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Review Article

N-butyl Cyanoacrylate Use in Various Neuroendovascular Diseases

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This review discusses the use of N-butyl cyanoacrylate (NBCA) in various neuroendovascular treatments. Despite the increase in the ONYX, NBCA continues to have significant usage. It is particularly useful for the treatment of arteriovenous malformations (AVM) and dural arteriovenous fistulas (dAVFs). Comparative studies have suggested that ONYX and NBCA are equally effective and safe for the treatment of AVM. However, the choice between the two depends on specific situations, such as the characteristics of the feeding arteries. NBCA is recommended for tortuous feeders, high-flow fistulous feeders, and feeders with a short margin of reflux, owing to the procedural risks posed by ONYX. The use of NBCA is also prominent in dAVF embolization. While achieving total occlusion solely with NBCA can be challenging, NBCA adheres to the vessel wall and encourages thrombus formation, aiding in fistula obliteration. In addition to AVM and dAVF, NBCA is used to treat chronic subdural hematoma and craniofacial vascular injuries. Embolization using NBCA is beneficial because of its deep penetration into the target tissue. For craniofacial injuries, NBCA embolization provides secure hemostasis within a short time. Neuroendovascular physicians should understand the characteristics of NBCA as a liquid embolic material and have expertise in the technical aspects of NBCA embolization, even in the ONYX era.

Keywords N-butyl cyanoacrylate, arteriovenous malformation, dural arteriovenous fistula, chronic subdural hematoma

Introduction

Since the implementation of ONYX as a liquid embolic material for arteriovenous malformations (AVM) and dural arteriovenous fistulas (dAVFs), the use of N-butyl cyanoacrylate (NBCA) as an embolization material has notably reduced, particularly in the context of arteriovenous shunt diseases. This trend can be attributed to the efficacy and success rates of ONYX, which have seemingly overshadowed the utility of NBCA in certain situations.

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However, this does not imply that NBCA has no role in neuroendovascular treatment. With its insurance listing in Japan in 2023, NBCA will continue to be used not only for AVMs and dAVFs but also for the treatment of other diseases. This review sheds light on the current status of NBCA in various neuroendovascular treatments. It provides an in-depth review of the existing literature and discusses the technical considerations that arise when NBCA is used as an embolization material. Furthermore, it aimed to map out potential future directions for NBCA usage, considering the continuous advancements in the field of neuroendovascular treatment.

NBCA Use in Brain AVM

In nationwide Japanese surveillance of AVM embolization between 2004 and 2009 (Japanese Registry of Neuroendovascular Therapy; JR-NET 1/2), NBCA was used in 74.2% of the cases.[1] However, subsequent surveillance between 2010 and 2014 (JR-NET 3) showed a 60.2% decrease in NBCA use.[2] By contrast, ONYX use increased from 5.5% to 41.5%. These trends indicate that the role of ONYX notably increased following its insurance reimbursement in Japan in 2008. The overall complication rates were 9.2% in JR-NET 1/2 and 13.1% for JR-NET 3. Although a direct comparison was not made, similar safety profiles were observed in both surveys.

Several studies have directly compared the safety and effectiveness of NBCA and ONYX as embolic materials for AVM. Loh et al. conducted a prospective multicenter randomized trial focusing on the effectiveness of embolization, defined as a size reduction of AVM by more than 50%. The results did not differ significantly (96% for ONYX vs 85% for NBCA).[3] The authors reported similar safety outcomes. Additional retrospective observational studies have suggested that the safety and effectiveness of ONYX and NBCA are comparable.[4,5] Overall, ONYX and NBCA are considered the two major liquid embolic materials for AVM.

However, these comparative studies did not address specific situations in which either NBCA or ONYX should be selected. In certain cases of embolization from specific feeding arteries, ONYX can present high procedural risks, and embolization with NBCA should be considered.

Tortuous feeders

The "plug and push" technique is often used to sufficiently penetrate ONYX into the nidus.[6] However, after creating a tight plug at the microcatheter tip, there is a risk of microcatheter entrapment.[7] When removing microcatheters from tortuous feeders, applying the necessary drag force to the microcatheter tip may be challenging. This could pose the risk of feeder artery straightening and subsequent hemorrhage due to perforator injury. To mitigate such risks, NBCA should be selected for the embolization of tortuous feeders.

High-flow fistulous feeders

In general, ONYX takes longer to adhere than NBCA. Therefore, there is a risk of excessive migration to the drainage side when embolizing fistulous feeders with ONYX. If the drainer is occluded without embolizing the nidus, it can lead to increased nidus pressure and periprocedural hemorrhagic complications. To secure the embolization material inside the feeder side, a high concentration of NBCA with a short polymerization time should be chosen.

Feeders having a short margin of reflux

To adequately infuse ONYX into the nidus, it is necessary to create a tight plug at the catheter tip. If the feeder artery has branches perfusing the normal brain near the catheter tip, a plug with a short reflux is made. However, the procedure is technically challenging. Instead, embolization with a simple NBCA push may pose a lower risk of normal-brain ischemia.

NBCA is typically mixed with Lipiodol for visibility in fluoroscopic images. The temperature and concentration of NBCA must be adjusted to control its behavior within the arteries. Warming the NBCA and Lipiodol mixture can decrease its viscosity.[8] By reducing the NBCA concentration, a longer curing time can be anticipated, allowing more material to be injected through the microcatheter.[9] However, prolonged injection times may result in excessive material migration to the venous side, potentially causing hemorrhage. In our retrospective analysis of AVM embolization, NBCA use was a risk factor for hemorrhagic complications, including asymptomatic ones.[10] Therefore, AVM embolization with NBCA should be performed under the supervision of expert neuroendovascular physicians who are knowledgeable and experienced in such technical nuances.[11] When performing adjunctive embolization preoperatively, it is crucial to discuss the goal of the procedure with the surgical team to avoid unnecessary risks.

ONYX, when used in embolization combined with stereotactic radiosurgery (SRS), contains a larger amount of metal, leading to more artifacts in follow-up images post-embolization.[12] A recent meta-analysis of 70 studies with 12088 patients suggests that this feature might reduce the success rate of SRS following Onyx embolization, although both ONYX and NBCA are associated with a lower rate of AVM obliteration than SRS alone.[13] By contrast, if targeted embolization of specific high-risk AVM components using minimal NBCA can be achieved, it could ensure safety during the latency period between SRS and nidus occlusion.[14,15] **Figure 1** depicts a case of targeted embolization, in which selective embolization of the nidus aneurysm was achieved using NBCA prior to SRS. Future studies are required to identify the patients who would benefit from neoadjuvant AVM embolization.[16] At present, it is important to have a detailed discussion with SRS physicians regarding which parts of the AVM should be embolized and to what extent.

NBCA Use in dAVF Embolization

Unlike AVM, total occlusion of dAVF can be achieved through endovascular embolization as the first-line treatment. Transarterial and transvenous embolization (TAE and TVE, respectively) are important treatment options to

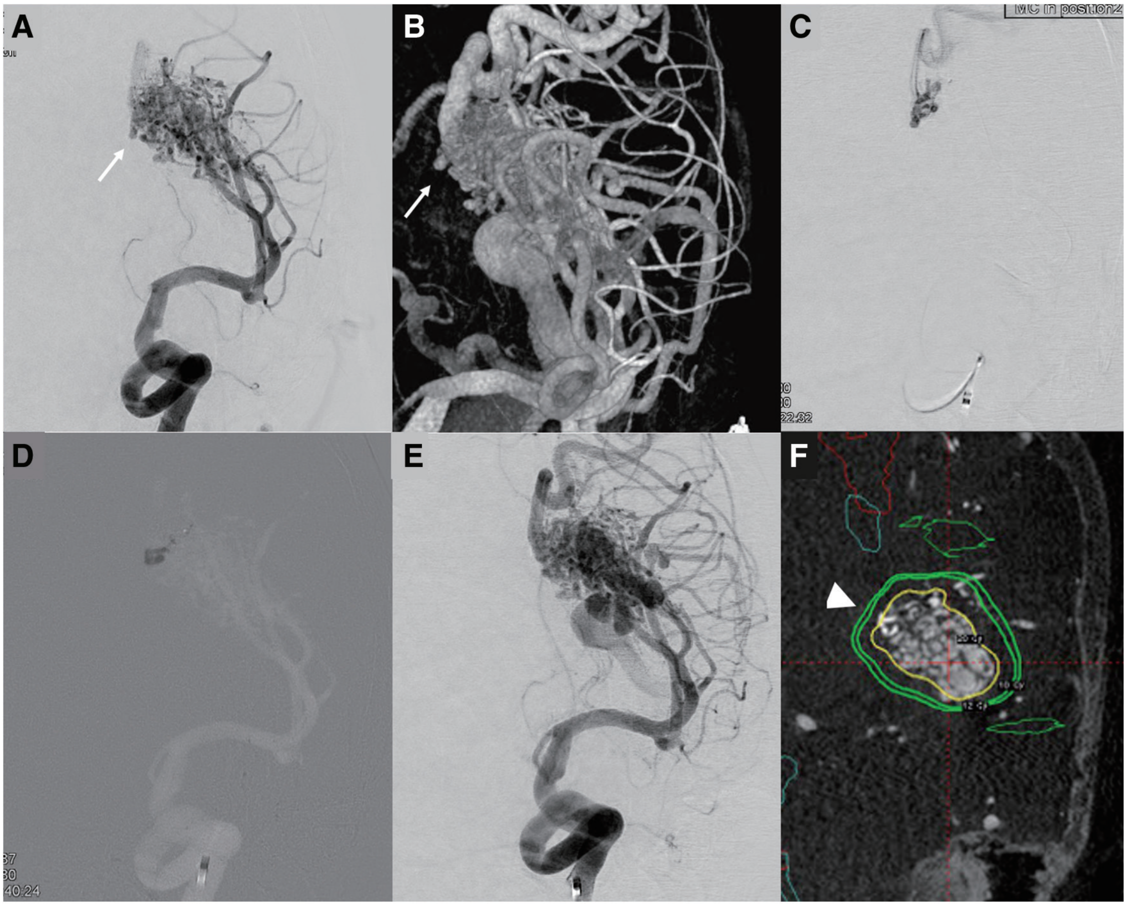

Fig. 1 A representative case of selective embolization combined with SRS. Angiography of the ruptured left insular AVM (maximal diameter 21 mm, Spetzler and Martin Grade 3) reveals an intranidal aneurysm (**A** and **B**, white arrows) at the medial edge of the nidus. (**A**) Left internal carotid angiography oblique view and (**B**) 3D rotational angiography. Prior to SRS, embolization targeting the aneurysm is performed. (**C**) The microcatheter is navigated to the artery feeding the intranidal aneurysm and (**D**) 33.3% of the NBCA injection successfully occluded the nidus component, leading to the aneurysm. (**E**) The aneurysm was well-occluded without occlusion of the drainer adjacent to the target lesion. (**F**) Three days after embolization, a single-session SRS is performed using 3D rotational angiography data post-embolization. Note the minimal artifacts of NBCA (white arrowhead). AVM, arteriovenous malformation; NBCA, N-butyl cyanoacrylate; SRS, stereotactic radiosurgery

eliminate the fistula and are chosen based on the angioarchitecture. Normally, TVE is not suitable for non-sinus-type dAVF (Borden type 3), and TAE is the standard treatment choice.

The JR-NET 3 study examined 1940 dAVF embolization procedures performed between 2010 and 2014. TAE was the only approach in 44% of cases, whereas TVE alone was chosen in 47% of cases.[17] Total and subtotal occlusions were attained in 55% and 91% of the cases, respectively. This study was conducted before the reimbursement of ONYX as an embolization material for dAVF in Japan in 2018. NBCA is the most frequently used embolic material for TAE, suggesting that NBCA is often utilized as an embolic material, but achieving total occlusion of the fistula solely with NBCA is frequently technically challenging.

One potential advantage of NBCA as an embolic material for dAVF is that it does not form casts inside the target artery. It adheres to the vessel wall and damages the vascular endothelium, thereby encouraging thrombus formation and secondary obliteration of the fistula.[11] To safely control the behavior of NBCA, it is crucial to position the microcatheter in the wedge position. By injecting NBCA under continuous flow-arrest conditions, undesired reflux to the tip of the microcatheter and excessive migration to the venous side can be avoided.[18]

Notably, ONYX is currently not reimbursed when used for the embolization of spinal dAVFs. This fistula is typically located in the inner layer of the spinal dura.[19] Hence, physicians must inject NBCA into the draining vein through a distally navigated microcatheter to achieve complete occlusion of the fistula.[20,21] Because feeder arteries at the dural surface are often small and tortuous, navigation and injection can be challenging. The safety and effectiveness of endovascular embolization

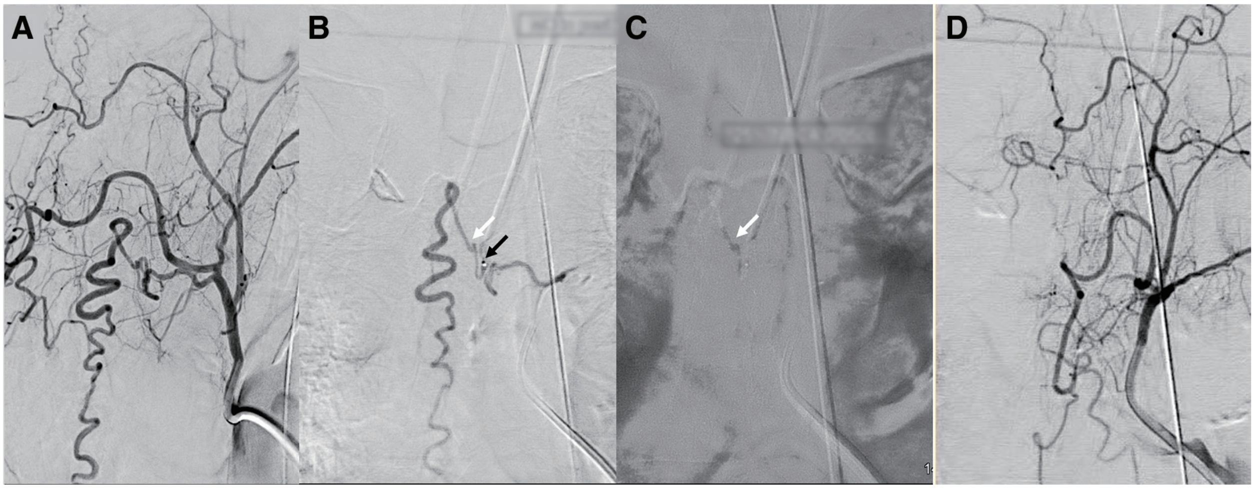

Fig. 2 NBCA embolization for spinal dAVF. Endovascular embolization was performed on a woman in her 80s for her spinal dAVF at Th4 level. (**A**) Pre-embolization angiography. (**B**) Injection from a microcatheter (black arrow) navigated close to the shunt point (white arrow) on the dura mater. (**C**) NBCA injection from the microcatheter. Note that the 25% NBCA well penetrated to the draining vein distal to the shunt point (white arrow). (**D**) Post-embolization angiography. With a single injection, the dAVF was completely obliterated. dAVF, dural arteriovenous fistula; NBCA, N-butyl cyanoacrylate

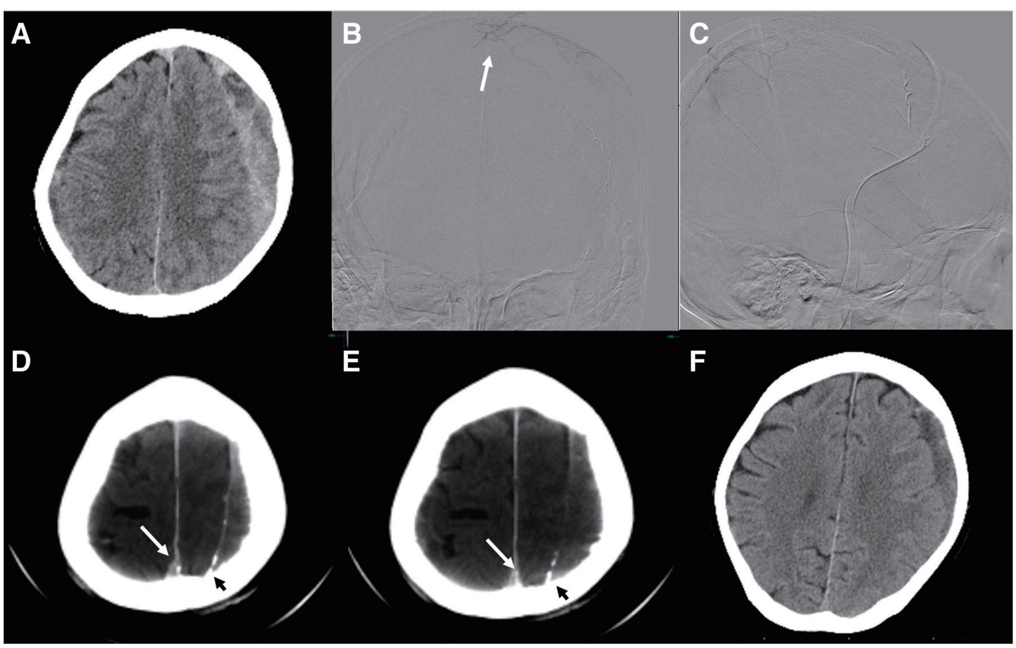

Fig. 3 MMAE for CSDH. (**A**) A male in his 50s, who complained of mild gait disturbance, was found to have a left CSDH. Due to his comorbidity, burr-hole drainage is not performed, and MMAE is conducted upfront instead. The blank roadmap during a 12.5% NBCA injection (**B**. AP view; **C**. lateral view) shows that the embolic material penetrates well to the midline (white arrow in **B**, labeled as "bright falx sign"). (**D** and **E**) Cone beam CT immediately after the embolization shows NBCA penetration to the midline (white arrows) and to the inner layer of the hematoma (black arrows). (**F**) Two months after the procedure, CT reveals a significant decrease in the hematoma volume. The patient's gait disturbance resolves immediately after the procedure. CSDH, chronic subdural hematoma; MMAE, meningeal artery embolization; NBCA, N-butyl cyanoacrylate

are inferior to surgical disconnection of the fistula.[22] The standard treatment of spinal dAVF is direct surgery. When surgery is not recommended for any reason, endovascular embolization using NBCA should be considered in expert centers. In the JR-NET 1/2 surveillance performed by Tsuruta et al., 98 spinal dAVF embolizations were registered, of which embolization using NBCA as the only material accounted for 66 (67.3%) cases. Total and subtotal occlusion of the fistula was achieved in 54.2% and 31.3% of the cases, respectively.[23] **Figure 2** depicts the successful endovascular embolization of a spinal dAVF in a woman in her 80s.

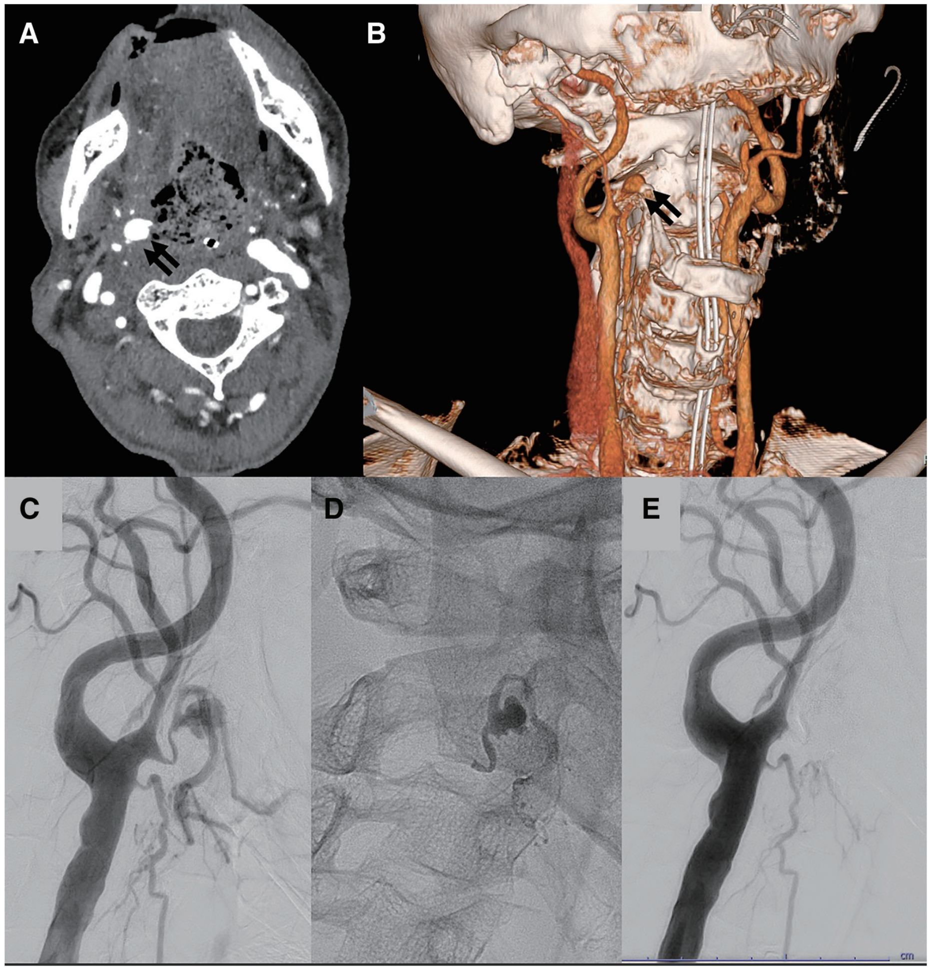

Fig. 4 A case of lingual artery pseudoaneurysm embolization. The patient was a man in his 60s who had undergone chemoradiation therapy for pharyngeal cancer. He was referred to our hospital due to recurrent oral bleeding. (**A**) Contrast-enhanced CT of the neck, axial view. (**B**) 3D reconstruction. A pseudoaneurysm (**A** and **B**, black arrows) at the proximal portion of his right lingual artery was suspected as the cause of bleeding, and endovascular embolization was performed. (**C**) Right common carotid angiography pre-embolization, lateral view. (**D**) The aneurysm is embolized with the parent lingual artery using 33% NBCA. (**E**) Common carotid angiography post-embolization. The aneurysm completely disappears. NBCA, N-butyl cyanoacrylate

NBCA Use in Other Neuroendovascular Treatment

Chronic subdural hematoma (CSDH)

The first case report of middle meningeal artery embolization (MMAE) to prevent CSDH recurrence after burr hole surgery was published by Mandai et al. in 2000.[24] Since the 2010s, both the procedures and reports on MMAE have increased. In the United States, the MMAE rate for CSDH has increased from 0.2% in 2012 to 3.7% in 2018.[25] Several meta-analyses have suggested that MMAE for CSDH is superior to conventional management for preventing hematoma growth and recurrence after surgical drainage.[26,27] As of 2024, several randomized controlled studies are underway to directly assess the safety and efficiency of MMAE compared to conventional management, including burr-hole drainage.[28–32]

Recent advancements in the understanding of the microvasculature of the dura mater have provided a theoretical rationale for the increase in MMAE.[33,34] Based on these anatomical insights, CSDH is now considered a vascular rather than a traumatic disease.[35,36] According to this theory, recurrent bleeding within the inner layer of the dura mater is the major cause of CSDH formation.[34] Therefore, when performing MMAE, it is crucial to allow the embolic agent to infiltrate the inner CSDH membrane. Liquid embolization materials, including low-concentration NBCA, are more beneficial than particle embolization materials because of their ability to penetrate deeply into the target tissue. Indeed, a single-center retrospective analysis reported that NBCA penetration into the midline (bright falx sign) was associated with earlier resolution of CSDH after MMAE.[37] In recent clinical trials, various liquid embolic materials, including ONYX and NBCA, are used in MMAE for CSDH.[38] In Japan, several MMAE case series have been recently reported using relatively low concentrations (12.5%–25%) of NBCA as the embolization material.[39–42] When injecting NBCA, meticulous care should be taken to avoid occluding the proximal part of the MMA, as proximal occlusion with liquid embolic material carries the risk of retinal ischemia due to potential anastomosis between the MMA and ophthalmic artery.[43] **Figure 3** shows a typical instance of MMAE utilizing NBCA, which demonstrates a reduction in CSDH after the procedure.

Craniofacial vascular injury

Catheter embolization of the affected artery is often warranted in cases of arterial injury and acute bleeding, particularly when direct surgical repair is challenging. Embolization using NBCA has been reported to achieve more secure hemostasis with a shorter procedure time in coagulopathic conditions than other embolic materials, such as particles and coils.[44] In the craniofacial regions, NBCA embolization in cases of the lingual or facial arteries has shown good results.[45–47] As vascular injury in these regions often leads to fatal airway obstruction, most cases are treated as emergency conditions. Therefore, neuroendovascular physicians should be proficient in these procedures. **Figure 4** illustrates a case of lingual artery pseudoaneurysm embolization in a patient with a history of pharyngeal cancer.

Conclusion

We introduced the use of NBCA in various neuroendovascular treatments. In AVM and dAVF, complete obliteration with NBCA alone is often difficult and may pose a substantial risk. When performing embolization, the treatment goal should be considered by a multimodality team. The advantage of NBCA is that immediate hemostasis can be achieved using a distally navigated, low-profile microcatheter. Neuroendovascular physicians should understand the characteristics of NBCA as a liquid embolic material and have expertise in the technical aspects of NBCA embolization, even in the ONYX era.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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