Cyanoacrylate Glue in Gastric Variceal Bleeding

S. Seewald[1]
P. V. J. Sriram[2]
M. Naga[3]
M. B. Fennerty[4]
J. Boyer[5]
F. Oberti[5]
N. Soehendra[1]

■ *The aim of the Expert Approach section is to contribute to the dissemination and standardization of new endoscopic procedures. Authors from three distinct geographic areas combine forces, sharing their experience to form a consensus of opinion. Readers' comments are welcome and will be published in the Mailbox which appears at the end of each Expert Approach article.* ■

For more than 15 years, the tissue glue cyanoacrylate (n-butyl-2-cyanoacrylate) has been successfully used in Europe and many other countries, but not in the United States, for the treatment of bleeding gastric varices. The use of cyanoacrylate for the treatment of esophageal and gastric varices via the percutaneous transhepatic route, was first described by Lundequist et al. [1]. Endoscopic injection of the tissue glue for gastric variceal bleeding was first reported in 1986 [2]. Due to its excellent efficacy [3–14] cyanoacrylate is considered to be the optimal initial therapy for gastric variceal bleeding by many clinicians worldwide, with the exception of the US. In Europe, cyanoacrylate has recently been approved for endoscopic use (Glubran®, GEM, Viareggio, Italy).

Despite its widespread use, there are still some controversies in the literature concerning technique, safety, and long-term results [15–17]. Embolization of the glue is a potential risk and a cause for concern, as evidenced in recent reports [18–20]. High rebleeding rates are related to incomplete obliteration of the varices. A rare and less severe complication is pyrexia. Instrument-related complications due to incorrect preparation include adhesion to the endoscope, sticking of the needle to the varix and obstruction of the injection catheter [21].

This article deals with the practical details of cyanoacrylate injection of bleeding gastric varices, including equipment, preparation, injection technique and follow-up. Close attention to and implementation of these technical recommendations will result in a safer and successful use of the tissue glue.

Institution
[1] Department of Interdisciplinary Endoscopy, University Hospital Hamburg-Eppendorf, Hamburg, Germany
[2] Asian Institute of Gastroenterology, Hyderabad, India
[3] Department of Internal Medicine, University of Cairo, Egypt
[4] Division of Gastroenterology, Oregon Health Sciences University, Portland, Oregon, USA
[5] Gastroenterology Unit, University Hospital, Angers, France

Corresponding Author
N. Soehendra, M.D. · Department of Interdisciplinary Endoscopy · University Hospital Hamburg-Eppendorf · Martinistrasse 52 · 20246 Eppendorf · Hamburg · Germany · Fax: +49-40-428034420 · E-mail: soehendr@uke.uni-hamburg.de

Bibliography
Endoscopy 2002; 34 (11): 926–932 © Georg Thieme Verlag Stuttgart · New York · ISSN 0013-726X

The tissue glue n-butyl-2-cyanoacrylate is a watery solution which polymerizes and hardens within 20 seconds in a physiological milieu and instantaneously upon contact with blood. This makes it ideal for obliterating vessels and controlling bleeding. However, the rapid solidification of the glue makes endoscopic application, through a relatively long injection catheter, technically difficult because of the risk of polymerization within the catheter. To prevent cyanoacrylate from solidifying too quickly, it is necessary to dilute it with the oily contrast agent Lipiodol® Ultra Fluid (Guerbert Roissy, France). Lipiodol® is not only compatible with the tissue glue for dilution but also allows fluoroscopic monitoring of delivery of the substance. However, one should be aware that overdilution of the glue prolongs the polymerization process and thus increases the risk of embolization. In our experience, the optimal proportions for the cyanoacrylate–Lipiodol® mixture are 0.5 ml : 0.8 ml. (Dr. Boyer and his group use a 1 : 1 mixture.)

Equipment and Preparation

Equipment (Table 1). During an active variceal bleed, an endoscope with a 6-mm working channel is ideal for easily evacuating blood and food residue from the stomach. For the glue injection itself, a therapeutic endoscope with a 3.7-mm working channel is preferable, since precise movement of the injection catheter and targeting of the bleeding varix are easier with this instrument compared with the 6-mm channel endoscope. The therapeutic endoscope has an additional small channel below the biopsy port, which connects with a water pump. This enables cleaning of the mucosal surface with a strong water jet so that the site of bleeding can be identified precisely. For the treatment of gastric varices, the endoscopy assistant should be well trained in the injection technique; another assistant is also required to hold the retroflexed endoscope firmly in an appropriate position. In the case of an actively bleeding varix, a second nurse is required for preparing the additional injection catheters and cyanoacrylate–Lipiodol® mixture. Since pulmonary aspiration is the most common serious and potentially lethal complication during massive variceal bleeding, the provision of separate, dedicated apparatus for oropharyngeal suction is mandatory. During an active bleed, endotracheal intubation may be required in order to protect the airways.

Table 1 Equipment needed

Large-channel endoscope (3.7-mm or 6-mm working channel)
Water irrigation pump
Lipiodol® Ultra Fluid
Distilled water
Goggles for eye protection

Injection catheters with a needle of 0.8 mm diameter and 8 mm length are ideally suited for glue injection. Additional sets must always be available because of the strong likelihood of catheter blockage after an injection. The injection needle should be checked before use, in vitro with the therapeutic endoscope in the retroflexed position, to ensure that the needle can be brought out and withdrawn completely without hindrance, when manipulated within the patient. If necessary, the outer sheath can be shortened as needed, to allow the needle to exit for at least 5 mm in the retroflexed position of the endoscope.

To prevent cyanoacrylate from adhering to the inner catheter of the injector, a few drops of Lipiodol® are injected into the catheter, which is then flushed with air to enable a small amount of Lipiodol® to remain coating the inner surface of the catheter (Dr. Boyer and his group use Vaseline oil to lubricate the sheath of the injection catheter to avoid damage to the channel of the endoscope). The mantle of the distal end of the endoscope should also be lubricated with Lipiodol® or silicone oil.

For controlling gastrointestinal hemorrhage, Glubran® is the preparation of n-butyl-2-cyanoacrylate which is approved in Europe, and which is used without any dilution. Compared

with pure n-butyl-2-cyanoacrylate such as Histoacryl® (B. Braun Dexon, Spangenberg, Germany), Glubran® polymerizes a little more slowly and thus it does not require the use of Lipiodol® except when fluoroscopic monitoring is needed. Due to the high viscosity of Lipiodol®, 2-ml syringes should be used to generate a higher injection pressure.

Distilled water is ideal for flushing the injection catheter following the injection of glue; normal saline solution should be avoided as it polymerizes the glue prematurely.

Care must be taken to protect the eyes of the patient and the clinical personnel. Goggles are required for eye protection during preparation and injection of the glue.

Preparation. In a 2-ml syringe, 0.5 ml Histoacryl® is mixed with 0.8 ml Lipiodol®. To minimize the risk of embolization, not more than 1 ml of the Histoacryl®–Lipiodol® mixture is injected into a gastric varix at a time (for esophageal varices, not more than 0.5 ml per injection should be applied). If more cyanoacrylate is required to achieve complete obliteration of large varices, injections have to be repeated in the same manner. For children, the individual amount of cyanoacrylate has to be reduced accordingly.

It is essential that the volume of the dead space of the inner catheter of the injector is known prior to injection. The dead space can be measured in vitro, by injecting distilled water. Usually the volume is about 0.8 ml for standard catheters. Since most of the Histoacryl®–Lipiodol® mixture is retained within the dead space, the injection of the mixture should be followed immediately by injection of 0.8 ml of distilled water to deliver the glue mixture in to the varix. (Dr. Boyer and his group use Lipiodol® instead of distilled water; however it should be taken into account that Lipiodol® is viscous and therefore more difficult to inject.) Once the needle is drawn out of the varix, the catheter must be flushed continuously with distilled water to keep it patent. For this purpose, it is necessary to prepare several 2-ml syringes filled with distilled water.

Injection technique (Figures 1–6). While fundic varices require the endoscope to be retroflexed, junctional varices can be optimally injected from a forward-viewing position. After the scope is positioned on the target varix, the injection catheter is advanced toward the varix to make a few dummy movements to determine the best injection site. Once the optimal injection site has been determined, keeping the tip of the catheter close to the varix, the needle is advanced to puncture the varix, and 1 ml of the Histoacryl®–Lipiodol® mixture is injected, followed immediately by 0.8 ml distilled water to deliver the glue from the dead space of the catheter. The endoscopy assistant announces the end of this second injection and simultaneously withdraws the needle into the catheter. Now, the endoscopist removes the injection catheter away from the varix and the endoscopy assistant begins to flush the needle continuously with distilled water to keep the needle patent for the next injection. During the injection procedure, the endoscopist continuously insufflates air in order to keep the gastric wall and any excess glue away from the tip of the endoscope. For the same reason, suction is

avoided for approximately 20 seconds after each injection. (For this purpose, Dr. Boyer and his group routinely disconnect the suction tube from the endoscope during the injection procedure. They also keep the needle in place after each injection for 20 seconds, awaiting optimal polymerization of the glue. One should however be aware of the risk of the needle's sticking in the varix.) After a few minutes the treated varix is palpated with the tip of the injection catheter to check the consistency; when it is hard, complete obliteration is indicated. A soft and supple varix requires further injections.

Paravariceal Injection

Variceal obliteration is achieved by strictly intravascular injection of tissue glue. Paravariceal injection induces tissue necrosis, which may lead to deep ulcer formation and even perforation. Early rebleeding occurs if the varix is not completely obliterated. To ensure intravariceal location, one could inject a few milliliters of distilled water to check the intravariceal position of the needle tip prior to glue injection. A mucosal bulge indicates paravariceal injection and the needle can be withdrawn and repositioned, whereas if no bulge appears this indicates intravariceal injection and the glue-mixture can be safely injected during the same puncture without withdrawing the needle.

Rebleeding

At 3–4 days after injection, necrosis develops around the site of injection, and rebleeding may occur from incompletely obliterated varices. It is therefore essential to ensure that varices are completely obliterated during the initial session. Complete obliteration of varices can be assessed by careful palpation using the injection catheter. Extensive fundic varices will require approximately 5–8 ml of the Histoacryl®–Lipiodol® mixture for complete obliteration. All visible feeding vessels should also be obliterated during the same session.

Pyrexia

Pyrexia may rarely occur after cyanoacrylate injection of gastric varices. This does not necessarily indicate infection and it usually subsides within 48 h. Routine prophylactic use of proton pump inhibitors is not indicated as its efficacy in accelerating the healing process of the ulceration has not been proved.

Embolism

Causes of increased risk of embolism during glue obliteration of fundic varices include the following:

a) The instillation of more than 1 ml Histoacryl®–Lipiodol® mixture per injection increases the risk. In Figure 7, venography under fluoroscopic monitoring demonstrates the extent of diffusion of 1 ml Histoacryl®–Lipiodol® mixture after injection, emphasizing the need for caution. If more glue mixture is needed to control the bleeding, further injections can be made in aliquots of 1 ml each.
b) When the dead space of the injecting catheter is flushed with distilled water to deliver the glue mixture into the varix, the instillation of an volume in excess of the dead space, under high pressure into the variceal collaterals, would increase the risk of embolization.
c) Overenthusiastic flushing of the needle with distilled water by the endoscopy assistant to prevent clogging of the needle, even before the needle is withdrawn from the varix leads to an increased risk.

Needle Sticking in the Varix

This complication can occur when the needle tip is accidentally dislodged from the catheter [21]. It could also occur if the needle tip were not promptly retracted from the varix after completion of the injection, in which case the tip of the needle could be trapped in the solidifying glue within the varix. Should such a mishap happen, it is important not to panic, and to wait for a few minutes to allow the glue to solidify completely and then the needle tip can usually easily be pulled out using a biopsy forceps. Premature attempts to pull out such a needle tip before the glue solidifies could result in the formation of a "sinus" track if the varix is incompletely obliterated. Spraying a small amount of glue on the site of the puncture will arrest any further oozing from the site.

Needle Blockage

To prevent the tissue adhesive from solidifying in the catheter, the Histoacryl®–Lipiodol® mixture must be injected rapidly in a coordinated manner, immediately followed by 0.8 ml distilled water. After the needle has been retracted from the varix, the catheter must be flushed immediately using plenty of distilled water. In the hands of an experienced assistant, one injector can be used for approximately four glue injections. Needle blockage is more common whenever undiluted cyanoacrylate is used.

Adherence of Glue to the Endoscope

To prevent this, the tip of the endoscope must be kept at a safe distance from the site of injection and air must be insufflated constantly during the injection, to keep the lumen from collapsing. Suction must be avoided immediately after injection. If Histoacryl®–Lipiodol® mixture sticks to the lens, the endoscope should be withdrawn and cleaned with ethanol immediately. We have never experienced damage to the endoscope when using the Histoacryl®–Lipiodol® mixture.

A "second-look" endoscopy is performed after 4 days to check for completeness of obliteration by careful palpation using the injection catheter. If the varix can be indented with the tip of the catheter, obliteration is not complete, and the injection has to be repeated. Lee et al. have shown that endosonographic (EUS) monitoring can be also useful for evaluating the quality of obliteration [11]. Over the next few weeks, the overlying mucosa sloughs off, and the glue is extruded from the varix like a cast into the gastric lumen within 3 months. Following the extrusion of the glue, the injection site re-epithelializes with scar formation. Surveillance endoscopy should be carried out every 3 or 6 months after successful obliteration, to check the long-term prevention of bleeding.

In the experience of the Hamburg group, primary hemostasis following cyanoacrylate injection was achieved in almost all cases of acute gastric variceal bleeding, with an early rebleeding rate of 2.2% [4]. Results in other studies were also similar [5–8,10–13]. Early rebleeding is mainly due to incomplete obliteration of the varices. In the first randomized trial comparing cyanoacrylate with band ligation in the management of gastric variceal bleeding, which was published recently, the rates of primary hemostasis were 87% vs. 45%, respectively [14]. In another study comparing cyanoacrylate with sclerotherapy using 5% ethanolamine oleate for the control of gastric variceal bleeding, the rate of hemostasis was 100% vs. 80% [9]. Over a period of 5 years, the cumulative rate of rebleeding was 7.6% in the cyanoacrylate group and 100% in the sclerotherapy group, respectively.

In the attempt to prove the superiority of glue injection over the other methods, by randomized controlled trials, before it is "scientifically approved" for wider use, the ethical aspect of such studies must be kept in mind, in that band ligation [14] as well as sclerotherapy [9,22,23] are hazardous when used in the treatment of bleeding gastric varices. Both these modalities only deal with a part of the large variceal conglomerates and thus do not lead to complete thrombosis of the vessel, eventually laying open the vessel when mucosal ulceration invariably follows. This risk is especially high in case of large fundic varices with extensive tributaries. From an ethical point of view, it is not justifiable to initiate further studies comparing glue injection with sclerotherapy or band ligation for the treatment of gastric variceal bleeding unless other data indicating the safety and effectiveness of these techniques for gastric varices are forthcoming.

Endoscopic sclerotherapy should not be combined with cyanoacrylate injection, as this would induce extensive and deep necrosis leading to rebleeding and perforation. When the appropriate technique is used, cyanoacrylate injection alone is sufficient to control acute gastric variceal bleeding and to simultaneously achieve complete variceal obliteration.

The most serious risk from intravariceal glue injection is embolization. There are several case reports of embolization of cyanoacrylate to lung, spleen and brain [18–20]. These potentially serious complications are rare. In a series of 317 patients treated with cyanoacrylate over a 5-year period, Gotlib et al. reported no such complication [24]. In the past 15 years, we have routinely used cyanoacrylate injection aggressively for the control of gastric variceal bleeding

and have encountered only a single case of cerebral embolization, in a patient with an undetected atrial septal defect. Presence of a right-to-left shunt predisposes to this rare complication.

Since most of the risks associated with cyanoacrylate are preventable, adherence to a standardized injection technique may help in minimizing the risk of potential complications and improve the long-term outcome for bleeding gastric varices.

[1] Lunderquist A, Borjesson B, Owman T et al. Isobutyl 2-cyanoacrylate (bucrylate) in obliteration of gastric coronary vein and esophageal varices. Am J Roentgenol 1978; 130: 1 – 5
[2] Soehendra N, Nam VC. Grimm H et al. Endoscopic obliteration of large esophagogastric varices with bucrylate. Endoscopy 1986; 18: 25 – 26
[3] Soehendra N, Grimm H, Nam VC et al. 10 years' experience with endoscopic sclerotherapy of esophagogastric varices. Chirurg 1989; 60: 594 – 598
[4] Soehendra N, Grimm H, Maydeo A et al. Endoscopic obliteration of fundal varices. Can J Gastroenterol 1990; 4: 643 – 646
[5] Fereds C, Dimopoulos C, Benakis P et al. N-butyl-2-cyanoacrylate (Histoacryl) plus sclerotherapy versus sclerotherapy alone in the treatment of bleeding esophageal varices: a randomized prospective study. Endoscopy 1995; 27: 355 – 357
[6] Thakeb F, Salama Z, Salama H et al. The value of combined use of N-butyl-2-cyanoacrylate and ethanolamine oleate in the management of bleeding esophagogastric varices. Endoscopy 1995; 27: 358 – 364
[7] Oho K, Iwao T, Sumino M et al. Ethanolamine oleate versus butyl cyanoacrylate for bleeding gastric varices: a nonrandomized study. Endoscopy 1995; 27: 349 – 354
[8] Battaglia G, Morbin T, Paternello E et al. Diagnostic et traitement endoscopique des varices gastriques. Acta Endosc 1999; 29: 116 – 117
[9] Ogawa K, Ishikawa S, Naritaka Y et al. Clinical evaluation of endoscopic injection sclerotherapy using n-butyl-2-cyanoacrylate for gastric variceal bleeding. J Gastroenterol Hepatol 1999; 14: 245 – 250
[10] Kind R, Guglielmi A, Rodella L et al. Bucrylate treatment of bleeding gastric varices. 12 years' experience. Endoscopy 2000; 32: 512 – 519
[11] Lee YT, Chan FK, Ng EK et al. EUS-guided injection of cyanoacrylate for bleeding gastric varices. Gastrointest Endosc 2000; 52: 168 – 174
[12] Huang YH, Yeh HZ, Chen GH et al. Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacryl) injection: long-term efficacy and safety. Gastrointest Endosc 2000; 52: 160 – 167
[13] Iwase H, Maeda O, Shimada M et al. Endoscopic ablation with cyanoacrylate glue for isolated gastric variceal bleeding. Gastrointest Endosc 2001; 53: 585 – 592
[14] Lo GH, Lai KH, Cheng JS et al. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. Hepatology 2001; 33: 1060 – 1064
[15] Sheikh RA, Trudeau WL. Clinical evaluation of endoscopic injection sclerotherapy using N-butyl-2-cyanoacrylate for gastric variceal bleeding. Gastrointest Endosc 2000; 52: 142 – 144
[16] Akahoshi T, Hashizume M, Shimabukuro R et al. Long-term results of endoscopic Histoacryl injection sclerotherapy for gastric variceal bleeding: a 10-year experience. Surgery 2002; 131: S176 – S181
[17] Karnam US, O'Loughlin CJ, Reddy KR. Bleeding gastric varices: stick to the sticky glue. Am J Gastroenterol 2002; 97: 199 – 200
[18] See A, Florent C, Lamy P et al. Cerebrovascular accidents after endoscopic obturation of esophageal varices with isobutyl-2-cyanoacrylate in 2 patients. Gastroenterol Clin Biol 1986; 10: 604 – 607
[19] Naga M, Foda A. An unusual complication of histoacryl injection. Endoscopy 1997; 29: 140
[20] Tsokos M, Bartel A, Schoel R et al. Fatal pulmonary embolism after endoscopic embolization of downhill esophageal varix. Dtsch Med Wochenschr 1998; 123: 691 – 695
[21] Bhasin DK, Sharma BC, Prasad H et al. Endoscopic removal of sclerotherapy needle from gastric varix after N-butyl-2-cyanoacrylate injection. Gastrointest Endosc 2000; 51: 497 – 498
[22] Trudeau W, Prindiville T. Endoscopic injection sclerosis in bleeding gastric varices. Gastrointest Endosc 1986; 32: 264 – 268
[23] Sarin SK. Long-term follow-up of gastric variceal sclerotherapy: an eleven-year experience. Gastrointest Endosc 1997; 46: 8 – 14
[24] Gotlib JP. Endoscopic obturation of esophageal and gastric varices with cyanoacrylate tissue adhesive. Can J Gastroenterol 1990; 9: 637 – 638