Bacteremia after endoscopic injection of N-butyl-2-cyanoacrylate for gastric variceal bleeding

Wen-Chi Chen, MD, Ming-Chih Hou, MD, Han-Chieh Lin, MD, Kwok-Woon Yu, MD, Fa-Yauh Lee, MD, Full-Young Chang, MD, Shou-Dong Lee, MD
Taipei, Taiwan

Background: Cyanoacrylate may form a barrier that prevents bacterial invasion when used in tissue. Because cyanoacrylate polymerizes within seconds on contact with aqueous media, it is used worldwide to arrest gastric variceal bleeding. The aim of this study was to determine the frequency of bacteremia after endoscopic cyanoacrylate injection for gastric variceal bleeding.

Methods: Patients with cirrhosis who underwent endoscopic cyanoacrylate injection for gastric variceal bleeding were included. Patients with cirrhosis who underwent upper endoscopy for nonvariceal upper GI bleeding were recruited as controls. Patients with infection before endoscopy were excluded. Blood was cultured in both groups. Injection needles and endoscope accessory channels were cultured in the cyanoacrylate injection group.

Results: More patients injected with cyanoacrylate had positive blood cultures in comparison with the control group (15/47 vs. 1/47, \( p < 0.0001 \)). In the cyanoacrylate injection group, the volume of blood transfused and Child-Pugh score were factors associated with the occurrence of bacteremia. Most episodes of bacteremia were transient, except for 1 patient who died of sepsis. Most of the microorganisms cultured from blood samples were identical to those cultured from injection needles (65%) and accessory channels (90%).

Conclusions: Endoscopic cyanoacrylate injection for gastric varices does not limit the spread of bacteria. The endoscope accessory channel was the major source of bacteria. Most episodes of bacteremia were transient and uneventful. (Gastrointest Endosc 2001;54:214-8.)

Gastric variceal bleeding is a serious complication of liver cirrhosis. Although gastric varices rupture less often than esophageal varices, the prognosis for the former is poorer than for the latter.\(^1\)\(^-\)\(^3\) Endoscopic injection with N-butyl-2-cyanoacrylate is used worldwide for the treatment of acute gastric variceal bleeding.\(^4\)\(^,\)\(^5\) Endoscopic injection of a conventional sclerosant for variceal bleeding has an associated rate of bacteremia that ranges from 0% to 50%.\(^6\)\(^-\)\(^10\) However, cyanoacrylate differs from conventional sclerosants in that it forms polymers within seconds, thus rendering hematogenous spread less likely. Some investigators claim that cyanoacrylate has in vitro antibacterial properties.\(^11\)\(^,\)\(^12\) Therefore, our theory was that cyanoacrylate injection might limit bacterial invasion and reduce the frequency of bacteremia. To test the hypothesis, this study was designed to compare the frequency of bacteremia after endoscopic injection of cyanoacrylate for gastric variceal bleeding with that after upper endoscopy for nonvariceal bleeding in patients with cirrhosis.

PATIENTS AND METHODS

All patients with cirrhosis seen from June 1998 to January 2000 with acute or recent gastric variceal bleeding who underwent endoscopic injection with N-butyl-2-cyanoacrylate were recruited for study. Patients with cirrhosis and nonvariceal upper GI bleeding who underwent upper endoscopy were recruited in a one-to-one match as control patients at the same time. Gastric variceal bleeding was defined as observed bleeding from a varix, blood clots adherent to the varices, the presence of a white nipple sign, fresh blood in the stomach with large varices, and variceal red color signs in the absence of other potential bleeding sites. Patients who had any infection or had received antibiotics within 72 hours before endoscopy were excluded. Patients were also excluded if any of the following were present before endoscopy: leukocytosis (white blood cell count >10,500/mm\(^3\)), body temperature higher than 38.5°C, or a positive blood culture.

Endoscopy and cyanoacrylate injection

After intramuscular injection with 20 mg hyoscine-N-butylbromide, and induction of topical pharyngeal anes-
Bacteremia after cyanoacrylate injection for gastric variceal bleeding


Bacteremia after cyanoacrylate injection for gastric variceal bleeding


A careful search was conducted for possible sources of bleeding. If a gastric varix proved to be the source, a 23-gauge disposable needle injector (EIS 01943, Top Co., Tokyo, Japan) was introduced by means of the accessory channel. The gastric varices were injected with a 1:1 mixture of 0.5 mL N-butyl-2-cyanoacrylate (Histoacryl blue, Braun, Melsungen, Germany) and 0.5 mL Lipiodol (Guerbet Laboratory, Aulnay-Sous-Bris, France). The mixture of Lipiodol and cyanoacrylate was prepared with aseptic technique by an assistant wearing sterile disposable gloves. Lipiodol was drawn into a sterile syringe from a bottle disinfected with povidone-iodine 70% isopropyl alcohol. The container of cyanoacrylate was also disinfected with povidone-iodine 70% isopropyl alcohol and cut with aseptic scissors. Cyanoacrylate was then drawn carefully into the syringe containing Lipiodol. No more than 6 injections were performed during each session. The needle injector catheter was then withdrawn and cut 5 cm from the tip for culture. A plain radiograph film of the abdomen was obtained in all patients within 12 hours of endoscopic treatment to verify the intravariceal injection of the cyanoacrylate. In the control group, endoscopic therapy was used to treat nonvariceal bleeding lesions as necessary.

Bacteriology

Blood for culture was obtained 5 minutes before endoscopy, and at 5 minutes, 3 hours, and 24 hours after endoscopy in both groups of patients. This included cleaning the forearm with povidone-iodine 70% isopropyl alcohol and drawing blood from separate veins in the forearm.

Five milliliters of blood was then inoculated into each blood culture bottle (BACTEC 6A and 7A, Becton Dickinson & Co., Spark, Md.). The blood culture bottles were placed in a culture system (BACTEC NR-860, Becton Dickinson). The tip of the needle injector and instrument accessory channel were cultured only in the cyanoacrylate group. The injector tip, cut off after the cyanoacrylate injection, was cultured over a blood agar plate (BAP). The BAP was placed in an incubator at 35.6°C. The accessory channel was cultured immediately after the endoscopy with a sterile swab that was directly inoculated onto a BAP, which was also placed in an incubator at 35.6°C. Ascites, if present, was tapped, analyzed, and cultured in blood culture bottles before the endoscopy to exclude the presence of spontaneous bacterial peritonitis in both groups. Spontaneous bacterial peritonitis was diagnosed if there were more than 250/mm³ polymorphonuclear cells in ascitic fluid that was culture positive. If the ascitic fluid culture was negative, the diagnosis was then based on the presence of more than 500/mm³ polymorphonuclear cells in the fluid together with characteristic signs such as fever and abdominal pain. Patients in both groups were treated with antibiotics as necessary after completion of cultures.

Statistical analysis

Results are given as mean ± SD. Continuous parameters were compared using the Student t test. Noncontinuous parameters were compared with the chi-square test. Logistic regression analysis was used to examine the risk factors for bacteremia and recurrent bleeding. Results were considered statistically significant if \( p < 0.05 \).

RESULTS

Fifty-two patients with 61 episodes of acute or recent gastric variceal bleeding and 50 patients with 52 episodes of nonvariceal bleeding were initially recruited. Eleven patients with 14 episodes of gastric variceal bleeding were excluded because of concomitant infection (urinary tract 3, spontaneous bacterial peritonitis 2, biliary tract 2, pneumonia 1), empirical use of antibiotics because of leukocytosis in 2, fever in 2, prophylactic use of antibiotics in 1 patient within 72 hours before endoscopy, and a positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before endoscopy. A positive blood culture before...
episodes and 45 patients with cirrhosis and 47 non-variceal bleeding episodes entered the study. The clinical characteristics of the patients in both groups were similar, except that a greater number of patients undergoing cyanoacrylate injection had hepatocellular carcinoma (Table 1). Thirty-three patients in the cyanoacrylate group and 27 control patients underwent emergency endoscopy within 24 hours after the initial hemorrhage. Patients in the cyanoacrylate injection group had a median of 2.0 (1-6) injections during each treatment session. In the control group, the sources of bleeding were as follows: gastric ulcer in 28 patients, duodenal ulcer in 12, esophageal ulcer in 5, and portal hypertensive gastropathy in 2. Twenty patients with 25 bleeding episodes (19 gastric ulcers, 6 duodenal ulcers) received epinephrine (1:10,000 dilution) injections for ulcer bleeding, and 2 patients with 2 gastric ulcer bleeding episodes were treated by heat probe coagulation.

**Bacteremia and bacteriology**

Blood cultures were positive during 15 of 47 (31.9%) bleeding episodes in patients receiving endoscopic injections of cyanoacrylate. The positive blood cultures after endoscopy were as follows: 7 sets taken at 5 minutes, 8 sets at 3 hours, and 5 sets at 24 hours. The hepatic function was classified as Child-Pugh C in 9, B in 3, and A in 3 patients with positive cultures. The causative microorganisms are listed in Table 2. Patients undergoing cyanoacrylate injection had a higher rate of bacteremia compared with those in the control group (15/47 vs. 1/47, \( p < 0.0001 \)). Blood culture yielded *Klebsiella pneumoniae* in 1 patient in the control group. Logistic regression analysis of all the factors in Table 1, the number of injections, and the volume of cyanoacrylate used for injection showed that the volume of blood transfused (OR 1.43: 95% CI [1.095, 1.860] \( p = 0.008 \)) and Child-Pugh score (OR 1.42: 95% CI [1.030, 1.966] \( p = 0.032 \)) were associated with bacteremia. Cultures from the tips of the injection needles were positive in 24 of 47 (51.1%) episodes (Table 2). Strains of bacteria cultured from the tip of the injection needle (65.0%) and accessory channels (90%) were almost always identical.

**Course and outcome**

Eighteen (38.3%) patients who received cyanoacrylate injections had transient fever (>37.5°C) within 24 hours after the procedure, and 9 of them had a high fever (>38.5°C). All episodes of fever subsided within 36 hours after endoscopy, except for 1 that lasted for 120 hours. Antibiotics were administered to 10 febrile patients. In the control group, 5 patients had mild fever and 1 had high fever. Three of these febrile patients received antibiotics. One patient with Child-Pugh C hepatic reserve, who had undergone endoscopic injection of cyanoacrylate, died as a result of procedure-related sepsis. No perforation of the stomach was found among patients in the cyanoacrylate group.

**DISCUSSION**

Bacteremia often coexists with acute variceal hemorrhage. Impaired function of the reticuloendothelial system, a low serum complement level, impaired cell-mediated immunity, and bacterial translocation in patients with cirrhosis are assumed to be the probable mechanisms. In addition to concomitant bacteremia, the traditional endoscopic injection of sclerosants for control of esophageal variceal hemorrhage also induces bacteremia. When used in tissue, cyanoacrylate forms a firm barrier that prevents bacterial invasion; this barrier has been beneficial in surgical practice. In contrast to the traditional sclerosing agents, cyanoacrylate is claimed to have an in vitro antimicrobial effect against gram-positive and gram-negative bac-

<table>
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<tr>
<th>Isolates</th>
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<th>Channel</th>
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<tr>
<td>Gram-positive bacteria</td>
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*Five patients had more than one set of positive blood cultures.
†Eight needle tip cultures produced more than one type of bacteria.
‡Eleven accessory channel cultures produced more than one type of bacteria.
teria. However, the frequency and clinical outcome of bacteremia in patients with gastric variceal bleeding who undergo endoscopic cyanoacrylate injections have never been assessed. Therefore, it is important to determine whether endoscopic injection of cyanoacrylate for gastric variceal bleeding limits the spread of bacteria, that is, whether there is an in vivo bacteriostatic effect. Because many patients with cirrhosis and upper GI bleeding may have occult infection, patients with leukocytosis or high fever before endoscopy were excluded. Only 1 patient in the control group had bacteremia. This result is comparable with the rate of bacteremia after upper endoscopy in most studies. Although half of the patients in the control group had epinephrine injections for peptic ulcer bleeding, the frequency of bacteremia was low. In contrast, transient bacteremia occurred in 30% of patients undergoing cyanoacrylate injection. This rate is comparable with that for endoscopic injection sclerotherapy, which ranges from 0% to 50%. This evidence is against the hypothesis that cyanoacrylate limits the spread of bacteria and has an in vivo bacteriostatic effect. However, it might be possible that bacteria escaped immediately into the blood stream before the polymerization of the cyanoacrylate.

Most of the strains of bacteria cultured from blood were identical to those obtained from the needle injector and accessory channel. This indicates that the injector needle, which is contaminated when introduced by means of the accessory channel, is the potential source of bacteremia after endoscopic injection with cyanoacrylate. Indeed, oral-pharyngeal contamination, the accessory channel, and a contaminated water supply are assumed to be the sources of infection associated with endoscopic injection sclerotherapy. The occurrence of bacteremia has been related to the length of the injection needle, but this was not evaluated in the present study.

The volume of blood transfused and Child-Pugh score were found to be risk factors associated with the occurrence of bacteremia; 1 patient with Child-Pugh C hepatic reserve died of sepsis. This is reasonable because patients with poor hepatic reserve have impaired reticuloendothelial and immune function. Severe hemorrhage also results in immunosuppression and increases the susceptibility to sepsis. These findings suggest that prophylactic administration of antibiotics may be required when performing endoscopic cyanoacrylate injection for gastric variceal bleeding in selected patients with advanced liver disease and severe hemorrhage.

It is difficult to keep the injection needle uncontaminated by the contents of the accessory channel, particularly in the emergency situation in which it is necessary to insert the injector again and again, and there is reflux of contaminated fluid or blood into the accessory channel. Use of a needle injector with a covered tip has been suggested as a way to decrease the frequency of bacteremia. However, this approach requires further study and verification.

In conclusion, an antimicrobial effect of cyanoacrylate was not observed in patients undergoing endoscopic injection with cyanoacrylate for gastric variceal bleeding. About 30% of these patients had transient bacteremia. Patients with advanced liver disease and severe hemorrhage are more prone to bacteremia. The accessory channel of the endoscope was the major source of bacteria. For patients with poor hepatic reserve and severe blood loss, the cost and benefit of the prophylactic use of antibiotics should be evaluated in a future trial.

REFERENCES


