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CLINICAL TRIALS AND THERAPEUTICS

Prophylactic use of antibiotics in endoscopic injection of tissue adhesive for the elective treatment of gastric varices: A randomized controlled study

Chengfeng Liu,*,[1] Lili Ma,[†,1] Jian Wang,* Feng Li,* Yujen Tseng,[‡] Tiancheng Luo,* Xiaoqing Zeng* and Shiyao Chen[§]

Departments of *Gastroenterology and Hepatology, [†]Endoscopy Center, [§]Gastroenterology and Hepatology, Endoscopy Center, Evidence-based Medicine Center, Zhongshan Hospital, Fudan University, and [‡]Department of Gastroenterology, Huashan Hospital, Huashan Hospital, Fudan University, Shanghai, China

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Correspondence
Dr Shiyao Chen, Department of Gastroenterology and Hepatology, Endoscopy Center, Evidence-based Medicine Center, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China.
Email: chen.shiyao@zs-hospital.sh.cn

Dr Xiaoqing Zeng, Department of Gastroenterology and Hepatology, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China.
Email: zeng.xiaoqing@zs-hospital.sh.cn

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[1]Chengfeng Liu and Lili Ma contributed equally to the manuscript and share first authorship.

Abstract

Background: Tissue adhesive injection is the first-line treatment for gastric varices rebleeding. Available studies are focused on antibiotic usage in emergency endoscopy, while the use of antibiotics in selective endoscopic tissue adhesive treatment remains controversial.
Methods: This is a randomized controlled study conducted in a tertiary referral hospital. Consecutive patients were enrolled from February 16, 2016, to November 19, 2016, and blindly randomized into two treatment groups. Patients in the prophylactic group received 2 g of cefotiam during endoscopic injection of tissue adhesive. All the subjects were observed for rebleeding, fever, and changes in laboratory indicators in hospital and post-discharge.
Result: One hundred and seven patients who received endoscopic therapy for gastroesophageal varices were included. Fifty-three patients were allocated to the antibiotic prophylactic group and 54 patients to the on-demand group. The two groups had similar baseline characteristics. The incidence of fever in hospital was 2/53 (3.8%) *vs* 9/54 (16.7%) ($P = 0.028$). Perioperative and postoperative clinical events were significantly lower in the antibiotic prophylactic group (5.7% *vs* 24.1%, $P = 0.018$; 7.5% *vs* 20.4%, $P = 0.050$). Inflammation indices were elevated on the first day after endoscopic therapy; however, no significant difference was observed between the two groups. The cumulative rebleeding free rate within 2 months was lower in the antibiotic prophylactic group (1.9% *vs* 9.3%, $P = 0.100$).
Conclusion: Our study illustrated that prophylactic use of antibiotics in selective endoscopic injection of tissue adhesive reduced the incidence of the total clinical events in perioperative period and had a trend towards lower rebleeding in 2 months.

Introduction

Gastroesophageal varices are a common clinical manifestation in patients with portal hypertension, with an annual incidence of 5–15%.[1] Variceal hemorrhage is often life threatening and can be detrimental to patient's quality of life. Although in certain cases, variceal bleeding can spontaneously resolve, the associated mortality rate is still at 20% within 6 weeks.[2] Treatment with tissue adhesives for gastric varices is the main treatment method to prevent variceal rebleeding.

Transient bacteremia frequently occurs after invasive treatment procedures such as sclerotherapy[3] or transcatheter chemo

embolization. Endoscopic treatment procedures are also associated with a risk of infection. The disease state of cirrhosis increases patient susceptibility due to intestinal flora shift and immune dysfunction, which increases incidence of comorbid infection.[4–7] However, infection rate after tissue adhesive treatment for gastric varices remains controversial.

Previous study showed that 10 (1.3%) of 753 patients developed sepsis after endoscopic tissue adhesive treatment, one (0.1%) developed spontaneous peritonitis, while 33 (4.4%) patients experienced rebleeding.[8] Another study showed that the incidence of infection after endoscopic tissue adhesive treatment was 3/41 (7.3%).[9] For patients with acute variceal hemorrhage, guidelines recommend the use of antibiotics to reduce the incidence of infection, rebleeding, and death for all patients with suspected or confirmed variceal bleeding secondary to portal hypertension.[1]

However, there is still controversy regarding preventive application of antibiotics in patients undergoing elective endoscopic treatment for gastric varices. There is no reliable statistics for clinical reference. Previous studies on cirrhosis infection are mostly retrospective studies with small sample size.

Therefore, we intend to explore the efficacy of prophylactic antibiotics usage in patients undergoing selective endoscopic treatment of tissue adhesive for gastric varices through the present randomized controlled clinical trial.

Methods

Patient selection. Patients with a history of variceal bleeding secondary to portal hypertension, admitted to our tertiary referral center (Zhongshan Hospital, Fudan University) between February 16, 2016, and November 19, 2016, were eligible for study inclusion. The exclusion criteria were as follows: (i) age < 18 or > 75; (ii) patients who did not receive endoscopic injection of tissue adhesives; (iii) contraindication of cefotiam, such as allergy or pregnancy; (iv) concurrent malignancies (patients with liver cancer were not excluded); (v) preoperative diagnosis of infection or patients who had received antibiotics prior to endoscopic treatment for severe ascites or other infections; (vi) acute gastroesophageal variceal bleeding (< 5 days); and (vii) refusal to participate in the study.

Randomization and study design. This is a randomized controlled clinical pilot study. Consecutively numbered opaque envelopes containing allocation generated by a computer were used for concealment. Two physicians who performed the procedure were blinded to outcome evaluations.

Patients who received endoscopic injection of tissue adhesive for gastric varices were randomized into two groups: the antibiotic prophylactic group and the on-demand group. Cefotiam is a second-generation cephalosporin with broad spectrum that can cover bacteria in endoscopic injection sclerotherapy.[10,11] Patients in the antibiotic prophylactic group received a single intravenous administration of 2 g of cefotiam prior to injection of cyanoacrylate. The control group received 100 mL of saline solution placebo. All subjects were observed for rebleeding, fever, and changes in laboratory indicators during hospitalization. After endoscopic treatment, antibiotics would only be prescribed to patients with fever (> 38 °C), significant increase in white blood cells ($> 10 \times 10^9$/L) or neutrophils ($> 80\%$), and variceal rebleed. All patients were followed for 2 months after the endoscopic procedure. A routine endoscopy examination was performed at the end of 2 months to evaluate the efficacy of the procedure.

We defined perioperative clinical events as fever, pain, or bleeding during hospitalization. If the patient failed to be discharged because of complications, complications and death during the hospital are also considered as perioperative clinical events. Postoperative clinical events were defined as additional antibiotics usage after endoscopic therapy or rebleeding within 2 months.

The primary outcomes were total clinical events (postoperative fever, infection, and additional usage of antibiotics). The secondary outcomes were rebleeding rate, survival rate within 2 months, and endoscopic follow-up after 2 months.

The study protocol was registered at http://www.clinicaltrials.gov (NCT02693951) and was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (approval no. B2015-168), in compliance with the Declaration of Helsinki. Written consents were obtained from all participants.

Endoscopic injection of tissue adhesive (N-butyl-cyanoacrylate). Esophageal varices (EV) were graded as follows: (i) grade 1: small, straight EV; (ii) grade 2: enlarged, tortuous EV occupying less than one-third of the lumen; and (iii) grade 3: large, coil-shaped EV occupying more than one-third of the lumen. Gastric varices were defined according to previous study.[12,13]

All treatments are performed under intravenous anesthesia. Propofol (Diprivan®; AstraZeneca, Cheshire, UK) was administered by bolus injection according to the protocol previously reported (0.25 mg/kg with additional doses of 20–30 mg when necessary, up to a maximum dose of 120 mg). To prevent tissue glue from obstructing the endoscopic channel and injection needle, the injection needle (Olympus, NM-200L-423, Tokyo, Japan) was exhausted with lauromacrogol before entering the endoscope. The Olympus GIF-XQ240/260 gastroscope was used to target varicose vein for treatment using the "sandwich" technique.[13] The needle is quickly flushed with lauromacrogol, followed by tissue adhesive (Beijing Compont Medical Devices Co., Ltd., Beijing, China) and then again by lauromacrogol.[13] The needle sheath is held in place for a few seconds and observed for bleeding. The target vein may be supplemented with surplus tissue adhesive when necessary. Proton-pump inhibitor was administered intravenously for 24–48 h postoperatively, followed by proton-pump inhibitor tablet for 2 months.

Statistical analysis. The SPSS 23.0 software (SPSSInc., Chicago, Illinois, USA) was used for statistical analysis. Continuous variables were expressed as means ± standard deviation and compared using Student's *t*-test. Qualitative data were described with constituent ratios, while intra-group comparisons were achieved using χ^2 or Fisher's exact test. Kaplan–Meier analysis was carried out to estimate the cumulative probability of rebleeding. Univariate or multivariate analyses were performed to assess potential risk factors for rebleeding by using Cox proportional hazard model analysis. All statistical analyses were two sided, and $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics. Three hundred and thirteen patients fulfilled the inclusion criteria between February 16, 2016, and November 19, 2016. Four patients refused the allocated intervention. After endoscopy, 107 patients who were not treated with tissue adhesive were excluded. Finally, 107 cases were included and randomized into two groups: 53 patients (age 53.45 ± 12.49 years, male 77.4%) in the antibiotic prophylactic group and 54 patients (age 55.76 ± 11.94 years, male 75.9%) in the on-demand group (Fig. 1). There was no significant difference of clinical baseline characteristics between the two groups (Table 1). All patients were followed up for 2 months without loss to follow-up.

Postoperative clinical manifestations and laboratory tests. The highest body temperature in the prophylactic antibiotic group was lower than that of the on-demand group (P = 0.034), and the incidence of moderate to high fever was significantly lower (P = 0.028) (Table 2). Blood culture test was performed in one of the patients in the on-demand group after a high-grade fever, but the result was negative. A total of nine patients in demand group patients had fever more than 38 °C after surgery. Three of them did not receive additional antibiotics for transient fever, without increase in white blood cells or neutrophil count. Another patient received antibiotics for postoperative bleeding. The incidences of additional antibiotics use during postoperative hospitalization were 5.7% in the antibiotic prophylactic group and 13% in the on-demand group, respectively (P = 0.168).

Perioperative clinical events. The incidence of perioperative clinical events and postoperative clinical events was significantly lower in the antibiotic prophylactic group than that of the on-demand group (5.7% *vs* 24.1%, P = 0.018; 7.5% *vs* 20.4%, P = 0.05) (Table 3). All inflammation indices were higher on the first day after endoscopic therapy, but these differences were not significant between the two groups (Table 4). There was no significant difference in the length of hospital stay between the two groups (4.59 ± 1.63 *vs* 4.30 ± 1.48 days, P = 0.757).

Rebleeding and survival. One (1.9%) patient in the antibiotic prophylaxis group *versus* five (9.3%) patients in the on-demand group developed rebleeding within 2 months. One patient in the on-demand group experienced hematemesis 1 day after endoscopic treatment and was discharged after conservative treatment. Gastric varix ulcers were the sources of rebleeding in three patients who received a repeat endoscopy after rebleeding. Analysis showed that patients with prophylactic antibiotics had a lower rate of rebleeding within 2 months than those who did not, but no statistical difference was reached (P = 0.1) (Fig. 2). On multivariate analysis, portal vein thrombosis and hepatocellular carcinoma were independent determinants of rebleeding (hazard ratio 6.557, 95% confidence interval, 1.066–40.330, P = 0.042; hazard ratio 16.255, 95% confidence interval, 1.452–181.990, P = 0.024) (Table S1). There were no deaths in the two groups within 2 months.

Review of gastroscopy. Thirty-three patients in the on-demand group and 44 patients in the antibiotic prophylactic group completed the gastroscopy during the follow-up period, and the median time to follow-up was 91 days (91 ± 68.5 days) and 94 days (94 ± 50.25 days), respectively. There was no significant difference in additional treatment and tissue adhesive extravasation between the two groups (P = 0.522, 0.608) (Table 5).

Discussion

Gastric varices and its association with portal hypertension were first mentioned in 1931. The incidence of gastric varices in patients with portal hypertension ranged from 18% to 70%.[14]

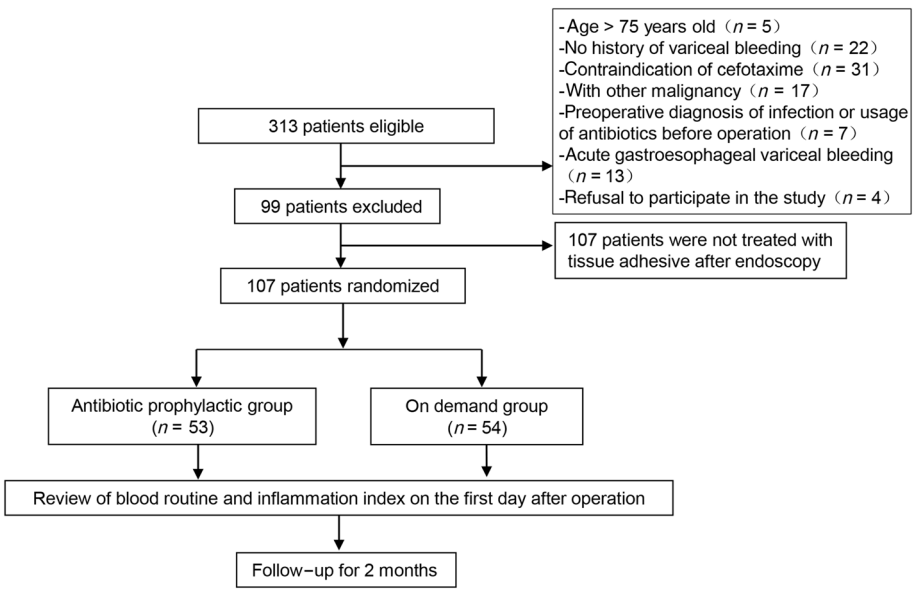

Figure 1 Study design (screening, randomization, and follow-up of subjects).

Table 1 Demographic and clinical characteristics

Variables	Antibiotic prophylaxis group (n = 53)	On-demand group (n = 54)	P value
Age (years ± SD)	53.45 ± 12.49	55.76 ± 11.94	0.331
Number of previous bleeding	2.15 ± 1.75	1.78 ± 1.48	0.235
Gender (male/female)	41 (77.4%)/12 (22.6%)	41 (75.9%)/13 (24.1%)	0.521
Child–Pugh class (A/B/C)	40 (75.5%)/13 (24.5)/0	36 (66.7%)/18 (33.3)/0	0.315
Concurrent HCC (absent/present)	49 (92.5%)/4 (7.5%)	48 (88.9%)/6 (11.1%)	0.383
Previous endoscopic therapy (absent/present)	25 (47.2%)/28 (52.8%)	25 (46.3)/29 (53.7%)	0.541
NSBB (absent/present)	50 (94.3)/3 (5.7)	52 (96.3)/2 (3.7)	0.632
PVT (absent/present)	45 (84.9)/8 (15.1)	41 (75.9)/13 (24.1)	0.306
Splenectomy (absent/present)	41 (77.4%)/12 (22.6%)	45 (83.3%)/9 (16.7%)	0.474
Diabetes (absent/present)	39 (73.6)/14 (26.4%)	44 (81.5%)/10 (18.5%)	0.228
RBC (10^{12}/L)	3.76 ± 0.81	3.58 ± 0.73	0.228
HGB (g/L)	101.23 ± 25.73	102.85 ± 26.04	0.746
PLT (10^9/L)	116.57 ± 104.21	108.5 ± 85.59	0.662
WBC (10^9/L)	3.54 ± 3.23	3.40 ± 1.77	0.775
NEUT (%)	57.22 ± 10.89	54.45 ± 13.27	0.241
EV (none/F1/F2/F3)	4 (7.5)/4 (7.5)/1 (1.9)/44 (83.0)	8 (14.8)/2 (3.7)/1 (1.9)/43 (79.6)	0.572
GV classification (1/2/3)	25 (47.2)/10 (18.9)/18 (34.0)	25 (46.3)/13 (24.1)/16 (29.6)	0.779
Tissue glue injection points	3.09 ± 1.46	2.89 ± 1.34	0.450
Tissue adhesive injection (mL)	2.38 ± 1.55	2.05 ± 1.03	0.195
Hospital day (days ± SD)	4.59 ± 1.63	4.30 ± 1.48	0.757

EV, esophageal varices; GV, gastric varices; HCC, hepatocellular carcinoma; HGB, hemoglobin; NEUT, neutrophil; NSBB, non-selective beta-blocker; PLT, platelet; PVT, portal vein thrombosis; RBC, red blood cell; WBC, white blood cell.

Table 2 Comparison of postoperative clinical events

Variables	Antibiotic prophylaxis group (n = 53)	On-demand group (n = 54)	P value
Body temperature (°C)	36.93 ± 0.48	37.19 ± 0.76	0.034*
Fever			
Present	2 (3.8%)	9 (16.7%)	0.028*
Absent	51 (96.2%)	45 (83.3%)	
Additional usage of antibiotics			
Present	3 (5.7%)	7 (13.0%)	0.168
Absent	50 (94.3%)	4 (87.0%)	
Usage of analgesics			
Present	2 (3.8%)	4 (7.4%)	0.348
Absent	51 (96.2%)	50 (92.6%)	
Early rebleeding (1st week)	0 (0.0%)	1 (1.9%)	0.505
Present	53 (100.0%)	53 (98.1%)	
Absent			
RBC (10^{12}/L)	3.93 ± 0.74	3.70 ± 0.70	0.126
HGB (g/L)	105.48 ± 23.58	106.70 ± 27.43	0.812
PLT (10^9/L)	107.46 ± 94.35	101.25 ± 79.69	0.721

*The highest body temperature and the incidence of moderate (38.1–39 °C) to high (39.1–41 °C) fever in the prophylactic antibiotic group were significantly lower than that of the on-demand group (P = 0.034, 0.028). HGB, hemoglobin; PLT, platelet; RBC, red blood cell.

Table 3 Comparison of postoperative total clinical events

Variables	Antibiotic prophylaxis group (n = 53)	On-demand group (n = 54)	P value
Perioperative clinical events			
Present	4 (7.5%)	13 (24.1%)	0.018*
Absent	49 (92.5%)	41 (75.9%)	
Postoperative clinical events			
Present	4 (7.5%)	11 (20.4%)	0.050*
Absent	49 (92.5%)	43 (79.6%)	

*The incidence of perioperative clinical events (fever, pain, and early rebleeding) and postoperative clinical events (additional antibiotics use and rebleeding in 2 months) is significantly lower in antibiotic prophylactic group than in the on-demand group (5.7% *vs* 24.1%, P = 0.018; 7.5% *vs* 20.4%, P = 0.05).

Gastric variceal hemorrhage is associated with a higher mortality rate compared with that of EV. Cessation of acute bleeding and preventing rebleeding are the key measures to improve survival and patient's quality of life. At present, endoscopic tissue glue injection has become the first-line treatment for gastric variceal bleeding. Our randomized controlled study displayed a significantly reduction of the incidence of the total clinical events in perioperative period and a trend towards lower rebleeding (1.9% *vs* 9.3%) in 2 months in the prophylactic group. However, there was no significant difference in inflammation indices after endoscopic therapy or additional treatment and tissue adhesive extravasation in the review of gastroscopy between the two groups.

Previous studies have shown that about 90% of patients will experience transient fever after endoscopic injection of tissue adhesive for the treatment of gastric varices.[15] However, the incidence of complications in the selective endoscopic tissue adhesive treatment is low. Chen *et al.*[11] investigated the incidence of infection after endoscopic injection of tissue adhesive. A clinical study including 94 individuals found that the positive rate of blood culture test in the tissue gel injection group was higher than that in the control group (15/47 *vs* 1/47, $P < 0.0001$). But only one patient died of sepsis, while most of the bacteremia was transient

Table 4 Comparison of preoperative and postoperative inflammation index

Variables	Antibiotic prophylaxis group (n = 53)	On-demand group (n = 54)	P value
WBC (10^9/L)			
Before	2.83 (1.84, 4.13)	2.99 (2.04, 4.45)	0.495
After	4.12 (3.39, 7.30) (n = 48)	4.65 (3.38, 6.58) (n = 53)	0.878
NEUT (%)			
Before	57.22 ± 10.89	54.45 ± 13.27	0.241
After	70.66 ± 9.11 (n = 48)	70.88 ± 9.91 (n = 53)	0.840
PCT (ng/L)			
Before	0.05 (0.04, 0.06) (n = 21)	0.06 (0.04, 0.085) (n = 20)	0.762
After	0.08 (0.035, 0.1) (n = 48)	0.1 (0.04, 0.2) (n = 47)	0.197
CRP (mg/L)			
Before	1.00 (0.50, 2.95) (n = 39)	0.75 (0.40, 2.70) (n = 34)	0.556
After	2.1 (1.4, 5.45) (n = 49)	1.9 (0.8, 4.1) (n = 51)	0.296
Endotoxin (pg/mL)			
Before	29.05 (8.29, 79.79) (n = 16)	9.57 (8.14, 18.17) (n = 8)	0.320
After	9.53 (7.71, 35.69) (n = 46)	9.5 (8.12, 19.02) (n = 49)	0.813

CRP, C-reactive protein; NEUT, neutrophil; PCT, procalcitonin; WBC, white blood cell.

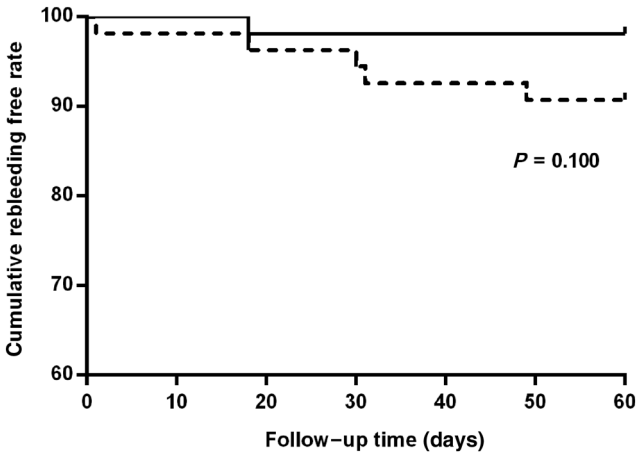

Figure 2 The cumulative rate of freedom from any source of rebleeding. ——, antibiotic prophylactic group; - - -, on-demand group.

and did not cause clinical events. A number of other studies[3,16] have found that the incidence of bacteremia or infection after endoscopic treatment for acute hemorrhage of esophagogastric varices was higher than that of elective patients. Patients with elective treatment rarely experience bacteremia or infection; therefore, it is not necessary to use antibiotics prophylactically. However, patients with acute bleeding have a high probability of developing bacteremia and require prophylactic use of antibiotics. Based on the present study results, we found that prophylactic use of antibiotics can reduce the incidence of postoperative fever and other clinical events, which is consistent with previous studies. In the study conducted by Rerknimitr *et al*., the injection point was limited to no more than 2, which is not consistent with our clinical situation. In our study, the average injection point was 2–3 points (1–8 points). Mucosal damage caused by excessive manipulation increased intestinal flora displacement, and sclerosing agents or tissue glue used for injection can potentially cause postoperative infection.[17]

Table 5 The effect of prophylactic antibiotics on patients' gastroscopy follow-up and additional treatment

	Antibiotic prophylactic group (n = 44)	On-demand group (n = 33)	P value
Endoscopic treatment			
Present	28 (70.0%)	23 (69.7%)	0.589
Absent	12 (30.0%)	10 (30.3%)	
Tissue adhesive injection			
Present	17 (42.5%)	13 (39.4%)	0.489
Absent	23 (57.5%)	20 (60.6%)	
Ligation			
Present	17 (42.5%)	14 (42.4%)	0.592
Absent	23 (57.5%)	19 (57.6%)	
Sclerotherapy			
Present	3 (7.5%)	1 (3.0%)	0.384
Absent	37 (92.5%)	32 (97.0%)	
Varices bleeding			
Present	2 (5.0%)	1 (3.0%)	0.573
Absent	38 (95.0%)	32 (97.0%)	
Tissue gel discharge ulcer			
Present	27 (67.5%)	23 (69.7%)	0.522
Absent	13 (32.5%)	10 (30.3%)	

Zhang *et al*.[18] compared endotoxin and procalcitonin (preoperative, 1 day after surgery and 7 days after surgery) in 32 patients with antibiotic use after endoscopic treatment and 18 patients without antibiotic use after surgery. The level of endotoxin and procalcitonin in the non-antibiotic group was significantly increased, suggesting a risk of infection. In addition, studies have suggested that persistent high levels of C-reactive protein in patients with decompensated cirrhosis are closely related to short-term mortality.[19] Studies by Christou *et al*. suggest that elevated white blood cells are one of the risk factors for community-acquired infections in patients with cirrhosis.[5] Our study found that all inflammation indices were higher on day 1 after

endoscopic therapy. But these differences were not significant between the two groups. Therefore, the more injection points, the greater the risk of intraoperative bleeding and bacterial invasion.

There were some limitations in the present study. First, no Child C patients were enrolled. In patients with poor liver function, the clinician will routinely use antibiotics before invasive procedures, which is consistent with previous studies, wherein need for prophylactic antibiotics is based on patient's liver function. Second, follow-up period and the sample size are not enough to show the effects in preventing rebleeding due to the low rebleeding rate (5.6% [6/107]) in 2 months. Bacterial infection was associated with rebleeding after gastric variceal bleeding, especially in those patients with higher Child–Pugh score and hepatocellular carcinoma.[20] Moreover, hepatic venous pressure gradient was also the factor that affect rebleeding after endoscopic treatment.[21] Preoperative hepatic venous pressure gradient can help with selection of patients at high risk of rebleeding. Further studies are needed to evaluate the efficacy of prophylactic use of antibiotics in selective endoscopic injection of tissue adhesive in a high-risk set.

Our study illustrated that prophylactic use of antibiotics in selective endoscopic injection of tissue adhesive reduced the incidence of the total clinical events in perioperative period and a trend towards lower rebleeding in 2 months. However, complications of endoscopic procedure are often closely related to patients' situation and operator's experience, which can differ between facilities. Therefore, in order to improve the representativeness of patients, a multicenter clinical research must be carried out.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Univariate multivariate analysis for rebleeding