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Technical Notes

Direct N-butyl-2-cyanoacrylate injections to the head and neck for percutaneous embolized devascularization

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ABSTRACT

Background: N-butyl-2-cyanoacrylate (NBCA) has been used for vascular malformations since the 1980s; however, few studies have looked at applications, procedural techniques, and outcome throughout many institutions. Herein, we review applications, procedural techniques, previous literature, and outcomes for the use of NBCA specifically through percutaneous technique in treating head and neck vascular pathology.

Methods: An extensive literature review using PubMed database with published literature containing "N-butyl-2-cyanoacrylate embolization," was performed. No date restrictions were used. Cross-checking of articles was conducted to exclude duplicate articles. The articles were screened for their full text and English language availability. We finalized those articles pertaining to the topic.

Results: The search yielded 1124 related articles. When comparing surgical resection to embolization with NBCA for cerebral AVMs, complications were similar in both groups and included hemorrhage (15%), residual AVM (6%), and cerebrospinal fluid leak (3%). Their mortality rate was 3% in both groups. Preoperative percutaneous embolization does show improved surgical outcomes.

Conclusion: NBCA is a fast-acting liquid embolic material used in the treatment of a variety of vascular malformations and lesions of the head and neck. Investigations surrounding the use of NBCA injections as a new alternative embolic agent began in the 1980's. Administration of NBCA has been shown to be useful in minimizing intraoperative blood loss and controlling acute hemorrhage. Performing percutaneous embolization with NBCA provides a successful alternative for surgeons when transcatheter embolization techniques may prove to be too difficult to perform. Embolization using NBCA will continue to play in integral role in the treatment of malignant lesions and vascular malformations. Continued research is warranted to improve safety, outcomes, and further develop clinical applications of NBCA.

Keywords: Arteriovenous malformation, Embolization, N-butyl-2-cyanoacrylate, Obliteration

INTRODUCTION

Cyanoacrylate glues are liquid alkyl-2-cyanoacrylae monomers that have the ability to form flexible polymers to soft tissues. N-butyl-2-cyanoacrylate (NBCA) is a class of cyanoacrylates which is a

group of adhesives that are fast-acting, due to their ability to form low viscosity fluids in a monomer state and polymerize instantly on contact with ionic substances. NBCA's are the most widely used liquid embolic material in the world. They are useful for a variety of brain and neck pathology such as arteriovenous malformations (AVMs).[10] AVM's are commonly treated with the use of NBCA's because unlike other materials such as acrylates NBCA's do not cause any catheter gluing.[20] NBCA's embolization was shown to be a feasible and effective method to control acute arterial hemorrhage.[14]

Isobutyl-2-cyanoacrylate (IBCA) was initially used, but then it was replaced by N-butyl 2-cyanoacrylate (NBCA) in the mid-1980s.[30] The nature of NBCA at high concentrations is very hard to manage because the polymerization time of NBCA can be prolonged however when diluted with other substances such as ethiodized oil or iophendylate, makes handling NCBA's much more convenient in utilizing for treatment.[30] Thus, diluted NBCA injections have provided another avenue for physicians to work with NBCA's for achieving proper polymerization times for effective treatment ranging between 0.2 and 5 s.[30] Highly concentrated NBCA glue was used before 1997 in some institution for AVM but effective obliteration was not be obtained. This caused movement toward diluted NCBA's.[30]

While many different treatment options are utilized in treating patients, knowing the effectiveness of this treatment is quite important. Herein, we will assess the applications for NBCA's, procedural techniques, and patient outcomes when using NBCA embolization.

PATIENT SELECTION

Percutaneous embolization of arterial and/or venous malformations, pseudoaneurysms, and other aberrant vasculature with NBCA has demonstrated high degrees of success for a variety of pathologies across a diverse population of patients.[13] With specific emphasis on pathologies of the head and neck, NBCA has proven an increasingly viable option to prevent anticipated hemorrhage before surgical resection of problematic vasculature or lesions or as an intervention to control acute hemorrhage. This is especially salient in the context of malignancy that predisposes individuals to developing pseudoaneurysms, AVMs, and other vascular anomalies secondary to tumorous growth or iatrogenic oncological therapies such as radiation.[4] Where traditional transcatheter embolization approaches face challenges from tortuous vasculature, atherosclerotic disease, and postoperative inflammatory changes, direct percutaneous delivery of sclerosants such as NBCA provide an alternative embolization technique with promising success rates.[34]

Although studies directly evaluating the use of NBCA in head and neck pathologies are limited in number, various prospective cohort studies and retrospective analyses have determined vascular lesion characteristics and criteria that favor successful outcomes of NBCA embolization therapy.[4,32,36] Conventionally, embolization using sclerotherapy with agents like NBCA has been used as an adjunctive therapy to surgical resection to minimize intraoperative blood loss; however, growing research has demonstrated higher rates of success with embolization therapy alone in treating problematic vascular aberrations.[36] Absolute indications for sclerotherapy with agents such as NBCA include active hemorrhage, lesions that compromise hemodynamic stability, and ischemia secondary to lesions with significant AV shunting.[18] Otherwise, sclerotherapy may be indicated for head and neck lesions that produce significant pain, ulceration, or deformity. Lesions with high flow are generally contraindicated for embolization therapy given increased rate of sclerosant dilution, reducing the success rate of embolization.[18]

Absolute indications or contraindications aside, appropriateness of NBCA percutaneous embolization therapy for head and neck lesions may be determined by considering a wide variety of lesion characteristics that contribute to the anticipated degree of intervention success [Figure 1].[32,36] In general, factors that are taken into consideration include a patient's preexisting chronic conditions and comorbidities, size of the lesion, location and depth of the lesion, proximity of the lesion to prominent vasculature, and vascular tributaries of the lesion, as outlined in the figure below.[36] In comparison to direct surgical resection or stereotactic radiosurgery, embolization therapy typically carries a higher success rate with fewer complications when the following criteria are met:[32,36]

- Small to medium-sized vascular lesion with clearly demarcated nidus
- Superficial lesion easily accessible with a percutaneous approach
- The lesion is not in direct contact with or extension to arteries such as the ICA or ECA with intracranial communication that would carry high risk of intracranial embolization of sclerosant material
- Lesions with few arterial feeders that allow for adequate reflux of NBCA along feeder vessels to block blood flow to the lesion
- Lesions without complex venous drainage to minimize post injection hemorrhage risk.

The decision to pursue direct percutaneous NBCA embolization of head and neck lesions is typically made when transcatheter approaches are impractical and surgical resection alone carries too high of a perioperative hemorrhage risk. A patient's comorbidities and the lesion's vascular characteristics as explained above must be thoroughly evaluated in great detail to determine the safety and likelihood of success of this type of intervention.

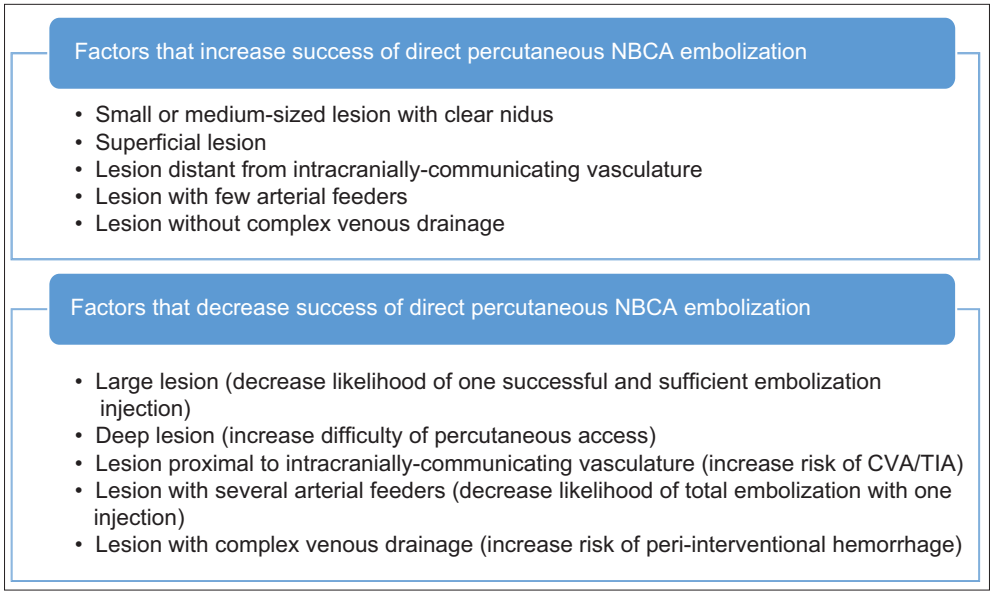

Figure 1: Lesion characteristics that contribute to the anticipated degree of direct NBCA injection success.

BRIEF OVERVIEW OF TECHNIQUES

NBCA is the most commonly used liquid embolic agent that due to its low viscosity can be percutaneous injected through a needle. NBCA is composed of liquid alkyl-2-cyanoacrylate monomers that rapidly polymerize on contact with ionic substances such as blood or water.[31] NBCA is administered in a mixture with ethiodol, a nonpolar vehicle that prevents polymerization, and tantalum power, which makes the solution radiopaque and also helps to slow polymerization, which begins immediately on contact with anions.[31] The rate of polymerization can be altered by varying the ratio of NBCA to ethiodol in solution.[31] A high NBCA:ethiodol ratio (1:1, 1:2) causes quicker polymerization.[11] Conversely, a low NBCA:ethiodol ratio (1:3, 1:4) prolongs the time for injection due to slower polymerization, which allows for a larger quantity of NBCA to be injected.[11] However, injecting solutions with a low concentration of NBCA increase the risk of distal embolism due to migration of the glue and subsequent polymerization past the target lesion.[11,16] Migration of glue into intracranial circulation can lead to serious complications, including stroke.[16]

Direct percutaneous injection of NBCA is used when transarterial catherization is not feasible or dangerous to perform, for example, with cases of tortuous vasculature or vessels with atherosclerotic plaques.[1] Percutaneous NBCA injection has several potential clinical applications in the head and neck region including embolization of arterial/venous malformations, pseudoaneurysms, and hypervascular tumors.[13] Therefore, the technique used for percutaneous injection of NBCA depends on the specifics of the clinical case. In general, blood-flow should be assessed with pre embolization angiography from multiple projections to prevent both reflux of the embolic agent and migration of NBCA due to high flow rates.[26] If necessary, flow stagnation can be achieved using temporary balloon occlusion.[16] Sonographic images of the vasculature are obtained to ensure proper placement of the needle, and NBCA is injected under real-time roadmap fluoroscopic guidance.[26] Post embolization angiography can be used after injection to evaluate success of devascularization.[26]

TRIALS, OUTCOMES, AND EFFECTIVENESS

Investigations surrounding the use of NBCA injections as a new alternative embolic agent began in the 1980's. Early work from interventional neuroradiologist concluded that clinically and biologically NBCA was an acceptable alternative to IBCA.[2] Since, NBCA has been a part of over 100 clinical investigations, throughout multiple specialties, to assess its effectiveness as a liquid embolic agent.[7,25,28,29] In this review, we highlight those investigations occurring in the head and neck.

Studies of embolization treatment with NBCA in head and neck lesions, specifically AVM, began in 1993 by Jafar *et al.* [Table 1].[3,12,15,22,24,27] Historically patients present with hemorrhage, epilepsy, headache, and/or neurological deficits. Before Jafar *et al.*, AVMs were not treated as regularly because the belief was that intervention was high risk. In their study, they compared surgical resection to embolization with NBCA as endovascular therapies for cerebral AVMs. Complications were similar in both groups and included hemorrhage (15%), residual AVM (6%), and cerebrospinal fluid leak (3%). Notable minor complications included edema, visual deficits, aphasia, and hemiparesis. Their mortality rate was 3% in both groups. These results

Table 1: Studies to date describing NBCA injections based on lesion type.

Studies	Year	Treatment approach	Early outcome	Late outcome
Jafar *et al.*[12]	1993	Surgery with embolization	Heroes Classification: 84% excellent outcome	Heroes Classification: 95% excellent outcome
DeMeritt *et al.*[5]	1995	Surgery with embolization	Glasgow scale>5: 70%	Glasgow scale>5: 87%
Wikholm[33]	1995	Embolization	11.2% occlusion	80% occlusion
Debrun *et al.*[3]	1997	Embolization Or surgery following embolization	N/A	5.56% cure rate Or 20.37% cure rate
Deruty *et al.*[6]	1998	Embolization with surgery Or Embolization with radiosurgery	N/A	100% cure rate Or 90% cure rate
Liu *et al.*[20]	2000	Preoperative embolization	47% patients had 75–99% obliteration	100% cure rate
Hartmann *et al.*[8]	2002	Embolization	6% mortality	86% no change in neurological status after treatment
n-BCA Trail Investigators[24]	2002	Embolization with NBCA versus PVA	N/A	Randomized trial showed that n-BCA is equivalent to PVA as a preoperative embolic agent for treatment of cerebral AVM
Yu *et al.*[35]	2004	Embolization	22% cure rate	100% rate of permanent cure of the initially complete embolization
Klurfan *et al.*[15]	2005	Embolization	Mortality rates of 1.1–3.7% and morbidity of 3.814%	30% cure rate
Li *et al.*[19]	2005	Embolization	0.7%, the mortality was 0.5% and the mild complication rate was 1.4%	33% cure rate
Raymond *et al.*[27]	2005	Embolization Or Embolization plus surgery or radiotherapy or both	22.6% overall complication rate	34% cure rate Or 66% cure rate
Ledezma *et al.*[17]	2006	Embolization Or Embolization plus surgery Or Embolization plus radiotherapy	Glasgow scale: 75% had excellent or good outcomes Or 93% Or 92%	N/A Or 96.8% had complete AVM obliteration Or N/A
Matsumoto *et al.*[22]	2007	Embolization of pseudoaneurysms case study	100% survival	N/A
Lv *et al.*[21]	2012	Embolization	19.7% Complete obliteration	Risk of hemorrhage was 3.8%
Deib *et al.*[4]	2017	Embolization oropharyngeal pseudoaneurysms two case study	100% permanent occlusion	N/A
Mendes *et al.*[23]	2018	Onyx transvenous embolization	2.5% mortality	92.6% cure rate 2.5% severe disability

were further supported by DeMeritt *et al*. showing that there was no significance difference in outcomes between both treatment groups. However, they noted that preoperative NBCA embolization improved postsurgical outcome.[5] Other groups took it a step further and showed that after 4 to 78 months post embolization with NBCA, there still was permanent occlusion of the AVMs.[33] However, later studies suggest that the overall initial cure with embolization alone is 20% due to the difficulty of getting 100% occlusion of the nidus with NBCA embolization techniques.[35] Because of this low initial cure rate with embolization alone, a combination approach where endovascular embolization is paired with surgery or radiosurgery is preferred. Current indications for embolization are: (1) curative embolization, (2) adjuvant embolization, and (3) palliative embolization.

With an increase in the use of NBCA, there was a parallel increase in conversations surrounding the safety of NBCA embolization. For the last decade, the efficacy and risks of NBCA were the focus of many clinical researchers. The results of several clinical papers suggest that NBCA in combination

with surgery can lead to a 100% cure rate. However, the risk of NBCA embolization is not negligible and should only be used as a reductive technique only when it is absolutely necessary to allow for complete cure of the AVM.[6] Some of the risks of NBCA include hemorrhage, stroke, neurological deficits, and mortality. About 14% of patients showed treatment-related neurological deficits measured by Rankin score while 2% had permanent neurological deficits.[8,19] While others report a 1.4% mild complication rate with ~9% having hemorrhages and strokes, the overall death rate has been reported to be 1-4%.[17,21] Hence, ~90% have good outcomes with NBCA, making it an acceptable treatment option for head and neck vascular or neoplastic lesions.[23] In addition, with the development of microcatheter technology and improved center's level of expertise, permanent occlusion, and improved outcomes with preoperative NBCA are promising and continue to push NBCA research and clinical use forward.

CONCLUSION

Embolization through direct percutaneous delivery of NBCA provides promising outcomes in the treatment of vascular malformations and lesions. As our treatment of vascular malformations of the head and neck continues to evolve, NBCA will continue to play a helpful roll in minimizing intraoperative bleeding of malignant lesions and assisting surgeons where traditional transcatheter embolization approaches face challenges. Although this procedure is not without risk of significant complication, performing the procedure in the guidance of trained surgeons provides favorable outcomes.

Over two decades later, we have extensive research on the use and outcomes of NBCA. Its expansion from abdominal to head and neck lesions has proven to reduce morbidity and mortality rates in AVM patients as well as cancer patients with hemorrhagic lesions, such as, ruptured pseudoaneurysms.[4] Regardless, the search for an even better embolic agent that can be reliably used without follow-up surgery persists. A 2020 agent that is a combination of NBCA and Lipiodol-Iopamidol has proven to meet this criterion and may serve as a new alternative liquid embolic material in the future.[9]

Continual research directly assessing NBCA's outcomes of vascular disorders and lesions will provide increasingly beneficial data to solidify NBCA outcomes. Further technical guidance and modifications may help improve the safety and success of percutaneous embolized devascularization with NBCA. In addition, future studies further developing applications for the use of NBCA injections may be of benefit in the clinical setting.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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