

## Glue for gastric varices: some sticky issues

The treatment of bleeding gastric varices is one of the final frontiers of flexible endoscopy—a chapter as yet incomplete in our textbooks. Hemostatic methods that use standard therapy for esophageal varices have not been found effective for gastric varices.<sup>1-3</sup> Due to their large size and extensive distribution, it is difficult if not impossible to eradicate gastric varices with sclerotherapy or band ligation. More importantly, tissue necrosis resulting from these endoscopic interventions can cause significant and sometimes disastrous complications.<sup>4</sup> Consequently, patients with gastric variceal bleeding are generally referred for a transjugular intrahepatic portosystemic stent shunt (TIPS) or surgical shunt procedure.

Conceptually, cyanoacrylate glue provides an ideal endoscopic treatment for gastric varices. Native cyanoacrylate is a liquid with a consistency similar to water and therefore lends itself to intravariceal injection. When added to a physiologic medium such as blood, the cyanoacrylate rapidly polymerizes, forming a hard substance. Thus, after injection into a varix, the cyanoacrylate plugs the lumen. This results not only in rapid hemostasis in cases of active bleeding, but it also prevents the recurrence of bleeding from the treated varix.

The use of cyanoacrylates for the treatment of gastric varices dates back over 2 decades. Lunderquist et al.<sup>5</sup> used it first in 1978 via a percutaneous transhepatic approach. In 1984, Gotlib and Zimmermann<sup>6</sup> in France described the first use of cyanoacrylate to treat esophageal varices. Soehendra et al.<sup>7</sup> in Germany were the first (1986) to treat gastric varices

with cyanoacrylate glue. In the 1990s, studies from endoscopy centers from around the world validated the efficacy and safety of cyanoacrylate treatment for varices.<sup>8-12</sup> Case series have highlighted the utility of cyanoacrylate treatment in specific clinical situations such as pregnancy,<sup>13</sup> and in children.<sup>13,14</sup> Control of active variceal bleeding has been reported to range from 93% to 100% of patients, and rates of recurrent bleeding have generally been below 30%.<sup>15</sup>

In this issue of *Gastrointestinal Endoscopy*, Huang et al.<sup>16</sup> from Taiwan and Lee et al.<sup>17</sup> from Hong Kong report impressive results using the cyanoacrylate glue, Histoacryl, for the treatment of bleeding gastric varices. In a series of 90 patients, Huang et al. achieved a 94% hemostasis rate at 1 week, with recurrent bleeding in 23% from 3 days to 16 months after the initial injection. Complications were minor. In a cohort of 54 patients, Lee et al. report a 96% primary hemostasis, with early (<48 hours) and late recurrence of bleeding in 7.4% recurrent bleeding in 18.5%, respectively. No serious adverse events were noted. In both studies, the treatment endpoint was complete obliteration of gastric varices. However, the methods for monitoring this endpoint differed. In the Taiwan study, instrumental palpation of the treated varix (soft versus hard) and radiographs (radio-opaque filling of the varix lumen) were used, whereas endoscopic ultrasound was used in the Hong Kong study.

Considering the large body of supportive published data, it is surprising that cyanoacrylate treatment is not more widespread. It continues to be regarded as investigational and is used routinely in only a few endoscopy centers worldwide. In the United States, Histoacryl is not approved by the FDA for clinical use. Has the time come for cyanoacrylate injection to become standard treatment for gastric varices? Are cyanoacrylates appropriate as “the first choice for bleeding gastric varices,” as suggested by Huang et al.?

The answer is a qualified “yes.” Most published data are retrospective. Detailed prospective data from well designed trials are still needed. Numerous issues require clarification and standardization: indications, equipment, injection technique, treatment protocol, and safety. Because TIPS is the standard of care for the treatment of gastric varices, randomized trials comparing cyanoacrylate injection with TIPS are warranted. Hemodynamically stable patients without active gastric variceal bleeding at the time of endoscopy are the best candidates for such studies. It is noteworthy that this comprised 94.4% of patients entered into the study of Huang et al.

### INDICATION

The term “gastric varices” encompasses a range of locations and morphology. Hence, the utility of cyanoacrylate treatment for gastric varices must be precisely defined according to these parameters. The classification of gastric varices by Sarin and Kumar<sup>18</sup> differentiates gastroesophageal (or junctional) varices from isolated gastric varices, which include fundal varices. This distinction is important, because sclerotherapy and band ligation yield better results in the treatment of junctional varices than fundal varices.<sup>19</sup> In a non-randomized trial by Oho et al.<sup>11</sup> in Japan, hemostasis after cyanoacrylate injection was found to be equal to that of sclerotherapy in patients with gastroesophageal varices, but significantly better (and the mortality rate significantly lower) in patients with fundal varices. Unfortunately, most studies of cyanoacrylates for gastric varices fail to provide subset analyses according to location or morphology. The gastric varices treated in the study of Huang et al. were fairly homogenous with a fundal location in 94% and a nodular or tumorous type in 94%. In the study of Lee et al., 50% of varices included in the “endosonography” arm were gastroesophageal in location, and a stratification of results according to location or morphology was not provided.

What is the role of cyanoacrylate injection for gastric varices not actively bleeding at endoscopy? This subgroup of patients can undergo TIPS electively, which carries a significantly lower morbidity and mortality than an emergent TIPS. However, the rate of recurrent bleeding after TIPS for gastric varices appears to be significantly higher than that for esophageal varices, ranging from 29%<sup>20</sup> to 53%.<sup>21</sup> Based on currently available data, cyanoacrylate injection is likely to produce equal or better results compared to TIPS, and at a significantly lower cost. Factors that increase the risk associated with TIPS including advanced liver disease, jaundice and renal failure favor the use of cyanoacrylate therapy.

Varices showing stigmata of bleeding must be differentiated from gastric varices that have never bled. Should non-bleeding gastric varices that accompany bleeding esophageal varices be “prophylactically” treated by cyanoacrylate injection? Further data on the risk of bleeding from gastric varices after an episode of an esophageal varix bleeding will be needed to answer this question. It is unclear whether eradication of esophageal varices increases the risk of bleeding from gastric varices. A number of variables will impact the decision whether to treat gastric varices prophylactically, including the location, size and presence of red signs, Child’s class, and the patient’s access to cyanoacrylate treatment in the event of sudden hemorrhage.

### Equipment and injection technique

There is currently no standardization of equipment or injection technique. Huang et al. used a 21 gm commercially available sclerotherapy injector: the size or type of injector were not mentioned by Lee et al.<sup>6</sup> The injector should have a Luer-lock metal fitting because, as Histoacryl is caustic to plastic and may crack a plastic hub. The dilution ratio of Histoacryl to Lipiodol has varied among studies, ranging from undiluted<sup>22</sup> to a 2:1 ratio.<sup>23</sup> Huang et al. used a 1:1 ratio, whereas Lee et al. used a 1:1.4 ratio. The dilution ratio increases if Lipiodol is used to flush the injector before injection. The rationale for diluting Histoacryl with Lipiodol is to delay the otherwise instantaneous polymerization reaction in order to complete the injection and remove the needle. A new cyanoacrylate homologue with a longer polymerization time is available in Europe and appears to be suitable for undiluted injection (Nib Soehendra, personal communication).

### Treatment protocol

It is essential to define the endpoint of treatment, as well as have a standardized protocol to achieve the endpoint. The goal of cyanoacrylate injection should be the obliteration of visible varices. The term “obliteration” more accurately describes the desired endpoint than “eradication,” because a varix occluded with cyanoacrylate may remain visible for many weeks. The completeness of obliteration deserves special emphasis, as cyanoacrylates induce mucosal necrosis at the site of injection.

The amount of Histoacryl required to achieve obliteration will vary depending on varix size and extent. In general, Histoacryl is injected in aliquots of 0.5 mL (content of 1 ampoule), which translates to 1 to 2 mL after dilution with Lipiodol. Obliteration

is tested by palpating the varix with the needle retracted. If “soft,” the varix is injected with an additional aliquot of Histoacryl.

Lee et al. evaluated EUS as a modality to monitor varix obliteration. To evaluate the usefulness of EUS, these investigators compared results in 2 groups of patients from two different periods. Unfortunately, this comparison based on consecutive time periods is flawed due to different treatment endpoints. During the first (1993 to 1996), Lee et al. treated gastric varices with Histoacryl according to an “on-demand” protocol with the endpoint of endoscopic hemostasis (rather than varix obliteration). During the second period (1996 to 1998), the treatment endpoint shifted to varix obliteration as defined by EUS (“absence of hypoechoic vascular channels in all parts of the stomach”). Not surprisingly, the rates of late-onset recurrent bleeding were significantly lower during the second time period. The investigators give endosonography credit for the improved results, although it remains to be proven whether the use of this imaging modality is superior to simple instrumental palpation in determining variceal obliteration.

What is the role of radiographs in the documentation varix obliteration? Because Lipiodol is radioopaque, varices filled with the cyanoacrylate mixture are well visualized radiographically. However, the ability of radiographs to distinguish intra- and perivariceal injection or document varix obliteration has never been studied. Fluoroscopy is occasionally used to monitor the intravariceal injection of cyanoacrylate. The use of a convex array echoendoscope to provide real-time monitoring of cyanoacrylate injection is technically possible but its benefit is questionable in comparison with endoscopy-guided injection.

### SAFETY

Cyanoacrylate injection has been found in large series to be remarkably safe. Nonetheless, case reports of severe complications related to embolization including cerebral stroke,<sup>24</sup> pulmonary embolism,<sup>25</sup> portal vein embolism,<sup>10</sup> splenic infarction<sup>26</sup> and retro-gastric abscess<sup>27</sup> have raised concern about safety. Further investigation is needed to minimize and hopefully eliminate the risk of embolization.

Neither Huang et al. or Lee et al. reported major complications, but embolization was seen. Lee et al. mentioned one patient who developed a cough and was found to have small pulmonary emboli on the chest radiograph. Similarly, Huang et al. noted embolic deposits on the chest radiograph of one patient who developed a cough after Histoacryl injection.

Battaglia et al.<sup>28</sup> in this issue of *Gastrointestinal Endoscopy* report 2 cases of visceral fistulae after Histoacryl injection, a previously unreported complication. One patient underwent treatment of gastric varices, which was complicated by an empyema of the left pleural cavity 6 months later. A fistulous connection between the gastric fundus and pleural cavity was documented. Operative exploration showed the gastric fundus to be adherent to the diaphragm with inflammation. This suggests that misguided injection of Histoacryl into the stomach wall may have caused this complication, as Histoacryl is known to be ulcerogenic to tissue. In the second case, Histoacryl injection of a bleeding esophageal varix was complicated by a fistulous tract to the right para-mediastinal region that ultimately resulted in fatal pulmonary abscesses. A large volume of sclerosant (24 mL of 1.5% polidocanol), however, had been injected both intra- and perivariceally before Histoacryl in an attempt to stop hemorrhage and this may have contributed to tissue injury.

The issue of safety also extends to equipment and personnel. Huang et al. reported a single case of clogging of the endoscope accessory channel, which required repair. Clogging occurred despite precautionary lubrication with silicone oil to prevent adherence of Histoacryl. All personnel should wear protective goggles to avoid serious eye injury as a result of accidental spraying of the cyanoacrylate.

### FUTURE STUDIES

The studies by Huang et al. and Lee et al. support the efficacy and overall safety of glue injection for gastric varices, validating previously published experience. However, many questions regarding the indications, equipment, technique, treatment protocol, and safety remain. What recommendations can we make for future studies? First, active bleeding must be distinguished from non-active bleeding. The hemostatic efficacy of glue injection coupled with the high mortality associated with non-endoscopic treatments are strong arguments in favor of glue injection as initial treatment in the patient with active bleeding. The optimal management of the stable patient without active bleeding needs further study (e.g., randomized trials comparing cyanoacrylate injection to TIPS). Second, the treatment of junctional varices must be distinguished from fundal varices. The outcome of endoscopic treatment using sclerotherapy or band ligation is different for these subsets of gastric varices. A randomized trial comparing cyanoacrylate injection to sclerotherapy or band ligation is warranted for junctional varices. Third, future studies must control for varix obliteration.

ation as the endpoint of treatment. The role of EUS to evaluate varix obliteration deserves further study. A randomized trial of instrumental palpation with and without EUS is recommended. Finally, future studies must address the risk of embolization. Although the risk is small, embolization can be fatal. Modifications of the injection technique and new cyanoacrylate compounds may reduce or eliminate this risk.

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