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Prevalence of gastric varices and results of sclerotherapy with N-butyl 2 cyanoacrylate for controlling acute gastric variceal bleeding.

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RAPID COMMUNICATION

Prevalence of gastric varices and results of sclerotherapy with N-butyl 2 cyanoacrylate for controlling acute gastric variceal bleeding

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Abstract

AIM: To study the prevalence, predictors and control of bleeding following N-butyl 2 cyanoacrylate (NBC) sclerotherapy of gastric varix (GV).

METHODS: We analyzed case records of 1436 patients with portal hypertension, who underwent endoscopy during the past five years for variceal screening or upper gastrointestinal (GI) bleeding. Fifty patients with bleeding GV underwent sclerotherapy with a mean of 2 mL NBC for control of bleeding. Outcome parameters were primary hemostasis (bleeding control within the first 48 h), recurrent bleeding (after 48 h of esophago-gastro-duodenoscopy) and in-hospital mortality were analyzed.

RESULTS: The prevalence of GV in patients with portal hypertension was 15% (220/1436) and the incidence of bleeding was 22.7% (50/220). Out of the 50 bleeding GV patients, isolated gastric varices (IGV-I) were seen in 22 (44%), gastro-oesophageal varices (GOV) on lesser curvature (GOV-Ⅰ) in 16 (32%), and GOV on greater curvature (GOV-Ⅱ) in 15 (30%). IGV-Ⅰ was seen in 44% (22/50) patients who had bleeding as compared to 23% (39/170) who did not have bleeding (P < 0.003). Primary hemostasis was achieved with NBC in all patients. Re-bleeding occurred in 7 (14%) patients after 48 h of initial sclerotherapy. Secondary hemostasis was achieved with repeat NBC sclerotherapy in 4/7 (57%). Three patients died after repeat sclerotherapy, one during transjugular intrahepatic portosystemic stem shunt (TIPSS), one during surgery and one due to uncontrolled bleeding. Treatment failure-related mortality rate was 6% (3/50).

CONCLUSION: GV can be seen in 15% of patients with portal hypertension and the incidence of bleeding is 22.7%. NBC is highly effective in controlling GV bleeding. In hospital mortality of patients with bleeding GV is 6%.

Key words: Gastric varices; Portal hypertension; N-butyl cyanoacrylate; Bleeding; Sclerotherapy

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INTRODUCTION

Gastric varix (GV) and its association with portal hypertension were first described in 1913[1]. Since then, there have been reports on different aspects of gastric varices including prevalence, bleed tendency and treatment options. The prevalence of GV in patients with portal hypertension varies from 18% to 70%[2,3], although the incidence of bleeding from gastric varices is relatively low ranging from 10% to 36%[3].

Management of GV presents is a challenging problem, because (1) since there is no consensus regarding the optimum treatment of GV, treatment tends to be empiric; (2) GV is not a homogeneous entity, and accurate classification defines its natural history and dictates its management; (3) although GV bleeding occurs less frequently than esophageal varix (EV) bleeding[4,5], whenever bleeding occurs it tends to be more severe and requires more red blood cell transfusions and has a higher mortality than EV bleeding[5]; (4) after control of acute bleeding, GV has a high rebleeding rate of 34% to 89%[6]; and (5) there is no consensus regarding subsequent sclerotherapy for prophylaxis against recurrent bleeding in GV patients. Optimal management of GV requires a multidisciplinary approach and close cooperation between gastroenterologists, interventional radiologists and the surgical team.

Sohendra *et al*[7] first reported in 1986 that bleeding from gastric varices could be controlled by sclerotherapy

using the tissue adhesive agent butyl cyanoacrylate. Since then several authors have used different sclerosing agents to achieve hemostasis in bleeding gastric varices, including N-butyl-2 cyanoacrylate (histoacryl)[4,8], 2-octyl cyanoacrylate[9], ethanolamine oleate injection[10], gastric variceal banding[11], thrombin[12], sodium tetradecyl sulfate[13]. However, N-butyl 2 cyanoacrylate (NBC) is the only promising agent.

Most reports on endoscopic treatment of bleeding gastric varices are small series, case reports, or retrospective reviews[14,15]. Not more than 1000 patients with bleeding GV have been treated with different sclerosing and coagulating agents. Cyanoacrylate injection can achieve primary hemostasis in 70% to 95% of patients with acute GV bleeding, with an early rebleeding rate ranging from 0% to 28% within 48 h[5,7,16]. Different doses of cyanoacrylate are used by different gastroenterologis ts[16,17]. Moreover, dilution ratio of NBC to lipoidal is different[18,19]. However, there is no consensus regarding effective dose and dilution of sclerosing agents.

This study was to analyze patients with GV in order to establish predictors of bleeding GV, and the efficacy and safety of NBC in treatment of bleeding GV.

Table 1 Clinical characteristics of patients with gastric varices

Characteristics	*n*	(%)
Number of patients	220	
Male:Female	141:79	(65:35)
Mean age (yr)	50 ± 11	
Etiology of GV		
HCV cirrhosis	155	(70)
HBV cirrhosis	38	(17.5)
NBNC	27	(12.5)
NCPHTN	9	
Alcoholism	5	
Budd-Chiari syndrome	1	
Wilson's disease	1	
Child-Pugh classification (A/B/C)	39/109/72	(18/49/33)
Types of gastric varices		
GOV-1	78	(35)
GOV-2	56	(25)
IGV-1	59	(27)
IGV-2	6	(03)
GOV-1 + GOV-2	14	(06)
GOV-2 + IGV-2	3	(1.5)
GOV 1+IGV 2	2	(01)
GOV 1 + IGV 1	2	(01)

MATERIALS AND METHODS

From March 2000 to March 2005, 1036 patients with portal hypertension underwent endoscopy in our hospital. Out of 220 GV patients with or without esophageal varices, 50 had active bleeding gastric varices which were treated with N-Butyl cyanoacrylate injection.

The cause of portal hypertension was defined on the basis of ultrasound and/or computed tomographic scan of abdomen along with Doppler ultrasound to study the patency and spleno-portal axis in all patients with bleeding GV.

The location of gastric varices was determined according to the classification described by Sarin and Kumar[3] and divided into gastroesophageal varices type 1 (GOV-1) GV continuing as an extension of esophageal varices on the lesser curve of the stomach), gastro-esophageal varices type 2 (GOV-2) on the greater curvature or fundal varices communicating with esophageal varices. Isolated gastric varices type 1 (IGV-1) and fundal varices within a few centimeters of the gastric cardia, or isolated gastric varices type 2 (IGV-2) and isolated ectopic gastric varices. Active bleeding was defined as bleeding or oozing of blood from a gastric varix, a clot or blackish ulcer or rent over a gastric varix, or the presence of distinct large gastric varices and absence of esophageal varices or other cause of gastrointestinal (GI) bleeding.

The clinical characteristics of patients including age, gender, Child-Pugh classification, type of varix, etiology and complications in patient with gastric varices were recorded and compared between groups with or without bleeding (Table 1).

Endoscopic sclerotherapy with n-butyl cyanoacrylate and lipoidal injection was performed by experienced endoscopists using a GIFQ160 gastroscope (Olympus, Tokyo, Japan). The sclerosant was injected into bleeding gastric varices using the 23 G disposable needle injector (Wilson Cook Medical Inc., Winston-Salem, NC).

The injection needle was primed with lipoidal (approximately 0.5 mL) to fill the dead space within the injection catheter. After the gastric varix lumen was punctured with the needle, 2 mL of NBC (histoacryl 100%) in aliquots of 1 mL, diluted in 0.5 mL lipoidal, was injected over 45-90 s, thus a dilution of 2:1 was achieved in all cases (Figure 1 and Figure 2). Distilled water was used to flush the injection needle before and after sclerotherapy. Additional NBC was not injected if bleeding was immediately controlled in patients. All patients received octreotide infusion (50 mg/per hour) at admission and continued for 3 d. All patients were given a proton pump inhibitor, initially intravenously for 48 h and then orally for 4-6 wk as per our endoscopy unit protocol.

Outcome measures

Primary hemostasis was defined as stability of vital clinical signs, no drop in hemoglobin concentration and no recurrent bleeding within the first 48 h after the initial sclerotherapy[16]. Re-bleeding was defined as hematemesis and/or melena, hypotension (a drop in systolic blood pressure of > 20 mmHg from baseline), fall in 2 gm/dL of hemoglobin and/or transfusion requirement of $\geqslant$ 2 units of packed red cells within that time.

Data analysis

Statistical interpretation of data was performed using Statistical Program for Social Sciences (SPSS) version 13. Results were expressed as mean ± SD for all continuous variables (e.g., age, gender, hospital stay, units of packed cells *etc.*) and numbers (percentage) for categorical data (e.g., gender, Child's class, *etc.*). Analysis was performed by using the independent *t*-test, chi-square test and Fisher's exact test wherever appropriate. $P < 0.05$ was considered statistically significant.

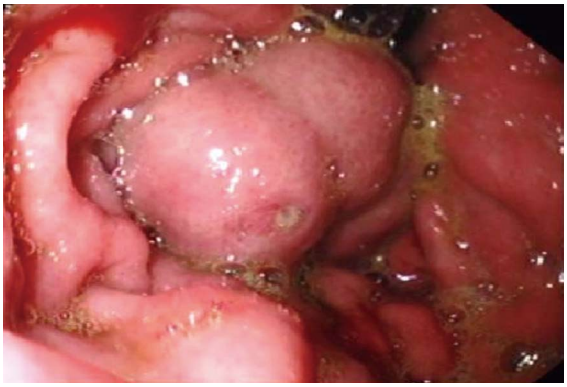

Figure 1 Isolated gastric varices with a nipple suggesting recent bleeding.

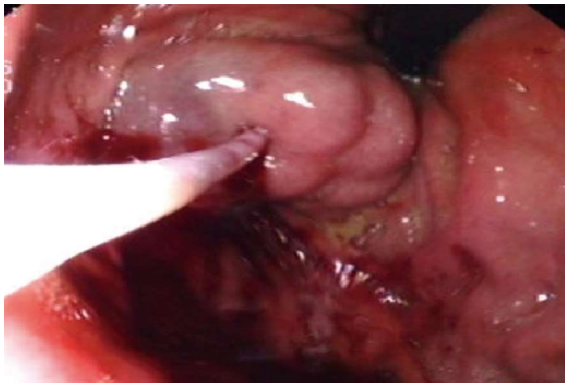

Figure 2 Injector needle with N- butyl cyanoacrylate in a large gastric fundal varix.

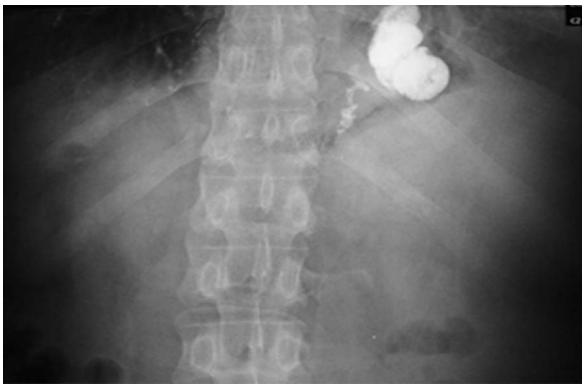

Figure 3 X-ray showing N-butylcyanoacrylate deposition in a gastric varix after sclerotherapy.

Table 2 Comparison between bleeding and non bleeding varices

Characteristics	Bleeding GV *n* (%)	Non bleeding GV *n* (%)	*P*
Age	50.48 ± 11.2	47.52 ± 12.7	0.14
Gender			
Male	30 (60)	111 (65.3)	
Female	20 (40)	59 (34.7)	0.49
Child Pugh class.			
A	12 (24)	27 (15.9)	
B	26 (52)	83 (48.8)	0.22
C	12 (24)	60 (35.3)	
Type of GV			
GOV- I	16 (32)	77 (45.3)	0.09
GOV-Ⅱ	15 (30)	58 (34.1)	0.58
IGV- I	22 (44)	39 (22.9)	< 0.01
IGV-II	0 (0)	11 (6.5)	0.06
Etiology of PHTN			
HBV	6 (12)	29 (17.1)	0.39
HCV	34 (68)	121 (71.2)	0.76
NBNC	6 (12)	21 (12.4)	0.94
Alcoholic	02 (2)	03 (1.8)	0.48
Non cirrhotic PHTN	01 (2)	08 (4.7)	0.59
Wilson's disease	01 (2)	00 (0)	0.06

RESULTS

The prevalence of bleeding gastric varices in patients with portal hypertension was 15% (220/1436) and the incidence of bleeding was 22.7% (50/220). The mean age of our patients with gastric varices was 50 ± 11 years, male patients accounting for 65% (141). The main etiology of bleeding gastric varices was hepatitis C-related cirrhosis in 34 (68%), followed by hepatitis B virus in 6 and non B non C cirrhosis in 6 (12%) patients, respectively. Alcoholic liver disease was found in 2 patients (4%), non cirrhotic portal hypertension in 1 patient and Wilson's disease in 1 patient, respectively. Twelve patients (24%) belonged to Child-Pugh A, 26 (52%) to Child-Pugh B, and 12 (24%) to Child-Pugh C.

Out of the 50 bleeding GV patients, IGV- I was seen in 22 patients (44%), GOV- I in 16 patients (32%), and GOV-Ⅱ in 15 patients (30%), concomitant GOV- I with GOV-Ⅱ in 3 patients. N-butyl cyanoacrylate (2 mL diluted in 1 cc lipoidal) was injected intravariceally in all patients with bleeding GV. The characteristics of bleeding and non bleeding gastric varices are shown in Table 2.

Among these 50 patients, 43 (86%) had active bleeding and 7 (14%) showed evidence of recent bleeding. Most varices (n = 48) were large (F3) according to Hashizume classification[20]. We compared bleeding and non bleeding GV and found that IGV- I was seen in 22/50 (44%) patients who had bleeding and in 39/170 patients (23%) patients who did not have bleeding (P < 0.003). Similarly, IGV-Ⅱ was observed in 0/50 (0%) and 11/170 (6.4%), GOV- I in 16/50 (32%) and 77/170 patients (45.2%) who did not have bleeding, GOV-Ⅱ in 15/50 (30%) and 50/170 patients (29.4%) who did not have bleeding from gastric varices, respectively.

The overall success rate for achieving primary hemostasis with NBC was 100% without recurrent bleeding within 48 h. A mean of 2.0 ± 0.5 cc NBC was injected in each patient.

Re-bleeding occurred in 7 (14%) patients after 48 h. Secondary hemostasis with repeat NBC sclerotherapy was achieved in 4 (57%) patients. Three patients died after repeat sclerotherapy: one during transjugular intrahepatic portosystemic stem shunt (TIPSS), one during surgery and one due to uncontrollable torrential bleeding. Treatment failure-related mortality rate was 6 % (3/50).

No major side effects occurred in most patients during and after NBC sclerotherapy. Three patients reported mild retrosternal chest pain which subsided within the next 24 h (Figure 3).

DISCUSSION

The overall incidence of gastric varices in patients with portal hypertension is 2%-70%[3]. Furthermore, we found that the incidence of bleeding from gastric varices in our patients is 22.7%, which is also similar to other reports[5].

In this study, the rate for primary hemostasis with NBC injection is consistent with the reported rate of 90% to 97% in other studies[8,14,16,21-23]. In our study, sclerotherapy with 2 mL NBC diluted in 1 mL lipoidal was effective in control of bleeding in all our patients during the first 48 h.

We used a higher dose of NBC with 2:1 dilution. Our technique avoids dilution of NBC, thus decreasing chances of migration and embolization as instantaneous polymerization is delayed.

It was reported that a hemostasis rate of 95% can be achieved without dilution of NBC, but serious side effects such as embolization may occur[24].

The risk of embolization increases with over dilution of cyanoacrylate which can slow down the process of polymerization. We avoided this problem by diluting 2 mL of NBC in 1 mL of lipoidal which was injected slowly over 45-90 s. Although the volume of injection was large, the side effects of a large volume were avoided and good hemostais was achieved by keeping a balanced dilution.

We also studied the predictors of the first gastric variceal bleeding, showing that the increased risk of bleeding is associated with larger varices including predominant IGV- I and GOV- I [5]. Kim *et al*[23] found that advanced Child-Pugh class and varix > 5 mm in size are associated with an increased risk of bleeding. Unlike esophageal varices, a high porto-systemic pressure > 12 mmHg does not cause GV bleeding, which is probably related to the high frequency of spontaneous gastro-renal shunts[17].

Cyanoacrylate therapy can improve and control re-bleeding. The high mortality rate is primarily a reflection of underlying advanced liver disease unaffected by the injection of cyanoacrylate[25,26]. This is further explained by a study of Kim *et al*[23] in which they prospectively followed a cohort of patients with gastric varices who did not undergo endoscopic therapy and found that the mortality rate is 35% over a median of 15 mo. Therefore, the role and efficacy of sclerotherapy for prophylaxis against recurrent bleeding are questionable.

In the present study, re-bleeding occurred after 48 h in 7 (14%) patients and was controllable in 4 (57%) with repeat injection of NBC. It was reported that the incidence of re-bleeding ranges from 23% to 35%[8,10,16]. However, Kind *et al*[14] reported that the incidence of re-bleeding is 15.5%.

Treatment failure-related mortality in our study was 6%, which is consistent with the reported mortality[16]. Another study showed that the mortality is 12.5% due to re-bleeding immediately after NBC sclerotherapy[8]. Kind *et al*[14] reported that the hospital mortality rate is 19.5% in patients with bleeding gastric varices.

In conclusion, endoscopic injection of NBC at a dilution of 2:1 appears to be effective and safe for the control of hemostasis in patients with bleeding gastric varices. If NBC is injected slowly, a large amount of NBC in proper dilution can be used without serious side effects.

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