Original Article

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Prospective Evaluation of the Safety and Feasibility of N-Butyl Cyanoacrylate Embolization

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Abstract

Purpose: Several studies have reported the benefits of embolization with N-butyl cyanoacrylate (NBCA); however, few of them have been prospectively studied. This study aimed to prospectively evaluate the safety and feasibility of NBCA embolization, including cases of coagulopathy and/or unstable hemodynamics.

Materials and Methods: This study involved a sample of 20 cases treated with NBCA embolization. Cases were excluded from the study if other embolic substances were considered more suitable, if NBCA embolization was utilized for cerebral and coronary vessels, or if the operators determined that NBCA use was unsuitable.

Results: There were no cases of severe adverse events specific to NBCA and embolization was successful in all cases.

Conclusion: NBCA embolization is a safe and feasible treatment option, even for cases of coagulopathy and/or unstable hemodynamics.

Key words: NBCA, embolization, bleeding, endoleak

Introduction

Percutaneous embolization is a commonly used procedure for treating various conditions affecting blood vessels. The devices and materials used for embolization include metallic coils, gelatin sponges, vascular plugs, microspheres, and n-butyl cyanoacrylate (NBCA), each of which has different characteristics. NBCA is a cyanoacrylate-based instant adhesive that is known to polymerize and adhere when in contact with anions in the blood; this property has recently been leveraged for intravascular embolization. The characteristics that distinguish NBCA from other embolic materials are that it is a liquid and can reach vessels distal to the catheter tip with the blood flow, it has a short time to achieve embolic effect[1)], the embolic effect tends to be maintained for a longer duration[2, 3)], it is useful even in patients with coagulopathy[4)], it has the ability to embolize vessels as a cast[5)], and it has the ability to control the extent of embolization by mixing it with lipiodol[6, 7)]. Nevertheless, NBCA has some specific difficulties. It is originally a medical adhesive; thus, backflow of NBCA around the catheter tip can cause the catheter to adhere to the vessel wall. If the mixing ratio with lipiodol is not appropriate or if NBCA flows back, it can embolize an undesired area. Therefore, some recommend that NBCAs should be used by experienced operators or with their assistance[2)].

Several benefits of NBCA embolization have been reported; however, only a few have been prospectively studied[8)]. In this study, we prospectively

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evaluated the safety and feasibility of NBCA embolization at a single center.

This study was approved by the institutional review board at St. Marianna University School of Medicine (approval number: 2520).

Materials and Methods

This study aimed to evaluate the safety and feasibility of embolization with NBCA in a small sample of 20 cases. It began in August 2015 and was completed after the 20th case. NBCA embolization was the treatment method in all the cases. When consent could be obtained for a case, a signed consent form was obtained for all cases. The investigators explained the study to the patients or their proxies using a consent document that included the purpose, methods, alternative treatments, and possible complications, as approved by the institutional review board, and obtained their free will consent in writing. For emergency cases where consent could only be obtained after the study, the purpose, methods, alternative treatments, and possible complications of the treatment were explained to the patient or his/her proxy as much as possible. Subsequently, patient consent was obtained and noted in the medical records.

Patients

In accordance with the characteristics of NBCA and the guidelines published by the Japanese Society of Interventional Radiology in 2014[2)], the inclusion and exclusion criteria for this study were set as follows.

The study included patients for whom embolization with metallic coils, gelatin sponges, vascular plugs, or microspheres was not expected to be adequate for bleeding, pseudoaneurysms, hypervascular tumors, and vascular lesions (such as aneurysms, vascular malformations, endoleaks after aortic stenting, and varicose veins) and arterial redistribution before transarterial treatment (in other words, embolization of other branches in order to concentrate the drug distribution in the targeted artery, such as in arterial injection chemotherapy). Specifically, the following situations were included in the study: 1) cases in which it was deemed difficult to reach the target lesion due to the condition of the vessels, because metallic coils or vascular plugs cannot be delivered to the target in such cases; 2) cases in which the condition of the blood vessels indicates a possible deviation of the metallic coils or vascular plugs; 3) cases in which it was deemed necessary to embolize blood vessels for long sections, such as vascular malformations and arteriovenous fistulas; 4) cases in which embolization time must be shortened; 5) cases in which the embolization effect must be maintained for a long duration; 6) cases with coagulopathy; and 7) situations in which NBCA must be used as an emergency evacuation, such as in cases of severe hemorrhage with unstable hemodynamics. Patients were excluded from the study if embolization with other embolic substances was deemed more useful, if NBCA embolization was used for cerebral and coronary vessels, or if operators determined that NBCA use was unsuitable for other reasons such as vascular anatomy. The operators determined the inclusion of the patients in this study according to the criteria mentioned above. Because it was expected that cases of severe bleeding would be included in the study, it was not possible to set further eligibility criteria that would limit the choice of embolizing materials to the operators.

Study discontinuation criteria

The criteria for discontinuing participation in the study were as follows: 1) patient withdrawal of consent; 2) discovery of patient ineligibility after enrollment; and 3) operator decision to discontinue treatment for other reasons. Severe NBCA-specific adverse events were promptly reported to the institutional review board and the Clinical Trial Subcommittee for permission to continue the study. The NBCA-specific adverse events were the adherence of the catheter to the vessel wall and the embolization of non-target vessels due to undesired NBCA spread. The serious adverse events were considered to be the following: need for additional treatments, prolonged hospitalization, permanent disability, life-threatening situation, or death.

Treatment Method

Interventional radiologists with at least eight years and sufficient experience with NBCA were enrolled as operators. The catheter or puncture needle was inserted at the target site via intravascular approach or percutaneously: catheterization was used in cases where it was deemed possible to approach the target intravascularly from nearby; in cases where the target was large and difficult to approach intravascularly, as in type 2 endoleaks, the needle was percutaneously punctured directly in the target under image guidance. A contrast agent was injected through the lumen of the catheter or needle to determine the mix-

Table 1. Patients Characteristics

Case	Age (years)	Sex	Indications	Coagulopathy	Hemodynamics
1	90	F	Leg bleeding	Yes	Unstable
2	62	F	Duodenal bleeding	N/A	Unstable
3-1	77	M	Type 2 endoleak	No	Stable
3-2	79	M	Type 2 endoleak	No	Stable
4	83	M	Type 2 endoleak	No	Stable
5	56	M	Pancreatic cancer bleeding	No	Unstable
6	30	M	Duodenal bleeding	Yes	Unstable
7	72	F	Retroperitoneal hemorrhage	Yes	Stable
8	43	F	Pelvic fracture	Yes	Unstable
9	68	M	Adrenal bleeding	No	Stable
10	80	F	Extraperitoneal hemorrhage	Yes	Unstable
11	79	M	Type 2 endoleak	No	Stable
12	89	F	Gastric bleeding	Yes	Unstable
13	52	F	Breast cancer	No	Stable
14	56	F	Breast cancer	No	Stable
15	86	M	Type 2 endoleak	No	Stable
16	71	M	Impending rupture of type 1a endoleak	No	Stable
17	75	M	Abdominal aortic aneurysm	No	Stable
18	50	F	Retroperitoneal hemorrhage	Yes	Unstable
19	88	M	Type 2 endoleak	No	Stable

M: male, F: female, N/A: Not Available

ing ratio of NBCA and lipiodol based on the distance to the target, vessel diameter, and flow velocity. The basis for the determination was that the higher the ratio of NBCA, the earlier the NBCA-Lip polymerizes after injection to achieve an embolic effect; while the lower the ratio of NBCA, the longer it takes to polymerize after injection and the farther the NBCA-Lip reaches the site to achieve an embolic effect. To prevent embolization in the catheter due to premature polymerization, the lumen of the catheter or puncture needle was flushed with a 5% glucose solution and NBCA-Lip was immediately injected under X-ray fluoroscopy or digital subtraction angiography (DSA). After injection, the catheter/puncture needle was immediately removed to prevent vessel wall adhesion. If necessary, the above procedure was repeated until complete embolization. The use of an adjunctive metallic coil or balloon catheter was also acceptable to better control the extent of embolization than that with NBCA alone.

Assessment

Assessment of safety and feasibility was determined by changes in physical findings, blood tests, and imaging studies. For safety evaluation, we evaluated NBCA-specific adverse events; the study was designed to include several cases of critical bleeding with severe systemic conditions, which are not appropriate for evaluating the safety of embolization. For the same reason, we did not define clinical success in this study. Instead, a satisfactory disappearance of blood flow in the embolized vessel on angiography or a filling enough NBCA into the endoleak sac indicated a successful embolization. As a rule, post-embolization evaluations were performed either on the same day or 1—7 days after embolization.

Results

From December 2015 to December 2017, 20 procedures were performed for 19 patients in this study. The patient characteristics and methods are shown in **Table 1** and the embolization sites and procedure methods in **Table 2**. Two procedures were performed for type 2 endoleak for one case (case 3). However, due to a 22-month interval between the procedures and the use of different techniques, they

Table 2. Embolization Sites and Procedure Methods

Case	Embolization sites	Approach	Adjunctive embolic materials
1	Branch of the popliteal artery Branch of the peroneal artery Branches of the posterior tibial artery	Transarterial	None
2	PSPDA	Transarterial	Metallic coils
3-1	Endoleak sac Lumber artery	Transarterial	Metallic coils
3-2	Endoleak sac Lumber artery	Direct puncture	Metallic coils
4	Endoleak sac IMA	Transarterial	Metallic coils
5	GDA	Transarterial	Metallic coils
6	Branches of GDA	Transarterial	None
7	Deep iliac circumflex artery	Transarterial	None
8	Internal iliac arteries	Transarterial	None
9	Subphrenic artery	Transarterial	Metallic coils
10	Lumber arteries	Transarterial	None
11	Endoleak sac IMA	Direct puncture Transarterial	None
12	Splenic artery	Transarterial	None
13	Internal mammary artery	Transarterial	Metallic coils
14	internal mammary artery	Transarterial	None
15	Endoleak sac	Transarterial	None
16	Endoleak sac	Transarterial	None
17	Intenal iliac artery	Transarterial	None
18	Lumber artery	Transarterial	None
19	Lumber arteries	Direct puncture	None

PSPDA: posterior superior pancreaticoduodenal artery, IMA: inferior mesentelic artery, GDA: gastroduodenal artery

were considered independent of each other. The study was terminated, as scheduled, after the twentieth case. The ages ranged from 30 to 90 years (mean 69.3 years). The patients included 10 males and nine females. Embolization was performed for different purposes: to control arterial bleeding in 10 cases, to embolize endoleaks after aortic stenting in seven procedures for six cases, to alter arterial distribution before transarterial chemotherapy for extensive breast cancer in two cases, and to embolize the internal iliac artery before aortic stenting for the remaining case. Seven patients had coagulopathy, and eight patients had hemodynamic instability; all of them had bleeding problems.

The embolized sites were endoleak sacs for six procedures in five cases, lumbar arteries for 5 procedures in 4 cases, gastroduodenal artery (GDA) or branches for two cases, internal iliac arteries for two cases, internal mammary arteries for two cases, arteries of the lower extremities for one case, posterior superior pancreaticoduodenal artery (PSPDA) for one case, internal mesenteric artery (IMA) for one case, subphrenic artery for one case, deep iliac circumflex artery for one case, and splenic artery for one case. The methods of approach to the site of embolization included the transarterial catheter approach for 17 procedures, direct puncture for two procedures, and their combination for one procedure. Seven procedures used adjunctive embolic material, all of which were metallic coils, and none of the procedures used balloon catheters as an adjunct.

There were no cases of severe adverse events specific to NBCA and embolization was successful for all cases.

Discussion

There have been reports on the use of NBCA as an intravascular embolic material for treating various diseases, such as embolization of aneurysms to prevent rupture[9], hemostasis for severe bleeding[10-13], embolization to control blood loss before surgical removal of hypervascular tumors[14, 15], embolization for vascular malformation[16-18], arterial redistribution before transarterial treatment[19], and embolization for endoleak after aortic stent placement[20, 21]. The use of NBCA embolization to treat cerebrovascular disease[16, 18] and varicose veins[22] has been reported by several prospective studies; however, only a few prospective studies have reported on its use to treat other diseases.

Sugawara et al. recently reported 64 cases treated with embolization using NBCA in a multicenter prospective study; the majority of these cases were active bleeding, pseudoaneurysms, vascular malformations, and arterial redistribution before transarterial treatment[8]. However, in that study, cases of disseminated intravascular coagulation (DIC) and unstable hypotension were excluded because they were deemed inappropriate for the evaluation of safety and usefulness, and cases of endoleaks after aortic stenting were excluded because they were challenging to evaluate for the embolic effect. In contrast, our study did not exclude these cases because we considered them to be inherently important for NBCA applications. Of the 10 cases of bleeding in our study, seven were associated with coagulopathy and eight with unstable hemodynamics, indicating that NBCA was more likely to be selected for cases of severe bleeding leading to coagulopathy and/or unstable hemodynamics. Furthermore, other than the bleeding cases, cases of endoleak after aortic stenting were the most common.

There have been several reports of adverse events specific to the use of NBCA, such as catheter adherence to the vessel wall resulting in catheter rupture[18, 23], NBCA fragment dispersion during catheter withdrawal and consequent non-target embolization[18], and non-target vessel embolization due to the unexpected peripheral spread of the NBCA or central overflow from the tip of the infusion catheter[18, 24, 25]. However, to the best of our knowledge, these reports only highlighted a few adverse events of NBCA and rarely indicated their frequency. The prospective study by Sugawara et al. reported that grade ≥ 3 adverse events, thought to be related to embolization, occurred in 17.2% of cases[8]. Embolization naturally results in ischemia of the dominant region as a trade-off for its efficacy. However, based on guidelines of the Japanese Society for Interventional Radiology, we focused on the undesired spread of the NBCA and catheter adherence to the vessel wall as NBCA-specific complications[2]. Adopting this definition, NBCA-specific adverse events described in the study by Sugawara et al. included only one case of non-target embolization (1.6%). In our current study, no NBCA-specific adverse events were observed.

In the prospective study by Sugawara et al., the success rates of embolization were reported to be 98.4% for cases and 99.0% for vessels. In contrast, embolization was successful for all cases in our current study, with a success rate of 100%. While several retrospective studies have already reported the usefulness of NBCA embolization for cases of coagulopathy or unstable hemodynamics[4, 12, 26], our current study is noteworthy because we have demonstrated in a prospective study that NBCA embolization can have a 100% success rate, even for patients with coagulopathy and/or unstable hemodynamics.

The lack of adverse events specific to NBCA and the high success rate of embolization in this study relative to previous reports can be attributed to the careful case selection since the final decision to use NBCA in this protocol depends on the decision of the individual operators. In addition, the embolization procedures were performed by experienced operators.

This study has some limitations. First, it was based on a few cases at a single center. Second, there may have been selection bias with the high rates of bleeding and endoleaks. Third, the selection of cases for NBCA embolization and technical factors such as the mixing ratio of NBCA-Lip and its injection location depends on the operator's experience and subjectivity. Fourth, adverse events caused by embolization were not evaluated. Finally, the observation period was short.

In conclusion, NBCA embolization is safe and feasible, even for cases of coagulopathy and/or unstable hemodynamics. In other words, our results also support the safety and feasibility of NBCA embolization in cases of severe bleeding in a prospective study.

Conflicts of Interest

The authors have nothing to disclose.

References

1) Oowaki H, Matsuda S, Sakai N, et al. Non-adhesive cyanoacrylate as an embolic material for endovascular neurosurgery. Biomaterials 2000; 21: 1039−1046.
2) Takeuchi Y, Morishita H, Sato Y, et al. Guidelines for the use of NBCA in vascular embolization devised by the Committee of Practice Guidelines of the Japanese Society of Interventional Radiology (CGJSIR), 2012 edition. Jpn J Radiol 2014; 32: 500−517.
3) Igarashi S, Izuchi S, Ishizuka B, et al. A case of pregnancy and childbirth after uterine artery embolization with a permanent embolic agent. Fertil Steril 2011; 95: 290.e9- 290.e11.
4) Yonemitsu T, Kawai N, Sato M, et al. Evaluation of transcatheter arterial embolization with gelatin sponge particles, microcoils, and n-butyl cyanoacrylate for acute arterial bleeding in a coagulopathic condition. J Vasc Interv Radiol 2009; 20: 1176−1187.
5) Luo CB, Teng MM, Chang FC, et al. Transarterial embolization of acute external carotid blowout syndrome with profuse oronasal bleeding by N-butyl-cyanoacrylate. Am J Emerg Med 2006; 24: 702−708.
6) Stoesslein F, Ditscherlein G, Romaniuk PA. Experimental studies on new liquid embolization mixtures (histoacryl-lipiodol, histoacryl-panthopaque). Cardiovasc Intervent Radiol 1982; 5: 264−267.
7) Takasawa C, Seiji K, Matsunaga K, et al. Properties of N-butyl cyanoacrylate-iodized oil mixtures for arterial embolization: in vitro and in vivo experiments. J Vasc Interv Radiol 2012; 23: 1215−1221.
8) Sugawara S, Arai Y, Sone M, et al. Phase II Trial of Transarterial Embolization Using an n-Butyl-2-Cyanoacrylate/Lipiodol Mixture (JIVROSG-0802). Cardiovasc Intervent Radiol 2019; 42: 534−541.
9) Guziński M, Kurcz J, Kukulska M, et al. Embolization of a True Giant Splenic Artery Aneurysm Using NBCA Glue - Case Report and Literature Review. Pol J Radiol 2015; 80: 155−158.
10) Extrat C, Grange S, Chevalier C, et al. Safety and efficacy of emergency transarterial embolization for mesenteric bleeding. CVIR Endovasc 2022; 5: 5. doi: 10.1186/s42155−021−00281-z
11) Haraguchi T, Hamaguchi S. Nonselective Bilateral Embolization of Internal Iliac Arteries with N-Butyl-2-Cyanoacrylate in Hemodynamically Unstable Patients with Pelvic Fracture. Interv Radiol 2021; 6: 37−43.
12) Park KJ, Shin JH, Yoon HK, et al. Postpartum hemorrhage from extravasation or pseudoaneurysm: efficacy of transcatheter arterial embolization using N-butyl cyanoacrylate and comparison with gelatin sponge particle. J Vasc Interv Radiol 2015; 26: 154−161.
13) Kodani M, Yata S, Ohuchi Y, et al. Safety and Risk of Superselective Transcatheter Arterial Embolization for Acute Lower Gastrointestinal Hemorrhage with N-Butyl Cyanoacrylate: Angiographic and Colonoscopic Evaluation. J Vasc Interv Radiol 2016; 27: 824−830.
14) Ishihara H, Ishihara S, Niimi J, et al. The safety and efficacy of preoperative embolization of meningioma with N-butyl cyanoacrylate. Interv Neuroradiol 2015; 21: 624−630.
15) Dossani RH, Waqas M, Rai HH, et al. Use of N-butyl 2-cyanoacrylate (nBCA) for preoperative tumor embolization. J Neurointerv Surg 2022; 14: neurintsurg-2021−017400. doi: 10.1136/neurintsurg-2021−017400.
16) Loh Y, Duckwiler GR, Onyx Trial Investigators. A prospective, multicenter, randomized trial of the Onyx liquid embolic system and N-butyl cyanoacrylate embolization of cerebral arteriovenous malformations. Clinical article. J Neurosurg 2010; 113: 733−741.
17) Liu HM, Huang YC, Wang YH. Embolization of cerebral arteriovenous malformations with n-butyl-2-cyanoacrylate. J Formos Med Assoc 2000; 99: 906−913.
18) n BCA Trail Investigators. N-butyl cyanoacrylate embolization of cerebral arteriovenous malformations: results of a prospective, randomized, multicenter trial. AJNR Am J Neuroradiol 2002; 23: 748−755.
19) Takizawa K, Shimamoto H, Ogawa Y, et al. Development of a new subclavian arterial infusion chemotherapy method for locally or recurrent advanced breast cancer using an implanted catheter-port system after redistribution of arterial tumor supply. Cardiovasc Intervent Radiol 2009; 32: 1059−1066.
20) Lagios K, Karaolanis G, Bazinas T, et al. Translumbar Infusion of N-Butyl Cyanoacrylate for the Treatment of Type II Endoleaks. J Vasc Interv Radiol 2018; 29: 826−832.

21) Horinouchi H, Okada T, Yamaguchi M, et al. Mid-term Outcomes and Predictors of Transarterial Embolization for Type II Endoleak After Endovascular Abdominal Aortic Aneurysm Repair. Cardiovasc Intervent Radiol 2020; 43: 696–705.
22) Vanlangenhove P, De Keukeleire K, Everaert K, et al. Efficacy and safety of two different n-butyl-2-cyanoacrylates for the embolization of varicoceles: a prospective, randomized, blinded study. Cardiovasc Intervent Radiol 2012; 35: 598–606.
23) Wakhloo AK, Perlow A, Linfante I, et al. Transvenous n-butyl-cyanoacrylate infusion for complex dural carotid cavernous fistulas: technical considerations and clinical outcome. AJNR Am J Neuroradiol 2005; 26: 1888–1897.
24) Serafin Z, Karolkiewicz M, Strzesniewski P, et al. Palliative percutaneous kidney embolization with enbucrilate in patients with renal cell carcinoma: safety and symptom control. Med Sci Monit 2007; 13 (Suppl 1): 98–104.
25) Mavili E, Donmez H, Ozcan N, et al. Endovascular treatment of lower limb penetrating arterial traumas. Cardiovasc Intervent Radiol 2007; 30: 1124–1129.
26) Patidar Y, Srinivasan SV, Singh J, et al. Clinical Outcomes of Transcatheter Arterial Embolization Using N-butyl-2-cyanoacrylate (NBCA) in Cirrhotic Patients. J Clin Exp Hepatol 2022; 12: 353–361.