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LABORATORY INVESTIGATION

Feasibility and Safety of *n*-Butyl Cyanoacrylate–Lipiodol–Iopamidol as an Alternative Liquid Embolic Material

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Abstract

Purpose To evaluate the feasibility and safety of *n*-butyl cyanoacrylate (NBCA)–Lipiodol–Iopamidol (NLI) as a liquid embolic material.

Materials and Methods In vitro, the ratio of NLI components was adjusted and the configuration of the mixtures was assessed visually in saline. In vivo, 14 wide-necked aneurysms were created on the common carotid and external iliac arteries of four female swine. Under balloon occlusion, 12 aneurysms were embolized with NLI prepared at a NBCA–Lipidol–Iopamidol ratio of 2:3:1 (NLI231), and two were embolized with NBCA–Lipiodol (NL) prepared at a NBCA–Lipiodol ratio of 1:2 (NL12) as a trial group. We performed angiography to evaluate the effectiveness of embolization and adhesion of the embolic material to the balloons or microcatheters.

Results In vitro, NLI231 (33% NBCA) was considered to be the optimal ratio for aneurysm embolization based on its configuration and stability. In vivo, embolization using NLI231 was successful and no adhesion between the embolic material and the balloons or microcatheters was observed in all 12 aneurysms. Embolization with NL12 was impossible in the other two aneurysms due to leakage and adhesion of NL.

Conclusion The configuration of NLI changed at each ratio. NLI231 is a feasible and safe liquid embolic material for balloon-assisted embolization of wide-necked aneurysms in swine.

Keywords *n*-Butyl cyanoacrylate · Lipiodol · Iopamidol · Balloon-assisted packing · Aneurysm · Embolization

Abbreviations

NBCA	*n*-Butyl cyanoacrylate
NL	NBCA–Lipiodol
NLE	NBCA–Lipiodol–ethanol
NLI	NBCA–Lipiodol–Iopamidol
NL12	NBCA–Lipiodol prepared at a ratio of 1:2
NLI231	NBCA–Lipiodol–Iopamidol prepared at a ratio of 2:3:1

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Introduction

Transcatheter embolization is the first-choice treatment for gastrointestinal bleeding, tumor bleeding, traumatic bleeding, postoperative bleeding, pseudoaneurysm rupture, visceral aneurysms, and arteriovenous malformations. Metallic coils, gelatin sponges, microspheres, and liquids like cyanoacrylate are currently used as the embolic materials. Metallic coils have two advantages: First, the embolization site is relatively easy to control using coils, and second, coil embolization is associated with a low risk of tissue damage [1–5]. However, disadvantages of metallic coils are that they are expensive, they require a long procedure time, and they are limited to embolization of sites that can be reached by the catheter, which typically restricts their use to proximal embolization [6]. Particulate embolic materials, such as gelatin sponges, may flow to the periphery of the arterial branch causing distal embolization and potentially tissue necrosis [7]. Another disadvantage of gelatin sponges is that hemostasis is dependent on secondary thrombi, which makes it difficult to achieve hemostasis in patients with a coagulopathy [8].

n-Butyl cyanoacrylate (NBCA) has been used as a liquid embolic material for transcatheter treatment of active bleeding and vascular malformation for many years, and its usefulness is widely reported [9–17]. NBCA is often mixed with Lipiodol (NBCA–Lipiodol; NL) to improve its visibility under X-ray fluoroscopy and to modify its polymerization speed [9–17]. As a liquid embolic material, NL has several advantages, including low cost and short procedure time. However, NL has strong adhesive properties and can cause adhesion between the catheter and the blood vessel wall or occlusion of the catheter lumen [18]. To overcome these problems, anhydrous ethanol was added to NL to yield the mixture NBCA–Lipiodol–ethanol (NLE), which is less adhesive than NL [19–22]. However, anhydrous ethanol is highly irritating and must be prepared separately, before mixing with NL. Considering these limitations of NL and NLE, we developed a liquid embolic material, NBCA–Lipiodol–Iopamidol (NLI) by adding a nonionic iodine contrast agent (Iopamirone) to NL. Iopamirone causes less irritation of blood vessels compared with anhydrous ethanol and does not need to be prepared separately. In addition, we hypothesized that NLI is less adhesive, enabling aneurysm embolization under balloon occlusion. In this study, we determined the optimal ratios of NLI components in vitro and evaluated the feasibility and safety of NLI in animal experiments.

Materials and Methods

Preparation of NLI

First, NL was prepared by mixing NBCA (Histoacryl, B. Braun, Melsungen, Germany) and Lipiodol (Ultra-Fluide®, Guerbet, Roissy, France) in a 2.5-mL syringe with a shaking or pumping method using a three-way stopcock. Next, Iopamirone (370 mg iopamidol/mL; Bayer, Leverkusen, Germany) was mixed with NL using a 2.5-mL syringe, using a pumping method with a three-way stopcock. The pumping frequency was 15 reciprocations in 15 s.

In Vitro Study

NLI was prepared at NBCA–Lipidol–Iopamidol ratios of 1:1:1 (NLI111), 1:2:1 (NLI121), 1:3:1 (NLI131), 2:2:1 (NLI221), 2:3:1 (NLI231), 2:4:1 (NLI241), and 1:2:0 (NL12) (Table 1). Each NLI mixture was injected into a cup filled with 100 mL of physiological saline through a 24 G needle. The configuration that each mixture formed was observed visually and was classified as a noodle-type, a single large droplet, medium droplets, and small droplets.

In Vivo Study

The animal experiment was approved by the institutional ethics review committee and was performed in accordance with the "Act on the Protection and Management of Animals" and the "Standards for the Care and Storage of Laboratory Animals and Alleviation of Pain" of Japan.

We used four healthy female swine weighing 50–52 kg. Preanesthesia was conducted with a combination of 5 mg/kg ketamine and 0.08 mg/kg atropine sulfate. General anesthesia was maintained with isoflurane gas via

Table 1 Ratios of the NLI components and their configurations in vivo

NBCA	Lipiodol	Iopamidol	Configuration
1	1	1	NT
1	2	1	SLD
1	3	1	MD
2	2	1	SLD
2	3	1	SLD/MD
2	4	1	MD
1	2	0	SD

NLI *n*-butyl cyanoacrylate (NBCA)–Lipiodol–Iopamidol, *NT* noodle type, *SLD* single large droplet; *MD* medium droplets; *SD* small droplets

intubation. Cardiac and respiratory data were monitored throughout the procedures. The common carotid arteries, external iliac arteries, and jugular veins were surgically exposed in each swine to create an aneurysm. First, the jugular vein, approximately 3 cm long, was removed and the resected piece of the vein was sutured onto the common carotid arteries and external iliac arteries under interrupted arterial blood flow. We created 14 aneurysms on the common carotid and external iliac arteries (Table 2).

In all swine, embolization of the aneurysms was performed immediately after their creation. First, 6 Fr sheaths (Radifocus Introducer II H, Terumo Clinical Supply, Gifu, Japan) were inserted via the bilateral femoral arteries, followed by a 4 Fr guide catheter (JB2, Medikit, Tokyo, Japan or 1CJ, Hanako Medical, Saitama, Japan). Preoperative angiography of the common carotid or external iliac artery was then performed using an X-ray system (Allura Xper FD 20, Royal Philips Electronics, Amsterdam, Netherlands). Next, a 2.1 Fr microcatheter (Virtus, Boston Scientific, Natick, MA) was inserted through the guide catheter, and the microcatheter was advanced into the aneurysm using a 0.016 in. microguidewire (Meister, Asahi Intecc, Aichi, Japan). A small amount of contrast agent was injected through the microcatheter to confirm that its tip was located in the aneurysm. Then, a 5 Fr balloon catheter (Mustang, Boston Scientific; 6 mm diameter, 40 mm long) was inserted through the sheath of the contralateral femoral artery and was placed at the neck of the aneurysm using a 0.035 in. guidewire (Radifocus Guide wire M, Terumo Clinical Supply, Gifu, Japan). A single polymer that forms single large droplets is most suitable for aneurysm embolization. Therefore, we selected NLI231, which has a single large droplet configuration, for this study (Fig. 1B). As a comparator, we used NL12 with the same concentration of NBCA (33% NBCA). To prevent polymerization of NBCA in the microcatheter, 5% glucose solution was injected into the microcatheter just before the injection of NLI231 or NL12. The balloon was inflated to 2 atm to prevent migration of NLI231 or NL12 outside the aneurysms. After inflating the balloon, NLI231 or NL12 was injected through the microcatheter using a 1-mL syringe (MEDALLION, Merit Medical, Salt Lake City, UT). The endpoint of embolization was defined as complete filling of the aneurysm with NLI or NL, as observed by angiography. Twelve aneurysms were embolized with NLI231, and the other two aneurysms were embolized with NL12 as a trial group (Table 2). After injecting NLI231 or NL12, the microcatheter was removed. The balloon occlusion time was 3 min. Subsequently, the balloon was deflated, and the balloon catheter was removed. Angiography was repeated using a guide catheter. We evaluated the state of the aneurysms, the effectiveness of embolization, migration of the embolic material, and adhesion of the embolic material to the balloons or catheters by comparing pre- and postoperative angiography.

Table 2 Outcomes of NLI231 and NL12 for aneurysm embolism in swine in vivo

		NLI or NL volume (mL)	Aneurysm			Leakage	Catheter adhesion	Embolization
			Diameter (mm)	Neck width (mm)	Dome-to-neck ratio			
1	NLI231	0.3	8.6 × 9.0	5.7	1.58	–	–	Complete
2	NLI231	0.2	6.2 × 7.4	4.1	1.8	–	–	Complete
3	NLI231	0.2	5.8 × 7.9	4.1	1.93	–	–	Complete
4	NLI231	1.4	12.3 × 14.9	8.3	1.8	–	–	Complete
5	NLI231	2.1	15.5 × 17.4	8.8	1.98	–	–	Complete
6	NLI231	0.7	10.7 × 11.4	6.4	1.78	–	–	Complete
7	NLI231	1.0	9.1 × 15.4	8.2	1.88	–	–	Complete
8	NLI231	1.3	14.0 × 14.2	8.4	1.69	–	–	Complete
9	NLI231	1.1	12.9 × 13.1	9.2	1.42	–	–	Complete
10	NLI231	0.3	8.1 × 8.9	4.6	1.93	–	–	Complete
11	NLI231	0.5	9.6 × 11.1	8	1.39	–	–	Complete
12	NLI231	0.4	9.1 × 9.4	5.1	1.84	–	–	Complete
13	NL12	0.5	10.1 × 10.9	7	1.56	+	+	NE
14	NL12	0.2	7.9 × 8.0	4.8	1.67	+	+	NE

NLI231 *n*-butyl cyanoacrylate (NBCA)–Lipiodol–Iopamidol prepared at a ratio of 2:3:1, *NL12* NBCA–Lipiodol prepared at ratio of 1:2, *NE* not evaluable

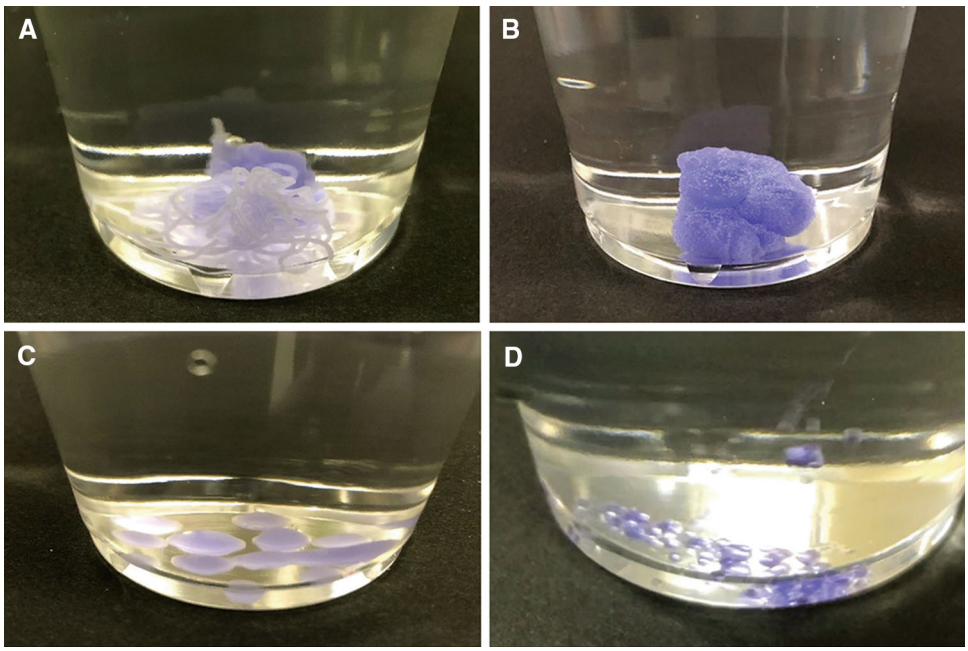

Fig. 1 Representative photographs showing the configurations of *n*-butyl cyanoacrylate (NBCA)–Lipiodol–Iopamidol (NLI) prepared at different ratios and NBCA–Lipiodol (NL). **A** NLI prepared at a ratio of 1:1:1 shows a noodle-type configuration. **B** NLI prepared at a ratio of 2:3:1 forms a single large droplet. **C** NLI prepared at a ratio of 1:3:1 forms medium droplets. **D** NL prepared at a ratio of 1:2 forms small droplets

Results

In Vitro Study

The configurations that the mixtures formed in saline solution were classified as follows: NLI111 as noodle type; NLI121 as a single large droplet; NLI131 as medium droplets; NLI221 as a single large droplet; NLI231 as a single large droplet/medium droplets; NLI241 as medium droplets; and NL12 as small droplets (Table 1, Fig. 1). The configuration of NLI changed at each ratio.

In Vivo Study

All 12 aneurysms were successfully embolized with NLI231. NLI231 did not leak into the parent artery or adhere to the catheters, which allowed us to remove the catheters from the artery. Postoperative angiography showed complete embolization of all 12 aneurysms (Fig. 2). In contrast, embolization was unsuccessful in two aneurysms treated with NL12 due to leakage of NL12 into the parent artery during embolization and catheter adhesion (Fig. 3).

Discussion

Our in vitro study revealed changes in the configuration of the NLI mixture in saline depending on the ratio of its components. These changes appear to be due to the effect of Iopamirone on the polymerization of NBCA. Iopamirone has numerous hydroxyl groups, which influence the polymerization of NBCA. The polymerization of NBCA starts slowly after adding Iopamirone to NL. This change is greatly affected by the relative Iopamirone content; increasing the Iopamirone content resulted in quicker polymerization of NL. At the highest tested Iopamirone content, the polymerization was rapid and NLI formed a noodle-type configuration. At the decrease in the Iopamirone content, NLI formed single large droplet, medium droplet, and small droplet configurations. When the Iopamirone content was unchanged, polymerization occurred quicker with increasing NBCA content. The single large droplet configuration is considered to be the most suitable configuration for aneurysm embolization because this configuration allows the mixture to extrude from the catheter into the aneurysm as a single mass. We hypothesized that, by injecting NLI in a single large droplet configuration, it is possible to embolize the aneurysm completely without leaving any gaps. Because the medium and small droplet configurations are smaller than the single large droplet configuration, NLI in the medium and small configurations is more likely to reach the periphery. Therefore, these configurations may be useful for emergency hemostasis of peripheral arteries that cannot be reached with a catheter. Because mixture NLI111 giving the noodle-type configuration has a high viscosity, it is difficult to inject it through a thin microcatheter.

In the in vivo study, all 12 aneurysms were completely embolized with NLI231 under balloon occlusion. NLI is unlikely to adhere to the balloon or catheters. We hypothesize that NLI polymerizes rapidly and forms a solid film on the surface, and this coating may reduce the anchoring effect between the substances and reduce

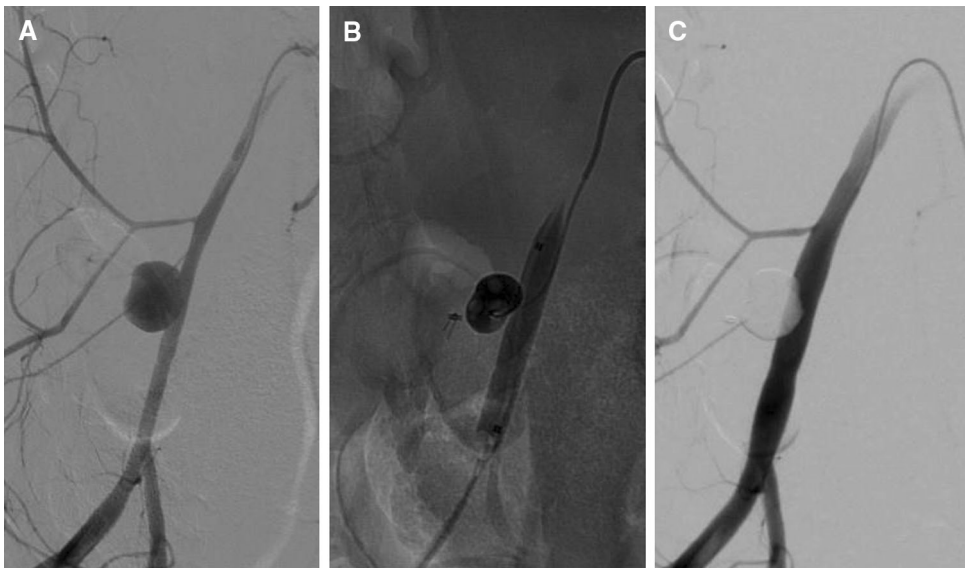

Fig. 2 Angiographic images obtained before, during, and after embolization of the aneurysm with *n*-butyl cyanoacrylate–Lipiodol–Iopamidol prepared at a ratio of 2:3:1 (NLI231). **A** Angiography before embolization showing the aneurysm on the right external iliac artery. **B** Angiography during embolization showing no leakage of NLI. **C** Angiography after embolization showing complete embolization of the aneurysm

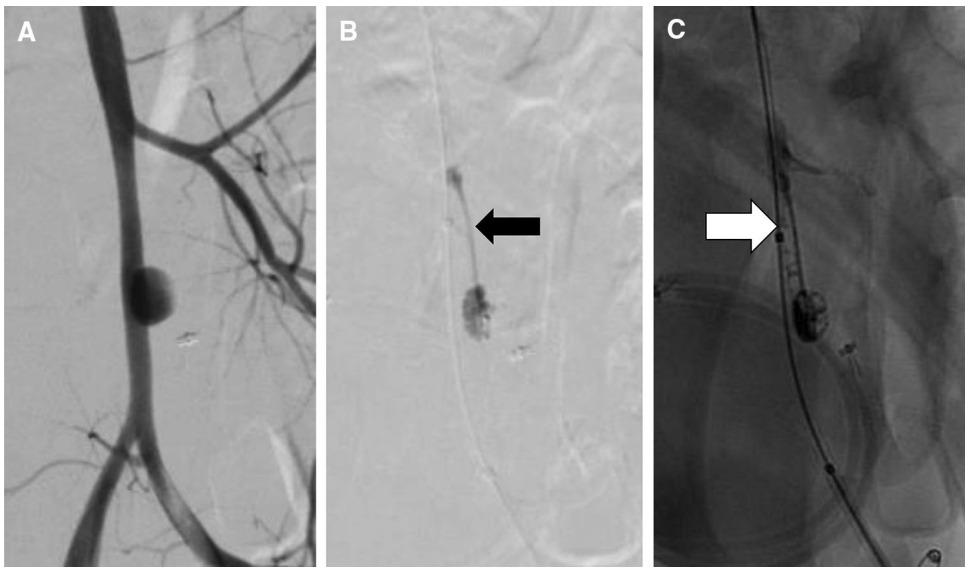

Fig. 3 Angiographic images obtained before, during, and after embolization of the aneurysm with *n*-butyl cyanoacrylate–Lipiodol prepared at a ratio of 1:2 (NL12). **A** Angiography before embolization showing the aneurysm on the left external iliac artery. **B** Angiography during embolization showing leakage of NL during the procedure (black arrow). **C** Angiography after embolization showing adhesion of NL12 to the catheter (white arrow)

adhesiveness. The low adhesion of NLI is similar to that of NLE. In clinical settings, embolization is performed using NLE because of its low adhesiveness [23–27]. Therefore, we believe that embolization with NLI, which also shows low adhesiveness, could be performed safely in clinical practice. We also suggest that switching anhydrous ethanol to Iopamirone could reduce adverse events due to irritation. However, embolization of the aneurysm with NL12 under balloon occlusion was impossible in the other two aneurysms. This result is consistent with results reported by Tanaka et al. [21]. For these two aneurysms, NL12 leaked out of the aneurysms into the parent arteries immediately after injection and adhered to the balloon catheter and the microcatheter. Therefore, the catheters could not be removed from the blood vessel, making it difficult to evaluate the effectiveness of embolization on angiography. Thus, our study confirmed that balloon-assisted embolization of wide-necked aneurysms with a highly adhesive material with an SS configuration, such as NL12, is not possible.

Our study has eight limitations to discuss. First, when preparing NLI, it is necessary to prepare NL first and then add the nonionic iodine contrast agent. This is because, when a nonionic iodine contrast agent is added to NBCA, polymerization starts immediately and NBCA solidifies. In addition, NL and nonionic iodine contrast agents cannot be mixed by shaking due to their high viscosity. Therefore, mixing must be done using a pumping method with a three-way stopcock. Second, the processing time of NLI231 is about 15 min. Therefore, if NLI231 is not used within 15 min after mixing, it cannot be injected through a microcatheter. Third, we could not use the same

microcatheters in the in vitro study due to a limited budget problem. Instead, we used a 24 G needle with an inner diameter similar to that of the microcatheter used in vivo. Furthermore, we used physiological saline instead of blood in the in vitro study. Fourth, the configuration of NLI changes at each ratio, although the reason is not clear. Fifth, a small number of animals were used and long-term evaluation may not be possible because of animal welfare considerations. Sixth, Iopamirone was used as the nonionic iodine contrast agent; the use of other nonionic iodine contrast agents needs to be investigated. Seventh, the occlusion time for embolization was 3 min. Future studies should assess the most suitable occlusion time and assess whether the balloon occlusion time can be reduced. Finally, embolization should be verified by rotating digital subtracting angiography or computed tomography. However, our experimental facilities do not have the equipment for this. Furthermore, we did not perform macroscopic or histologic examination of the aneurysms.

Conclusion

The configuration of NLI changed at each ratio. NLI231 is a feasible and safe liquid embolic material for balloon-assisted embolization of wide-necked aneurysms in swine.

Compliance with Ethical Standards

Funding This study was not supported by any funding.

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval All applicable international, national, and institutional guidelines for the care and use of animals were followed. And all procedures performed in this study involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

Informed Consent Informed consent is not required for this type of study.

Consent for Publication Consent for publication is not required for this type of study.

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