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BRIEF ARTICLE

Factors influencing clinical outcomes of Histoacryl® glue injection-treated gastric variceal hemorrhage

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Abstract

AIM: To determine the factors associated with clinical outcomes and complications of Histoacryl® glue injection for acute gastric variceal hemorrhage.

METHODS: Patients who presented to the Siriraj Gastrointestinal Endoscopy Center with active gastric variceal bleeding and were admitted for treatment between April 2008 and October 2011 were selected retrospectively for study inclusion. All bleeding varices were treated by injection of Histoacryl® tissue glue (B. Braun Melsungen AG, Germany) through a 21G or 23G catheter primed with lipiodol to prevent premature glue solidification. Data recorded for each patient included demographic and clinical characteristics, endoscopic findings, clinical outcomes in terms of early and late re-bleeding, mortality, and procedure-related complications. Data from admission (baseline) and post-treatment were comparatively analyzed using stepwise logistic regression analysis to determine the correlation between factors and clinical outcomes.

RESULTS: A total of 90 patients underwent Histoacryl® injection to treat bleeding gastric varices. The mean age was 55.9 ± 13.9 (range: 15-88) years old, and 74.4% of the patients were male. The most common presentations were hematemesis (71.1%), melena (12.2%), and coffee ground emesis (8.9%). Initial hemostasis was experienced in 97.8% of patients, while re-bleeding within 120 h occurred in 10.0%. The presence of ascites was the only factor associated with early and late re-bleeding [odds ratio (OR) = 10.67, 95%CI: 1.27-89.52, P = 0.03 and OR = 4.15, 95%CI: 1.34-12.86, P = 0.01, respectively]. Early procedure-related complications developed in 14.4% of patients, and were primarily infections and non-fatal systemic embolization. Late re-bleeding was significantly correlated with early procedure-related complications by univariate analysis (OR = 4.01, 95%CI: 1.25-12.87, P = 0.04), but no factors were significantly correlated by multivariate analysis. The overall mortality rate was 21.1%, the majority of which were related to infections. The factors showing strong association with higher mortality risk were elevated total bilirubin (OR = 16.71, 95%CI: 3.28-85.09, P < 0.01), a large amount of transfused fresh frozen plasma (OR = 1.001, 95%CI: 1.000-1.002, P = 0.03), and late re-bleeding (OR = 10.99, 95%CI: 2.15-56.35, P = 0.02).

CONCLUSION: Histoacryl® injection is a safe and effective hemostatic method for treating gastric variceal hemorrhage. Patients with compromised liver, including ascites, have a higher risk of re-bleeding.

Key words: Histoacryl; Gastric varices; Clinical outcome; Complications; Hemorrhage

Core tip: Acute gastric variceal hemorrage is associated with a high mortality rate which accounts for one third of the patients. Histoacryl® injection has been reported as one of the effective procedures for treating this condition. The present study investigated patients presenting with acute gastric variceal hemorrage and found that Histoacryl® injection was a safe and highly effective hemostatic method for treating gastric variceal hemorrhage with 97.8% initial hemostasis; only a 10% early re-bleeding rate and a 14.4% procedure-related complication rate were found. The risk factors for re-bleeding were compromised liver status and presence of ascites.

INTRODUCTION

Bleeding from esophagogastric varices is the second most frequent etiology of upper gastrointestinal hemorrhage and is associated with high rates of mortality, even up to five years after the initial episode. In addition, the clinical management procedures used to resolve the bleeding can themselves cause complications, such as infection or tissue injury, that increase the patient's risk of re-bleeding episodes and mortality. The condition and its treatment can be further complicated by the presence of underlying or concomitant diseases. In fact, more than 80% of reported cases have concomitant liver disease, including portal hypertension and cirrhosis[1-5].

Variceal band ligation is regarded as the most effective standard treatment for bleeding esophageal varices. However, this procedure has proven largely ineffective in treating gastric varices, producing a low rate of hemostasis (reports range from 26%-71%) but having a high rate of re-bleeding (from 60%-90%)[1-5]. While bleeding gastric varices are substantially less common than those involving the esophageal tissues (accounting for only about 20% of cirrhotic patients), they are invariably related to massive hemorrhaging and significant complications. Moreover, the mortality rate for bleeding gastric varices is about 30%. Other treatment procedures, such as endoscopic sclerotherapy, have shown equally unsatisfactory outcomes; endoscopic band ligation is reported to produce hemostasis in only 45% of cases and to have a 31% re-bleeding rate[1]. The available hemostatic modalities with the best rates of successful application are: Histoacryl® tissue adhesive (2-N-butyl-cyanoacrylate; B. Braun Dexon, Spangenberg, Germany) injection, transarterial intrahepatic portosystemic shunting (TIPS), and balloon-occluded retrograde transvenous obliteration (B-RTO). Of these three, Histoacryl® injection represents the most commonly used treatment for initial acute gastric varices, with TIPS or B-RTO applied subsequent to Histoacryl® injection failure. The preference for Histoacryl® injection is largely due to liver status-related contraindications affecting TIPS and B-RTO, as well as their inconvenience for application in emergency care clinical settings[1-10].

Since its introduction in 1984[3], widespread use of Histoacryl® has shown that this agent can successfully resolve bleeding gastric varices. Recent evaluation of the accumulated reports of complications arising in Histoacryl®-treated patients, such as systemic embolization, end-organ infarction, visceral fistula, and bacteremia, have also indicated this adhesive is relatively safe and effective[1,9-13]. A few small case series from Germany, the United Kingdom, Italy and Uruguay have shown 88%-98% initial hemostasis with only a 1% rate of severe complications, such as systemic embolization, and a re-bleeding rate of 10%-29%[4-10]. Studies from China and Korea reported 95%-100% success rates but a similar range of re-bleeding rates at 1-year follow-up[6-13]. However, no studies to date have identified the factors related to clinical outcome of gastric variceal hemorrhage following Histoacryl® treatment. Therefore, we performed the current retrospective analysis to evaluate the correlation of clinical and/or demographic characteristics to clinical outcome and procedure-related complications.

MATERIALS AND METHODS

Patient selection and clinical procedures

The medical records of the Siriraj Gastrointestinal Endoscopy Center were searched to identify all patients who presented with active gastric variceal bleeding and underwent Histoacryl® injection treatment between April 2008 and October 2011. Data recorded at admission (baseline) and during the subsequent hospitalization and follow-up examinations were recorded, including demographic and clinical characteristics, endoscopic procedures and findings, and clinical outcomes in terms of early and late re-bleeding, mortality, and procedure-related complications. The study was carried out with pre-approval by the Siriraj Institutional Review Board (No. Si001/2012).

Each gastric varices case was classified as GOV1, GOV2, IGV1 or IGV2, according to the strategy described by Marques *et al*[13]. All of the cases were diagnosed as acute gastric variceal bleeding. The clinical setting was classified as emergency when the procedure was carried out within 24 h of the bleeding episode, and as urgent in the case of self-limited bleeding. All patients underwent the treatment procedure within the initial admission period, and no patient was released and re-admitted for the treatment. Achievement of initial hemostasis was defined by stable vital signs and absence of re-bleeding within 24 h. Re-bleeding was defined by the presence of active bleeding from the treated varices directly observed by endoscopy (using forward-viewing gastroscopes GIF 1T145, GIF XTQ 160, or GIF Q180; Olympus, Tokyo, Japan) or indicated by melena/or hematemesis with concurrent hemoglobin decrease of > 2 mg/dL. Re-bleeding was defined as early if it oc-

curred within 120 h after the index procedure, and as late if it occurred within two weeks after the index procedure.

A standardized Histoacryl® injection method was used according to the recommendations of Seewald *et al*[14]. A working solution of Histoacryl® was generated by mixing 0.5 mL with 0.8 mL of lipiodol (Guerbert, Roissy, France). The injection catheter (21G or 23G Interject™; Boston Scientific, Spencer, IN, United States) was first primed with 0.8-1.2 mL of lipiodol to prevent premature solidification of the Histoacryl®. Then, the bleeding gastric varix was punctured and the working solution was injected, followed immediately by 1.0-2.0 mL of sterile distilled water to ensure delivery of the entire working solution volume into the varix. The needle was retracted and immediately flushed with sterile distilled water to maintain patency. Then, the varix was probed with the injection catheter and if it was found to have remained soft, an additional 1.3 mL injection was initiated to achieve complete obliteration (defined as absolute firmness of the injected varix). All of these procedures were carried out without the aid of fluoroscopic monitoring. All procedures were carried out by experienced gastroenterologists or by second-year gastroenterologist trainees under the supervision of an experienced gastroenterologist.

Post-operative monitoring included clinical and laboratory examinations to identify development of complications. Most patients received continuous intravenous infusion of vasopressors (Octreotide, Sandostatin®) for three to five days following the procedure. Complications identified during routine examinations, and not based on clinical symptoms and signs, were classified as minor, and included abdominal pain, chest discomfort, or embolization. Complications identified upon examination in response to clinical signs and symptoms were classified as major, and included systemic embolization; major complications required further treatment and extended hospitalization by about three days. Furthermore, complications that occurred within 24 h of the procedure were classified as early, while those that occurred within two weeks of the procedure were classified as late.

Statistical analysis

Statistical analysis were carried out by the SPSS software, version 13.0 (SPSS, Inc., Chicago, IL, United States). Descriptive data are reported as mean ± SD or as percentage. The Student's *t* test and the χ^2 test were used to assess differences between groups. Forward stepwise logistic regression analyses, both univariate and multivariate, and receiver operating characteristic curve (ROC) analysis were used to determine the correlation between factors and clinical outcomes. A two-tailed *P* value > 0.05 was considered as statistically significant.

RESULTS

A total of 90 cases of gastric variceal hemorrhage treated by Histoacryl® injection were analyzed. The majority of the cases were male (*n* = 62, 74.4%). The average pa-

tient age was 55.9 ± 13.9 (range: 15-88) years old. The most frequent clinical presentations were hematemesis (71.1%), melena (12.2%), coffee ground vomiting (8.9%), and hematochezia (6.7%). One-third of the patients presented with concomitant hypotension, while one-fifth had clinical signs of hepatic encephalopathy and about one-third had concurrent hepatocellular carcinoma (HCC). According to Child-Pugh classification, 20.0% of patients had class A liver status, while 46.7% and 32.2% had class B and C liver status, respectively. According to scoring for model of end-stage liver disease (MELD), the median MELD score for all patients was 10 and the scores ranged from 6 to 28. Nearly all cases of portal hypertension were caused by cirrhosis related to various etiologies, including alcoholism (34.4%), chronic hepatitis B infection (28.9%), chronic hepatitis C infection (14.4%), non-alcoholic steatohepatitis (2.2%), cryptogenic factors (12.2%), and other factors (7.8%). Only one patient had non-cirrhotic portal hypertension.

Ninety percent of the total patients with bleeding gastric varices required blood transfusion prior to endoscopy or during hospital admission. Seventy-three percent of the procedures were carried out as emergency endoscopic treatments. The gastric varices cases represented GOV1 (44.4%), GOV2 (33.3%), IGV1 (21.2%) and IGV2 (1.1%). Two-thirds of the patients had concurrent esophageal varices, but no cases showed evidence of esophageal index bleeding.

The mean volume of Histoacryl® working solution delivered per procedure was 3.12 mL. Initial hemostasis was achieved in 97.8% of the procedures. The average hospital stay was nine days. Early re-bleeding occurred in 10.0% of the total patients, but 21.1% of patients experienced late re-bleeding. Early complications occurred in 14.4% of the total cases, and included subclinical systemic embolization (4.4%), aspiration pneumonia (5.5%), spontaneous bacterial peritonitis (1.1%), and other infection (3.3%). A total of 19 patients died during the follow-up period, and 80.0% of the deaths were attributed to HCC or advanced cirrhosis (all of which had been treated conservatively). The remaining deaths were related to the gastric varices re-bleeding.

The patients' baseline characteristics are shown in Table 1, and data related to the procedure and clinical outcome, including complications, are shown in Table 2. The first clinical outcome considered in univariate and multivariate analyses was re-bleeding, and both early and late episodes were analyzed. As shown in Tables 3 and 4, the factors associated with early re-bleeding by univariate analysis were presence of ascites [odds ratio (OR) = 10.90, 95%CI: 1.30-91.51, *P* = 0.01] and concurrent HCC along with a large volume of transfused packed red cells (PRC) (6.89 ± 3.85 units, *P* < 0.01) (OR = 4.95, 95%CI: 1.14-21.50, *P* = 0.05). The factors correlated with late re-bleeding by univariate analysis were presence of ascites (OR = 4.25, 95%CI: 1.37-13.17, *P* = 0.01) and concurrent HCC in general (OR = 2.98, 95%CI: 1.05-8.46, *P* = 0.04). However, multivariate analysis identified only the

Table 1 Patient baseline characteristics and clinical presentation *n* (%)

Clinical factor	*n* = 90	mean ± SD
Age, yr		55.9 ± 13.9
Male sex	67 (74.4)	
Clinical presentations		
Hematemesis	64 (71.1)	
Melena	11 (12.2)	
Hematochezia	6 (6.7)	
Coffee ground	8 (8.9)	
Not reported	1 (1.1)	
Vital signs at presentation		
Normal	49 (54.4)	
Tachycardia	7 (7.8)	
Hypotension	34 (37.8)	
Etiology of cirrhosis		
Alcoholism	31 (34.4)	
Chronic hepatitis B	26 (28.9)	
Chronic hepatitis C	13 (14.4)	
Nonalcoholic steatohepatitis	2 (2.2)	
Cryptogenic	11 (12.2)	
Other	7 (7.8)	
Liver status by Child-Pugh classification		
Class A	18 (20.0)	
Class B	42 (46.7)	
Class C	29 (32.2)	
Concurrent hepatocellular carcinoma		
Yes	29 (32.2)	
Blood transfusion		
Yes	81 (90.0)	
Transfusion volume		
Packed red cells, units		3.5 ± 2.8
Fresh frozen plasma, mL		890.9 ± 1183.4
Endoscopic setting		
Emergency	66 (73.3)	
Urgent	24 (26.7)	

Table 2 Procedures, clinical outcomes, and complications *n* (%)

Procedures and clinical factors	*n* = 90	mean ± SD
Type of gastric varix		
GOV1	40 (44.4)	
GOV2	30 (33.3)	
IGV1	18 (20.0)	
IGV2	1 (1.1)	
Combination of variceal type	1 (1.1)	
Size of gastric varices, cm		2.1 ± 0.9
Concurrent esophageal varix		
No	28 (31.1)	
Yes	62 (68.9)	
Bleeding stigmata observed by endoscopy		
Yes	71 (78.9)	
Initial hemostasis		
Yes	88 (97.8)	
Early re-bleeding		
Yes	9 (10.0)	
Late re-bleeding		
Yes	19 (21.1)	
Early complications		
No	77 (85.6)	
Non-significant systemic embolization	4 (4.4)	
Pneumonia	4 (4.4)	
Spontaneous bacterial peritonitis	1 (1.1)	
Infection elsewhere	3 (3.3)	
Late complications		
No	88 (97.8)	
Infection elsewhere	1 (1.2)	
Mean aliquot used/procedure		3.0 ± 1.7
Follow-up clinical status		
Dead	19 (21.1)	
Worsening	3 (3.3)	
Stable	8 (8.9)	
Improved	60 (66.7)	
Causes of death (*n* = 19)		
Bleeding-related	4 (4.4)	
Infection	9 (10.0)	
Liver failure	1 (1.1)	
Cardiovascular diseases	2 (2.2)	
Renal failure	1 (1.1)	
Bowel gangrene	2 (2.2)	

presence of ascites as correlated with early re-bleeding (OR = 10.67, 95%CI: 1.27-89.52, P = 0.03) and late re-bleeding (OR = 4.15, 95%CI: 1.34-12.86, P = 0.01).

The second clinical outcome considered in univariate and multivariate analyses was mortality at the last follow-up. As shown in Table 5, the factors significantly correlated with mortality by univariate analysis were presence of ascites (OR = 3.09, 95%CI: 1.05-9.12, P = 0.04), elevated total bilirubin (8.50 ± 6.71 mg/dL, P < 0.01) (OR = 16.7, 95%CI: 3.28-85.09), concurrent HCC (OR = 2.98, 95%CI: 1.05-8.47, P = 0.03), high volume of transfused PRC (5.68 ± 3.32 units, P < 0.01) or fresh frozen plasma (1934.0 ± 1850.78 mL, P < 0.01), emergency endoscopic setting (OR = 0.17, 95%CI: 0.01-0.92, P = 0.02), high volume of Histoacryl® injection (4.13 ± 1.99 mL, P < 0.01) (OR = 2.28, 95%CI: 2.32-108.72, P < 0.01), early re-bleeding (OR = 20.12, 95%CI: 3.72-108.32, P < 0.01) and late re-bleeding (OR = 10.32, 95%CI: 3.35-34.91, P < 0.01). Multivariate analysis showed correlations with mortality only for total bilirubin (OR = 16.71, 95%CI: 3.28-85.09, P < 0.01), large volume of transfused fresh frozen plasma (OR = 1.001, 95%CI: 1.000-1.002, P = 0.03), and late re-bleeding (OR = 10.99, 95%CI: 2.15-56.35, P = 0.02).

The last clinical outcome considered in univariate and multivariate analyses was procedure-related complica-

tions. As shown in Table 6, univariate analysis identified only one factor as correlated with procedure-related complications: late re-bleeding (OR = 4.01, 95%CI: 1.25-12.87, P = 0.04). However, the multivariate analysis did not identify any factors as significantly correlated with this clinical outcome.

ROC analysis of total bilirubin correlation with mortality indicated that the cut-off level was > 4.5 mg/dL (area under the curve was 0.926). Classification of the patients into two groups according to this cut-off level followed by multivariate analysis identified total bilirubin > 4.5 mg/dL as significantly correlated with mortality (OR = 7.25, 95%CI: 2.39-22.02, P < 0.01).

DISCUSSION

In our study, the majority of patients with gastric variceal hemorrhage had underlying decompensated liver cirrhosis and presented with hematemesis. Surprisingly, only one-third of the patients presented with active bleeding

Table 3 Factors related to early re-bleeding

Factors	Early re-bleeding							
			Univariate			Multivariate		
	Yes (*n* = 9)	No (*n* = 81)	*P* value	95%CI	OR	*P* value	95%CI	OR
Decompensated liver diseases								
Yes	9	62	0.19					
MELD score > 12	3	19	0.69					
Encephalopathy	3	24	0.33					
Ascites	8	33	0.01[1]	1.30-91.51	10.9	0.03[1]	1.27-89.52	10.67
Concurrent HCC								
Yes	6	23	0.05	1.14-21.50	4.95			
Transfusion volume								
PRC, unit	6.89 ± 3.85	3.09 ± 2.56	< 0.01[1]			0.04[1]	1.12-116.0	11.41
FFP, mL	1943.33 ± 1064.61	773.69 ± 1142.92	< 0.01[1]			-	-	-
Type of gastric varix								
GOV	7	63						
IGV	2	17	0.99					
Mean GV size, cm	2.16 ± 0.70	2.12 ± 0.88	0.88					
Mean aliquot number/procedure	3.88 ± 1.72	2.93 ± 1.72	0.146					
Endoscopic red stigmata								
Yes	9	69	0.19					

[1]Statistically significant difference. HCC: Hepatocellular carcinoma; MELD: Model of end-stage liver disease; PRC: Packed red cell; FFP: Fresh frozen plasma; OR: Odds ratio.

Table 4 Factors related to late re-bleeding

Factors	Late re-bleeding							
			Univariate			Multivariate		
	Yes (*n* = 19)	No (*n* = 71)	*P* value	95%CI	OR	*P* value	95%CI	OR
Decompensated liver diseases								
Yes	18	53	0.19					
MELD score > 12	5	17	0.92					
Encephalopathy	7	10	0.07					
Ascites	14	27	0.01[1]	1.37-13.17	4.25	0.01[1]	1.34-12.86	4.15
Concurrent HCC								
Yes	10	19	0.04[1]	1.05-8.46	2.98	-	-	-
Transfusion volume								
PRC, unit	5.00 ± 3.59	3.06 ± 2.36	< 0.01[1]			-	-	-
FFP, mL	1648.68 ± 1720.18	688.11 ± 906.73	0.03[1]			-	-	-
Type of gastric varix								
GOV	14	56	0.89					
IGV	5	15						
Mean GV size, cm	2.05 ± 0.76	2.15 ± 0.89	0.67					
Mean aliquot number/procedure	3.17 ± 1.75	2.98 ± 1.74	0.69					
Endoscopic red stigmata								
Yes	17	54	0.55					

[1]Statistically significant difference. HCC: Hepatocellular carcinoma; MELD: Model of end-stage liver disease; PRC: Packed red cell; FFP: Fresh frozen plasma; OR: Odds ratio.

and as hemodynamically unstable. This examination of 90 cases treated by Histoacryl® injection revealed that almost all patients required blood transfusion prior to the endoscopic procedure or during the subsequent hospital admission, and that the most common types of gastric varices were GOV1 and GOV2. Moreover, concurrent esophageal varices and HCC were frequently present in these patients. In 2005, Noophun *et al*[15] reported a similar retrospective study of 24 Thai patients who presented with gastric variceal hemorrhage and were treated with Histoacryl® injection. In that study population, initial hemostasis was achieved in 58% of patients and 29% ex-

perienced re-bleeding; however, these findings were quite different from the other studies in the literature, which were reporting success rates as high as 90%-100%[2-17]. In our present study population, initial hemostasis was achieved in 97.8%. However, the rates of early and late re-bleeding were lower than those reported in the previous studies (10% and 20%, respectively, *vs* 12%-54%)[2-5]. One previous study by Wang *et al*[7] had reported that about 10% of Histoacryl® extrusion occurs within the first week after injection, and suggested that this phenomenon might be related to re-bleeding of the gastric varices. Therefore, we hypothesize that the early re-

Table 5 Correlation analysis of factors associated with mortality at final follow-up

Factors	Yes (*n* = 19)	No (*n* = 71)	Univariate			Multivariate		
			P value	95%CI	OR	*P* value	95%CI	OR
Age, yr	56.4 ± 3.34	55.8 ± 1.65	0.95					
Decompensated liver diseases								
Yes	18	53	0.10					
MELD score > 12	8	14	0.06					
Ascites	13	28	0.04[1]	1.05-9.12	3.09	-	-	-
Encephalopathy	6	11	0.29					
Total bilirubin, mg/dL	8.50 ± 6.71	2.73 ± 2.93	< 0.01[1]			< 0.01[1]	3.28-85.09	16.7
Concurrent HCC								
Yes	10	19	0.03[1]	1.05-8.47	2.98	-	-	-
Transfusion volume								
PRC, unit	5.68 ± 3.32	2.87 ± 2.28	< 0.01[1]			-	-	-
FFP, mL	1934.00 ± 1850.78	611.76 ± 724.89	< 0.01[1]			0.03[1]	1.000-1.002	1.001
Type of gastric varix								
GOV	14	56	0.54					
IGV	5	14						
Mean GV size, cm	1.97 ± 0.74	2.16 ± 0.89	0.38					
Mean aliquot number/procedure	4.13 ± 1.99	2.76 ± 1.57	< 0.01[1]			-	-	-
Early re-bleeding								
Yes	7	2	< 0.01[1]	3.72-108.3	20.12	-	-	-
Late re-bleeding								
Yes	8	11	< 0.01[1]	3.35-34.91	10.32	< 0.01[1]	2.15-56.35	10.99

[1]Statistically significant difference. HCC: Hepatocellular carcinoma; MELD: Model of end-stage liver disease; PRC: Packed red cell; FFP: Fresh frozen plasma; OR: Odds ratio.

Table 6 Correlation analysis of factors associated with procedure-related complications

Factors	Yes (*n* = 16)	No (*n* = 74)	Univariate			Multivariate		
			P value	95%CI	OR	*P* value	95%CI	OR
Age, yr	55.92 ± 12.56	56.06 ± 19.69	0.97					
Decompensated liver diseases								
Yes	14	57	0.19					
MELD score > 12	8	14	0.14					
Encephalopathy	1	16	0.06					
Ascites	8	33	0.79					
Concurrent HCC								
Yes	5	24	0.90					
Mean GV size, cm	2.28 ± 0.99	2.09 ± 0.83	0.44					
Mean aliquot number/procedure	2.87 ± 1.50	3.06 ± 1.79	0.71					
Early re-bleeding								
Yes	4	5	0.49					
Late re-bleeding								
Yes	7	12	0.04[1]	1.25-12.87	4.01			

[1]Statistically significant difference. HCC: Hepatocellular carcinoma; MELD: Model of end-stage liver disease; OR: Odds ratio.

bleeding cases in the present study population might be associated with early glue extrusion.

Procedure-related complications following Histoacryl® injection developed in 13.9% of the current study's population. This rate is slightly lower than the rate of 15% reported by Fry *et al*[11]. One of the most concerning complications of endoscopy is fatal systemic embolization[8-27]; fortunately, no cases of severe systemic embolization developed in the current study population, despite the average amount of Histoacryl® working solution used per case being about 3 mL. Most of the cases of embolization complications in the current study did not

manifest any significant clinical symptoms and/or signs, and were incidentally detected by lipiodal staining in chest X-ray or computed tomography scan. None of the fatal consequences of systemic embolization, which include organ infarction and abscess formation, developed in this study population. Thus, the collected data suggest that Histoacryl® injection is an effective and safe option for treating active or recent gastric variceal hemorrhage.

The overall post-procedure mortality in the current study's population was similar to that reported from previous studies[2-11]. We noted that one-half of the patient deaths were associated with infections, with hospital-

acquired pneumonia or ventilator-associated pneumonia being predominant. Moreover, the infections occurred despite the use of prophylactic antibiotics. We believe that the pneumonic infections, in particular, might have resulted from incidental aspiration that occurred during the active bleeding condition or were secondary consequences of bacteremia[25]. Thus, this complication might be prevented by extending the antibiotic prophylaxis schedule, by performing early endotracheal intubation to prevent aspiration, or by using a needle fitted with a covered-tip catheter to reduce contamination.

Previously, Chang *et al*[2] investigated the factors which might affect clinical outcomes of patients who underwent Histoacryl® injection for gastric variceal hemorrhage. Although only 9% of that study population was represented by patients with gastric variceal hemorrhage, the two predictive factors of re-bleeding identified were a large amount of PRC transfusion and high MELD scores. Another study of 118 Taiwanese patients with gastric variceal hemorrhage identified concomitant HCC as associated with early re-bleeding[5]. In particular, advanced cancer stage, newly-developed HCC, active bleeding, and high MELD score were reported as being associated with poor outcome. To date, however, no study has reported predictive factors for early re-bleeding in cirrhotic patients with active gastric variceal hemorrhage. In the present study, the presence of ascites was the only factor associated with both early and late re-bleeding in patients with active gastric variceal hemorrhage treated by Histoacryl® injection. Therefore, we propose that these re-bleeding episodes may have been related to pre-existing defects in the liver status. Ascites are one of the items considered in the Child-Pugh scoring system of liver status, yet neither the Child-Pugh score nor the MELD score was found to be significantly correlated with re-bleeding in the current study population.

A large amount of transfused PRC was identified as another potential predictive factor of re-bleeding, which is logical since this factor corresponds to the severity of active bleeding at the initial presentation for which surgery is indicated. Yet another factor, concurrent HCC, was correlated with both early and late re-bleeding by univariate analysis only, and the correlation was lost in multivariate analysis. It is possible that our relatively small study population size limited our ability to detect the true correlation, and future study with a larger population might confirm the predictive nature of this factor. Surprisingly, the endoscopic finding of recent bleeding signs, such as red nipple or white nipple, or even the type and size of GV itself, including the amount of injected Histoacryl®, could not be used as the predictors for re-bleeding in the present study. In addition, late re-bleeding was identified as a potential predictive factor of procedure-related complications, but again the significant correlation was lost in multivariate analysis. Because infections accounted for more than half of complications occurring in the current study population, we hypothesized that the processes of re-bleeding and infection may each represent both cause and effect; for example, the bleeding site might be a portal by which

pathogenic agents achieve more systemic distribution, or the infection itself might trigger a bleeding episode in already weakened tissues further damaged by the actions of inflammatory cytokines.

The mortality rate of patients with bleeding gastric varices has been previously shown to be related to the amount of blood transfusion and the patient's liver status (Child-Pugh score and MELD score). The present study showed that a larger amount of transfused fresh frozen plasma, elevated total bilirubin level (> 5 mg/dL), and late re-bleeding were significantly correlated with mortality. Therefore, we hypothesize that the risk of mortality for a patient with gastric variceal hemorrhage following treatment with Histoacryl® injection is associated with pre-existing liver conditions, severity of the index bleeding, and development of infectious complications. Concurrent HCC and MELD score may also influence mortality, but studies with larger populations are needed to confirm their role.

Some limitations exist in the present study design that may affect generalization of our findings. First, this was a retrospective study in which the decision making of treatment strategy depended on the endoscopist who was in charge on the day of the procedure. However, all of the endoscopists were trained in a standardized protocol for Histoacryl® injection. Second, some of the re-bleeding patients diagnosed with advanced HCC or decompensated liver disease were managed noninvasively. Conservative treatment can be associated with a higher mortality rate and may have impacted our mortality data. Lastly, the relatively small population size of the current study may have weakened the power of detecting true correlations; studies with larger populations are required to confirm our findings.

Histoacryl® injection is an effective and safe treatment option for gastric variceal hemorrhage. Neither the type or size of gastric varices, the amount of Histoacryl®, nor the injection technique were associated with rates of re-bleeding, complications, or mortality. However, the severity of index bleeding and a pre-existing decompensated liver status, especially the presence of ascites or elevated total bilirubin, are associated with the rates of re-bleeding and mortality.

COMMENTS

Background
Gastric variceal hemorrhage is an uncommon cause of upper gastrointestinal bleeding, and is mostly related to portal hypertension; however, this condition is associated with very high rates of morbidity and mortality. Injection of Histoacryl® tissue adhesive (N-2-butyl-cyanoacrylate) can achieve hemostasis, but is also associated with development of life-threatening procedure-related complications, such as fatal systemic embolization, and appreciable rates of re-bleeding. To date, there are limited data regarding the factors associated with the clinical outcomes of Histoacryl® injection to treat bleeding gastric varices.

Research frontiers

In this article, the authors evaluate the factors associated with clinical outcomes of gastric variceal hemorrhage treated by Histoacryl® injection. These data may help to identify patients at greater risk of experiencing re-bleeding episodes following treatment and those who will benefit from closer clinical monitoring for an extended period of time following the surgical procedure.

Innovations and breakthroughs

Initial hemostasis was achieved in 97.8% of bleeding gastric varices patients treated with Histoacryl® injection. The rate of early (within 120 h of procedure) re-bleeding was 10.0%, and the rate of late (within two weeks of procedure) re-bleeding was 21.1%. The overall complication rate was 13.9%, and the majority of cases that died were associated with infection. The factors associated with adverse clinical outcome involved the patients' liver status, and the procedure itself appeared to be much less involved.

Peer review

The authors performed a retrospective analysis of patients with acute gastric variceal hemorrhage to determine the factors associated with clinical outcomes and complications of Histoacryl® injection. The Histoacryl® injection procedure and compound were effective and safe for treating gastric variceal hemorrhage, achieving a high rate of hemostasis while producing low rates of re-bleeding and procedure-related complications. The clinical outcomes were mostly associated with liver status of the patients during the index bleeding episode. The results provide insights into the underlying etiologies of re-bleeding following treatment and may help to identify patients at higher risk of re-bleeding and mortality.

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