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Revised abstract

Background: Gastric variceal bleeding is associated with a high mortality rate, and sclerotherapy using N-butyl-2-cyanoacrylate is the treatment of choice. The risk of recurrent bacteremia after N-butyl-2-cyanoacrylate injection has rarely been reported. We aimed to evaluate the frequency of this complication following injection of N-butyl-2-cyanoacrylate in a real-world setting.

Methods: We analyzed retrospective data from a single-center cohort of patients with liver cirrhosis who underwent N-butyl-2-cyanoacrylate injection for the treatment of bleeding gastric varices from January 2010 to March 2021. Recurrent bacteremia was defined as repeated bacteremia caused by the same microorganism after the resolution of the first event occurring at least two weeks from the date of the final positive blood culture of the first event.

Results: A total of 232 patients receiving 338 sessions of N-butyl-2-cyanoacrylate injection were enrolled. For the purpose of this study, we excluded patients (n=39) with a follow-up duration of less than 3 weeks. We included 193 patients with liver cirrhosis and gastric variceal bleeding who received 298 sessions of N-butyl-2-cyanoacrylate injection and were followed up for ≥21 days. All patients received antibiotics prophylaxis; third-generation cephalosporins were used. The average age of patients was 60.0 ± 12.3 years and the mean Model for End-Stage Liver Disease (MELD) score was 13.5 ± 5.4. Of the patients following cyanoacrylate injection, 60 patients developed primary bacteremia at a median of 323 (interquartile range, 66–932) days from N-butyl-2-cyanoacrylate injection. Nine out of 60 patients developed recurrent bacteremia following sclerotherapy with N-butyl-2-cyanoacrylate. The identified organisms were: Extended-Spectrum β-Lactamase (ESBL)-producing *Escherichia coli* (3), ESBL-producing *Klebsiella pneumoniae* (2), non-ESBL-producing *Klebsiella pneumoniae* (2), *Pseudomonas aeruginosa* (1), and *Methicillin-resistant Staphylococcus aureus* (1). The median number of episodes of recurrent bacteremia per patient was 2 (range, 2–5) during the median 972 (range, 78–1997) days of follow-up. Four of these nine recurrent bacteremia patients died.

Conclusion: Recurrent bacteremia occurred in 4.7% of cirrhotic patients following cyanoacrylate injection for the treatment of gastric variceal bleeding. Foreign-body-type infection of the polymerized N-butyl-2-cyanoacrylate should be suspected in patients who had received previous endoscopic treatment with N-2-butyl-cyanoacrylate and fails to disclose another source of infection.

Background

- Gastric variceal bleeding is a serious complication of liver cirrhosis
- Endoscopic injection with N-butyl-2-cyanoacrylate is used worldwide for the treatment of acute gastric variceal bleeding
- Oral-pharyngeal contamination, the accessory channel, and a contaminated water supply are assumed to be the sources of infection associated with endoscopic injection sclerotherapy
- N-butyl-2-cyanoacrylate (NBC; Histoacryl):
 - Polymerizes from liquid glue to a plastic cast on contact with blood in the varix
 - Forms polymers within seconds, thus rendering hematogenous spread less likely
 - In vitro antibacterial properties → cyanoacrylate injection might limit bacterial invasion and reduce the frequency of bacteremia?
- Patients with active and recent bleeding may be susceptible to bacterial invasion through a defective variceal wall
- The foreign body of a glue plug offers an ideal surface for bacterial colonization which becomes a reservoir for continuous bacterial dissemination
- 30% of patients who underwent GVO had transient bacteremia and most infections were self-limited
- Recurrent or apparent bacteremia is rarely reported

Methods

- Study design and hospital setting**
 - Retrospective, single center chart review study
 - Study period: January 2010 to March 2021
- Inclusion criteria**
 - Liver cirrhosis who underwent endoscopic N-butyl-2-cyanoacrylate (Histoacryl®) injection for the treatment of bleeding gastric varices
 - N=232
- Exclusion criteria**
 - Patients (n=39) with a follow-up duration of less than 3 weeks from N-butyl-2-cyanoacrylate injection
 - Patients with a documented bacterial infection on the day of varix bleeding
- Outcome definitions**
 - Primary bacteremia was defined as positive blood cultures without another associated infection and clinical signs of infection after N-butyl-2-cyanoacrylate injection
 - Common skin contaminants (*diphtheroids*, *Bacillus spp.*, *Propionibacterium spp.*, coagulase-negative *Staphylococci*, *Aerococcus spp.*, *Micrococcus spp.*) were counted as contaminants unless blood cultures were positive on two separate occasions or if there were clinical signs of infection
 - Recurrent bacteremia was defined as a subsequent episode of bacteremia after the resolution of the first episode occurring ≥14 days from the last date of the positive blood culture of the first event
 - Persistent bacteremia was defined as at least 5 days of positive blood cultures after implementation of appropriate treatment
 - Multidrug-resistant infections were classified as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus*, vancomycin-resistant *Enterococci*, extended-spectrum β-lactamase (ESBL) producing Gram-negative bacilli, and Gram-negative bacilli that are resistant to multiple classes of antimicrobial agents

Results

Table 1. Baseline characteristics

Variable	All patients (n=193)	Primary bacteremia (n=60)	No primary bacteremia (n=123)	P value
Age (years)	60.0 ± 12.3	59.6 ± 11.3	60.1 ± 12.7	0.78
Male, n (%)	146 (75.6%)	47 (78.3%)	99 (74.4%)	0.69
Etiology of liver disease				
HBV	38 (19.7%)	9 (15.0%)	29 (21.8%)	0.22
Alcoholic	110 (57.0%)	33 (55.0%)	77 (57.9%)	
HBV+Alcoholic	8(4.1%)	2 (3.3%)	6 (4.5%)	
HCV	14 (7.3%)	8 (13.3%)	6 (4.5%)	
Unknown	23 (11.9%)	8 (13.3%)	15 (11.3%)	
Presence of hepatocellular carcinoma	47 (24.4%)	17 (28.3%)	30 (22.6%)	0.49
Child-Pugh classification				
A	68 (35.2%)	19 (31.7%)	49 (36.8%)	0.72
B	98(50.8.0%)	33 (55.0%)	65 (48.9%)	
C	27(14.0%)	8 (13.3%)	19 (14.3%)	
MELD	13.5 ± 5.4	13.7 ± 5.3	13.4 ± 5.4	0.70
WBC count (x10 ⁹ /L)	8.4 ± 4.6	8.7 ± 5.0	8.2 ± 4.4	0.48
Hemoglobin (g/dL)	8.8 ± 2.1	8.9 ± 1.9	8.8 ± 2.3	0.92
Platelet count (x10 ⁹ /L)	100.2 ± 57.8	95.8 ± 60.9	102.3 ± 56.5	0.47
Albumin (g/dL)	2.8 ± 0.6	2.9 ± 0.5	2.8 ± 0.6	0.90
Bilirubin (mg/dL)	2.4 ± 2.8	2.3 ± 2.3	2.3 ± 2.7	0.909
Prothrombin time (INR)	1.5 ± 0.5	1.4 ± 0.3	1.5 ± 0.5	0.75
Creatinine (mg/dL)	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	0.64
Sodium (mEq/L)	139.2 ± 4.0	139.5 ± 4.5	139.3 ± 4.2	0.56
Systolic BP (mmHg)	110.1 ± 22.5	111.2 ± 21.4	109.6 ± 23.0	0.66
Mean injection volume (cc)	1.8 ± 0.8	1.9 ± 1.1	1.7 ± 0.7	0.18
Mean follow-up duration (days)	912.1 ± 904.5	943.3 ± 890.4	898.0 ± 913.8	0.75

Data are presented as mean±SD or number (%)
MELD, Model for end-stage liver disease; BP, blood pressure

Table 2. Characteristics of nine patients with recurrent bacteremia after endoscopic injection of N-butyl-2 cyanoacrylate for bleeding gastric varices

Patient No.	1	2	3	4	5	6	7	8	9
Age/sex	F/38	53/M	65/M	60/M	45/M	48/M	83/F	71/M	31/M
Cultured organisms	<i>E. coli</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>K. pneumoniae</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>K. pneumoniae</i>	<i>S. aureus</i>
Microbiological characteristics	ESBL	ESBL	ESBL	ESBL	ESBL	Cefotaxime-sensitive	Ceftazidime-sensitive	Cefotaxime-sensitive	Methicillin-resistant
Episodes of bacteremia meeting study ² criteria		2	5	2	3	3	2	2	4
Relapse/Reinfection	Relapse	Relapse	Relapse	Relapse	Relapse	Relapse	Reinfection	Relapse	Relapse
Interval (days)	68	10	43	17	17	47	121	25	25
No. of endoscopic injection	2	1	2	3	4	3	1	3	2
Amount of injected N-butyl-2 Cyanoacrylate	2.5	1.5	1.5	3.5	2	2.5	2.5	1	1.5
Other underlying condition	DM	DM	DM, Pul TB	DM, IPF	DM	DM, HCC	DM, HCC	DM, HCC	HCC
Prognosis	Death	Death	Death	LT	Alive	Death	Transfer to LTCF	Transfer to LTCF	LT

The interval is the period between the first bacteremia episode and endoscopic injection of N-butyl-2 cyanoacrylate.
The amount of injected N-butyl-2 cyanoacrylate is used for the first endoscopic hemostasis.
DM, diabetes mellitus; TB, tuberculosis; HCC, hepatocellular carcinoma; LTCF, long-term care facility; LT, Liver transplantation; Pul TB, pulmonary tuberculosis; IPF, idiopathic pulmonary fibrosis; ESBL, extended-spectrum β-lactamase
In patient 52, *Klebsiella pneumoniae* caused recurrent bacteremia, and then anaerobic GPC, GPB, and *Enterococcus faecalis* were identified.

- 89 isolates were cultured from 60 patients with primary bacteremia after N-butyl-2-cyanoacrylate injection
- 46 episodes of gram-positive blood stream infection
 - coagulase-negative staphylococci (26.1%), species of *Streptococcus* (19.6%), *Enterococcus faecium* (17.4%), *Staphylococcus aureus* (13.0%), other *Enterococcus* species (10.9%), and other microorganisms (6.5%)
- 43 episodes of gram-negative blood stream infection
 - Escherichia coli* (44.2%), *Klebsiella pneumoniae* (32.6%), *Enterobacter cloacae* (4.7%), *Pseudomonas aeruginosa* (4.7%), and other species (14.0%).

Conclusion

Recurrent bacteremia occurred in 4.7% of cirrhotic patients following cyanoacrylate injection for the treatment of gastric variceal bleeding. Foreign-body-type infection of the polymerized N-butyl-2-cyanoacrylate should be suspected in patients who had received previous endoscopic treatment with N-2-butyl-cyanoacrylate and fails to disclose another source of infection.