Review Article

Endoscopic cyanoacrylate injection in gastric varices

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Abstract

Gastric varices are the second most common cause of upper-gastrointestinal bleeding in patients with portal hypertension. Endoscopic cyanoacrylate injection is one of the methods to treat gastric variceal bleeding. It has a high initial haemostatic response, high obliteration rate, and low rebleeding and mortality. Techniques and dose of injection are varies. Serious and uncommon complication of endoscopic phenomena is thromboembolic phenomena. Endoscopic cyanoacrylate injection should be considered as primary treatment for gastric variceal bleeding.

Key words: Gastric varices, Cyanoacrylate injection, Endoscopic treatment

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Introduction

Gastric varices (GVs) are the second most common cause of upper-gastrointestinal bleeding in patients with portal hypertension. The prevalence of GVs varies from 18 - 70% in patients with portal hypertension and GV bleeding occurs in 10 - 35% of acute variceal bleeding.[1, 2] Mean portal pressure in GVs is lower than esophageal varices (EVs) because GVs have larger size and often present shunts.[1] GV bleeding can occur even with porto-systemic pressure gradient less than 12 mmHg.[3] Compared with EV bleeding, morbidity and mortality is higher in GV bleeding. Mortality from GV bleeding ranges from 10 - 30%.[1] In addition, 35-90% of patients with GV bleeding rebleed after spontaneous remission.[1, 2, 4] Risk factors of GV bleeding include larger size (more than 5 mm.), presence of red signs, location of GVs (IGV 1 > GOV 2 > GOV 1), large nodular varix, presence of portal hypertensive gastropathy, hepatocellular carcinoma, and advance stage of cirrhosis.[1 - 3, 5, 6] The most important predictor of bleeding is the size of varices.[4] Bleeding from GVs should be considered if there is active spurt or ooze, adherent clot, a large gastric varix, no esophageal varix and no other source of bleeding.[3, 7] Nowadays, optimal management of GV bleeding remains undefined due to lack of large RCTs.

Classification of gastric varices

Sarin classification[1] is the most widely used because it is easy to use, has good correlation with pathophysiology, and guides treatment. GOV 1 is an extension of esophageal varix along the lesser curvature of the stomach and GOV 2 is an extension of esophageal varix along the greater curvature of the stomach. Isolated GVs are located either in the fundus (IGV 1) or in other parts of the stomach (IGV 2). IGV 1 usually arises with spleno- or gastro-renal shunts. Isolated splenic vein thrombosis should be excluded in patients with IGV 1 because splenectomy is the proper treatment. GOV 1 is the most common type of GV.[5, 8] Bleeding GVs occur 78%, 55% and 10% in IGV 1, GOV 2 and GOV 1 respectively.[9] Fundal varices (GOV 2 and IGV 1) are the most challenging varices to treat.[4]

Initial management

In acute variceal bleeding, endotracheal intubation should be placed in the airway of compromised patients. Fluid resuscitation with isotonic solution is needed. Blood transfusion is targeted at hemoglobin 8 g/dl.[10] Restrictive strategy (transfusion when the haemoglobin fell below 7 g/dl) has significantly higher probability of survival than liberal strategy (transfusion when the haemoglobin fell below 9 g/dl) in patients with Child-Pugh A and B cirrhosis.[11] Antibiotic prophylaxis should be given. Even if there is no data available about the efficacy of vasoactive agents in GV bleeding, it should be used. Balloon tamponade is not effective for bleeding from fundal varices. Linton-Nicholas tube which has 600 mL single gastric balloon may be used.[12]

Cyanoacrylate injection

Cyanoacrylate (CA) used as GV treatment was firstly reported by Sohendra et al., in 1986.[13] CA is a monomer that consists of a reactive cyano group and alkoxycarbonyl group of variable carbon chain length.[14] After contact with hydroxyl ions in water, CA undergoes rapid polymerization.[1, 2] Two types of CAs are used in GI endoscopy (N-butyl-2-CA and Ocrylate). N-butyl-2-CA (Enbucrilate) has 4-carbon alkyl groups and is marketed as Indermal (Covidien, Mansfield, MA) and Histoacryl (B. Braun Medical, Bethiehem, PA). Glubran 2 (GEM s.r.l., Viareggio, Italy) contains Enbucrilate plus methacryloxy supholane. Ocrylate (2-octyl CA) has 8-carbon alkyl groups and is marketed as Dermabond (Johnson & Johnson, New Brunswick, NJ).[13] Histoacryl is more commonly used. A CA with shorter alkyl group has rapid polymerization time and can result in premature solidification of CA in the needle or entrapment of the needle within varix. Enbucrilate needs to be injected rapidly over seconds. Dilution with Lipiodol slows the rate of solidification, which reduce the risk of catheters adhesion to the endoscope, allowing radiologic confirmation of injection and identify embolization. Glubran 2 and Ocrylate have longer polymerization time than Enbucrilate which does not require dilution with Lipiodol. CA should be kept in the refrigerator. Experts suggest the term

of obturation or obliteration for GVs treated by CA rather than eradication because it can be seen after effective treatment.[2] Techniques for injection vary depending on type of CA and local expertise.

Histoacryl can be used with or without dilution. Dilution with Lipiodol (0.5 mL of Histoacryl with 70% Lipiodol 0.5 - 0.8 mL) is preferred.[4, 6] Some experts suggest using 2 mL syringe with a Luer lock to allow rapid injection and to prevent spraying.[15] A therapeutic endoscope with a 3.7 mm working channel is suggested.[16] A large-bore disposable sclerotherapy injection needle (21 - 22 G, 6 - 8 mm long) is used and it may be flushed with Lipiodol before the injection to prevent glue adherence. Silicone oil or other similar compounds may be used to coat the tip of the endoscope to minimize the risk of glue adherence. Goggles for eye protection of patient and staff from splashed of CA during preparation and injection is advised.[4, 15] CA is injected intravariceally. Some expert advices to inject it at the side of varix first, and follow by an injection at the dome which has the highest pressure and high speed of blood flow.[4] During the injection, CA should flow without resistance. CA should be injected rapidly and followed by distilled water or normal saline 1-2 mL to clear the working channel and then the needle is slowly withdrawn. Some experts prefer distilled water over normal saline because they are concerned about coagulation of CA with normal saline.[4] It is recommended to injection less than 2 mL per session to reduce the risk of glue embolization.[1, 2, 4, 15] Injection can be repeated until hemostasis is achieved. No data about optimal volume of injection, it depends on the size of varix. Catheter pull sign and red catheter sign may be helpful.[17] Positive catheter pull sign means solidified varix moves toward the endoscope during needle withdrawal. If blood is seen in the outer catheter, the varix is not solidified (positive catheter pull sign). Endoscope should be cleaned rapidly after the injection. Subtotal occlusion of varix occurs immediately and total occlusion occurs within hours. The overlying mucosa slough off and glue extrudes into the gastric lumen about 1 month after injection. Glue cast extrudes completely 3 months after injection. Repeat endoscopy to assess gastric varix obturation (GVO) should be done but data about optimal timing is lacking. Endoscopy is generally performed 2 to 4 weeks after an initial session.[5, 7] To check GVO, hub of injection with needle kept in or biopsy forceps press on gastric varices gently. Endoscopy should be performed every 3 to 6 months after GVO.

Primary prophylaxis with cyanoacrylate injection

A study of 33 patients with high risk GV revealed that all patients achieving obliteration after CA injection and 95% of patients achieving eradication. Two patients developed immediate bleeding. GV recurrence is 14% and rebleeding rate is 8%.[18] A randomized trial comparing GVO with beta–blocker and no treatment showed that bleeding-related mortality is 0, 10 and 24% respectively ($p = 0.034$) and the overall mortality is 7, 17, and 26% respectively ($p = 0.003$). Complication is not different.[19] Data about primary prophylaxis with CA injection is insufficient to make the recommendation and more studies are needed.

Cyanoacrylate injection in acute or recent GV bleeding

In most series, initial hemostasis of GVO is 80 - 100% and the rebleeding rate is ranging from 4 - 35.2%. (Table 1) When comparing with sclerotherapy, GVO has a higher initial hemostasis, higher obliteration rate, lower rebleeding rate, and lower mortality. (Table 2) GVO is better than band ligation in terms of initial hemostasis and rebleeding rate. (Table 3)

Table 1 Initial hemostasis, rebleeding and mortality of cyanoacrylate injection for gastric varices[20 - 48]

	Medication	No. of patients	Initial hemostasis (%)	Rebleeding (%)	Mortality (%)
Kind R et al. 2000	NBCA	174	97.1	early 15.5 late 14.9	19.5
Huang YH et al. 2000	NBCA	90	94.4	23.3	2.2
Dhiman RK et al. 2002	NBCA	29	100	10.3	20
Tomohiko Akahoshi et al. 2002	NBCA	52	96.2	40	4
Greenwald BD et al. 2003	NBCA	44	97.7	18 (1 year)	18 (1 year)
Phadet et al. 2005	NBCA	24	58	12.5	12.5
Jae Woo Kim et al. 2006	NBCA	86	93	16.1	45.4 (34 months)
Cheng LF et al. 2007	NBCA	635	95.2	8	5 (1 year)
Khalid et al. 2007	NBCA	50	100	14	6
Caldwell SH et al. 2007	NBCA	92	NA	17 (1 year)	25 (1 year)
Belletrutti PJ et al. 2008	NBCA	34	93.8	24.2	17.6
Paik CN et al. 2008	NBCA	121	90.9	13.2	11.6
Stefen Seewald et al. 2008	NBCA	131	100	early 0 late 6.9	0
Petruska Marques et al. 2008	NBCA	48	87.5	early 20.5 late 20.5	43.9
Yan-Mei Wang et al. 2009	NBCA	148	96.2	early 6.2 late 8.1	3.3
Jaber Al-Ali et al. 2010	NBCA	37	95	early 8 late 28	28.6
Liu-Fang Cheng et al. 2010	NBCA	753	NA	4.4	6.5
Takahiro Sato et al. 2010	NBCA	129	100	NA	NA
Gourdas Choudhuri et al. 2010	NBCA	170	82.3	14.5	11.7
Ajay Kumar et al. 2010	NBCA	170	84.8	23.4	8.8
Rajoriya N et al. 2011	NBCA	31	100	10 (1 year)	23 (1 year)
Yasar Tuna et al. 2011	NBCA	15	100	13.3	6.7 (5 years)
Eun Jun Kang et al. 2011	NBCA	127	98.4	18.1	14.8
Varayu et al. 2013	NBCA	90	97.8	early 10 late 21	21.1
Chung Hwan Jun et al. 2014	NBCA	455	96.9	35.2	6.8
Atif Saleem et al. 2011	OCA	62	93	6	23
Arsian Kahloon et al. 2014	OCA	41	100	14.4	19.5
Daniel S et al. 2004	OCA	25	100	4	12
Fernanda Prata et al. 2009	CA	23		4.3	21.7

NBCA N-butyl-2-CA, OCA 2-octyl CA, CA Cyanoacrylate, NA not mentioned

Table 2 Initial hemostasis, rebleeding and mortality of cyanoacrylate injection compared with sclerotherapy for gastric varices[49 - 51]

	Medication	No. of patients	Initial hemostasis (%)	Rebleeding (%)	Mortality (%)
Ogawa et al. 1999	Ethanolamine VS NBCA	38	52.4 VS 100	76.6 VS 7.3	72.2 VS 44
Oho K et al. 1995	Ethanolamine VS NBCA	53	67 VS 93 (P 0.014)	25 VS 30 (P 0.921)	67 VS 38 (P 0.043)
Shiv K Sarin et al. 2002	Alcohol VS CA	37	62 VS 89 (P < 0.05)	33 VS 27 (P NS)	3 VS 1

NBCA N-butyl-2-CA, CA Cyanoacrylate, NS not statistically significant

Table 3 Initial hemostasis, rebleeding and mortality of cyanoacrylate injection compared with band ligation for gastric varices[52 - 55]

	Medication	No. of patients	Initial hemostasis (%)	Rebleeding (%)	Mortality (%)
Gin-Ho Lo et al. 2001	NBCA VS pneumatic ligator	31 VS 29	87 VS 45 (P 0.03)	31 VS 54 (P 0.0005)	9 VS 14 (P 0.05)
Pen-Chung Tan et al. 2006	NBCA VS pneumatic ligator	49 VS 48	93 VS 93 (P = 1)	22 VS 43.7 (P 0.44)	16 VS 14.5
El Amin H et al. 2010	NBCA VS Band ligation	75 VS 75	91 VS 81	6 VS 16	5 VS 1
Marcel Tantau et al. 2014	NBCA VS Band ligation	19 VS 18	100 VS 88.9 (P 0.43)	31.6 VS 72.2 (P 0.03)	10.5 VS 11 (P 0.75)

NBCA N-butyl-2-CA

From two case series, GVO is less effective than Transjugular Intrahepatic Portosystemic Shunt (TIPS) in achieving GVO, with a lower initial hemostasis and higher rebleeding.[56, 57, 58] Other studies have shown that GVO is equally effective when comparing with TIPS.[59, 60] TIPS has higher long term morbidity and higher cost than GVO.[60]

A randomized trial demonstrated that GVO is less effective than portocaval shunt in achieving permanent control of hemostasis.[56] Balloon-Occluded Retrograde Transvenous Obliteration (BRTO) is the procedure to obliterate GV by injection of sclerosant via the catheter which pass through gastrorenal or gastrocaval shunt to the GV. Complete obliteration of GV is ranging from 77 - 100%. Rebleeding after BRTO is about 0 - 15%.[5] GVO has similar efficacies to BRTO but GVO has higher rebleeding rate.[61] A prospective study comparing GVO with Percutaneous Transhepatic Variceal Embolization (PTVE) showed that GVO has higher rebleeding rate but the cumulative survival is not statistically different.[62]

When combining GVO with band ligation, initial hemostasis is 88.9% and rebleeding rate is 33.3%. Survival at 5 years is 63%.[63] Small case series have demonstrated that GVO combined with BRTO has no rebleeding or recurrent GV.[64] A small study of combining CA and ethanol showed that the initial hemostasis was 100% and rebleeding rate is 30%.[65]

Nowadays, data about the proper dose of CA injection is scarce. A randomized controlled trial comparing 0.5 with 1 mL of CA in patients with acute GV bleeding demonstrated that 1 mL of CA is not better than 0.5 mL in the terms of survival, treatment failure, rebleeding, and complication.[66]

From the available data, AASLD and BAVENO V recommend endoscopic CA injection as the first line treatment for GV bleeding.[67, 68]

Secondary prophylaxis with cyanoacrylate injection

A randomized trial comparing GVO with GVO and beta blocker showed that mortality and rebleeding are not statistically different[69]. Another study revealed that combining GVO and beta blocker result in lower mortality than GVO alone but rebleeding rate is not different.[70]

Complications of CA injection

Multiple complications from CA injection have been reported but their incidence is low. Severe complications, of which the physician should be concerned, are systemic thromboembolic phenomena (cerebral, pulmonary, coronary, renal, portal, splenic, and superior mesenteric vessels).[1, 5, 9, 12, 71] Risk factors of thromboembolic phenomena are large injection volume, dilution of CA with Lipiodol, excessive rapid injection, rapid speed of injection, presence of shunts (gastrorenal and hepatopulmonary syndrome) and IGV 1.[6, 7, 10, 72] Other complications are pyrexia, abdominal pain or discomfort, rebleeding from extrusion of glue cast, gastric ulcer, mesenteric hematoma associated with haemoperitoneum and bacterial peritonitis, recurrent and prolonged bacterial sepsis due to retained embolised glue casts, visceral fistulization, acute kidney injury, adrenal abscess, retroperitoneal abscess, pericarditis, chest pain and dysphagia.[2, 5, 12, 13, 73, 74] Instrument damage from glue contamination, including occlusion the working channel and glue adherence to the tip of endoscope are usually a cause of concern. Mortality from CA injection is 0.5%. Most of the complications can be prevented by standardizing the technique.

Conclusion

Endoscopic CA injection has a high initial haemostatic response, high obliteration rate, and low rebleeding and mortality. It should be used as a first line treatment in GV bleeding. More studies regarding techniques for injection and proper dose are needed. Serious complication of CA injection should be of concern. In addition, combining CA injection with other treatments is inconclusive. Thus, CA injection may be considered for primary prophylaxis of GV with high risk features.

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บทคัดย่อ

การรักษาหลอดเลือดขอดที่กระเพาะอาหารด้วยการฉีดยา cyanoacrylate ทางการส่องกล้อง

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สาขาโรคระบบทางเดินอาหาร ภาควิชาอายุรศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ

Gastric varices เป็นสาเหตุของเลือดออกในทางเดินอาหารส่วนต้นจากภาวะความดันในหลอดเลือดดำ portal สูงที่พบบ่อยเป็นอันดับสอง การฉีดยา cyanoacrylate ทางการส่องกล้องเป็นวิธีหนึ่งของการรักษาภาวะเลือดออกจาก gastric varices ในปัจจุบันข้อมูลเกี่ยวกับวิธีการฉีดยา cyanoacrylate และปริมาณยาที่เหมาะสมยังมีหลากหลาย การศึกษาเกี่ยวกับการฉีดยา cyanoacrylate ทางการส่องกล้องพบว่าสามารถหยุดภาวะเลือดออกได้ดี ทำให้ gastric varices ยุบลง เลือดออกซ้ำลดลงและมีอัตราการเสียชีวิตลดลง ภาวะแทรกซ้อนที่รุนแรง คือ การเกิด thromboembolism ซึ่งพบไม่บ่อย การฉีดยา cyanoacrylate ทางการส่องกล้องถือเป็นวิธีการรักษาอันดับแรกของภาวะเลือดออกจาก gastric varices

คำสำคัญ: Gastric varices, การฉีดยา cyanoacrylate ทางการส่องกล้อง, การส่องกล้องทางเดินอาหารส่วนต้น