

Endoscopic management of gastric variceal bleeding with cyanoacrylate glue injection: Safety and efficacy in a Canadian population

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BACKGROUND: Gastric variceal bleeding (GVB) is a major cause of morbidity and mortality among patients with portal hypertension. Endoscopic band ligation and standard sclerotherapy have been used but have significant limitations. Decompression through transjugular intrahepatic portosystemic shunt insertion has been shown to be effective. Gastric variceal injection therapy with a commercially available cyanoacrylate glue is less invasive than transjugular intrahepatic portosystemic shunt insertion and has recently been shown to be effective for acute hemostasis.

OBJECTIVE: To assess the immediate and long-term outcomes of cyanoacrylate glue injection therapy for GVB.

METHODS: A retrospective chart review was conducted to identify patients treated with cyanoacrylate injection for GVB at two tertiary care hospitals over a period of six years. The outcomes assessed included complications, acute hemostasis, rebleeding rate and all-cause mortality.

RESULTS: Thirty-seven patients (60% men) underwent cyanoacrylate glue injections for GVB. The median follow-up period was 14 months and included 29 patients (eight were lost to follow-up). Initial hemostasis was achieved in 35 patients (95%). No significant complications from cyanoacrylate injection were observed. Early rebleeding was rare (8%) and late rebleeding occurred in only 28% of patients. The all-cause mortality rate was 28.6% during the median follow-up period.

CONCLUSION: The data suggest that cyanoacrylate injection therapy is safe and effective for the prevention of short- and long-term bleeding from gastric varices. Furthermore, although these patients had significant comorbid disease, survival in the follow-up time period was greater than 70%.

Key Words: Cirrhosis; Cyanoacrylate; Fundal varices; Sclerotherapy; Transjugular intrahepatic portosystemic shunt

Variceal bleeding is a frequently encountered and often catastrophic complication of portal hypertension, accounting for up to one-third of deaths in patients with cirrhosis. Successful management of a variceal bleed relies on early diagnosis and prompt institution of therapy using a combination of aggressive resuscitation, pharmacological treatments to reduce portal pressure and endoscopic intervention to target the source of bleeding. In most cases, bleeding arises from varices in the lower esophagus; hemostasis can be

La prise en charge endoscopique des saignements de varices gastriques par injection de colle cyanoacrylate : L'innocuité et l'efficacité au sein de la population

HISTORIQUE : Les saignements de varices gastriques (SVG) constituent une cause majeure de morbidité et de mortalité chez les patients ayant une hypertension portale. On utilise la ligature élastique endoscopique et la sclérothérapie standard, mais elles comportent des limites importantes. Il est établi que la décompression par insertion d'un shunt intrahépatique portosystémique par voie transjugulaire est efficace. La thérapie par injection des varices gastriques au moyen d'une colle cyanoacrylate commerciale est moins efficace que l'insertion de ce type de shunt. Son efficacité a récemment été démontrée contre l'hémostase aiguë.

OBJECTIF : Évaluer les issues immédiates et à long terme de la thérapie par injection de colle cyanoacrylate pour traiter les SVG.

MÉTHODOLOGIE : Les chercheurs ont procédé à l'analyse rétrospective des dossiers pour repérer les patients traités par injection de cyanoacrylate pour résorber des SVG dans deux hôpitaux de soins tertiaires sur une période de six ans. Les issues évaluées incluaient les complications, l'hémostase aiguë, le taux de reprise des saignements et la mortalité toutes causes confondues.

RÉSULTATS : Trente-sept patients (60 % d'hommes) ont subi des injections de colle cyanoacrylate en raison de SVG. La période de suivi médiane était de 14 mois et incluait 29 patients (huit ont été perdus au suivi). On a obtenu une hémostase initiale chez 35 patients (95 %). On n'a observé aucune complication importante imputable à l'injection de cyanoacrylate. La reprise rapide des saignements était rare (8 %) et leur reprise tardive ne se produisait que chez 28 % des patients. Le taux de mortalité toutes causes confondues s'élevait à 28,6 % pendant la période de suivi médiane.

CONCLUSION : D'après les données, la thérapie par injection de cyanoacrylate est sécuritaire et efficace pour prévenir les saignements à court et à long terme causés par des varices gastriques. De plus, même si ces patients avaient d'importantes maladies comorbides, la survie pendant la période de suivi dépassait les 70 %.

achieved using sclerotherapy or, more commonly, endoscopic variceal band ligation. Bleeding from gastric varices occurs less frequently, with a reported two-year incidence of approximately 25% in patients with portal hypertension; however, it typically poses a greater management challenge, with higher reported transfusion requirements, rates of rebleeding and mortality (1).

As with esophageal varices, endoscopic therapy for gastric varices can be used to achieve hemostasis, although the

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TABLE 1
Patient characteristics (n=37)

Variable	n (%)
Median age, years (range)	60 (34–78)
Men	22 (60)
Women	15 (40)
Liver disease	
Viral	7 (18)
Alcohol	18 (46)
Viral and alcohol	14 (36)
Cryptogenic	3 (8)
Metabolic	1 (3)
Primary biliary cirrhosis	1 (3)
Autoimmune hepatitis	1 (3)
Other	4 (11)
Portal vein thrombosis	1 (3)
Comorbidities	
Diabetes mellitus	11 (30)
Peptic ulcer disease	5 (14)
HIV	4 (11)
Renal failure	2 (5)

Due to rounding, percentages do not always total 100%

procedure can prove to be challenging to the endoscopist and the high risk of rebleeding often encourages the early use of more invasive approaches such as transjugular intrahepatic portosystemic shunt (TIPS) insertion. Furthermore, few large studies of endoscopic therapy for gastric variceal bleeding (GVB) have been performed, thereby limiting the development of clinically useful management guidelines (2).

Injection of the tissue glue N-butyl-2-cyanoacrylate can be used to treat GVB and may be more effective than band ligation or alcohol injection, as well as being more cost effective than TIPS insertion (3-5). Its use remains relatively limited, however, and concerns regarding its safety profile are often raised, particularly the risk of embolic complications. It has been our practice to use cyanoacrylate for GVB for almost 10 years. We report our experience, with particular regard to efficacy in the cessation of bleeding, complications and long-term mortality.

METHODS

The study evaluated the use of cyanoacrylate injection for GVB at two tertiary care teaching hospitals in Vancouver, British Columbia (Vancouver General Hospital and St Paul's Hospital) over a six-year period (2001 to 2006). Patients treated with cyanoacrylate injection were identified by the examination of prospectively maintained endoscopy records. Demographic and clinical data were recorded following review of medical records including the etiology of the portal hypertension, comorbidities, medication use and history of shunt procedures. Endoscopic reports were retrieved, and data regarding the volume and number of cyanoacrylate injections were collected. Outcomes recorded included hemostasis, rebleeding (early and late), transfusion requirements after glue injection, procedure-related complications, the need for further intervention including TIPS and all-cause mortality.

Variceal injection was performed using cyanoacrylate tissue glue (Histoacryl, B Braun Melsungen AG, Germany) mixed with an equal volume of lipiodol contrast medium (Lipiodol Ultra Fluid, Therapex, Canada). The injection technique is similar to one that was previously described (6) and uses a

23-gauge, 7F, 240 cm Marcon-Haber MH-1-240 injection needle (Cook, USA). Briefly, the injector needle is initially primed with lipiodol (1.3 mL). A 1 mL mixture of histoacryl/lipiodol is used to replace the lipiodol in a catheter initially primed with 100% lipiodol. Once the vein is localized, the needle is placed into the varix and 1 mL of histoacryl/lipiodol is injected using a lipiodol flush (approximately 1.3 mL). The needle is then removed from the vein. Slightly before injection, suction is usually disconnected to ensure no aspiration of cyanoacrylate glue into the endoscope channel. One millilitre of glue is injected at each injection site, with two to three injections typically used per endoscopic therapy session.

RESULTS

Thirty-seven patients treated with cyanoacrylate injection for GVB were identified (Table 1). All had portal hypertension secondary to liver disease, with the exception of one patient who had a congenitally absent portal vein. All patients were studied in the general medical wards, except one patient who was seen in the intensive care unit. At the time of admission, 12 patients (32%) were on regular beta-blockers, five (14%) were taking acetylsalicylic acid, four (11%) were using regular nonsteroidal anti-inflammatory drugs and one (3%) was using warfarin for a mechanical aortic valve.

In patients treated with cyanoacrylate injection, the indication for endoscopy was active bleeding in 32 cases (86%), while five (14%) were referred for definitive management of previously bleeding gastric varices. In addition to gastric varices, esophageal varices were identified in 27 patients (73%).

In patients with active bleeding, hemostasis was achieved in 35 (95%) with a single cyanoacrylate injection session. One patient required repeat glue injection within 48 h of the initial procedure due to ongoing active bleeding. In another patient, GVB could not be treated endoscopically because visibility was severely compromised by active bleeding. In this case, surgical treatment was required and a portocaval shunt was inserted. Bleeding continued postoperatively and repeat endoscopy identified the bleeding varix, which was injected with cyanoacrylate. However, bleeding recurred once again, requiring salvage surgery with splenectomy, partial pancreatectomy and partial gastrectomy, which were successful.

Two patients (5%) developed immediate bleeding from their gastric varices at the site of glue injection. In one patient, there was significant bleeding; therefore, intravenous octreotide was initiated and the patient underwent repeat glue injection 1 h after the original procedure, with cessation of bleeding. This patient was observed in the intensive care unit overnight and discharged home the following day without further complications. In the other patient, there was only minor oozing at the injection site. The patient was admitted to the medicine service overnight; the following day, further glue injection yielded good results.

Follow-up data were available for 29 patients (78%; mean follow-up 14 months, range zero to 70 months). During this time period, late rebleeding from gastric varices (more than 72 h postendoscopic intervention) occurred in eight patients (28%); one experienced two separate episodes at six- and eight-month intervals. The time lapse between initial therapeutic intervention and recurrent bleeding in the remaining cases was less than two weeks in two patients, one month for one patient,

between eight and 12 months in three patients and 19 months in one patient. Urgent repeat endoscopic cyanoacrylate injection was performed in six patients. Due to ongoing bleeding, splenic artery embolization followed by splenectomy and partial pancreatectomy was required in one case, while TIPS insertion was required in another. One patient experienced resolution of bleeding with intravenous octreotide administration alone, with glue injection not repeated until follow-up endoscopy four weeks later.

One patient (3%) developed bleeding from what was believed to be gastric ulcerations induced by cyanoacrylate injection performed one month previously. The ulcer was not bleeding at the time of endoscopy and, therefore, did not require endoscopic intervention; however, a second glue injection to the underlying gastric varix was performed at the time.

Hemostasis was typically achieved using less than 5 mL of cyanoacrylate suspension in total, with only one patient (3%) requiring a greater volume. Postprocedural transfusion data were available for 33 patients. Excluding the patient who underwent salvage splenectomy, for whom the volume of blood transfused could be quantified due to the use of a cell saver, the average transfusion requirement following glue injection was 0.58 units (zero to seven units) during hospitalization.

In the 29 patients for whom data were available, a mean of 0.83 repeat glue injections were required during the entire follow-up period. Twelve patients did not require repeat glue injection, 11 required one repeat glue injection, five required two repeat injections and one patient required three repeat injections. Follow-up endoscopic evaluation was performed on two patients before hospital discharge, and on 12 patients within six weeks of the initial intervention for what were considered high-risk gastric varices. Repeat glue injection was performed in six of these patients (43%) on this first follow-up for fundal varices that did not, endoscopically, appear obliterated.

There was no clinical evidence of pulmonary emboli related to cyanoacrylate injection therapy. Through electronic medical records at both Vancouver General and St Paul's Hospital, mortality data were available from the time of study enrollment until study conclusion for 35 patients who resided locally. During the study period, all-cause mortality was 28.6% (10 of 35). The remaining two patients were visiting Canada from abroad and both did well with one-year follow-up; however, further follow-up was not possible.

DISCUSSION

Our experience with cyanoacrylate glue injection for the management of patients with GVB suggests that it is both safe and effective. Hemostasis was achieved initially in 35 patients (95%) with active bleeding. Rebleeding occurred in only three patients (8%) during the same hospital admission, with one patient requiring salvage splenectomy and another requiring TIPS insertion. These results mirror the findings of larger international studies in which cyanoacrylate use was also associated with high rates of efficacy when examined alone and when compared with other treatment modalities, with initial hemostasis rates frequently approaching 100% (7-15).

No significant complications of cyanoacrylate injection were observed, specifically peripheral embolization of polymerized glue or clinically significant tissue necrosis. Although rare, serious complications of glue injection have been widely

reported, including cases of fatal pulmonary embolism (16,17). In a large study of 635 patients (9), complications of glue injection occurred in 5.2%, including early rebleeding in 3.1%, although embolic complications were observed in only 0.5%. The lack of such complications in our group was likely a reflection of the relatively small cohort studied. Other factors that may have been important include the availability of experienced nursing staff and the routine use of low-volume glue injections (less than 1 mL per injection) because many reported complications may be related to procedural factors or the volume of glue used.

Our study is limited by both its retrospective design and the small cohort size; however, the cases studied represented the total number of patients requiring endoscopic treatment of gastric varices at two large tertiary referral hospitals including the regional liver transplant centre. As such, our data likely mirror the results of other similar-sized centres in North America and internationally.

We routinely arrange a follow-up endoscopy for all patients who have fundal varices glued. This is typically arranged four to eight weeks following the procedure. The present study was performed because the authors believed that many of these patients did poorly and that many of them died of either comorbid disease or, alternatively, of underlying liver disease. The authors speculated that perhaps the 'glue' injections were simply prolonging lives that eventually succumbed to underlying disease in the near future. To the contrary, we determined that early rebleeding was rare and late rebleeding occurred in only 28% of patients. Additionally, 29 of 37 patients (78%) with a mean of 14 months of follow-up were doing well. Although some may suggest that this is poor follow-up, the present study was retrospective in nature and patients with significant liver disease are often difficult to follow over the long term. The survival data were actually much better than we initially anticipated. One of the initial concerns was that the benefit of cyanoacrylate injection therapy might be extremely limited if patients died of underlying liver disease shortly thereafter. We found the opposite – that most patients survived – at least in the median 14-month follow-up period, and most appeared to be very functional at that stage.

We believe that these data suggest that this type of therapy is safe and effective, not only to prevent short-term bleeding, but also in the prevention of long-term bleeding from these varices. Additionally, the patients in the present study (which includes all of our patients with fundal varices during this time period) appeared to do well in the follow-up time period over the ensuing year. The complication rate is high and tertiary care involvement in the care of these patients is recommended; however, with appropriate management, these patients can survive and do well over the long term with this therapy.

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