Online October 17, 2024
Journal of Neuroendovascular Therapy 2025; 19: 2024-0055
DOI: 10.5797/jnet.ra.2024-0055

Review Article

NBCA: Basic Knowledge

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Various types of embolic substances are used in endovascular therapy, and understanding their characteristics, including shape and kinetics, is essential for proper use. Cyanoacrylate is a typical liquid embolization agent that can be applied to many cerebral neurovascular lesions. It is injected as a mixture with ethiodized oil to provide radiopacity and regulate the polymerization rate. This review describes the characteristics, action mechanisms, techniques of use, and potential pitfalls of using cyanoacrylate-ethiodized oil mixtures for embolization.

Keywords NBCA, embolic material, transcatheter embolization

Introduction

Embolic materials for endovascular treatment are particles or liquids that are released through a catheter to occlude target vessels mechanically or biologically. N-butyl-2 cyanoacrylate (NBCA), initially commercialized as an adhesive, was recently approved in Japan as an embolic agent for endovascular therapy.[1] NBCA has been used as an embolization agent for decades, but it still requires the surgeon to gain significant experience and proficiency to perform embolization procedures safely and efficiently. This article discusses the properties, action mechanisms, rules of use, and potential pitfalls of embolization with NBCA.

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Received: May 30, 2024; Accepted: August 27, 2024
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Characteristics of Cyanoacrylate for Medical Use

Cyanoacrylate was discovered in the 1940s as a chemical that bonded things upon contact and was later commercialized as an instant adhesive. Cyanoacrylate is a liquid with low viscosity in its monomer state, and when it comes into contact with anions, it polymerizes to form a polymer that hardens and bonds.[2] There are various types of cyanoacrylates differentiated by the alkyl groups in their structure. They are used for industrial, household, medical, and other applications based on their properties (**Fig. 1**). Among them, butyl cyanoacrylate and octyl cyanoacrylate are suitable for use in living organisms because their polymers are flexible, odorless, and less toxic. These cyanoacrylates, which have larger alkyl groups, polymerize more slowly than those with smaller alkyl groups, release less heat during polymerization, and are less toxic to tissue.[3] Cyanoacrylate was first used medically to stop bleeding and repair the skin. In the 1990s, 2-octyl-cyanoacrylate was first approved by the United States Food and Drug Administration (FDA) as a skin surface adhesive.

In the endovascular field, cyanoacrylate has been widely used as a liquid embolic material since the 1970s and 1980s, when it was employed to treat cerebral arteriovenous malformations (AVMs).[4,5] However, prior to 2000, the intravascular use of cyanoacrylate was off-label.

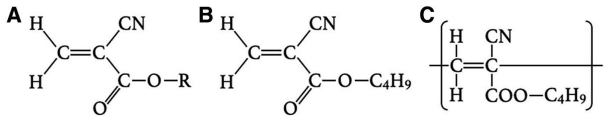

Fig. 1 The chemical structure of monomeric cyanoacrylate (**A**). The R represents an alkyl group. The monomeric (**B**) and polymeric (**C**) forms of NBCA are also shown. NBCA, N-butyl-2 cyanoacrylate

NBCA for Endovascular Treatment

Histoacryl (B.Braun, Tuttlingen, Germany), which is composed of NBCA, was initially marketed as a surgical adhesive like other cyanoacrylate and has since been used for endoscopic sclerotherapy of esophagogastric varices and hemostasis of bleeding disorders. Histoacryl for endovascular therapy is a mixture of NBCA (clear and colorless) and blue dye (D&C violet No. 2). Histoacryl is currently the most widely used commercialized NBCA in endovascular therapy, but Trufill (Cordis, Miami Lakes, FL, USA) and Glubran2 (GEMSRL, Viareggio, Italy) were available on the market prior to Histoacryl.[6)]

Trufill, like Histoacryl, contained only NBCA and was FDA-approved solely for the preoperative embolization of cerebral AVMs in 2000. Glubran2 was European conformity (CE)-marked in 2005 as an embolic agent and has been used in Europe. Glubran2 is a mixture of NBCA and metacryloxysulpholane, which suppresses the heat of polymerization and prolongs the polymerization time. It does not adhere to blood vessels and has a lower inflammatory response and toxicity than NBCA alone.[7)] However, neither Trufill nor Glubran2 is available in Japan.

In March 2022, Histoacryl was approved as a vascular embolization material under the Pharmaceutical Affairs Law in Japan,[1)] and it can now be used for transcatheter embolization procedures in systemic organs, including cerebrospinal and head and neck vessels. In neurology, NBCA is indicated for a wide range of diseases, including brain AVMs, spinal AVMs, dural arteriovenous fistulas (dAVFs), head and neck tumors, brain tumors, and hemorrhagic lesions. In the following sections, NBCA will be described with reference to Histoacryl.

NBCA is a radiolucent material that instantly polymerizes and hardens upon contact with blood, making safe and accurate embolization difficult when used alone.[8)] To overcome these drawbacks, it is commonly injected mixed with ethiodized oil (Lipiodol; Guerbet, Villepinte, France), a nonionic oil-based contrast agent that does not polymerize with NBCA and can be easily mixed in any ratio. As discussed below, the NBCA polymerization time can be adjusted by changing the mixing ratio, which is a significant advantage of using NBCA as a liquid embolization material.

Tantalum may be added to achieve radiopaque properties, especially when NBCA is used in high concentrations, but this is not a common practice. Tantalum delays the onset of polymerization and should be mixed only immediately before use.[8)]

In vivo Behavior of NBCA

As NBCA is injected into a blood vessel, it reacts with anions in the blood and starts to polymerize, forming a hardened NBCA "cast" that matches the shape of the target vessel. This cast fills the vessel lumen, thereby disrupting blood flow. Since the NBCA cast itself blocks blood flow, it can occlude blood vessels even when thrombus formation does not occur, for instance, when blood clotting ability is impaired.

The polymerization time varies greatly depending on the mixing ratio of NBCA and Lipiodol; the higher the ratio of NBCA, the shorter the polymerization time, and the lower the ratio, the longer the polymerization time. Pure (100%) NBCA takes 0.087 seconds to cure upon contact with plasma.[9)] In vitro experiments show the following polymerization times for different NBCA to Lipiodol ratios: 3.2 seconds at 1:1, 4.7 s at 1:2, and 7.5 s at 1:3.[10)]

When NBCA is injected mixed with Lipiodol, pathological studies show that Lipiodol is present in the center of the vessel while hardened NBCA is deposited on the vessel wall side.[10,11)] The reaction heat generated during the polymerization of NBCA damages the vessel wall, resulting in acute necrotizing vasculitis.[12,13)] This leads to a chronic granulomatous process with the accumulation of foreign body giant cells and fibrosis within approximately 30 days.[4,14,15)]. Inflammatory changes in the vessel wall produce scarring and fibrosis, which enhance the embolic process.[16)] Fibrosis progresses slowly, and histologically, it has been reported that extrusion of the adhesive out of the vessel and the development of capillaries in the embolized vessel wall have been observed. Inflammatory changes have been reported not only in the vessels but also in the perivascular tissue.[17)]

Cyanoacrylates have also been used during neurovascular open surgeries, such as coating aneurysm walls and fixing vessels in microvascular decompression procedures. However, this extravascular usage of cyanoacrylates can

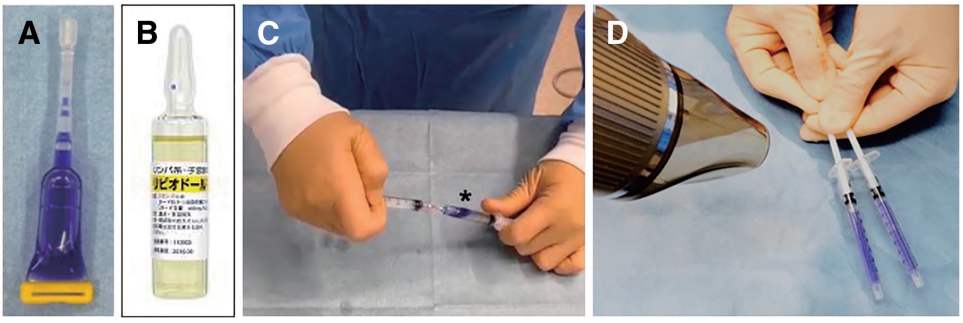

Fig. 2 Visual appearances and preparation of a mixture before embolization. (**A**) Histoacryl 0.5 mL vial and (**B**) Lipiodol 10 mL vial. (**C**) Histoacryl and Lipiodol are mixed in a plastic luer-lock syringe (asterisk). (**D**) The mixture is warmed with a hair dryer for 1 minute just before the injection.

result in arterial stenosis, occlusion, or dissection.[18,19] Thus, NBCA can be considered vascular toxic. NBCA has been proven to be mutagenic but not carcinogenic.[20]

Rules of Injection

Positioning of the microcatheter

The microcatheter is primarily used for injection. Its tip should be advanced as far as possible, as close to the embolized area as feasible. Superselective contrast is then performed through the microcatheter to assess blood flow velocity, distance to the lesion, whether the catheter tip is wedged, and whether feeding vessels of normal tissue can be visualized. Based on these factors, the infusion rate of NBCA and the mixing ratio of NBCA and Lipiodol are determined. It is of note, however, that the kinetics of NBCA injection differ from those of contrast agents due to the combination of NBCA's adhesive properties and the viscosity of Lipiodol.

Dilution and preparation of the NBCA–Lipiodol mixture

The rate of polymerization of NBCA depends on the mixing ratio of NBCA and Lipiodol; the higher the percentage of NBCA, the stronger the adhesion (**Fig. 2A–2C**). For embolization of short segments or when blood flow is fast, a high concentration (33%–50%) of NBCA is preferable. Conversely, for longer distances to the lesion, the greater distal reach of NBCA, and slower blood flow, lower concentrations (10%–25%) of NBCA are more appropriate (**Tables 1** and **2**, and **Fig. 3**).[8,21] When low-concentration NBCA is used, the proportion of oil-based contrast media is higher, which increases the viscosity of the mixture and hinders its accessibility to distal sites. To overcome this, the mixed solution may be heated to reduce viscosity (**Fig. 2D**).

Table 1 Selecting the concentration of mixture according to the situation

Variables	Concentration of NBCA	
	High	Low
Catheter position	Close to lesion	Away from lesion
Catheter tip	Wedged	Free
Blood flow	Fast	Slow
Occlusion site	Short and thick	Long and thin
Injection time	Short	Long

NBCA, N-butyl-2 cyanoacrylate

Table 2 Approximate concentration of mixed solution for each neurovascular disease

Disease	Concentration (%)
Tumor	10–25
dAVF	20–33
AVM	25–50
High flow fistula	50–75

AVM, arteriovenous malformation; dAVF, dural arteriovenous fistula

Injection

Injection should be performed under fluoroscopy or a blank roadmap. To prevent polymerization of the adhesive within the catheter, flush the catheter with 5% dextrose solution (D5) to remove ionic material (contrast media or blood). Flushing out the contrast media is also important to accurately recognize the start of the inflow of the NBCA and Lipiodol mixture.

Two methods can be used for NBCA injection: free-flow injection and controlled-flow injection. Free flow, also called flow-dependent injection, is a method of administering NBCA directly into the bloodstream. This technique requires smaller amounts of material but carries a risk of unexpected scattering of material to the distal vessels. As the NBCA reaches the distal portion and occlusion progresses gradually, the blood flow velocity also decreases, and the infusion rate must be reduced accordingly. Controlled-flow injection is a method that involves wedging the microcatheter or using a micro-balloon catheter

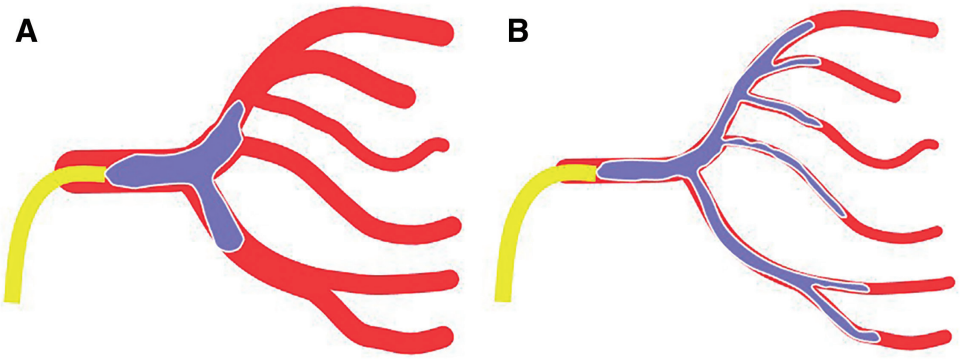

Fig. 3 A scheme showing the difference in behavior depending on the concentration. (**A**) A high-concentration of NBCA polymerizes and hardens immediately upon contact with blood, thus occluding short segments and functioning as a proximal embolic material. (**B**) Low-concentration NBCA polymerizes as it flows in the bloodstream, resulting in deep penetration away from the catheter tip. NBCA, N-butyl-2 cyanoacrylate

to reduce or block blood flow. Under this flow-controlled situation, NBCA can be injected similarly to the Plug-and-Push technique used for ethylene vinyl alcohol (EVOH) copolymer injection. A balloon-guiding catheter or detachable coils may also be used to control blood flow.

Removal of the microcatheter

The endpoints of the injection are when the NBCA has adequately embolized the lesion, refluxed proximal to the catheter tip, or entered an unplanned vessel. Low concentrations of NBCA can be injected multiple times, but essentially, injection is a 1-time procedure that cannot be redone. The microcatheter should be removed promptly before its tip is trapped by the NBCA cast. It is also advisable to apply negative pressure in the catheter lumen to prevent the dispersal of adherent NBCA during catheter removal.[22] However, it must be noted that excessively rapid extraction of the catheter may create negative pressure and pull the NBCA cast back proximally.

Technical Tips and Potential Pitfalls

One common technical issue is the premature polymerization of the glue proximally before the NBCA penetrates to the required depth. Warming the mixture promotes more peripheral delivery even with a high percentage of ethiodized oil.[23] Mine et al. showed that the viscosity of the mixtures of NBCA and ethiodized oil at 60°C was about 4 or 5 times lower than those at 4°C.[24] Another merit of warming is that the injection pressure into the microcatheter decreases with the lowering of the viscosity. It makes the injection more stable and safer.

A method that can aid in achieving more distal embolization is the "flood technique,"[25,26] which involves continuous positive pressure flushing with D5 from a guide catheter or a distal access catheter. Flushing the distal vascular bed with a nonionic solution slows NBCA polymerization, allowing deeper penetration of the mixture and more distal embolization.[8]

An injection from a wedged catheter or balloon-microcatheter carries the risk of NBCA straying into other sites via intrinsic vascular anastomoses that are not depicted on angiography. Careful observation is necessary during injection, and it is useful to have multiple observers sharing observation points for the behavior and reach of the NBCA. Because NBCA is toxic to blood vessels, as mentioned above, excessive NBCA infusion into normal branches distributed in the skin and mucosa should be avoided. This can cause vascular endothelial damage and inflammation, resulting in erosion and ulcer formation.

Generally, occlusion of vessels by NBCA is considered permanent, but there have been reports of recanalization.[27,28] This may be due to cast resorption or migration in cases of low NBCA concentrations or partial occlusion.[4,13]

Clinical Experiences

Since NBCA has been widely used as a vascular embolization agent for the past 40 years, a wealth of knowledge has been accumulated. In Japan, guidelines for the proper use of liquid embolic substances, NBCA and EVOH, have been issued to ensure their safe use.[1,3] The Japanese Registry of Neuroendovascular Therapy (JR-NET), a database based on a multicenter, retrospective, observational study, has shown positive results for a variety of cerebrovascular lesions.

For the treatment of brain AVM, a total of 987 embolization procedures were reviewed from JR-NET1 and 2 databases from 2005 to 2009.[29] NBCA alone or NBCA plus other embolization materials were used in 732 cases (74.2%). The primary endpoint, a modified Rankin Scale (mRS) score of 0–2 at 30 days postoperatively, was obtained in 790 patients (80.1%). The technical success rate of the procedure in all patients, including those using embolic materials other than NBCA, was good at 98.8%.

In the JR-NET3 database, which contains cases from 2010 to 2014, 1042 embolizations in 780 cases of brain AVM were analyzed.[30] Preoperative embolization was performed 638 times (61.2%), pre-radiosurgery 160 times (15.4%), targeted embolization 144 times (13.8%), and radical embolization 87 times (8.3%). The embolization materials used were NBCA 627 times (60.2%), EVOH 432 times (41.5%), and coil 165 times (15.8%). In this study, the technical success rate of total embolization was 98.2%, with good results (mRS 0–2) at 30 days postoperatively in 71.3% of patients. In a meta-analysis of 103 studies evaluating outcomes with NBCA or EVOH for unruptured AVMs, the neurologic outcome was 5.2% and 6.8% in the NBCA and EVOH groups, respectively. The AVM complete occlusion rate was 13.7% in the NBCA group and 24% in the EVOH group.[31]

From the JR-NET3 database, 2121 embolization procedures for dAVF were also analyzed.[32] Of these, 818 (44%) underwent transarterial embolization alone, and 527 (61%) used NBCA. Univariate analysis showed that the use of NBCA was not associated with complications. A good technical success rate of 98.0% was achieved for the procedure in all patients, including those with embolic material other than NBCA, and complications were observed in 7.7% of cases.

For spinal cord vascular lesions, NBCA is currently the standard embolization material used, and the efficacy of EVOH is unknown.[33] From the JR-NET2 and 3 databases, 172 cases of spinal dAVF were analyzed.[34] Curative treatment was planned in 79.1% of cases, and NBCA was the main embolic agent. Overall, 60.5% of patients had a favorable outcome (mRS 0–2) at 30 days, the primary endpoint. On multivariate analysis, only complete shunt occlusion was associated with postoperative neurological improvement.

For the embolization of intracranial tumors, 1018 cases were analyzed from the JR-NET2 database.[35] Complications were observed in 1.48% of cases, with embolization of non-meningioma tumors being associated with complications in multivariate analysis. In addition, 1545 patients who underwent intracranial tumor embolization were analyzed from the JR-NET3 database.[36] Liquid embolic material was used in 627 patients (40.6%), with NBCA considered the primary embolic material. In all patients, the primary endpoint of a good outcome (mRS 0–2) at 30 days was achieved in 89.5% of cases. Complications were observed in 3.7% of patients, and on multivariate analysis, risk factors for complications were embolization of target vessels other than the external carotid artery and the use of liquid embolic material.

Embolization of the middle meningeal artery (MMA) for chronic subdural hematoma (CSDH) has become widespread as an effective treatment since it was first reported in 2000.[37] MMA embolization is used as both a standalone treatment and as an adjunct to surgical evacuation of hematoma.[38,39] MMA is currently embolized with several kinds of materials, such as coils, polyvinyl alcohol (PVA), NBCA, and EVOH. Sioutas et al. reviewed a total of 18 studies, including 507 cases of MMA embolization with liquid embolization materials, namely NBCA and EVOH.[40] The rate of hematoma size reduction was good at 97%, radiographic recurrence was 3%, reoperation was 3%, and the overall complication rate was 1%. A meta-analysis comparing embolic agents for MMA embolization was conducted, analyzing 31 studies with 1134 patients.[41] There was no difference in the recurrence rate (5.0% for PVA, 4.0% for NBCA, and 6.9% for EVOH) and procedural complication (1.8% for PVA, 3.6% for NBCA, and 1.6% for EVOH) based on the embolic agent.

Conclusion

Safe and optimal endovascular treatment with liquid embolization material requires practical expertise and experience. Embolization with NBCA is an effective treatment for various lesions not only in the cerebrospinal cord and head and neck region but also in the entire body. With NBCA now officially approved as a vascular embolization material, the range of indications and demand for it is expected to expand. Because NBCA has properties and advantages not found in other liquid embolic materials, embolization with NBCA requires accurate evaluation of vascular anatomy, careful attention to the technical details of injection, making the material radiopaque with Lipiodol, and modulation of the polymerization rate based on the surgeon's knowledge and skills.

Disclosure Statement

All authors have no conflict of interest.

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