THE OUTCOME OF CYANOACRYLATE THERAPY IN GASTRIC VARICES

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ABSTRACT

Background: Gastric variceal bleeding is associated with significant morbidity and mortality in patients with portal hypertension. Currently, endoscopic injection of cyanoacrylate is the mainstay of therapy for gastric varices. Despite the extensive worldwide use, there are still differences related to the technique, safety, and the outcome.

Methods: This hospital based prospective study was carried out among 43 patients with active gastric variceal bleeding or signs of recent haemorrhage on endoscopic examination at Department of Gastroenterology, Yangon General Hospital. These patients underwent endoscopic treatment with limited appropriate volume of equal mixture of N-butyl-2-cyanoacrylate and lipiodol. The immediate haemostasis, rebleeding rate and complications were reviewed. Endoscopic surveillance was carried out at two weeks and three months after treatment.

Results: The primary haemostasis was achieved in 97.7%. The overall rebleeding rate at 3 months after therapy was 16.4%, of which 5% was early rebleeding and 11.4% was late rebleeding. The rate of primary haemostasis and rebleeding were not related to severity of hepatic function, type and size of gastric varices. The treatment failure related mortality was 2.3%. Variceal obliteration was successful in 93% of patients after first endoscopic session and it was achieved in all patients with two endoscopic sessions. The rates of adverse events were acceptably low.

Conclusion: The endoscopic injection of cyanoacrylate therapy was effective for immediate haemostasis of bleeding gastric varices as well as obliteration of varices which contributes to less rebleeding and better short term survival.

Keywords: gastric varices, isolated gastric varices type 1(IGV1), gastroesophageal varices type 2 (GOV2), *N*-butyl-2-cyanoacrylate, haemostais, rebleeding

INTRODUCTION

Gastric variceal haemorrhage is an important cause of gastrointestinal bleeding in patients with portal hypertension. Gastric varices (GVs) are less common than oesophageal varices. However, bleeding tends to be more severe, more difficult to treat, requires more transfusions and has a higher mortality rate than oesophageal variceal bleeding.[1]

Gastric varices represent an inhomogeneous entity morphologically, tomographically and haemodynamically. Gastroesophageal varices type 1 (GOV1) is the commonest variant, accounting for 74% of all gastric varices, while gastroesophageal varices type 2 (GOV2), isolated gastric varices type 1(IGV1) and isolated gastric varices type 2 (IGV2) constitute 16%, 8% and 2%, respectively. The frequency and severity of bleeding from GVs depend on their location. The risk of bleeding is greater with fundal varices (IGV1 78%, GOV2 55%) than with lesser curve varices (GOV1 28% and IGV2 10%).[2]

There is no universal consensus on the therapy of choice for bleeding GV and initial treatment

modalities have varied worldwide. Treatment with cyanoacrylate glue and balloon occluded retrograde transvenous obliteration (BRTO) are the preferred first line treatment option in Europe with transjugular intrahepatic portosystemic shunt (TIPS) being used as the salvage therapy of choice for uncontrolled bleeding. BRTO is the standard first line treatment for bleeding GV while glue (N-butyl-2-cyanoacrylate) or TIPS are second line therapies in Japan.[3]

N-butyl-2-cyanoacrylate is a class of synthetic glue; 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 haemostasis and prevention of rebleeding. [4]

There is currently no standardization of equipment or injection technique. The dilution ratio of NBC to lipiodol has varied among studies, ranging from undiluted to a 2:1 ratio. Restricting injection volume probably has reduced the occurrence of infective and embolic complications while achieving excellent haemostasis. However, the best way to titrate injection volume to the size of a GV during routine gastric variceal obturation remains unclear.[4] Cyanoacrylate injection has been used for management of GV in Myanmar for nearly one decade but there is no locally published literature describing the technique, dosage, efficacy and outcomes of this procedure. In this study, the injection volume, dilution ratio with lipoidol will be adjusted to aim at maximizing obliteration and minimizing complications. Therefore, the safety, efficacy in the immediate cessation of bleeding, prevention of rebleeding after adjusted dose glue injection in gastric variceal bleeding can be addressed.

MATERIALS AND METHOD

This hospital based prospective study was carried out among patients with active gastric variceal bleeding or signs of recent haemorrhage on endoscopic examination at Department of Gastroenterology in Yangon General Hospital. The study aimed to determine the outcome of low dose cyanoacrylate therapy in patients with gastric variceal bleeding. Forty three patients with gastric variceal bleeding underwent endoscopic treatment with limited appropriate volume of an equal mixture of N-butyl-2-cyanoacrylate and lipiodol. The immediate haemostasis, rebleeding rate and complications were reviewed. Endoscopic surveillance was carried out at two weeks and three months after treatment. The size and obliteration of gastric varices, recurrence or development of new gastric varices or esophageal varices and appearance or worsening of portal hypertensive gastropathy were assessed at follow up endoscopy.

FINDINGS

The age of study population ranged from 31 to 73 years old with a mean age of 55 years (SD 10.7).The majority of patients were males 69.8%.

Liver cirrhosis was the underlying cause of gastric varices in all patients and non-cirrhotic portal hypertensive cause was not detected in this study. In terms of severity of liver cirrhosis, 13 patients (30.2%) belonged to Child-Pugh A, 21 patients (48.8%) to Child-Pugh B, and 9 patients (21%) to Child-Pugh C.

According to Sarin's classification of gastric varices, IGV1 were detected in 11 patients (25.6%) and GOV2 in 32 patients (74.4%).

Distribution of the size of gastric varices among study population was : (0.8-1.6 cm) in 20 patients (46.5%), (1.7-2.4 cm) in 15 (34.9%) and (2.5-3.2 cm) in 8 (18.6%).

The indications for gluing were: active bleeding in 3 patients (7%) and recent bleeding in 40 patients (93%).Gastric variceal bleeding was contributed to 11.2 % of variceal bleeding and 6.9% of all upper gastrointestinal bleedings.

Table (1) Immediate outcome of bleeding gastric varices after cyanoacrylate therapy

Immediate outcomes	n/N	Percentage (95% CI)
Primary haemostasis among patients with active bleeding gastric varices	2/3	66.7 (9.4 – 99.1)
Primary haemostasis among patients with signs of recent haemorrhage	40/40	100
Overall primary haemostasis	42/43	97.7 (87.7 – 99.9)
Obliteration of gastric varices	40/43	93.0 (80.9 – 98.5)

Of the three patients with active bleeding at the time of endoscopy, primary haemostasis was achieved in two patients (67%). One patient died within 48 hours after endoscopic therapy due to failure of primary haemostasis with uncontrolled rebleeding. Forty patients had stigmata of recent bleeding and primary haemostasis was successfully accomplished in all patients. The overall primary haemostatic control was 97.7% of the patients. Among 43 patients, obliteration of gastric varices was achieved in 40 patients (93%).

Table (2) Outcomes of bleeding gastric varices at two weeks after cyanoacrylate therapy

Outcomes	n/N	Percentage (95% CI)
Early rebleeding	2/39	5.1 (1 – 17)
Obliteration of gastric varices	36/39	92.3 (79.1 – 98.4)
No change in size of gastric varices	25/39	64.1 (47.1 – 78.8)
Decrease in size of gastric varices	14/39	35.9 (21.2 – 52.8)
Aggravation or appearance of portal hypertensive gastropathy	0/39	0
Appearance of oesophagealvarices	0/39	0

*****3 patients lost follow up and 1 patient death

At 2 weeks endoscopic follow up, three patients were lost to follow up and one patient died. Of 39 patients, 2 patients (5%) experienced early rebleeding. Size of gastric varices was not changed in 25 (64%) and size was decreased in 14 (35.9%). There was no aggravation or appearance of portal hypertensive gastropathy and esophageal varices.

Table (3) Outcomes of bleeding gastric varices at three months after cyanoacrylate therapy

*7 patients lost follow up and 1 patient death

Outcomes	n/N	Percentage (95% CI)
Late rebleeding	4/35	11.4 (3.2 – 26.7)
Obliteration of gastric varices	35/35	100
No change in size of gastric varices	7/35	20.0 (8.4 – 36.9)
Decrease in size of gastric varices	28/35	80.0 (63.0 – 91.5)
Aggravation or appearance of portal hypertensive gastropathy	1/35	2.9 (0.07 – 14.9)
Appearance of oesophagealvarices	2/35	5.7 (0.7 – 19.2)
Extra endoscopic session of injection	7/43	16.3 (6.8 – 30.7)

At three months after cyanoacrylate therapy, another four patients were lost to follow up. Among 35 patients attending follow up, late rebleeding occurred in four patients (11.4%) and it was controlled with repeated injection. Obliteration of gastric varices was achieved in all patients. The size of gastric varices was not changed in 7 (20%) and the size was decreased in 28 (80%). Portal hypertensive gastropathy was appeared in one patient (2.9%) and esophageal varices in two patients (5.7%).

At the end of follow up, total seven patients required extra glue injection for early and late rebleeding and incomplete obliteration. The rate of primary haemostasis and rebleeding were not statistically associated with severity of hepatic function, type and size of gastric varices.

Complications of the procedure occurred in 16 patients (37.2%), including pyrexia in 9.3% and ulceration at the site of injection in 27.9%. No symptomatic glue embolism and thrombosis were found.

DISCUSSION

In this study, 3 (7%) had active bleeding (spurting or oozing) and 40 (93%) had stigmata of recent variceal haemorrhage at the time of endoscopy. Most patients in this study did not have really active bleeding during the endoscopic procedure. This may be due to the infusion of vasoactive agents given to many patients on the emergency basis.

During study period, gastric varices were responsible for 11.2% of all variceal bleeding and 6.9% of upper GI bleeding. Therefore, the bleeding from gastric varices is less common than from esophageal varices but it carries the higher mortality.[5]

In the present study, the risk of gastric variceal bleeding was not related to severity of liver disease but variceal size > 5 mm was associated with risk of bleeding.

The location of gastric varices was determined according to classification described by Sarin. IGV1 were detected in 11 patients (25.6%) and GOV2 in 32 patients (74.4%). The GOV2 was more common variant than IGV1 among fundal gastric varices.

Immediate outcome of bleeding gastric varices after cyanoacrylate therapy

The primary haemostasis was achieved in 97.7% which was comparable to or better than that in other series.

In this study, the primary haemostasis was independent of the types of gastric varices *(P=0.553)*, size of gastric varices *(P=0.385)* and hepatic function (Child-Pugh score) *(P=0.145)*. Marques et al (2008) also reported that the severity of cirrhosis did not impact rates of immediate haemostasis and it were 100% even amongst Child Pugh C cirrhotics because tissue adhesives do not depend on intrinsic mechanisms of coagulation, which are impaired in cirrhotics.[6]

Variceal obliteration was successful in 93% of study population after first endoscopic session and the previous studies reported that it ranged from 80% to 100% with one injection session. In this study, it may be over or under estimated because obturation of gastric varices was detected by blunt palpation of the varix by hub of injector or closed tip of biopsy forcep. As a result of the deep seated location of gastric varices in the submucosal layer of the stomach, residual GV are difficult to detect. Mucosal ulceration and scarring after sclerotherapy also make subsequent endoscopic assessment of variceal patency more difficult. So, detection of gastric variceal obliteration by EUS Doppler monitoring and fluoroscopy is more accurate than the standard practice of evaluating vascular patency by injection catheter palpation.

Outcome of bleeding gastric varices at 2 weeks and 3 months after cyanoacrylate therapy.

The early rebleeding rate was 5%. The early rebleeding rate after endoscopic treatment with cyanoacrylate has been reported to vary between 0% to 23%. The result in this study was very similar to that in the pilot study of 44 patients by Greennwald et al (2003), the study of 148 patients by Wong et al (2007) with 5% and 6.2% respectively.[7,8]

The late rebleeding occurred in 11.4 %. The overall rebleeding rate at 3 months after therapy was 16.4%, of which 5% occurred within 6 weeks classified as early rebleeding and 11.4% occurred after 6 weeks of treatment as late rebleeding. The rebleeding rates after endoscopic treatment of gastric varices with tissue adhesives have been reported to vary between 10 to 50 %, by Akahoshi et al (2002). It suggests that recurrent bleeding is problematic and still occurred in a significant proportion of the patients although endoscopic injection of cyanoacrylate is effective in the immediate control of bleeding.[9]

The rebleeding rate in the present study was independent of Child-Pugh class *(P=0.931)*, the size *(P = 0.655)* and the type of the varix*(P = 0.181)*. In the series of 48 patients by Marques et al (2008) and 174 patients by Kind et al (2000) have reported that patients with worse liver function and larger size of varix were most likely to rebleed. However, in another study, Haung et al (2000) failed to show the correlation between rebleeding rate and hepatic function. It was most likely due to small number of patients (14 patients) with Child Pugh C cirrhosis in Haung et al and 9 patients in the present study.[6,10,11]

In this study, follow up was scheduled up to 3 months after treatment and the rate of rebleeding after this period was not assessed.

The treatment failure related mortality rate was 2.3% (1/43). The literature reports a treatment

failure related mortality rate of 2% to 4%, which is similar to the present study. [2,12]

Decreased size of GV was observed in 14 (35.9%) at 2 weeks and 28 (80%) at 3 months. The eradication rate and the recurrence of the index varix could not be demonstrated in present study because of short duration of follow up and it is difficult to accurately estimate eradication time because histoacryl cast usually remain within varices for varying amount of time. The histoacryl cast ultimately sloughed in most cases, but a few just shrank in size.

The appearance of portal hypertensive gastropathy was noted in only one patient and esophageal varices were aggravated in two patients at the 3 month endoscopy. Therefore, cyanoacrylate therapy is not commonly associated with either aggravation or appearance of portal hypertensive gastropathy and oesophagealvarices because it does not affect on portal blood flow and portal pressure gradient. [13]

At the end of follow up, the extra endoscopic sessions and glue injection were needed in total seven patients for early rebleedding (1 case), late rebleeding (4 cases) and incomplete obliteration (2 cases). The volume of cyanoacrylate injected per endoscopic session ranged from 0.5 ml to 1.5 ml in this study.

Complications of gluing gastric varices

Complications of the procedure occurred in 16/43 patients (37.2%), including pyrexia in 9.3 % and ulceration at the site of injection in 27.9%. Symptomatic systemic complications like pulmonary embolism, cerebral embolism, portal vein embolism, thrombosis and splenic infarction were not observed. Asymptomatic emboli were not systematically sought radiographically in this study and so it was possible that small subclinical emboli may have occurred.

The lack of such complications in this study might be due to relatively small sample size. The other important factors include procedural factors. The occurrence of systemic embolization has been associated with a large volume of injection, the speed of injection and the existence of the shunt. Rapid injection may cause increased intravariceal pressure and induce migration of histoacryl before full polymerization. In this study, it was injected in limited but appropriate volumes. With an equal amount of lipoidol in mixture, the injection speed was usually limited.

CONCLUSION

The study showed that cyanoacrylate injection was effective for the treatment of actively bleeding gastric varices or varices that have recently bled. High rate of immediate haemostasis was achieved, often with obliteration of varices with lowest effective dose, within the first session of treatment. Rate of immediate haemostasis was independent of hepatic function, the size and the type of gastric varices. Complete variceal obliteration was essential to achieve good outcome. It required relatively few treatment sessions and low injection volume.

The data demonstrated that it had acceptable rebleeding rate which was controlled with repeated injection. The risk of rebeeding was also independent of hepatic function, type and size of varices.

The rate of serious adverse events were acceptably low. Generally it was a safe method in the hands of experienced endoscopists who were familiar with intravascular sclerotherapy.

This treatment modality was also a rapid, low cost and simple therapeutic option for gastric variceal bleeding.

From this study, it can be concluded that cyanoacrylate injection was relatively safe and effective for immediate haemostasis and prevention of rebleeding of gastric varices.

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