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Review Article

Is glue embolization safe and effective for gastrointestinal bleeding?

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A B S T R A C T

Transcatheter arterial embolization using N-butyl-2-cyanoacrylate (NBCA) for gastrointestinal arterial bleeding enables higher cessation rate and lower recurrent bleeding rate compared with conventional embolic materials including gelatin sponge, metallic coil, and polyvinyl alcohol (PVA) particle. Glue embolization is particularly effective in patients with coagulopathy. Even in the lower gastrointestinal tract, ischemic bowel complications by glue embolization are comparable to other agents. Glue embolization is also effective for arterial esophageal bleeding without any serious ischemic complications although the anatomy of the esophageal artery is complex and varied. For bleeding after abdominal surgery such as pancreaticoduodenectomy or hepatic lobectomy, interventional radiologists should be careful with indicating glue embolization because the presence of fewer collateral vessels can easily result in serious ischemic complications. Modified glue such as Glubran 2 (NBCA associated with methacryloxyfulfane) can reduce the risk of ischemic complication due to its less thermal reaction, but the outcomes seem unsatisfactory.

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Keywords: Cyanoacrylates; Gastrointestinal hemorrhage; Therapeutic embolization

Introduction

Transcatheter arterial embolization (TAE) with a gelatin sponge, metallic coils, polyvinyl alcohol (PVA), or a combination of these agents is widely used for management of acute gastrointestinal (GI) tract bleeding.^{1–5} Although effective in the majority of cases, these methods fail to achieve adequate hemostasis in some cases for a variety of reasons, including inability to adequately reach the bleeding site, collateral circulation after embolization, or recanalization of the embolized vessels, particularly in patients with coagulopathy.^{1,2,6–11}

N-butyl-2-cyanoacrylate (NBCA) (Histoacryl; B. Braun, Mel-sungen, Germany) is an alternative permanent liquid embolic material and tissue glue that was approved by the U.S. Food and Drug Administration for use in cerebral arteriovenous malformations in 2000. According to previous reports that describe the use of glue embolization for the treatment of GI tract bleeding,^{10,12–16} NBCA, which allows rapid and permanent embolization with fast polymerization when it comes into contact with blood, has several advantages compared with other embolic materials. First, NBCA can be injected through a microcatheter into small and tortuous

arteries and collateral circulation, which are often too difficult to access and embolize with a microcoil. NBCA can also enable simultaneous embolization of collateral vessels connected to the bleeding focus, which can prevent residual bleeding from retrograde collateral flow. Second, because NBCA does not depend on the biological coagulation process for its therapeutic effect, it is also useful in patients with coagulopathy. In cases of coil or PVA particle embolization, occlusion of vessels or pseudoaneurysms is dependent on thrombosis rather than the embolic material itself, and the coagulation function of the patient is critical for the ultimate success of the embolization procedure for bleeding. Encarnacion et al⁷ reported that embolization was 2.9 times more likely to fail in patients with coagulopathy and that death from bleeding after embolization was 9.6 times more likely to occur in this group.

In this article, we review the literature and discuss the safety and efficacy of glue embolization for GI tract bleeding, including arterial esophageal bleeding, pancreatitis related bleeding, and postoperative bleeding, as well as assess the utility of modified glue.

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Techniques of Glue Embolization

Techniques of glue embolization, including indication, infusion point, glue mixture ratio, endpoint of infusion, and combination of other embolic agents if necessary, are not significantly different in various literatures as described below.

Diagnostic angiography is first performed to identify the bleeding site. Taking the risk of ischemic injury after embolization into consideration, the microcatheter is advanced as close to the bleeding site as possible. Mixture ratios of iodized oil (Lipiodol; Andre Guerbet, Aulnay-sous-Bois, France) to NBCA varies, depending on the distance from the tip of microcatheter to the bleeding point, vessel size, and blood flow velocity. The NBCA mixture ratio is also guided by the polymerization times described by Pollak and White¹⁷ who suggested that the estimated *in vivo* polymerization time for NBCA to iodized oil mixtures between 1:1 and 1:4 was 1 to 4 seconds, with a linear relationship between time and mixture ratio. More practically, if the microcatheter can be delivered close to the bleeding point, a higher concentration of NBCA mixture is administered, and if the catheter cannot be placed at the corresponding vessel, a lower concentration of NBCA mixture is injected at the proximal segment. The end point for the injection is extravasation of the mixture from the bleeding site or filling of the pseudoaneurysm with or without appearance of anastomotic channels. Immediately after the cast of the target vessel or pseudoaneurysm is visualized under fluoroscopy, the microcatheter is quickly removed to prevent adherence of the catheter tip to the vessel wall and discarded without flushing. In some cases, initial coil embolization at a non-target vessel is performed prior to glue embolization in order to prevent end-organ damage. When there is high blood flow and a long distance to the bleeding site, coils are used for flow control prior to NBCA administration.

Clinical Outcomes and Complication

Kim et al¹⁸ published a systematic review on transcatheter arterial embolization using NBCA as a main embolic agent in upper and lower GI tract bleeding. The clinical success rate and complication rate of glue embolization were 81.1% (210 of 259) and 1.9% (5 of 259) in the upper GI tract, and 86.9% (152 of 175) and 4.6% (8 of 175) in the lower GI tract, respectively. According to previous reports on embolization using conventional embolic agents (i.e., coils, gelfoam, and PVA particles), the clinical success rate and complication rate were 48% to 89% and 4% to 17% in the upper GI tract, and 68% to 92% and 3% to 24% in the lower GI tract, respectively.^{2,7,19-22} Although these published studies about conventional embolic agents are relatively old, glue embolization can be concluded as effective and safe, achieving a high rate of cessation, preventing recurrent bleeding.

Post-procedural bowel ischemic complication including erosion, ulcer, and necrosis is 1.9% in the upper GI tract and 4.6% in the lower GI tract, according to a previous review article.¹⁸ Yata et al²³ reported a relative high rate of ischemic complication (30.0%; 3 of 10 patients receiving endoscopic evaluation after glue embolization both in the upper and lower GI tract). However, in their study postprocedural endoscopy was performed more compared with other studies, therefore in other studies, asymptomatic and subclinical ischemia might not have been identified. Regardless, serious ischemic complication requiring surgery seems to be very limited after glue embolization. Previous experimental studies suggest that embolization involving four or more vasa recta carries an increased risk of substantial ischemic bowel damage.^{24,25} Kodani et al²⁶ compared embolized vasa recta on angiogram and

ischemic complication on colonoscopy after glue embolization for lower GI tract bleeding, and suggested that glue embolization of even one vasa rectum with more than two branches can induce ischemic complication without any symptoms.

On the other hand, NBCA has a very specific drawback, which is the potential adhesion of the catheter tip to the vessel wall. NBCA should be administered by a skillful operator. If an inexperienced doctor is attempting glue embolization, a low concentration of NBCA mixture should preferably be used because of its prolonged polymerization time. Based on current literature, adhesion was not found as a complication.

Glue Embolization after Abdominal Surgery

Particularly in patients with a past history of abdominal surgery including pancreaticoduodenectomy or hepatic lobectomy, interventional radiologists should be careful with an indication and procedure of glue embolization. Hepatic artery or gastroduodenal artery (GDA) stump is occasionally associated with GI tract bleeding. Previous studies²⁷⁻³⁰ have described that hepatic failure can occur (0%–66%) after hepatic arterial embolization and is often fatal. In general, hepatic failure after hepatic arterial embolization has been attributed to the presence of portal vein stenosis or poor arterial supply of the liver. However, the correlation between the hepatic failure and the presence of portal vein stenosis is controversial. According to the article by Sato et al,³¹ hepatic complication was eight times more likely to occur in cases with no hepatic collaterals involving hepatic, replaced, or accessory hepatic arteries, than in cases only with nonhepatic collaterals via splanchnic arteries, including gastric, phrenic, and adrenal vessels. However, the correlation between the embolization outcome and the presence of portal vein stenosis was not significant. To prevent hepatic failure after endovascular treatment, stent graft placement is preferable for preserving peripheral flow.³²⁻³⁴ Gwon et al³² reported endovascular management of extrahepatic artery hemorrhage after pancreaticobiliary surgery, and compared between transcatheter arterial embolization and stent-graft placement, and concluded that stent-graft placement is better than TAE for preserving intrahepatic arterial flow without rebleeding from the extrahepatic artery. However, in emergency procedures, the artery is often too spastic for a delivery system of stent graft placement to be advanced, and embolization is therefore chosen. In embolization, glue injection is challenging because glue flowing into the peripheral hepatic artery can induce hepatic failure under conditions with poor collateral network. Glue should play a supporting role for other embolic materials such as coil or vascular plug rather than as a main embolic material in these situations.

Arterial Esophageal Bleeding

In arterial esophageal bleeding, glue embolization is also useful without any associated serious complications. Aoki et al³⁵ reported five cases of arterial esophageal bleeding in esophageal cancer patients. In this series, glue embolization could successfully arrest bleeding in all five patients without any evidence of procedure-related complications such as esophageal infarction and recurrence of arterial esophageal bleeding. All the patients had a bleeding esophageal artery that originated directly from the aorta. Park et al³⁶ reported five cases of arterial esophageal bleeding caused by benign lesions. The bleeding esophageal artery directly originated from the aorta in four patients and from the left inferior phrenic artery in one patient. Angiographic and clinical success was achieved in all five patients with no evidence of procedure-

related complications such as esophageal infarction. Interventional radiologists should be aware of variations in the arterial blood supply of the esophagus when investigating a bleeding focus. The arterial blood supply of the esophagus is divided into three parts. Primarily, the descending branches of the inferior thyroid artery supply the cervical esophagus. Branches of the bronchial arteries, and one or two esophageal arteries that arise directly from the aorta, supply the midthoracic portion. Lastly, branches of the left gastric or left inferior phrenic arteries supply the distal portion.^{37,38} Branches of the subclavian, thyroidea ima, common carotid, or superior thyroid arteries may also supply the cervical esophagus. Branches of the right third or fourth intercostal arteries may also supply the midthoracic esophagus. Branches from the celiac, splenic, short gastric, or left hepatic arteries may supply the distal esophagus.³⁷ As the esophageal arteries form collateral capillary networks before they penetrate the esophageal muscle layer and perfuse the submucosa,³⁹ they can cause back bleeding (hemorrhaging from potential collateral channels) that is of concern in the case of proximal embolization using coils or microcoils.

GI Tract Bleeding Associated with Pancreatitis or Post Pancreaticoduodenectomy

Compared with arterial esophageal bleeding, GI tract bleeding associated with pancreatitis or post pancreaticoduodenectomy is more commonly encountered. Reported incidences of pseudoaneurysms associated with acute or chronic pancreatitis range from 10% to 17%, and mortality rate from pseudoaneurysms in such patients is approximately 20%.⁴⁰ Furthermore, reported incidences of arterial hemorrhage after pancreatic surgery range from 2% to 5%, and reported mortality rates from postoperative hemorrhage range from 18% to 60%.⁴⁰ Thus far, case series on glue embolization at the GDA or its branches are limited. Izaki et al⁴¹ performed 12 glue embolizations for pseudoaneurysms complicating pancreatitis or pancreatectomy. They mentioned that coagulative necrosis does not occur because NBCA does not permeate capillaries. The same team evaluated the safety of glue embolization in a swine model in terms of histological changes in the pancreas, and concluded that selective glue embolization caused localized ischemic necrosis without clinically significant pancreatitis.⁴²

Modified Glue

During the last two decades, several cyanoacrylate formulations have been developed. Recently, there have been several reports on endovascular treatment using NBCA associated with methacryloxysulfolane (NBCA-MS) (Glubran 2; GEM Srl, Viareggio, Italy) from Europe.^{43–45} NBCA-MS has its peculiar characteristics. Polymerization begins 1 to 2 seconds after application and completes within 60 to 90 seconds. The polymerization reaction generates a temperature of approximately 45°C,^{46,47} which is lower than that of pure cyanoacrylates,^{48,49} and causes very limited damage to the surrounding tissue. In contrast, other cyanoacrylates generate temperature of 80°C to 90°C, causing more inflammation and, rarely, tissue necrosis and deep ulcers or fistulas.⁵⁰ According to the report by Abdulmalak et al,⁴⁴ who treated non-variceal GI tract bleeding using NBCA-MS, there was no post-procedural ischemic complication, but clinical success was achieved in 17 of 28 patients (60.7%) while clinical failure was observed in the remaining 11 of 28 patients (39.3%).

The clinical outcome and recurrent bleeding rate seem to be unsatisfactory, and therefore NBCA-MS may not be considered as an alternative to NBCA. We think that the advantages of NBCA-

MS as a less exothermic reaction and a less destruction of the vascular endothelium may be the reason of higher rate of clinical failure as a result of inadequate vessel occlusion. The use of ethylene vinyl alcohol copolymer (Onyx; ev3, Plymouth, MN, USA), which polymerizes more slowly and has less catheter adherence than NBCA, is feasible and effective for peripheral interventions.⁵¹ However, the use of this agent is not approved in some countries including Japan. In recent years, a mixture of NBCA, Lipiodol, and ethanol (NLE) has been introduced and has different characteristics from those of the typical mixtures of NBCA and Lipiodol (NL).⁵² NLE may have multiple advantages over NL for adhesion, such as accelerated polymerization and low risk of adhesion to the microcatheter. Although experimental studies have been found,^{52–55} there are no reports on the clinical use of NLE for GI tract bleeding. If NLE is proven to be safe and effective, any interventional radiologists can easily tolerate and achieve cessation.

Conclusions

Glue embolization is an effective treatment for GI tract bleeding, particularly in cases with coagulopathy. Ischemic bowel complications by glue embolization are comparable to other embolic agents. Glue embolization is also effective for arterial esophageal bleeding although the anatomy of esophageal artery is complex and varied. For bleeding after abdominal surgery, interventional radiologists should be aware of indicating glue embolization because ischemic complications may easily occur when there are fewer collateral vessels. A modified glue which can be used more safely than NBCA is expected in the future.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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