCA · Phase II study

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Introduction

N-butyl-2-cyanoacrylate (NBCA) acts as an embolic material due to its polymerization reaction with anions in the blood, regardless of coagulopathic conditions, followed by cast and thrombus formation [1–6]. The ratio of NBCA to ethiodized oil in a preparation affects polymerization time in vessels and provides controllability of the penetration into the target vessels [7]. NBCA is currently widely used in vascular interventions for aneurysm, vascular malformation, bleeding, arterial redistribution, portal vein embolization, endoleak after endovascular aortic repair (EVAR) or thoracic EVAR (TEVAR), palliative treatment for polycystic kidney, and other pathophysiologies [1, 2, 5–23]. However, in most countries, other than for cerebral arteriovenous malformation and fistula embolization, NBCA is used on an off-label basis for other indications. The main reason for this is the lack of evidence required to meet the existing regulatory recommendations.

Most of the reports on the use of NCBA to date are retrospective studies [1, 2, 6–11, 13–18, 21–28], and there are few prospective studies focused on the efficacy and safety of NBCA in embolization [15, 22, 23]. Therefore, it is critical that evidence meeting the regulatory recommendations, in the form of a prospective clinical trial, is collected.

The purpose of this multicenter, prospective study was to evaluate the embolic effect and safety of NBCA in various clinical settings, with a view to the approval of NBCA for TAE.

Materials and Methods

Patients

The inclusion criteria were as follows: (1) active bleeding or pseudoaneurysm (associated with any cause), (2) true aneurysm, (3) arteriovenous malformation, (4) arteriovenous fistula, or (5) need for arterial distribution before transarterial treatment (e.g., embolization for the right gastric artery before chemoinfusion therapy for hepatic tumor). In all patients, indication of embolization using NBCA was determined based on angiographic results. Patients in whom failure of embolization with other embolic material was confirmed on angiography in the same session were also included. Exclusion criteria were: (1) cerebral arteriovenous malformation, (2) cerebral aneurysm, (3) disseminated intravascular coagulation (DIC), (4) unstable hypotension (shock index $\geq$ 1.5), and (5) endoleak after EVAR/TEVAR. Patients with cerebral arteriovenous malformation were excluded because prospective reports have been published regarding TAE using NBCA for cerebral arteriovenous malformation [8, 9]. Cerebral aneurysm was excluded because coil is generally used in embolization for cerebral aneurysm and TAE using NBCA is not adopted. Patients with DIC and unstable hypotension were also excluded because these patients are not appropriate candidates for evaluating safety and efficacy of embolization with NBCA due to their existing deteriorated condition. It may be challenging to evaluate the embolic effect of NBCA on angiography in patients with endoleak after EVAR/TVAR due to the complex anatomy of targeted vessels; therefore, these patients were also excluded.

All participating institutions obtained approval from the relevant institutional review board, and informed consent was obtained from all the enrolled patients.

Study Design

This study was a multicenter phase II trial performed by Japan interventional Radiology in Oncology Study Group (JIVROSG). Informed consent was obtained from each patient who was thought to be a candidate for the present study. Patients were consequently registered via the Internet during angiography when the use of NBCA was determined based on angiography results. In all patients, embolization using NBCA was performed after patient registration.

Embolization procedures were performed by board-certified, interventional radiologists (Fig. 1). Conventional angiography was obtained through the parent catheter, and the target vessel was identified. A microcatheter was advanced to the target vessel and flushed with glucose solution just before injection of NBCA. After flushing microcatheter, NBCA diluted with lipiodol (2–10 times) was injected selectively. Microcatheters were removed immediately after the injection of NBCA. Pre- and post-embolization angiography was recorded to evaluate the embolic effect.

The embolic effect was evaluated by an Independent Response Evaluating Committee composed of 3 interventional radiologists with 15, 20, and 28 years of experience in embolization procedures. Angiography findings were evaluated, and the embolic effect was judged by consensus. Embolization was judged as effective when the distal blood flow of the target vessel was completely blocked.

Indications for embolization, hematological data, and the shock index were documented before embolization. Technical results of angiography and embolization, intraoperative adverse events, postoperative adverse events, hematological data after embolization (within 24 h, 2–7 days later, and 21–35 days later) were also evaluated. Patients were followed up for 4 weeks after embolization.

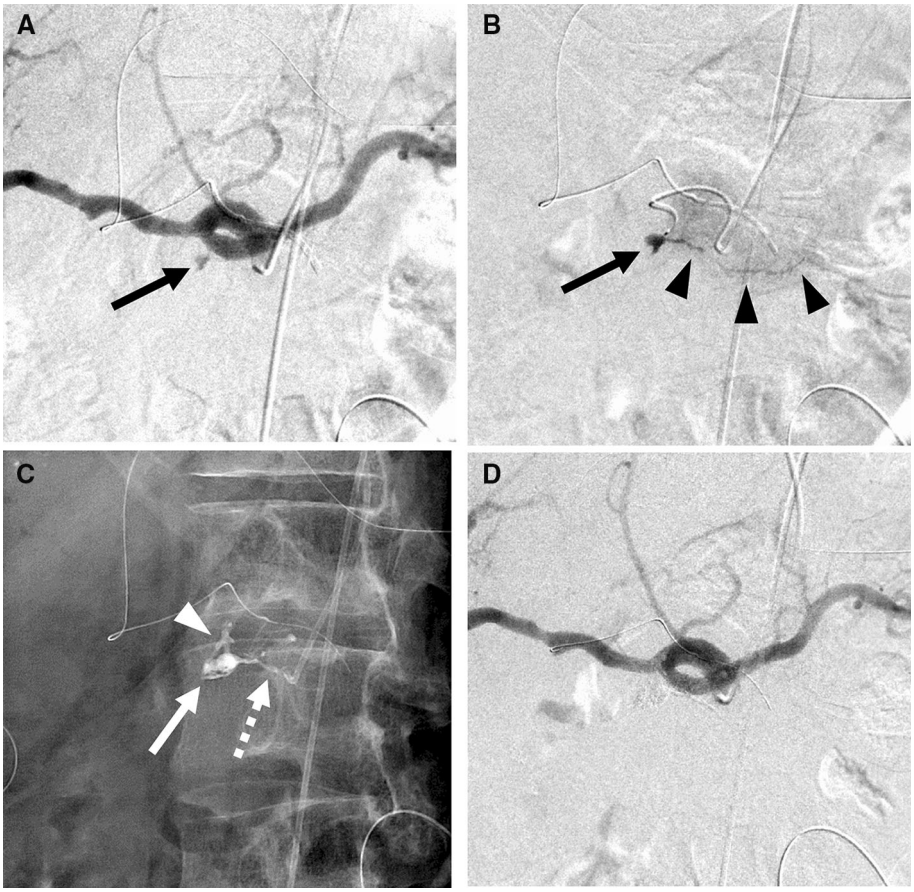

Fig. 1 A 74-year-old male who underwent pylorus preserving pancreatoduodenectomy 9 days before had hemoperitoneum and angiography was performed. **A** Angiography of the celiac artery before TAE. Pseudoaneurysm in the dorsal pancreatic artery arising from the splenic artery (arrow) was visualized. **B** Selective angiography of dorsal pancreatic artery using microcatheter before TAE. Pseudoaneurysm (arrow) and peripheral artery (arrow heads) of the dorsal pancreatic artery was depicted. Microcatheter could not be advanced more distally. **C** Fluoroscopic image after TAE using NBCA. Cast of NBCA–lipiodol mixture distributes distal (dotted arrow), inside (arrow) and proximal (arrow head) of pseudoaneurysm. **D** Angiography of the celiac artery after TAE. Disappearance of pseudoaneurysm was confirmed on the angiography

Endpoints

The primary endpoint was the success rate of embolization with a per-patient analysis. In patients who underwent embolization for multiple vessels, embolization was judged as successful when all target vessels were embolized effectively. Embolization was deemed to have failed in a patient if the embolic effect was insufficient in 1 or more vessels. Secondary endpoints were safety and success rate of embolization per vessel. Safety was evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4 [29]. Events for which grading increased by 1 or more after embolization were regarded as adverse events.

Statistical Analysis

Previous reports have suggested that the efficacy of embolization using NBCA is $> 80\%$ [1, 2, 10–12], and a treatment efficacy of at least 50% was expected in the current study. Therefore, with H1; $p = 0.08$, H0; $p = 0.05$, using a two-sided t test and an alpha error of 0.05, a sample size of 19 patients would provide greater than 80% power to detect the difference in efficacy. Conversely, the clinically acceptable incidence of severe or unpredictable adverse events was deemed to be $< 5\%$. A sample size of 59 patients was calculated based on an adverse events rate of $< 5\%$ with a 95% confidence interval (CI). Consequently, 59 patients were required to test the efficacy and safety of embolization using NBCA in this phase II study. Because emergent cases would also be enrolled in the study, we planned to enroll a total of 65 patients to allow for a 10% rate of dropout from the study.

Results

From June 2014 to April 2016, 83 patients were evaluated for possible entry into this study and 65 patients were enrolled based on angiographic findings from 16 institutions (Supplementary Table 1), (Table 1). Embolization with NBCA was accomplished in all patients. One patient was excluded from the full analysis set (FAS) because arterial embolization was performed for venous gastrointestinal bleeding caused by pancreatic cancer, which conflicted with the inclusion criteria of the study. Another patient underwent arterial embolization with NBCA before registration of the patient; hence, that patient was excluded

Table 1 Patient characteristics in the phase II trial of transarterial embolization using an NBCA/lipiodol mixture (N = 64)

Characteristics	
Age in years [median (range)]	61 [24–75]
Sex (male/female)	39/25
Indications for embolization[a]	
Active bleeding/pseudoaneurysm	21
True aneurysm	1
Vascular malformation	14
Arteriovenous fistula	1
Arterial redistribution before transarterial treatment	26
Shock index[b]	
< 0.5	0
0.5–1.0 <	18
1.0–1.5 <	3
≥ 1.5	0

[a]One patient who underwent transarterial embolization for venous gastrointestinal bleeding was excluded from the evaluation of the success rate of embolization due to conflict with the inclusion criteria

[b]Results of 21 patients who underwent TAE using NBCA for active bleeding/pseudoaneurysm on an emergency basis are shown

Table 2 Characteristics of transarterial embolization in 63 patients and 103 vessels

Characteristics	Number	(%)
Region of target vessels		
Head and neck	14 vessels	(13.6)
Chest	6 vessels	(5.8)
Abdomen and pelvis	66 vessels	(64.1)
Limbs	17 vessels	(16.5)
Number of target vessels in each patient		
1	36 cases	(57.1)
2	19 cases	(30.2)
3	5 cases	(7.9)
4	2 cases	(3.2)
5	None	(0)
6	1 case	(1.6)
Embolic material other than NBCA		
Yes	27 patients	(42.9)
	37 vessels[a]	(35.9)
No	36 patients	(57.1)
	66 vessels	(64.1)

NBCA *n*-butyl-2-cyanoacrylate

[a]Coil in 34 vessels and polidocanol in 3 vessels prior to embolization with NBCA

from the FAS and the safety analysis set due to violation of the protocol. Consequently, 63 patients and 103 vessels were evaluated as the FAS (Table 2). Mean dilution ratio of NBCA was 30.3% (median, 33.3%; range, 10.0–66.7%). Embolic materials other than NBCA were used prior to NBCA in 27 patients and 37 vessels (coils for 34 vessels and polidocanol for 3 vessels), and in these patients subsequent embolizations using NBCA were performed due to insufficient initial embolic effect. Safety was evaluated in 64 patients, excluding the 1 patient who underwent embolization before registration.

Success Rate of Embolization Per Patient

The efficacy of embolization was deemed effective in all target vessels in 62 out of 63 evaluable patients (98.4%; 95% CI, 91.5–100.0). In one patient, effectiveness was not evaluable because angiography was not performed after embolization, and thus, embolization could not be deemed successful.

Success Rate of Embolization Per Vessel

Embolization was evaluated as successful in 102 out of 103 vessels; thus, the success rate per vessel was 99.0% (95% CI, 94.7–100.0). One vessel was not evaluable because of the lack of post-embolization angiography in the same patient as described in the previous section.

Safety

Forty-one severe adverse events (grade 3 or above as defined by the CTCAE version 4) occurred in 22/64 patients (34.4%; 95% CI, 17.0–36.5) (Table 3). Twelve severe intraoperative or postoperative adverse events, which may have been related to embolization using NBCA, occurred in 11 patients. Intraoperative adverse events included nontarget embolization ($n = 1$), pain ($n = 1$), vasovagal reflex ($n = 1$), and bleeding ($n = 1$) in 4 patients. No life-threatening AE or treatment-related death (≥ grade 4) occurred during the procedure. Postoperative hematological adverse events related to embolization using NBCA were grade 4 elevated aspartate aminotransferase (AST) ($n = 2$), grade 3 elevated AST ($n = 1$), grade 4 elevated alanine aminotransferase (ALT) ($n = 1$), grade 3 elevated ALT ($n = 1$), and grade 4 elevated serum amylase ($n = 1$). Since 1 patient had elevation both of AST and of ALT after TAE, 4 patients had grade 3/4 elevation of AST/ALT after TAE. Among these 4 patients, embolized arteries were the replaced right hepatic artery for arterial distribution in 1 case, the right inferior phrenic artery for arterial distribution in 1 case, the gastroduodenal artery and the replaced left hepatic for arterial distribution in 1 case, and splenic artery for bleeding caused by acute pancreatitis in 1 case. The patient who had grade 4 elevation of serum amylase had received TAE for first jejunal artery for bleeding

Table 3 Adverse events grade 2 or above

Adverse event	Grade 2		Grade 3		Grade 4		Grade 5	
	Number	(%)	Number	(%)	Number	(%)	Number	(%)
Nonhematologic adverse events								
Fever	4	(6.3)	–	–	–	–	–	–
Pain	9	(14.1)	1	(1.6)	–	–	–	–
Urticaria	–	–	1	(1.6)	–	–	–	–
Anemia	11	(17.2)	4	(6.3)	–	–	–	–
Nausea	1	(1.6)	–	–	–	–	–	–
Vasovagal reaction	–	–	1	(1.6)	–	–	–	–
Intraoperative hemorrhage	–	–	1	(1.6)	–	–	–	–
Intraoperative vascular injury	1	(1.6)	–	–	–	–	–	–
Postoperative hemorrhage	1	(1.6)	–	–	–	–	–	–
Intra-abdominal hemorrhage	–	–	1	(1.6)	–	–	–	–
Hematoma	1	(1.6)	–	–	–	–	–	–
Nontargeting embolization	–	–	1	(1.6)	–	–	–	–
Skin ulceration	–	–	1	(1.6)	–	–	–	–
Stroke	2	(3.1)	–	–	–	–	–	–
Duodenal stenosis	1	(1.6)	–	–	–	–	–	–
Ventricular arrhythmia	–	–	1	(1.6)	–	–	–	–
Nervous system disorder	1	(1.6)	–	–	–	–	–	–
GVHD	–	–	–	–	–	–	1	(1.6)
Hepatic failure	–	–	–	–	–	–	1	(1.6)
Sudden death NOS	–	–	–	–	–	–	1	(1.6)
Total (events)	32		12		–		3	
Hematological adverse events								
AST increased	5	(7.8)	4	(6.3)	3	(4.7)	–	–
ALT increased	3	(4.7)	4	(6.3)	2	(3.1)	–	–
ALP increased	2	(3.1)	–	–	–	–	–	–
Cr increased	1	(1.6)	1	(1.6)	–	–	–	–
Serum amylase increased	–	–	–	–	1	(1.6)	–	–
Blood bilirubin increased	8	(12.5)	1	(1.6)	–	–	–	–
Hypoalbuminemia	12	(18.8)	1	(1.6)	–	–	–	–
Hyponatremia	–	–	3	(4.7)	–	–	–	–
Hyperkalemia	–	–	1	(1.6)	–	–	–	–
Hyperglycemia	8	(12.5)	1	(1.6)	–	–	–	–
Reduced white blood cell count	1	(1.6)	2	(3.1)	1	(1.6)	–	–
Reduced platelet count	4	(6.3)	1	(1.6)	–	–	–	–
Total (events)	44		19		7		–	

GVHD graft-versus-host disease, *NOS* not otherwise specified, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *Cr* creatinine

caused by recurrent duodenal cancer. Postoperative non-hematological adverse events related to embolization using NBCA were grade 3 skin ulceration ($n = 1$) and grade 3 urticaria ($n = 1$). The patient who had skin ulceration did not recover on 30 days after TAE, and index finger of right hand was amputated lastly. All of the other patients recovered from adverse events except 3 patients who died within 30 days after TAE mentioned below. Other adverse events were deemed to be unrelated to embolization.

Three patients died after embolization using NBCA (5 days, 11 days, and 20 days after TAE, respectively). Two patients died due to deterioration of primary disease (graft-versus-host disease and hepatic failure due to hepatocellular carcinoma). One patient received embolization using NBCA for duodenal bleeding caused by trauma and underwent surgical repair for duodenal perforation 4 days after embolization. Intraoperative findings revealed no ischemic change in the duodenum, and it was considered

that the cause of perforation was trauma. However, this patient had a sudden cardiopulmonary collapse 20 days after embolization and died. A definitive cause of death could not be determined via autopsy.

Discussion

In the present multicenter, prospective study, embolization using NBCA exhibited a high success rate (98.4%) per patient and a high efficacy rate (99%) per vessel. NBCA has been widely used as an embolic material in various vascular interventions [1, 2, 5–23], but robust evidence is yet to be established. A few prospective studies investigating embolization using NBCA for cerebral arteriovenous malformation or varicoceles have been reported [8, 9, 21], but evidence pertaining to the safety and efficacy of NBCA and its embolic effect in situ in other fields is limited. TAE using NBCA for bleeding or pseudoaneurysm has been adopted for various pathophysiologies, such as iatrogenic bleeding [6, 10, 12, 24], traumatic bleeding [6, 17, 25], pseudoaneurysm caused by pancreatitis [12], nasal bleeding [1], hemoptysis [26], and gastrointestinal bleeding [2, 18], and the associated efficacy rates were 95–100% [1, 2, 6, 10, 12, 25]. In previously reported studies, the success rates of arterial redistribution before transarterial treatment were also high, 93.0–99.3% [11, 23]. However, all of these were retrospective case series studies. The high success rate of the present prospective study, which included various clinical settings and regions in the body, suggests equivalent efficacy to that found in these previous studies; therefore, the study yielded robust evidence pertaining to embolic effect of NBCA.

Adverse events including hematological adverse events grade 3 or above were found in 22 patients (34.4%). The reason for the high incidence of adverse events was that the study included patients with various conditions, such as trauma or postsurgical bleeding, prior to NBCA embolization. Twelve adverse events grade 3 or above, which were thought to be related to TAE, occurred in 11 patients (17.2%), and all of them were predictable clinically. Four patients had grade 3/4 elevation of AST/ALT, and 1 patient had grade 4 elevation of serum amylase elevation relating to TAE using NBCA, but all of these hematological adverse events were tolerable since these hematological parameters dropped to the range before TAE within 30 days after TAE. Previous reports suggest that various adverse events may be associated with TAE including nontarget embolization such as cerebral infarction [27], spinal cord infarction [28], pain [26], fever [22], gastrointestinal ischemia followed by ulceration, perforation or stenosis [2, 18], cholecystitis [22], splenic infarction [7], renal infarction [24], soft tissue injury [20], peripheral nerve injury [20], and pancreatitis [30]. Nontarget embolization might be caused by overflow of NBCA to proximal vessels, migration of NBCA upon withdrawal of a microcatheter, or unintended inflow of NBCA through a collateral vessel. Other adverse events, including local pain, bleeding, nausea/vomiting, and fever, and adverse events specific to NBCA, such as intravascular fixation of the microcatheter [9], secondary vascular rupture after withdrawal of a fixed catheter [25], and disrupted and residual microcatheter [9], have been reported. In the current study, there were no adverse events related to fixation of the catheter caused by NBCA. Procedure-related death did not occur in the current study. Three patients died during the follow-up period, but in all patients the cause of death was deterioration of the primary disease. Therefore, the results of the current study suggest that TAE using NBCA is safe and that the ensuing adverse events are acceptable clinically.

Various embolic agents including coils, plugs, particles, and liquid materials have been used for vascular intervention, and they are used as appropriate depending on pathophysiology, vascular anatomy, the condition of patients, and the characteristics of each embolic material [7, 31–33]. NBCA is a liquid embolic material, and it is used to complement insufficient embolic effects of a coil alone [10, 23] or when a microcatheter cannot be advanced to the ideal position for coil embolization [2, 7, 12]. The present study included patients with such clinical situations we encounter in the real-world clinical practice settings. Because the embolic effect of NBCA does not depend on the coagulation status of the patient, NBCA is also reportedly a reliable embolic material for patients with coagulopathic conditions such as DIC [6]. Additionally, the depth of embolization can be controlled by changing the polymerization time by modifying the ratio of NBCA to ethiodized oil [7]. This characteristic of NBCA can be utilized to overcome the shortcomings of other embolic materials. In contrast, experience and skill are required to handle NBCA properly because nontarget embolization or intravascular fixation of the microcatheter can occur [9, 10, 21, 25]. In the present study, embolization using NBCA was performed by certified interventional radiologists in various clinical contexts including emergent cases with bleeding or pseudoaneurysm, arteriovenous malformation, arteriovenous fistula, and arterial redistribution before transarterial treatment, and whether to use NBCA was decided based on angiography results. Furthermore, NBCA was used in addition to other methods when the embolic effect of another embolic material used prior was insufficient in 27/63 patients (42.9%) and 37/103 vessels (35.9%). Consequently, success rates of 98.4% per patient and 99.0% per vessel were obtained. These results endorse the outstanding characteristics of NBCA and suggest that it

can be used effectively in various clinical settings as long as it is used by experienced interventional radiologists who possess the required technical skills.

One of the limitations of the current study was the exclusion criteria. Because DIC was excluded from the study, we could not evaluate the efficacy of NBCA in patients with coagulopathy. However, the condition of patients with DIC is generally poor and clinically unstable, and thus, they are not suitable candidates for a clinical trial designed to evaluate the efficacy and safety of an embolic agent or method. Notably, the current study included emergent cases with bleeding or pseudoaneurysm, and we selected patients who were viable candidates for TAE and could foreseeably tolerate the procedure, and we followed patients up for 4 weeks based on vital signs (e.g., monitored whether their shock index was less than 1.5). Patients involving endoleak after EVAR/TEVAR were also excluded from the present study, in which angiography was required before and after TAE to evaluate the efficacy of TAE using NBCA. Arteries responsible for endoleak can be tortuous and difficult to cannulate. Therefore, angiography after TAE using NBCA for evaluating the efficacy of embolic effect might not always be easy to achieve in such patients; hence, the current study excluded patients with endoleak after EVAR/TEVAR. The second limitation of the study was the short follow-up period of 4 weeks, which is not sufficient for the evaluation of late complications such as intestinal stricture, which may occur more than 4 weeks after TAE [18, 30]. However, most complications caused by embolization using NBCA occur in the early period after TAE [18, 26–28, 30]; therefore, we adopted a follow-up period of 4 weeks to evaluate the safety of TAE using NBCA. The third limitations were its heterogeneity of indication for TAE, diversity of interventions, and same follow-up regimen. However, one of the purposes of the current study was to evaluate embolic effect of NBCA in the target vessels based on angiographic findings. Therefore, we considered that inclusion of diverse conditions and interventions could attest embolic effect of NBCA and match the purpose. The fourth limitation was including patients in whom other embolic material was used. Use of other embolic materials would confuse the evaluation of embolic effect of NBCA. However, NBCA is often used as additional embolic material when the other embolic materials failed to accomplish embolization in real world, and failure of embolization using other embolic materials was confirmed on angiography before the use of NBCA in all cases in the current study. Therefore, authors considered that including patients whose embolization using other embolic materials was ineffective would suit the purpose of the current study. In conclusion, this prospective multicenter clinical trial clearly revealed that the efficacy of TAE using NBCA was extremely high and adverse events were clinically acceptable.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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 Informed consent was obtained from all individual participants included in the study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

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