Gluing Gastric Varices in 2012: Lessons Learnt Over 25 Years

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Bleeding from gastric varices (GV) continues to pose a challenge to the endoscopist and no consensus has been reached on the best way for treating these patients. Gastric variceal obturation (GVO) with the tissue adhesive, *N*-2-butyl-cyanoacrylate (NBC), is considered the treatment of first-choice for this condition in most parts of the world. The liquid monomer polymerizes into a solid cast, obturating the vessel within 10–20 s of coming in contact with ionic solutions such as blood. Gastric variceal obturation achieves hemostasis in over 90% of patients with active bleeding, eradicates GV in over 80% of these patients, and re-bleeding occurs in 3–30%. These results are comparable with those of transjugular intrahepatic portosystemic shunting (TIPS; over 90% hemostasis in acute bleeding with re-bleeding in 15–30%). Though, there has been no direct comparison with GVO, balloon-occluded retrograde transvenous obliteration of GV (BRTO) achieves near 100% obliteration with recurrence in 0–10% and is superior to TIPS for hemostasis in active bleeding when used in combination with transcatheter sclerotherapy. Several complications have been described for GVO including thromboembolic complications which occur in 0.5–4.3% and may be devastating in some. Many of the complications and the variability in results of GVO can be attributed to variations in injection technique. The use of a standardized injection technique has been reported to achieve 100% hemostasis and obliteration with 6.9% re-bleeding and no embolic complications. Gastric variceal obturation with NBC continues to be the first-choice therapy for GV bleeding outside Japan. Adherence to a standard injection technique will maximize hemostasis and eradication of GV while minimizing complications of therapy. (J Clin Exp Hepatol 2012;2:55–69)

HISTORICAL BACKGROUND

The cyanoacrylates are a family of fast-acting adhesives that are widely used in industry and have been finding novel uses in veterinary and medical practice. The prototype is methyl-2-cyanoacrylate (MCA). Its ethyl, butyl, and octyl congeners share the adhesive properties. Methyl-2-cyanoacrylate was invented by Harry Wesley Coover Jr and Fred Joyner in 1942, while working for Kodak Laboratories to develop materials for making transparent gun sights (Figure 1). Although not appropriate for gun sights, MCA could glue together many materials with great strength and rapidity. This new adhesive was developed as 'Eastman 910' by Kodak and marketed a few years later as the first true 'super glue'.[1] As the market expanded in the 1960s, other brands, made by mixing different cyanoacrylates with some other substances, were introduced on the market, including 'Loctite Quick Set 404', 'Superbonder', and 'Permabond'. Coover was inducted into the National Inventors' Hall of Fame in 2004[2] for his pioneering work

Figure 1 Harry Wesley Coover Jr (1917–2011) shortly before being awarded the National Medal of Technology and Innovation by Barack Obama in 2010.

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Abbreviations: BRTO: balloon-occluded retrograde transvenous obliteration; EUS: endoscopic ultrasound; EV: esophageal varices; GV: gastric varices; GVO: gastric variceal obturation; MCA: methyl-2-cyanoacrylate; NBC: *N*-2-butyl-cyanoacrylate; OCA: 2-octylcyanoacrylate; TIPS: transjugular intrahepatic portosystemic shunting
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with the 'superglues' and was honored with the National Medal of Technology and Innovation by President Barack Obama in 2010. He died of natural causes at his home in Kingsport, Tennessee, on March 26, 2011. Sadly, Eastman Kodak, founded in 1889, has filed for bankruptcy in January 2012.[3]

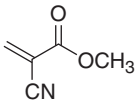
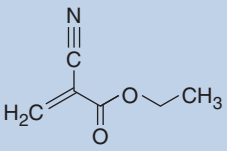
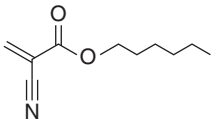
CHEMISTRY

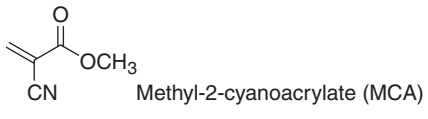
In the presence of water, specifically hydroxyl ions (OH^-), MCA, and the other cyanoacrylates polymerize rapidly (Figure 2) in an exothermic reaction, forming long, strong chains and changing from a watery liquid to a hard, brittle acrylic plastic. Degradation is by hydrolysis and results in the formation of smaller oligomers, cyanoacetate, and formaldehyde, which are irritant to the skin and other tissues. Acetone is a widely available solvent capable of softening cured cyanoacrylate. Other solvents include gamma-butyrolactone, nitromethane, and methylethyl ketone.[4] Properties of some of the commonly used industrial and medical grade cyanoacrylate glues are summarized in Table 1.

MEDICAL USES OF CYANOACRYLATE GLUES

Cynoacrylate glues are used topically for sutureless closure of skin wounds and as skin sealants, in ophthalmology, ENT, dentistry and orthopedics, and for obturation of bleeding or abnormal vessels such as varices, aneurysms, pseudoaneurysms, hemangiomas, and arterio-venous malformations.[5–9]

Table 1 The superglue family.

Name	Formula	Structure	MW (Da)	Acronym	Brand name	Manufacturer
Industrial grade						
Methyl-2-cyanoacrylate	$C_5H_5NO_2$		111	MCA	Krazy Glue	
Ethyl-2-cyanoacrylate	$C_6H_7NO_2$		125	ECA	Super Glue	
Methyl methacrylate				MMCA		Embolotherapy spheres for hemangiomas, arteriovenous malformations (AVMs)
Medical grade						
N-butyl-2-cyanoacrylate	$C_8H_{11}NO_2$		153	NBCA	Histoacryl Nectacryl Endocryl	B Braun Melsungen AG, Germany Dr. Reddy's Laboratory, Hyderabad, India Geno Pharmaceuticals Ltd., Mumbai, India
Isobutyl-2-cyanoacrylate	$C_8H_{11}NO_2$			IBCA		Injection embolotherapy for arteriovenous malformations (AVMs), hemangiomas
2-octylcyanoacrylate			209	OCA	Dermabond	Medical grade skin adhesive, gastric varices



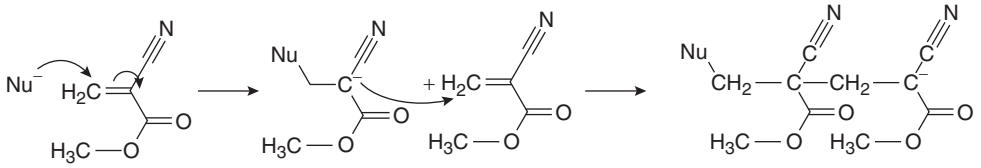


Figure 2 Polymerization of methyl-2-cyanoacrylate.

Skin and Wound Sealant

Cyanoacrylate glue has been used as a skin sealant and hemostatic agent since the 1960s. Even while an application to use Dr. Coover's glue for sealing wounds was pending before the United States Food and Drug Administration (FDA), it was used in Vietnam in 1966, where it saved many lives. It was very effective as a battlefield hemostatic spray to stop bleeding from chest, abdominal, and limb wounds, allowing time for paramedical staff to shift the wounded back to base hospital.[1]

N-butyl-2-cyanoacrylate (NBC) was the only commercially available cyanoacrylate tissue adhesive until 1998. Although, it is effective in closing superficial lacerations, the adhesive becomes brittle after polymerizing and fractures when used over skin creases or long incisions, thus limiting its use to areas of low tension. Though breaking strength in skin wounds closed with NBC is similar to that in wounds repaired with 5-0 monofilament sutures after 5–7 days, on day 1, it is only about 10–15% of that in a sutured wound. *N*-butyl-2-cyanoacrylate has been used widely in plastic surgery with good cosmetic outcomes (e.g., upper lid blepharoplasty, facial skin closure, and scalp wound closure).[4,5]

In 1998, the US FDA approved 2-octylcyanoacrylate (OCA) for closing wounds and surgical incisions in humans and, in 2001, for use as a barrier against common bacterial microbes including certain staphylococci, pseudomonads, and *Escherichia coli*. It has improved flexibility and its three-dimensional breaking strength is 3 times that of NBC, allowing its use on longer incisions. 2-octylcyanoacrylate is marketed under the brand names *Traumaseal* and *Dermabond*.[3]

Ocular Uses

Since 1959, when cyanoacrylate adhesive was introduced in ophthalmology[1] and sutureless ocular surgery using Eastman 910 (MCA) was described,[6] the use of tissue adhesives has gradually become standard treatment for corneal perforation, descemetocele, stroma thinning, wound leak, and exposure keratopathy, conditions in which surgical treatment is dangerous and uncertain. Today, although no tissue adhesive for ocular use has been approved by the US FDA, glue is widely used for these ocular indications in some European referral centers.[7]

Vascular and Other Uses

N-2-butyl-cyanoacrylate has also been extensively used for obturation of varices by endoscopic injection or transvenous embolization and for obturation of vascular malformations such as hemangiomas and arterio-venous malformations. Cyanoacrylate glues also find use in orthopedic surgery, dental and oral medicine (Soothe-n-Seal), veterinary medicine (Nexaband), and for home use as LiquiBand® or liquid bandage. It has even been explored as a potential treatment for emphysema, where it can be used to seal off diseased lung passages without the need for invasive surgery.

Safety and Toxicity

Industrial toxicity is related to fumes from vaporized cyanoacrylate monomers that irritate sensitive membranes in the eyes, nose, and throat. About 5% of the population can become sensitized to cyanoacrylate fumes after repeated exposure, resulting in flu-like symptoms, asthma, and allergic skin reactions. These risks can be minimized by using MCA in well-ventilated areas. In vivo tissue toxicity is related to the irritant properties of the breakdown products of the cyanoacrylates. The least toxic is OCA which degrades very slowly due to its longer organic backbone and is preferred for sutures. Its lower reactivity and slower degradation translate into lower concentration of polymer breakdown products in surrounding tissues resulting in less inflammation and less skin irritation.[4]

GLUE INJECTION FOR GASTRIC VARICES

Introduction

Management of gastric variceal bleeding continues to be a clinical challenge and, despite availability of several effective endoscopic, interventional radiologic and surgical therapies, there is no general consensus regarding the optimal management strategy for this condition. Endoscopic gastric variceal obturation (EGVO) with intravariceal injection of the tissue adhesive agent NBC, originally described in 1986,[10,11] is the first-choice therapy for bleeding GV in Europe and most parts of Asia outside Japan[12,13] though there are only a few reports from USA where NBC is not approved for this indication. Gastric variceal obturation is readily available in most parts of the world, is very effective for both acute GV bleeding (GVB) and elective therapy for obliteration of GV, and is also significantly cheaper than interventional radiologic options.[14] However, despite its proven efficacy, reservations persist related to variability in reported results, particularly in re-bleeding rates, and the small but significant risk of sinister local and systemic complications. Variability in results and in occurrence of complications maybe attributed to differences in techniques and regimens between different workers. Development and implementation of a standardized technique aimed at maximizing obliteration and minimizing complications will optimize results of this valuable technique. The chemistry of cyanoacrylate glue, the conventional technique for glue injection, and its variations and data on efficacy and complications of GVO will be reviewed in detail, along with data regarding efficacy of interventional radiologic modalities for the management of GVB. Alternative endoscopic therapies for GVB[15,16] and interventional radiologic approaches to the management of GVB have been reviewed in detail elsewhere.[17,18] Recently, improvements upon the

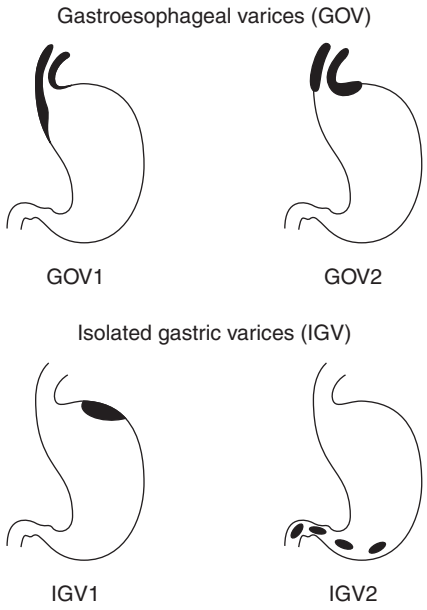


Figure 3 The Sarin classification of gastric varices.[21]

conventional technique for GVO with NBC, using endoscopic ultrasound (EUS) guidance for obliteration of the 'inlet' vessel feeding large, complex GV[19] and transesophageal coiling and gluing of fundal varices with OCA[20] have been reported and may provide results superior to the conventional technique practiced currently. In a series of 30 patients with gastric fundal variceal (GFV) bleeding, this innovative technique was able to achieve hemostasis in 100%, GFV eradication in 96% in a single session, without any embolic complications and with 16.6% recurrent bleeding that was not from GFV.

Classification of Gastric Varices

Gastric varices are reported in 20% (5–33%) of patients with portal hypertension either alone or with esophageal varices (EV). Sarin et al have classified them according to their location and relationship to EV (Figure 3).[21] Gastroesophageal varices type 1 (GOV1) are extensions of EV along the lesser curvature, seen in about 70% of patients. Gastroesophageal varices type 2 (GOV2) extend into the fundus and tend to be longer and more tortuous. Isolated GV occur in the absence of EV and maybe located in the fundus (IGV1) where they tend to be tortuous and complex, or in the body, antrum, or around the pylorus (IVG2). Hashizume et al[22] have described GV according to their *form* which maybe tortuous (F1), nodular (F2), or tumorous (F3) and *location* which may be locus anterior (La), posterior (Lp), lesser curvature (Ll), and greater curvature (Lg) of the cardia and the fundic area (Lf).

Imaging for Gastric Varices

Although, most often, endoscopic evaluation of GV provides adequate information for diagnosis and management, cross-sectional imaging can be useful in certain special situations. The computed tomography (CT) portography, contrast-enhanced MR angiography, and multidetector CT (MDCT) have been used to determine the extraluminal extent of large GV and to determine completeness of obturation of the entire GV complex, particularly when balloon-occluded retrograde transvenous obliteration (BRTO) and its variations are used.[23,24]

In patients with suspected GV, EUS, particularly when combined with color Doppler, is the most useful and informative second investigation after standard endoscopy. In patients with giant gastric folds, differentiation between GV and other causes such as gastric cancer, gastric lymphoma, Menterier's disease, and gastric lymphangiectasis is best done with EUS. All patients with GV have anechoic tortuous varicose veins in the submucosal layer. While EUS images of gastric lymphangiectasis are very similar, GV are readily distinguished from gastritis (regular thickening confined to the mucosa and submucosa), lymphoma, and adenocarcinoma (marked thickening of muscularis propria, with or without changes in the other layers).[25] Color Doppler signals can demonstrate a continuous venous hum and pulsatile flow in GV, while no signal is demonstrable in Menetrier's disease, gastrointestinal stromal tumors (GIST), or lymphoma.[26] Informative morphologic indices can also be determined by EUS such as blood flow velocity in the GV (significantly higher with F3 GV and with prior GVB) and gastric wall thickness (significantly reduced in GV with red-color sign or erosions).

'Deep' Varices

Endoscopic ultrasound has added a new dimension to grading of varices and assessment of bleeding risk by introducing the concept of 'deep varices', defined as dilated intramural venous channels adjacent to the muscularis propria ('deep' periesophageal/perigastric varices) or extramural channels outside the muscularis propria ('deep' paraesophageal/paragastric varices). Since 'deep' varices are not detected on routine endoscopy and significantly increased risk of bleeding has been reported among patients with cirrhosis having large (>5 mm) 'deep' varices, their detection is of more than academic interest. Interestingly, a recent study of 33 patients being evaluated for liver transplantation has reported discord between presence of large EV/GV and large 'deep' EV/GV. Although, large EV on endoscopy (33%) and large 'deep' EV on EUS (both para and periesophageal; 36%) were equally common, large, 'deep' EV were present without large EV in 42% and large 'deep' GV were present without large GV in 58% patients. These observations suggest that EUS may find a place in the routine evaluation of GV particularly in patients being evaluated for LT.[27]

The same workers have reported that previous banding may increase the risk of developing large 'deep' esophageal and GV. 'Deep' EV, large GV (>5 mm), and large 'deep' GV

occurred significantly more commonly (60%) in patients previously banded for EV and now with grade II/III EV than in the not-banded group (20%; $P=0.04$).[28]

Natural History

Gastric varices have been known to be present in portal hypertension since 1913,[10] yet their natural history is poorly documented. Though GV bleed less frequently than EV, typically, GVB is more severe, more difficult to control, re-bleeding is more common and mortality is higher. While overall risk of bleeding from GV is 25% in 2 years, in fundal varices it ranges from 55% to 78%, with a bleeding-related mortality in 45%.[21] Risk factors for gastric variceal hemorrhage include size of fundal varices (large [>10 mm] > medium [5–10 mm] > small [<5 mm]), presence of localized reddish mucosal spots or areas on the surface of the GV at endoscopy and Child class (C > B > A).[29,30] Hemodynamic factors contributing to an episode of GVB have not been studied as well as for EV. Though, in general, the well-known relationship between variceal size, wall thickness, wall tension, and intravariceal pressure prevails in GV as for EV, there are also some differences. Portal venous pressure in patients with GV is usually lower than in patients with EV.[31,32] Portosystemic pressure gradient of >12 mmHg is not necessary for GVB, probably due to the large, high-flow gastrorenal shunts (GRS) that decompress GV in about 85% of these patients.[33,34]

Treatment of Gastric Varices

Data comparing different endoscopic, interventional radiologic and surgical treatment modalities for the management of bleeding from GV are scanty and no consensus has been reached regarding the optimal management strategy for this condition. Gastroesophageal varices type 1, which are extensions of EV, are eradicated by endoscopic band ligation (EBL) or endoscopic injection sclerotherapy (EIS) for EV. Isolated GV type 1 secondary to isolated splenic vein thrombosis are readily treated by splenectomy. Gastroesophageal varices type 2 may be partially eradicated but IGV type 1 do not respond at all to EBL or EIS for EV.[12]

Endoscopic Gastric Variceal Obturation

N-2-butyl-cyanoacrylate is a watery liquid that transforms into a solid state when added to a physiological medium containing hydroxyl ions, such as blood. When injected into a varix, the glue polymerizes instantaneously and hardens into a rock hard substance, thereby obturating the lumen of the varix, achieving rapid hemostasis and prevention of re-bleeding. Over time, with the erosion of the overlying mucosa, the glue cast is extruded into the lumen. A recent study reported that this happened within 1 year in all patients. Early extrusion, within 1 week, was noted in 12.1% and was associated with early re-bleeding in half of these patients (6.2%). During serial follow-up, glue extrusion was noted in 42.8% after 2 weeks, in 27.9% after 3 months, and in 28.9% after 6 months though late re-bleeding, 2–18 months after injection, occurred in only 8.1%.[35] However, in at least one case, the glue cast was reported to be still present as late as 3 years after glue injection.[36]

Efficacy of N-2-butyl-cyanoacrylate Injections for Gastric Varices

In the last 25 years, experience with >3000 patients has been reported in over 35 case series, many of which are summarized in Table 2.[14,35,37–66] The median rate for achieving primary hemostasis with NBC injection in actively bleeding GV has been reported in 30 of 32 series reviewed and was 95.2% (range 71–100%) while the median rate for complete variceal obliteration, reported in only 15 of 32 series, was 87% (range 51–100%) in one to three sessions. Median rate of re-bleeding, reported in 30 of 32 series, was 16% (range 0–58%) during mean follow-up periods ranging from 3–116 months while the median rate for early re-bleeding, within 48 hours of injection, was reported in only 8 of 32 series and was 6.8% (range 0–20.5%). Embolic complications, reported in 17 series, occurred at a median rate of 1.0% (range 0–4.3%) while infective complications occurred in only 4 of the 16 series in which they were reported (median rate 0%; range 0–10%). Median procedure-related mortality, reported in 27 series, was 6% (range 0–44%). This heterogeneity in results reflects variability in techniques and regimens over the last 25 years. Complete obliteration of GV was not performed as a routine in many series and the wide variability in re-bleeding rates reflects both incomplete GV eradication and the long follow-up period after completion of therapy in many series. Embolic and infective complications were not reported in many of the early series.

Two randomized controlled trials have shown that NBC injection is superior to EIS both with alcohol[30] and with ethanolamine oleate[67] while another trial showed superiority of NBC over EVL[68] in the treatment of acute GVB. Hemostasis in active bleeding was achieved in >90% of cases with NBC compared with 62% for alcohol injection, 57% for ethanolamine oleate injection, and just 40% for EVL. The only prospective comparison of transjugular intrahepatic portosystemic shunting (TIPS) with GVO[47] reported comparable GV obliteration rate but significantly higher re-bleeding rate (38% vs 11%, $P<0.05$) in the GVO group. However, this study has been criticized because the results for GVO were inferior to the results in other reported series. Gastric varices obliteration was achieved in only 51% compared with the standard figure of ~80% while re-bleeding rate of 38% after NBC injection was unusually high compared with other published series (median 16%; range 0–58%) (Table 2).

Table 2 Outcome of *N*-2-butyl-cyanoacrylate injection for fundal varices.

Series	Number	Hemostasis (%)	Obliteration (%)	Re-bleeding (%)	Embolism (%)	Infection (%)	GVO-related mortality (%)	Follow-up (mo)
Ramond et al[37] (1989)	49	93	–	58	–	–	30	12
Oho et al[38] (1995)	29	93	–	25	–	–	38	14
D'Imperio et al[39] (1996)	54	90.9	87	3.7	–	–	9.5	6
Miyazaki et al[40] (1998)	16	83.3	–	–	–	–	–	51
Ogawa et al[41] (1999)	17	100	–	7.5	–	–	–	60
Kind et al[42] (2000)	174	97.1	75	Early 15.5 Late 12.8	0	0	19.5	36
Lee et al[43] (2000)	R* 54 OD† 47	96.3 95.7	79.6 –	7.4 12.8	0 –	0 –	1.9 6.4	16.8 –
Huang et al[44] (2000)	90	94.4	–	23.3	0	0	2.2	13
Iwase et al[45] (2001)	37	100	–	16	–	–	43	31
Lo et al[47] (2001)	31	87	51	13	–	–	6	14
Akahoshi et al[46] (2002)	52	98.2	–	35	–	–	4	28.1
Dhiman et al[48] (2002)	29	100	93.1	10.3	3.4	0	3.4	–
Sarin et al[49] (2002)	9	89	100	22	0	0	10	15.4
Greennwald et al[50] (2003)	44	95	–	Early 5 Late 18	0	0	23	12
Mahadeva et al[14] (2003)	23	96	–	30	4.3	0	24	6
Noophun et al[51] (2005)	24	71	–	10	4.1	8.2	25	8.3
Kim et al[52] (2006)	86	93	–	16	0	0	–	11
Cheng et al[53] (2007)	635	95.2	76.9	Early 3.1 Late 8.0	1.0	0.5	8	3–116
Joo et al[54] (2007)	85	98.6	–	Late 28.2	3.5	–	1.4	25.4
Mumtaz et al[55] (2007)	50	100	–	14	–	–	6	–
Belletrutti et al[56] (2008)	34	93.8	84	11.7	2.1	10	2.1	11
Seewald et al[57] (2008)	131	100	100	Early 0 Late 6.9	0	0	6.1	25.8
Fry et al[58] (2008)	33	88	–	15	3.3	–	3.3	9
Marques et al[59] (2008)	48	87	–	Early 20.5% Late 20.5%	–	–	44	18
Martins et al[60] (2009)	23	–	87	4.3	–	–	4.3	25.4
Wong et al[26] (2007)	148	96.2	70.2	Early 6.2 Late 8.1	0.6	–	–	13.1
Kumar et al[61] (2010)	87	84.8	89	23.4	–	–	7.2	16
Al-Ali et al[62] (2010)	37	95	–	Early 8 Late 28	0	0	0	14
Sato et al[63] (2010)	129	100	93	0**	3.1	0	0	–
Choudhuri et al[64] (2010)	170	82.3	90	14.5	0	0	5.7	30.7
Rajoriya et al[65] (2011)	31	100	–	16	0	0	0	35
Kang et al[66] (2011)	127	98.4	100	18.1	1.5	3.0	–	10.8
Median (%)	95.2	87	16	1	0	6	–	–
Range (%)	71–100	51–100	0–58	0–4.3	0–10	0–44	–	–

N = 2633 patients in 32 series.
**R*: repeat injection with intention to eradicate; †OD: on demand when re-bleeding occurred; **recurrent GV in 14.2%, no re-bleeding on FU.
FU: fluorouracil; GV: gastric varices; GVO: gastric variceal obturation.

COMPLICATIONS OF *N*-2-BUTYL-CYANOACRYLATE INJECTIONS

Complications due to glue injections can be local, occurring at the site of injection, or systemic, which may be infective or embolic.

Local Complications

Giant ulceration at the site of injection has been ascribed to paravariceal or intramural glue injection.[69] At times, ulceration may involve the full thickness of the esophagus and result in sinus formation from the esophageal wall.[70] Impaction of the needle tip in the glue cast was reported with the use of undiluted glue for active bleeding and was attributed to premature glue solidification in the tip of the injector.[39,48]

Chief among local complications is bleeding during the procedure as well as early and late re-bleeding. Uncontrolled bleeding from the site of injection after withdrawal of the needle has been noted in patients with high-risk GV, that is, large, tumorous, F3 varices with red spots in patients with Child's C liver function. Though, usually controlled by repeating glue injections into the varix mass, uncontrolled bleeding may be fatal[61] or may need TIPS, surgical shunt, or major resectional surgery.[62] Laceration of the varix, after forcible removal of an injector impacted in the glue cast, can cause torrential bleeding that may be fatal.[39,48] Re-bleeding rates have ranged between 3.7% and 58%.[37,39] Early re-bleeding, reported in 0–20.5% patients,[57,59] occurs from GV that have not been completely eradicated and has been related to early extrusion of the glue cast within 7 days of injection. Early re-bleeding occurred in half of the 12.1% patients with early extrusion in a series of 148 NBC injections.[35] Antibiotic prophylaxis after the first episode of gastroesophageal variceal hemorrhage using quinolones[71] or third-generation cephalosporins[72] has been shown to decrease re-bleeding, particularly early re-bleeding rates, in two prospective randomized trials. Late re-bleeding, variously reported as re-bleeding after 48 hours, 1 week,[35] or 6 weeks[72] after glue injection, also occurs from incompletely eradicated GV, is unrelated to extrusion of the glue cast,[35] can occur at any time during follow-up and is managed in the same way as the index bleed.

Systemic Complications

Pyrexia and mild abdominal pain were the commonest complications after NBC injection and were, respectively, noted in 33% and 17% of patients in a recent series.[64] Fever does not necessarily indicate infection and usually settles within 24–48 hours.[57] Transient bacteremia is not uncommon after glue injection.[73] In a cohort of 47 patients who underwent NBC injection, 15 had a positive blood culture; the organism was similar to that cultured from the needle tip and accessory channel of the endoscope.[74] Some workers have suggested that the bacteremia may be related to the acute variceal bleed rather than the glue injection.[75] A few reports have described recurrent bacteremia from an infected glue conglomerate in the GV this has been successfully treated with repeated courses of antibiotics.[76,77] A recent report described GVO complicated by pyogenic spleno-portal thrombosis which led to persistent *Klebsiella pneumoniae* septicemia. The glue plug is a foreign body that offers an ideal surface for bacterial colonization and becomes a reservoir for continuous bacterial dissemination.[78] Rarely abscesses may form in distant organs. Two cases of adrenal abscesses presenting 4–6 months after glue injection with fever, chills, abdominal pain, and costovertebral angle tenderness have been reported. These were likely related to venous stasis in the adrenal gland caused by a glue cast in the adrenal vein that had probably embolized through a gastrorenal or a gastrocaval shunt.[79] An inflammatory tumor of the pancreas, not identified by advanced imaging techniques, was diagnosed in a patient explored with a provisional diagnosis of advanced pancreatic cancer and splenic vein occlusion 2 years after glue injection, when an encapsulated abscess with surrounding necrosis was found.[80] In another recent case, migration of the cyanoacrylate plug to the inferior vena cava and left renal vein through a GRS appeared to have been followed by thrombus formation on the plug surface. Embolization of the colonized thrombus to the pulmonary vasculature resulted in multiple lung abscesses.[81] Antibiotic prophylaxis with third-generation cephalosporins reduced infection rate (3.2% vs 15.5%, $P=0.026$) following gastric variceal hemorrhage.[72] According to current recommendations of the ASGE Standards of Care Committee, prophylactic antibiotics must be administered to all patients with cirrhosis and acute variceal bleeding.[82]

Embolization of the injected material is a serious complication of glue injections. Pulmonary embolism (PE) after NBC injection, the most feared systemic complication, was first reported in 1989[83] and has also been reported even after injections of OCA.[84] It occurs in about 1% (range 0–4.3%) of patients receiving NBC injections.[50,57] Emboli are detected by chest radiograph, lung perfusion scans or by noncontrast-enhanced CT scans but may be obscured by contrast enhancement. In a retrospective Korean study of 140 patients receiving glue injections, PE were detected in six (4.3%) patients and were nonfatal.[85] Minor episodes of PE after glue injection may be asymptomatic or result in mild self-limiting symptoms such as coughing, tachycardia, or chest pain. Occasionally, breathlessness or episodes of desaturation may occur during the procedure that persists for several hours. Massive PE is catastrophic and may result in immediate collapse after injection with major cardiovascular instability, acute right heart failure, cardiac arrest, and death on

the table.[86,87] Autopsy has confirmed the presence of glue in the pulmonary artery and its branches.[87] Other serious embolic complications include thrombosis of the portal vein, splenic vein, superior mesenteric vein, left renal vein, iliac vein, inferior vena cava, and splenic infarction as well as coronary and cerebral emboli.[51,88–90]

Factors Contributing to Complications

Though not prospectively validated, factors that appear to influence thromboembolic complications following glue injections can be patient-related or technique-related. Patient-related factors include the presence of large GV with draining gastrorenal (GRS), gastrocaval (GCS), and gastrolienorenal shunts (GLRS). Before complete obturation of a large GV occurs following the glue injection, unpolymerized or partially polymerized glue can be washed away into the systemic circulation through these large, high-flow shunts, which are present in up to 85% of all cirrhotics,[34] and gets trapped in the pulmonary circuit producing embolic complications.[86] Abnormalities such as patent foramen ovale, atrial septal defect, arterio-venous malformation, or ectatic pulmonary capillaries in cirrhotics allow paradoxic coronary and cerebral embolization. Several technique-related factors have a bearing on thromboembolic complications. Dilution of cyanoacrylate by lipiodol is the single most important factor and has been implicated in almost all reported cases of thromboembolic complications. It is needed to delay polymerization and prevent premature solidification of glue; however, overdilution prolongs the polymerization process and increases the risk of embolization.[57] A recent series found no case of clinically significant distal embolization in 261 NBC injections made with undiluted NBC, that is, without lipiodol.[61] In another study, the endoscopist switched from diluted NBC to undiluted NBC midway through the study after noticing embolic complications with diluted NBC and then reported no embolic complications with undiluted NBC.[48] However, using undiluted NBC does not insure against embolism; D'Imperio et al[39] reported distant embolic complications in 2 of 80 patients injected with undiluted NBC. In a retrospective analysis, embolic complications were associated with injection of larger volumes of glue (4.2 mL vs 1.8 mL, $P<0.05$).[85] A trend toward higher injection volumes in the patients with embolic complications was also noted in another study (mean 4.3, range 2.5–8.0 mL in 4 patients with emboli vs mean 3.2, range 1.5–8.0 mL in 129 patients without emboli).[80] Using distilled water in volumes greater than the dead space of the injection catheter to flush the glue into the varix increases the risk of distant embolism.[91] Finally, inappropriate speed of injection, either too fast, which elevates intravariceal pressure, or too slow, which allows polymerization before variceal obturation, favors embolization.[86]

Technique for Injection

Preparation for Injection

The endoscopist would be well advised to double check the equipment available and rehearse the steps of the procedure before beginning a glue injection session for a patient with active or recent gastric variceal bleeding.

Some workers have recommended the use of a therapeutic forward-viewing endoscope with a 3.7 mm or a 6.0 mm instrument channel for glue injections.[57] However, in practice, most endoscopists continue to use the conventional diagnostic instrument with a 2.8 mm instrument channel due to familiarity and easy availability.

The preferred injection catheter is a 240 cm long, 7 F catheter with a transparent Teflon sheath. The needle tip has a diameter of 21G (~0.8 mm) and is 5–8 mm long, to allow penetration into the GV.[15] However, injectors with a metallic spring coil sheath that resists kinking in the retroflexed position, allowing easier needle advancement, and injectors with 23G needles have also been used.[61,62] It is useful to measure the dead space of the inner catheter by saline flushing (0.8 mL, Optiflo, Boston Scientific, Boston, USA; 1.3 mL, MH-1-240, Cook, USA; 1.8 mL, Devon Innovations, Bangalore, India) so that volumes needed for priming and for flushing the catheter are known. Several injectors should be handy while tackling large GV which usually need multiple injections. Efficient assistance with rapid exchange of blocked injection catheters and scope cleaning may make the difference between success in achieving hemostasis or failure.

Cyanoacrylate glue generally used for GV injection is NBC, available as Nectacryl® and Endoacryl® (Table 1); Histoacryl® and Dermabond® (OCA) are not readily available in India. *N*-2-butyl-cyanoacrylate may be injected neat[53] or mixed with the iodized radiopaque contrast agent, lipiodol (Lipiodol® Ultra Fluid, Guerbert Roissy, France) in the proportion of 1:1[35] or 0.5:0.8.[57] This not only enables radiographic visualization of obturated varices but also delays solidification by 15–20 s which, while facilitating GV injection, also increases the chances of distal embolization. In contrast, undiluted NBC solidifies within 10–12 s after coming in contact with blood.[61]

Eye protection with goggles is essential for all those involved with the procedure since accidental splatter of glue into the eyes of the endoscopist, nursing assistant, or the patient can be fraught with major inconvenience and serious consequences. Although reports of the deleterious effects of eye splatter and its management are lacking in literature, it is useful to bear in mind that none of the chemicals used for removal of glue from the endoscope or accessories are safe for human use and should not be applied to the skin or the eyes after glue splatter. Nevertheless, it is also important to bear in mind that cyanoacrylate congeners are regularly used as sealants in ocular surgery for corneal perforations, sealing corneal cataract wounds,

glaucoma surgery and bleb leaks, retinal detachment surgery, and macular hole surgery. The glue is extruded as the superficial epithelial layers are shed in 1–2 weeks, so it is unlikely that permanent damage to the eye will result from inadvertent glue splatter. Protecting the endoscope by applying silicone oil to the scope tip, flushing the instrument channel with it, and promptly cleaning the scope tip and channel on withdrawal after an injection will prevent damage to the instrument channel, distal end, and the lens system by unintended glue solidification. Oil-based contrast agents, simethicone, or even olive oil have also been used for this purpose.[35] Acetone softens cured cyanoacrylate and facilitates removal in case of such solidification. To ensure that the endoscope channel is not blocked with aspirated cyanoacrylate glue, suction should be disconnected slightly before injection, the endoscope removed after each injection, the injector cut from the proximal Luer lock end before withdrawal from the tip, and the channel and distal end cleaned before re-insertion.[62]

The Injection

The technique of glue injection was originally described by Soehendra,[10,11] has recently has been standardized by Soehendra's group[57] and has been variously modified by different workers.[61,62] Most GV injections are done in the bleeding-free interval soon after a bleed or in unbled but high-risk GV; fewer are done during active GVB. Steps of the procedure are summarized in Table 3.

Most often, GVO is done using a mixture of NBC and lipiodol. *N*-2-butyl-cyanoacrylate is diluted with lipiodol in the proportion of 0.5 mL NBC and 0.8 mL lipiodol[57] or 0.5 mL NBC and 0.5 mL lipiodol.[35] The injector is first flushed with lipiodol and then primed with a mixture volume equal to the dead space volume of the needle. Once the needle punctures the varix, 1 mL of the NBC–lipiodol mixture is quickly pushed into the varix, the injector is rapidly withdrawn and is flushed into the lumen with lipiodol or distilled water.[15,35,61] Some endoscopists prefer to keep the needle within the varix for 15–20 s after the injection to allow complete solidification. A feeling of slight resistance on attempting to retract the needle within the catheter, the so-called '*catheter tug sign*', suggests that solidification is complete and that there is little chance of immediate bleeding. Reflux of blood into the transparent Teflon catheter when the needle is retracted, the *'red catheter sign',* suggests that the varix has not solidified fully and may spurt when the needle is pulled out (TS Chandrashekhar, 2011, personal communication). While delayed withdrawal is more likely to be associated with varix solidification and absence of bleeding from the injection site, it is also likely to result in a blocked catheter and, rarely, in needle tip impaction within the solidified glue cast.[37,42] Withdrawal immediately after completing the injection will avoid needle impaction in the glue cast and may salvage the needle for additional injections but may also be associated with a spurt from the varix.

After the Injection

After completing the injection, the endoscope is removed and cleaned. It is then re-inserted and blunt palpation of the injected varix is done to check for solidification. In case softening is still present, the varix mass and its

Table 3 Summary of technique for glue injection.

1.	Antibiotic prophylaxis should be used before *N*-2-butyl-cyanoacryrate glue (NBC) for gastric varices Quninolones and third-generation cephalosporins have been found to be effective in controlled trials.[63,64,74]
2.	If NBC and lipiodol mixture are used, they should be mixed in an optimal proportion, i.e., 0.5 mL of NBC with 0.8 mL of lipiodol[49] or 0.5 mL NBC with 0.5 mL lipiodol.[27] Undiluted NBC may be used instead of the mixture.[53]
3.	The needle is first flushed with lipiodol, then primed with the NBC–lipiodol mixture. The varix is punctured and desired volume of the mixture is injected smoothly and rapidly into the varix. The needle is then retracted and flushed into the lumen with lipiodol or distilled water. Excessive flushing should be avoided.
4.	When neat NBC is used, the needle is first flushed with distilled water, priming is avoided, chosen volume of NBC is injected into the varix, and the injector flushed with distilled water (second flush).
5.	Injections should be placed strictly intravariceally. Paravariceal injections should be avoided.
6.	Volume of the NBC–lipiodol mixture should be restricted to 1 mL. Injection may be repeated in 1 mL aliquots in case of spurting from GV after injection, 'red catheter sign', absence of complete solidification on blunt palpation, and to obturate feeding vessels.[49] However, some workers report using larger volumes (2–4 mL per injection) in patients with 'large' GV.[27,56]
7.	The endoscope must be cleaned and lubricated and the injector changed after each injection, taking precautions described earlier. This should be done as quickly and efficiently as possible in patients with active bleeding.
8.	The volume of NBC–lipiodol mixture used should be restricted to 4–5 mL per session, if possible.
9.	Endoscopic examination should be repeated after 3–4 days and parts of the GV complex and feeders that have not been obturated should be injected. Sessions may be repeated in this manner until the endoscopist is satisfied that all endoscopically identifiable parts of the GV have been obturated.
10.	Periodic follow-up to confirm persistence of obliteration of GV is recommended. Though data do not support the use of non-selective beta blockers for primary or secondary prophylaxis, prophylactic gastric variceal obturation (GVO) may be useful for recurrent GV.

feeding vessels are injected again. Depending on its size, each varix is injected with 0.5–1 mL of NBC-lipiodol.[50] Complete obliteration of all tributaries is desirable in the same session or at the earliest, to prevent early re-bleeding. Injections into the varix mass are also repeated in case of a 'red catheter sign' or a spurt after needle withdrawal. Most experts do not inject >2 mL in a single varix at one time, do not inject >2–3 sites in a single session, and do not exceed a total volume of 4–5 mL per session. After the initial control of bleeding, repeat endoscopy is usually performed after a few days for treating the remaining GV.[46]

Variations in Technique

When glue injection is done during active bleeding, priming with the NBC–lipiodol mixture is omitted to avoid premature solidification at the injector tip. After the first flush with lipiodol, 1.0 mL of the mixture is injected into the varix, followed immediately by a second flush with 0.8 mL (or a volume equal to the dead space of the catheter) of lipiodol or distilled water to deliver the entire glue from the catheter into the varix, after which the needle is retracted and flushed into the lumen. Injections into the varix mass are repeated in 0.5–1.0 mL aliquots until hemostasis is achieved. Injections for complete eradication of the GV are usually done in another session a few days later.

The volume of the mixture injected at one time is variable and often depends on the size of the GV. While most workers use no more than 2.0 mL of the mixture per injection, others have reported using 3.0[35] or 4.0 mL,[64] continuing the injection until the varix appears engorged.[35] However, large volume of injection has been considered as the second most important factor in producing distal embolization.[63]

Some workers prefer to use undiluted NBC for GV injection.[61] The technique of injection is as detailed above except that the first flush of the injector is with distilled water, it is not primed with NBC, and undiluted or 'neat' NBC, not mixed with lipiodol, is used for the variceal injection. This is followed by the second flush, also with distilled water. Despite rapid retraction of the needle and flushing into the lumen, the catheter usually gets blocked when neat NBC is used.

Priming the injector with NBC–lipiodol mixture after the first flush with lipiodol allows exactly 1.0 mL, or the chosen volume, to be injected into the GV, no second flush is needed and the final 0.8 mL of the mixture (or volume equal to the dead space of the catheter) remains in the injector. However, premature solidification within the catheter is a problem in the actively bleeding patient. If priming is not used, the volume delivered into the GV is > 1.0 mL or the chosen volume since, during the injection, first a volume of distilled water or lipiodol equal to the dead space of the catheter, used for the first flush, enters the GV and then the chosen volume of the mixture or neat NBC is pushed through with the second flush.

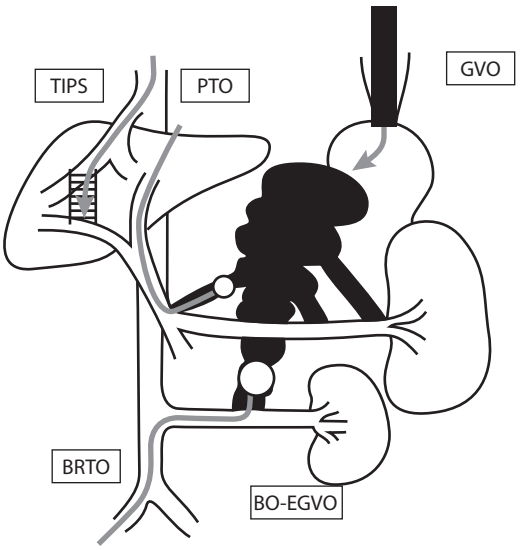


Figure 4 Transvenous routes for the treatment of gastric fundal varices. Percutaneous transhepatic obliteration (PTO), transjugular intrahepatic portosystemic shunt (TIPS), balloon-occluded retrograde transvenous obliteration (BRTO), balloon-occluded endoscopic gastric variceal obturation (BO-EGVO) and gastric variceal obturation (GVO) using *N*-2-butyl-cyanoacryrate glue (NBC).
Adapted from Kameda et al.[110]

CHOICE OF THERAPY FOR GASTRIC VARICES

There is no universal consensus on the therapy of choice for bleeding GV. Though both GVO with cyanoacrylate glue and interventional radiologic procedures such as TIPS, BRTO, and its variants are first-line treatment options, current guidelines in USA[12] and Europe[13] recommend GVO as the preferred initial intervention, with TIPS being used as the salvage therapy of choice for uncontrolled acute GVB despite glue injection, though percutaneous transhepatic obliteration of GV (PTO) and modified PTO have also been used for this purpose.[88,93] Transjugular intrahepatic portosystemic shunting (TIPS) maybe used as first-line therapy in the absence of facilities for gastric glue injection. Today, in Japan, BRTO is the standard first-line treatment for bleeding esophagogastric varices while GVO with glue or TIPS are second-line therapies.[94,95]

Gastric varices bleeding can be managed by a variety of interventional radiologic procedures (Figure 4). The PTO of GV was the first interventional radiologic procedure practised for the treatment of ruptured varices.[92] Modified PTO using sclerosant and metallic coils[93,96] is used to embolize GV more selectively than the original PTO. Intrahepatic portosystemic shunting placement is currently the second-line treatment for bleeding esophagogastric varices.[93,96] It achieves excellent hemostasis in acute GVB, with bleeding control rates of 90–96%. However, re-bleeding rates have ranged from 20% to 30%.[97,98] Only a few studies have compared TIPS with glue injections. While 2 studies, one retrospective,[14] the other prospective,[99] reported equal efficacy for initial hemostasis, no difference

in survival or complication rates but significantly higher re-bleeding in the cyanoacrylate arm compared with the TIPS arm (38% vs 11% and 35% vs 20%, respectively), in the most recent retrospective comparison between TIPS and cyanoacrylate therapy for gastric variceal bleeding, hemostasis, re-bleeding, and mortality rates were similar between the 2 groups though the TIPS group had a significantly higher incidence of encephalopathy.[100] However, TIPS was considerably more expensive than cyanoacrylate therapy.[14] Patients with GV, who have a lower portocaval pressure gradient and extensive spontaneous portosystemic shunts, may respond poorly to TIPS.[32] Early reports from several workers had reported that bleeding from GV was more difficult to control with TIPS than bleeding from EV.[101–103] However, a prospective study comparing salvage TIPS in patients with uncontrolled gastric fundal vs uncontrolled esophageal variceal bleeding showed similar efficacy in the two conditions.[97]

Balloon-occluded Retrograde Transvenous Obliteration

Balloon-occluded retrograde transvenous obliteration has become the treatment of choice in Japan for obliteration of GV in patients with a GRS.[96,97] It has nearly 100% success in obliterating GV, is very safe, with negligible rates of embolic or infective complications, and has a low degree of invasiveness.[31,104,106] Long-term results are excellent with recurrent varices reported in only 0–10% of patients while bleeding rates are even lower.[31,93,106] Prophylactic treatment with BRTO can effectively prevent GV rupture and improve patient survival.[107] Though it is primarily an elective procedure unsuited for acute GVB, BRTO with transcatheter coiling and sclerotherapy can control GVB better than TIPS.[93]

Transvenous retrograde obliteration of GV may be performed by two approaches: the transjugular and the transfemoral (Figure 4). The former is called transjugular retrograde obliteration[104] and the latter BRTO.[105] While transjugular retrograde obliteration is less invasive than BRTO and is very effective in eradicating GV, the high occurrence rate of new EV is a problem. This is thought to be due to increased portal venous pressure resulting from obliteration of high-flow GRS during transjugular retrograde obliteration. Partial splenic embolization decreases splenic blood flow and portal venous pressure.[108] Though these EV can easily be treated with EIS or EBL, a recent study has shown that partial splenic embolization followed by transjugular retrograde obliteration of GV, while achieving 100% obliteration, resulted in significant reduction in the occurrence of new EV (45% vs 9%, $P<0.05$) compared with transjugular retrograde obliteration alone.[109]

The BRTO is performed through GRS, which exist in 85% of GV[34]; absence of a GRS has been regarded as a limitation to BRTO. However, BRTO has been performed even in the absence of a GRS if the drainage or the outlet vein is connected directly to the inferior vena cava. A number of different supply or inlet veins feed the GV, including left gastric vein (21.7%), short gastric vein (18.8%), and the retrogastric vein (59.4%); however, a recent study reported that among 13 of 15 (86.7%) patients without GRS, the subphrenic vein was connected to the inferior vena cava as the drainage vein.[110] A transfemoral occlusive balloon catheter placed in this drainage vein allowed the GV to be obturated by a mixture of NBC and lipiodol. When the drainage vein is not connected to the inferior vena cava, modified PTO is a good option for the treatment of GV without GRS, and good results have been reported.[93,96] Balloon-occluded EGVO (BO-EGVO) has also been used in patients with GV without GRS,[111] though its use is limited only to cases for which other methods are not suitable.

Unsettled Issues in Gastric Variceal Bleeding

Although over the past quarter of a century, many areas of concern regarding cyanoacrylate glue injection for GV have been clarified, some issues remain unsettled.

Tailoring Injection Volume to Gastric Varices Size

Using a standardized technique for GVO, restricting injection volume to 1 mL of NBC or mixture probably has reduced the occurrence of infective and embolic complications while achieving excellent hemostasis in the hands of some workers.[46] However, intraprocedure bleeding due to a spurt from the varix after retraction of the needle suggests that the volume of glue used has been inadequate for obturating that varix. Such spurting may obscure vision resulting in failure to complete the injection and leading to uncontrolled bleeding. Though 'large' GV are generally defined as >10 mm in diameter,[12] it is not uncommon to encounter GV much larger than this size. Intuitively, it would appear that large GV need larger volumes of glue and a higher number of sessions for obturation,[88] though large injection volumes have been associated with increased frequency of distal embolization.[66] Indeed, some workers have reported the successful use of 2–4 mL volumes of NBC or mixture per injection for large GV, without any major embolic complications.[35,64] However, the best way to titrate injection volume to the size of a GV during routine GVO remains unclear. Limiting injection volume when drainage through gastrorenal or gastrocaval shunts is detected under fluoroscopic monitoring, obturation of the 'inlet vessel' feeding a large GV mass with small volumes of glue under endosonographic monitoring[112] and PTO[93] or balloon-occluded GVO, where transvenous balloons are used to occlude GRS and GCS followed by endoscopic injection of large volumes of cyanoacrylate glue to obliterate the GV complex,[111] are different methods for delivering large volumes of glue to a large varix while eliminating the risk of embolic complications. However, combining

these complex interventional radiologic procedures with routine EGVO is difficult in most hospitals.

Re-bleeding after Gastric Variceal Obturation

While early re-bleeding after GVO has been related to incomplete obturation, early extrusion of the glue plug and presence of infections,[35,73] the causes of late re-bleeding, remain unclear. Incomplete obturation of GV, fresh collateralization, and recanalization of obturated vessels remain possible mechanisms. Obturation of GV after glue injection is satisfactorily ascertained by blunt palpation of the varix and repeated sessions to inject unobliterated GV may have reduced risk of re-bleeding.[57] However, following a few sessions of GVO, it may be difficult to differentiate small GV or feeders from gastric rugae and folds, a situation which may be resolved with the use of EUS. Innovative EUS-guided procedures such as obliteration of the 'inlet' vessel feeding a large, complex GV[19] and transesophageal coiling and gluing of fundal varices[20] may help to eliminate the risk of late re-bleeding from GV.

Avoiding Thromboembolic Complications

Minimizing if not eliminating thromboembolic complications of glue injections continues to be a major goal. Modifications in technique that have reduced these complications include avoidance of overdilution with lipiodol when using the mixture of NBC and lipiodol, using undiluted or 'neat' NBC, reducing the volume of glue used to 1 mL per injection, using a moderate speed of injection, and avoiding excessive flushing.[57,61,86,91] Determining risk factors for thromboembolic complications in the individual patient may allow tailoring therapy for GV accordingly. Thus, if EUS detects large gastrorenal and gastrocaval shunts, using interventional radiologic techniques that allow control over these shunts, such as BRTO and BO-GVO for obliteration of GV, will eliminate these complications.

Primary Prophylaxis for Gastric Varices Bleeding

The use of nonselective beta blockers has not been shown to be effective in the primary or secondary prophylaxis of GVB. However, prophylactic GVO is widely practised for high-risk GV, that is, varices >1 cm with either red signs or advanced liver disease (Child B or C). The 1-year risk of bleeding in a Child C cirrhotic with red marks on a large fundal varix is estimated at 65%.[112] A prospective controlled study reported that prophylactic GVO with NBC ($n=25$) was superior to prophylaxis with nonselective beta blockers (NSBB; $n=24$; $P=0.042$) and to no treatment ($n=25$; $P=0.024$) in preventing bleeding from previously unbled GV (IGV1 and GOV2 after EV eradication).[15] Very recently, a prospective randomized study revealed that adding NSBB therapy provided no benefit for secondary prevention of bleeding or reducing mortality in patients undergoing repeated GVO. Ninety-five patients with acute GVB were randomized into two groups after achieving primary hemostasis with GVO, one being continued on GVO till obliteration while the other group received additional NSBB. This confirms the long-held belief that NSBB are not useful in the secondary prophylaxis of GVB.[113]

Finally, there is a need to introduce greater levels of uniformity not only in the way that the technique of GVO is practiced but also in standard definitions and in reporting of results and complications of GVO.

CONFLICTS OF INTEREST

All authors have none to declare.

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