Safety and Efficacy of Lipiodol and N-Butyl Cyanoacrylate (N-BCA) Combination for Vascular Embolization

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Abstract

Purpose The aim of this study was to evaluate the safety and efficacy of the combination of Lipiodol and N-butyl cyanoacrylate (N-BCA) for vascular embolization.

Methods Patients with various vascular pathologies, eligible for embolization using a combination of Lipiodol and N-BCA, were included in this ethical committee–approved prospective multicenter study. Adverse events (AEs) during the procedure and up to 30 days were recorded and categorized into minor or major (AE classification by the Society of Interventional Radiology). Depending on the targeted volume of vascular occlusion of the lesion, lesions were classified into four groups (group 1: <50% target volume; group 2: 50–75%; group 3: 75–99%, and group 4: 100%). Consistency between the targeted and actual vascular occlusion achieved after embolization was assessed.

Results One hundred and twenty-four patients were enrolled. All underwent at least one procedure, and 12 required a second procedure. No AEs were noted during the procedure, while 42 AEs occurred in 23 patients (18.5%) after and during the follow-up period. Two minor AEs in one patient (0.8%) were related to the mixture, and 26 AEs in 16 patients (12.9%) were related to the procedure (mostly minor A, 30.8% or B, 42.3%). The most frequent procedure-related AE was postembolization syndrome (4.8%). Nonfatal serious AEs related to the procedure occurred in two patients. The actual vascular occlusion was equal to or greater than the targeted volume in 119/135 lesions (88.1%) following the first procedure and in 11/13 lesions (84.6%) following the second procedure.

Conclusion Lipiodol and N-BCA combination is safe and highly effective for vascular embolization.

Keywords
- embolization
- N-BCA
- Lipiodol

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Introduction

Vascular embolization is a minimally invasive image-guided procedure to obtain a temporary or permanent and partial or complete occlusion of blood vessels for a variety of clinical indications, including active bleeding, varices, vascular malformations, and benign and malignant tumors.[1–4] It is also used preoperatively for resectable tumors to reduce operative bleeding or to prepare organs for resection.[5,6] Vascular embolization has the advantage of a lower rate of complications and superior outcomes compared to open surgery.[7] Depending on the clinical scenario, different embolic materials could be used, including mechanical occlusion devices (such as coils) for large vessel embolization, particulates for small vessel embolization, and liquid/gel embolic materials (such as alcohol and N-butyl-2-cyanoacrylate [N-BCA]) for both large and small vessel embolization.[8]

Ethyl esters of iodized fatty acids of poppy seed oil (Lipiodol Ultra Fluid, Guerbet, Aulnay-sous-Bois, France) is a radiopaque contrast material extensively used in interventional radiology. Lipiodol contains 480 mg/mL of iodine, has a viscosity of 34 to 70 mPa·s at 20°C, and is slightly denser than water (1.28 g/cm^3 at 20°C).[9] Lipiodol mixed with N-BCA has been used for vascular embolization since the 1980s.[10,11] Lipiodol increases the polymerization time of the mixture, hence limiting risks of clogging of the catheters; allows viscosity adjustment of the mixture to the lesion angioarchitecture and blood flow; and most of all allows the fluoroscopic visualization of the embolic mixture due to iodine radiopacity. The ratio of Lipiodol to N-BCA is empirically decided by the interventional radiologist depending on blood vessel diameter, blood flow velocity, and the distance between the microcatheter tip and the target.[12] Despite its advantages, vascular embolization could be associated with some complications, the most frequent being pain and postembolization syndrome (PES).[13,14] More rare but serious complications could occur, including pulmonary embolism and hemorrhage.[15–17] This study aimed to assess the safety and efficacy of the combination of Lipiodol and N-BCA for vascular embolization in Indian patients with various clinical conditions and to meet the postmarketing obligation of the Drug Controller General of India (DCGI).

Materials and Methods

Study Design and Population

This is a prospective, multicenter, open-label, single-arm, postmarketing study conducted on Indian patients requiring vascular embolization as part of therapeutic/palliative strategy for their disease from November 2017 to May 2021. The study was approved by the independent ethics committee of each site and authorized by the DCGI. This study was performed in compliance with the Declaration of Helsinki and with the Indian Good Clinical Practice guidelines. All patients provided informed consent. The study was registered on ClinicalTrials.gov (NCT02625389).

All the patients included were 18 years old or above (age range: 18–69 years) and presented with vascular lesions/anomalies, such as vascular malformations (arterial, venous, arteriovenous, fistula) or tumors (benign such as angiomyolipoma, uterine fibroid, hemangioma or malignant such as angiosarcoma) eligible for vascular embolization using selective transarterial catheterization using the Lipiodol and N-BCA mixture, and were not treated previously with this approach. Patients presenting with known contraindications to vascular embolization (i.e., severe coagulation disorders, and infectious syndrome) or on beta-blockers, metformin, interleukin II, or anticoagulant therapy were excluded from the study. Those with acutely bleeding lesions were also excluded from the study.

A first embolization procedure was performed on the same day or within 7 days after enrolment, and a second optional embolization procedure was performed, if needed, within 30 days after the first procedure. A safety follow-up was performed up to 30 days after the last procedure. The mixture was injected into the lesion after super-selective cannulation of arterial feeders and at a ratio of 1:4 to 4:1 (Lipiodol to N-BCA) as decided by the investigator. The total volume of Lipiodol used during embolization depended on lesion size but did not exceed 15 mL.

Safety Evaluation

The primary outcome of this study was safety assessment of the Lipiodol and N-BCA mixture assessed by calculating the rate of patients experiencing adverse drugs reactions (ADRs) during the procedure after administration of the mixture (ADRs related to the mixture). As a secondary safety outcome measure, the rate of adverse events (AEs), regardless of a causal relationship, was also collected during the study from the time of the first administration of the mixture to the end of the follow-up period. Based on their severity, the AEs were categorized into mild (symptom awareness but without significant interference in daily activities or clinical consequences), moderate (disruption of daily activities or had clinical consequences), or severe (inability to carry out daily activities and/or AE had definite clinical consequences) and further translated as per the Society of Interventional Radiology (SIR) classification as minor (A–B) or major (C–F) complications.[18] Additionally, the seriousness of these AEs was assessed.[19]

Efficacy Evaluation

Based upon the targeted volume of vascular occlusion (percentage of the lesion expected to be embolized safely during the embolization procedure as decided by the interventional radiologist based on the pre-embolization angiogram, the clinical situation, and local practice), all the lesions planned for embolization were grouped into four groups (group 1: target embolization $<$50% of the lesion; group 2: target embolization 50–75% of the lesion; group 3: target embolization 75–99% of the lesion; and group 4: target embolization 100% of the lesion).

Postembolization, based on the actual vascular occlusion achieved (percentage volume of the lesion that was embolized), lesions were again regrouped into four groups (group 1: $<$50% of the lesion got embolized; group 2: 50–75% of the

lesion got embolized; group 3: 75–99% of the lesion got embolized; and group 4: 100% of the lesion got embolized). To assess the efficacy of the mixture, consistency between the targeted and actual vascular occlusion was evaluated by comparing the pre-embolization target volume and actual vascular occlusion volumes in each group.

Statistical Methods

The sample size was determined based on the specified requirement of 125 participants set by the DCGI. Only descriptive statistics were used to report all data collected in the study. Quantitative variables were summarized in tables including sample sizes, means, and standard deviations (SDs). Qualitative variables were described in terms of percentages of the number of patients or lesions considered.

Results

Overall, 132 patients were included in 16 centers, and 8 patients were prematurely discontinued from the study due to either withdrawal of consent (4 patients) or cancellation of the procedure (4 patients). In all, 124 patients received the mixture for a first embolization procedure, and 12 underwent a second embolization procedure. All 124 patients who received the mixture completed the study (►**Fig. 1**). The mean (SD) age of the patients who received the mixture was 34.2 (±13.6) years, and 55.6% of them were females (►**Table 1**).

Safety Results

Primary criterion: No AEs and ADRs were reported during the embolization procedure when the patient was in the procedure room.

Secondary criteria: Overall, 23 patients (18.5%) reported a total of 42 AEs after leaving the procedure room and up to 30 days from the last procedure. Sixteen patients (12.9%) had 26 AEs related to the embolization procedure (►**Table 2**). An AE-targeted medical therapy was needed for 17 patients (73.9%). Two patients needed AE-targeted surgical therapy (cannula site changed in one patient, ventriculoperitoneal shunt and external ventricular drain in the second patient). The most frequently reported AEs were PES in six patients (4.8%), injection site pain in three patients (2.4%), and pyrexia and skin necrosis in two patients each (1.6%). All except pyrexia were considered related to the embolization procedure. All other AEs were reported in one patient (►**Table 2**).

As per the AE classification by the SIR, most AEs were graded as minor A complications (10/42, 23.8%) or minor B complications (23/42, 54.8%). Six AEs (7.1%) were graded as major C complications, and three AEs were reported as major D complications (3/42, 4.8%).

Only one patient (0.8%) with arteriovenous malformation (AVM) experienced two nonserious ADRs: pregangrenous changes in the skin over embolized lesions with blister formation. Both occurred 6 days after the procedure and were of mild intensity. They required an ADR-targeted medication and resolved without sequelae (minor B complications). In two patients, three nonfatal serious AEs (SAEs) were reported, considered related to the embolization procedure and not related to the mixture. Out of three SAEs, two life-threatening SAEs (hydrocephalus and a cerebellar infarction) leading to prolongation of hospitalization were noted 2 days after the procedure in a 56-year-old patient treated for a posterior fossa AVM (major D complications). The patient developed severe and serious cerebellar infarction that was visible on magnetic resonance imaging, and which happened

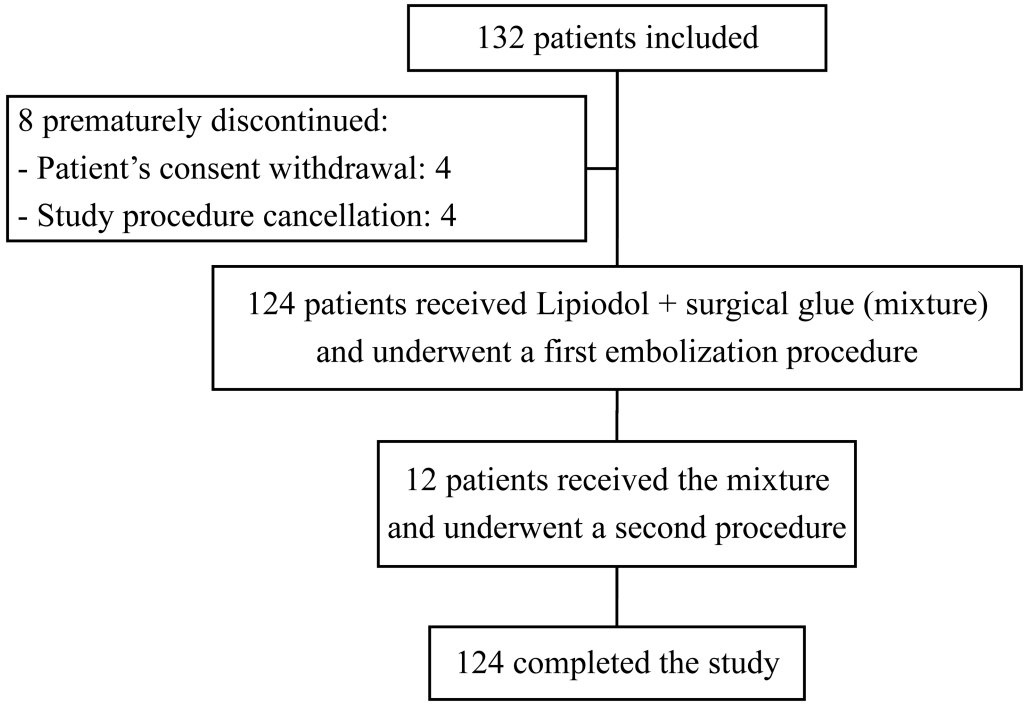

Fig. 1 Flowchart of patients undergoing vascular embolization.

Table 1 Demographic characteristics of patients

Parameter	Total ($N = 124$)
Age (y)	
Mean (SD)	34.2 (13.6)
Median	31
Minimum; maximum	18; 69
Gender	
Male	55 (44.4%)
Female	69 (55.6%)
Weight (kg)	
Mean (SD)	56.1 (10.5)
Median	55
Minimum; maximum	34; 86
Height (cm)	
Mean (SD)	159.9 (10.0)
Median	160
Minimum; maximum	131; 183
Body mass index (kg/m^2)	
Mean (SD)	21.93 (3.49)
Median	21.7
Minimum; maximum	15.1; 33.3

Abbreviation: SD, standard deviation.

Table 2 Adverse events related to the embolization procedure

	Patients ($N = 124$)
At least one adverse event	16 (12.9%)
Postembolization syndrome	6 (4.8%)
Injection site pain	3 (2.4%)
Skin necrosis	2 (1.6%)
Catheter site swelling	1 (0.8%)
Injection site swelling	1 (0.8%)
Lower abdominal pain	1 (0.8%)
Dysphagia	1 (0.8%)
Burning sensation	1 (0.8%)
Cerebellar infarction	1 (0.8%)
Dyskinesia	1 (0.8%)
Hydrocephalus	1 (0.8%)
Blisters	1 (0.8%)
Back pain	1 (0.8%)
Mastication disorder	1 (0.8%)
Pain in extremity	1 (0.8%)
Hypertension	1 (0.8%)
Nontarget organ ischemia	1 (0.8%)
Vertigo	1 (0.8%)

due to the reflux of the mixture into the posterior cerebellar artery. The hydrocephalus and the neurological and functional consequences of the cerebellar infarction resolved within 62 days. The third SAE leading to prolongation of hospitalization was noted in an 18-year-old patient being treated for an AVM of the upper lip. While injecting the mixture into the superior labial artery, reflux of the mixture occurred into an inferior labial artery, leading to local skin necrosis in the nontarget area (major D complication). Signs and symptoms of this SAE were noted 7 days after the procedure and resolved in 46 days.

Efficacy Results

One hundred and thirty-eight lesions in 124 patients were treated by embolization on one occasion. One hundred and fourteen patients were treated for one lesion, six patients for two lesions, and four patients for three lesions. Most of these lesions were AVMs (66.7%) or other vascular neoplasms (9.4%; ►**Table 3**). Most of these lesions were localized in the skin and subcutaneous tissues (43.5%), bone and other internal soft tissues (20.3%), urinary system (9.4%), liver (8.0%), or reproductive system (7.2%; ►**Table 3**). Endocryl (n-butyl-2-cyanoacrylate, Samarth Life Sciences, Mumbai, India) was used for 124 lesions (89.9%), while Histoacryl (n-butyl-2-cyanoacrylate, B. Braun, AG, Melsungen, Germany) was used for embolization of 12 lesions (8.7%). The brand name of the N-BCA glue was not specified for two lesions. In one patient, in addition to the mixture, another embolic material (i.e., implant) was used during the first embolization procedure. The most often used Lipiodol/N-BCA ratios for embolization were 4:1 (38.5%), 3:1 (14.6%), and 1:1 (14.2%). The mean (SD) duration of the procedure was 54 ($\pm$38) minutes.

The actual vascular occlusion percentage was available only for 135 of 138 lesions, as for 3 lesions, investigators did not provide information about the actual percentage of vascular occlusion achieved after embolization. The actual percentage of vascular occlusion for lesions after the first embolization procedure met the pre-embolization target in 100 out of 135 lesions (74.1%), exceeded the pre-embolization target in 19 lesions (14.1%), and was lower than the target score in 16 lesions (11.9%). Therefore, the actual vascular occlusion achieved was equal to or higher than the pre-embolization target in 119 lesions (88.1%). On further analysis, the actual vascular occlusion percentage corresponded to the pre-embolization target in 10 of 12 lesions (83.3%) for postembolization group 1 lesions, in 13 of 20 lesions (65.0%) for postembolization group 2 lesions, in 35 of 44 lesions (79.5%) for postembolization group 3 lesions, and in 42 of 59 lesions (71.2%) for postembolization group 4 lesions (►**Table 4**).

A second embolization procedure was performed for 13 lesions in 12 patients (mostly AVMs), exclusively with Endocryl: 1 lesion in 11 patients and 2 lesions in 1 patient. The most often used Lipiodol/N-BCA ratio was 3:1 (36.6%). The mean (SD) duration of the procedure was 55 (33) minutes.

Table 3 Type of lesions to be treated

	Patients ($N = 124$)	Lesions ($N = 138$)
Type of lesion		
Arteriovenous malformation	84 (67.7%)	92 (66.7%)
Other vascular neoplasm	11 (8.9%)	13 (9.4%)
Arteriovenous fistula	4 (3.2%)	4 (2.9%)
Infantile hemangioma	3 (2.4%)	3 (2.2%)
Aneurysm	2 (1.6%)	2 (1.4%)
Noninvoluting congenital hemangioma	2 (1.6%)	2 (1.4%)
Angiosarcoma	1 (0.8%)	1 (0.7%)
Arterial malformation	1 (0.8%)	1 (0.7%)
Venous malformation	1 (0.8%)	1 (0.7%)
Other[a]	15 (12.1%)	19 (13.8%)
Location of lesion[b]		
Skin and subcutaneous tissues	55 (44.4%)	60 (43.5%)
Bone and other internal soft tissues	27 (21.8%)	28 (20.3%)
Urinary system	11 (8.9%)	13 (9.4%)
Liver	8 (6.5%)	11 (8.0%)
Reproductive system	10 (8.1%)	10 (7.2%)
Lung	4 (3.2%)	5 (3.6%)
Intracranial intra-axial tissues	2 (1.6%)	2 (1.4%)
Spleen	2 (1.6%)	2 (1.4%)
Spinal cord	1 (0.8%)	1 (0.7%)
Stomach	1 (0.8%)	1 (0.7%)
Other[c]	5 (4.0%)	5 (3.6%)

[a]Including liver or neck hemangioma, uterine fibroid, and hypertrophied bronchial arteries.
[b]Sum of locations is more than the number of patients as few patients were having lesions at multiple locations.
[c]Including the left branchial and left axillary artery, occipital artery, right lateral chest wall, gluteal region, scrotum, left groin, and pelvis.

Table 4 Actual and target vascular occlusion/lesion obliteration percentage for the first embolization procedure

Actual vascular occlusion percentage	Target vascular occlusion percentage				
	<50%	≥50 and <75%	≥75 and <100%	100%	Total lesions ($N = 138$)
<50%	10	1	1	0	12 8.7%
	83.3%	8.3%	8.3%	0.0%	
≥50 and <75%	0	13	4	3	20 14.5%
	0.0%	65.0%	20.0%	15.0%	
≥75 and <100%	0	2	35	7	44 31.9%
	0.0%	4.5%	79.5%	15.9%	
100%	1	0	16	42	59 42.8%
	1.7%	0.0%	27.1%	71.2%	
Missing	0	1	2	0	3
Total	11 8.0%	17 12.3%	58 42.0%	52 37.7%	138 100.0%

The actual vascular occlusion after the second embolization procedure met the target in 6 of 13 lesions (46.2%), exceeded the target in 5 lesions (38.5%), and was lower than the target in 2 lesions (15.4%). The actual lesion obliteration/vascular occlusion was equal to or higher than the target score in 11 lesions (84.6%). The actual lesion

obliteration percentage corresponded to the target score in 2 of 2 lesions with an obliteration percentage of less than 50%, 1 of 2 lesions with an obliteration percentage between ≥50 and less than 75%, 2 of 5 lesions with an obliteration percentage between ≥75 and less than 100%, and 1 of 4 lesions with an obliteration percentage of 100%.

Although vascular embolization was initially planned to be performed in this study using a selective transarterial route only (as per study protocol), the embolization of the portal vein in one patient with a liver neoplasm planned for liver resection was performed via a percutaneous portal vein access. It was, therefore, reported as a protocol deviation. Of note, this patient also had complete obliteration of the portal vein branches in the desired part of the liver after the procedure, achieving a 100% technical success rate.

Discussion

Our study has demonstrated a favorable safety profile of the lipiodol and N-BCA mixture, with most reported AEs being mild to moderate (SIR minor A or B complications) and mostly unrelated to the mixture. In addition, the study revealed a high success rate in achieving the desired vascular occlusion, with 87.8% of treated lesions having equal to or better than the targeted vascular occlusion.

In the present study, AVMs accounted for most treated lesions (i.e., 66.7%). In a study performed on patients with craniofacial venous vascular malformations (low-flow vascular malformation), preoperative embolization via direct puncture and injection of N-BCA achieved complete embolization in 8 of 13 patients (62%) and partial embolization in the remaining 5 patients (38%). All patients underwent a successful surgical resection.[20] Another randomized study reported 79.4% of cerebral AVM nidus reduction after embolization with N-BCA/Lipiodol, comparable to that reported after embolization with polyvinyl alcohol (PVA) microparticles (86.9%).[21] In the current study, the actual vascular occlusion/lesion obliteration percentage was equal to or higher than the target in 88.1% of the treated lesions following the first procedure and 84.6% following the second procedure. No information regarding the need for surgical resection of the AVM after embolization was recorded. The high lesion obliteration/vascular occlusion rate in the present study, which included patients treated for various indications according to real-world clinical practice settings, suggests equivalent efficacy to that reported in previous studies.[21–23]

In the present study, AEs considered related to the mixture were reported in only one patient, and the incidence of AEs related to the procedure was 12.9%. Most of the AEs related to the procedure were mild or moderate (96.2%). Other studies reported a complication rate between 9 and 16% for AVM embolization.[24–26] PES is a postinflammatory clinical syndrome comprising symptoms such as pain, fever, nausea, and vomiting. In the current study, the rate of PES was 4.8%. In the literature, PES could be reported as such, and the incidence could vary depending on the indication of the procedure, with higher incidences (18–86%) reported with the embolization of bone metastases.[13,27,28] In a phase II study on vascular embolization for various indications (excluding cerebral AVM), the rate of AEs of grade 3 (severe AEs) or above (based on common terminology criteria for adverse events (CTCAE) version 4) that could be related to the procedure was 17.2%, including many symptoms related to PES. The high rate of grade 3 AEs, as compared to the present study, could be explained by the inclusion of patients with traumatic or postsurgical bleeding.[29]

Embolotherapy for skin and subcutaneous AVM is usually associated with increased risk of skin necrosis, as reported in several studies.[13,30] In the current study, two patients reported pregangrenous skin changes and mild skin necrosis (1.6%), which resolved after treatment. The use of the N-BCA/Lipiodol mixture for vascular embolization could be associated with a risk of possible uncontrolled reflux during the injection with consequent ischemic complications.[31,32] Previous reports suggested that nontarget embolization such as cerebral or spinal cord infarction could occur with vascular embolization.[24,33,34]

This study has a few limitations. No clinical success endpoint, as therapeutic or palliative procedure, was defined in this study. The primary aim of this study was to assess the safety of the vascular embolization procedure. Nevertheless, consistency between target and actual lesion obliteration was assessed as technical measure of efficacy of the Lipiodol/N-BCA mixture. Long-term follow-up was not performed. However, complications encountered with vascular embolization occurred mostly within the first weeks after the procedure.[29,35] The incidence of rebleeding was not specifically assessed, but the systematic reporting of AEs did not identify such an event. The study primarily focused on AVM treatment, while a limited number of other lesions such as arteriovenous fistulas, hemangiomas, and aneurysms were included in the study. This limited representation of different lesion types hampers the ability to generalize the study findings.

Conclusion

In conclusion, the Lipiodol and N-BCA mixture had a favorable safety profile for vascular embolization, with no AEs reported during the procedure, and two mild AEs related to the mixture reported after the procedure. Additionally, vascular embolization with the Lipiodol and N-BCA mixture demonstrated a high success rate in achieving the desired vascular occlusion, indicating its effectiveness in treating the targeted lesions.

Ethical Approval

The study was approved by the ethics committee of each site independently and authorized by the DCGI.

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None.

Conflict of Interest

Dr. Raghunandan Prasad reports support by Guerbet (payment was made to the institution). All the other authors report no conflict of Interest.

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