Risk of rebleeding from gastroesophageal varices after initial treatment with cyanoacrylate: a systematic review and pooled analysis.

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Abstract
Background Cyanoacrylate alone or in combination with other interventions, can be used to achieve variable rates of successes in preventing rebleeding. Our study aims to assess the pooled risk of gastric and esophageal varices rebleeding after an initial treatment with cyanoacrylate alone and/or in combination with other treatments, by systematic review of literature and pooled analysis.

Methodology PubMed, EMBASE, SCOPUS and the Cochrane library were searched for studies that reported the risk of rebleeding during the follow-up period after treatment of gastric or esophageal varices with either cyanoacrylate alone or in combination with other treatments. Standard error, upper and lower confidence intervals at 95% confidence interval for the risk, were obtained STATA Version 15 which was also used to generate forest plots for pooled analysis. Random or fixed effect model was used depending on the heterogeneity (I2).

Results A total of 39 studies were found to report treatment of either gastric or esophageal varices with either cyanoacrylate alone or in combination with other treatments. When gastric varices are treated with cyanoacrylate alone, the risk of rebleeding during the follow-up period is 0.16(Confidence Interval: 0.13-0.18). When combined with lipiodol; polidocanol or sclerotherapy the rebleeding risks are 0.13 (CI:0.03-0.22), 0.10(CI:0.02-0.19) and 0.10(CI:0.05-0.18), respectively. When combined with percutaneous transhepatic variceal embolization; percutaneous transhepatic variceal embolization; endoscopic ultrasound guided coils; or with ethanolamine, the rebleeding risk are 0.10(CI:0.03-0.17), 0.10(CI:0.03-0.17), 0.07(CI:0.03-0.11) and 0.08(CI:0.02-0.14), respectively. When esophageal varices are treated with cyanoacrylate alone, the risk of rebleeding is 0.29(CI:0.11-0.47). When combined with percutaneous transhepatic variceal embolization; sclerotherapy; or band ligation, the risks of rebleeding are 0.16(CI:0.10-0.22), 0.12(CI:0.04-0.20) and 0.10(CI:0.04-0.24), respectively. When combined with transjugular intrahepatic portosystemic shunt; or ethanolamine, the risks of rebleeding are 0.06(CI:-0.01-0.12) and 0.02 (CI:-0.02-0.05), respectively.

Conclusion In treating both gastric and esophageal varices, cyanoacrylate produces better results in terms of lower risk of rebleeding when combined with other treatments than when used alone. The combination of cyanoacrylate with ethanolamine or with endoscopic ultrasound guided coils produces lowest risk of rebleeding in esophageal and gastric varices, respectively. We call upon randomized trials to test these hypotheses.

Introduction
Liver cirrhosis is the leading cause of portal hypertension which in turn, leads to portal hypertension and gastrointestinal varices. Up to 17% of liver cirrhosis patients will develop esophageal varices, while 15% will develop gastric varices. Up to 30% gastroesophageal varices will bleed within 2 years (1). Bleeding from varices is one among gastrointestinal emergencies that account for majority of mortalities and morbidities among portal hypertension patients despite the cause (2). About 50–80% of patients who survive the first episode of variceal hemorrhage will have a recurrent early or late rebleeding episode (3). Up to 20% of patients with rebleeding a episodes will not survive (4).

From an older literature, half of variceal hemorrhages would stop spontaneously however, the risk of rebleeding and mortality increases significantly (5). Current studies, however, report that, in patients with cirrhosis Child-Pugh of class C or with hepatic venous pressure of higher than 20millimeters of mercury are less likely to spontaneous stoppage of bleeding. These patients would require interventional hemostatic measures with pharmacological drugs such as octreotide, somatostatin and beta blockers; endoscopic sclerotherapy, band ligation or tissue adhesives injection; and/or shunting by surgery or by transjugular intrahepatic portosystemic shunt to achieve hemostasis. A selective combination of these approaches has also been reported (1). Different hemostatic approaches differ in terms of their success rates in achieving hemostasis, preventing rebleeding and reducing mortality and morbidity. With advancing technology, each approach has evolved, and tissue adhesives have increasingly being used as the first line of therapy during the last decades (6, 7).
Also known as “tissue glue“, tissue adhesives were approved by the United States of America’s Food and Drug Authority in 1998, however, there have been previous studies reporting their use as back as the year 1981 (8). Primarily containing n-butyl-2 cyanoacrylate or 2-octyl cyanoacrylate, tissue adhesives are liquid monomers that undergo chemical reactions upon contact with moisture, to form polymers that can strongly attach to tissue (9). Despite a number of reported complications associated with their use such as embolism and needle impaction (10), cyanoacrylate has been reported to have higher hemostasis and lower rebleeding rates than traditional band ligation and sclerotherapy in gastroesophageal varices (2). Moreover, they have been reported to have antibiotic activity towards gram-positive bacteria (11).

Cyanoacrylate can be used alone or in combination with other interventions, to achieve variable rates of successes in hemostasis, reducing mortality and prevention of rebleeding. Our study was aimed at assessing the overall risk of gastroesophageal rebleeding after an initial treatment with cyanoacrylate alone and/or in combination with other treatments, by systematic review of literature and pooled analysis.

**Methods**

**Eligibility criteria**

The current study involved participants with bleeding gastroesophageal varices who underwent hemostasis by cyanoacrylate injection alone or in combination with other treatments. Observational and interventional studies reporting the risk of rebleeding after hemostasis treatment were included. Expanding the external validity, eligible English published literature from across the world were included.

**Information sources**

Four online databases, namely PubMed, EMBASE, SOPUS and the Cochrane library were systematically searched with no time range specified. Secondary referencing of eligible studies extended the search scope. The last search was conducted on 4th March 2020.

**The search**

Advanced search tool employing MeSH and keywords, was utilized in all three online databases. Using PubMed, advanced search was done as; (((((cyanoacrylate[MeSH Terms]) AND endoscopic hemostasis[MeSH Terms]) AND esophageal varices[MeSH Terms]) OR gastric varices[MeSH Terms])) AND reble*. The search was repeated as; (((adhes*) AND endosc*) AND varic*) AND reble*. The searches were independently performed by two authors; ZH and JS. Results were exported to EndNote X9 (Build 12062) which kept track of references.

**Study selection process**

Two authors screened titles and abstracts of all articles from online database searches to identify the most relevant articles in line with our study question. The relevant articles were sought for full texts and final included studies were identified after thorough reading full text articles to assess inclusion and exclusion criteria. This process was done by two authors; ZH and JS with the third author, TL assisting to resolve discrepancies. The search, screening and study identification process is summarized in Figure 1.

**Data extraction**

Before data extraction process from full-text articles meting eligibility criteria for inclusion, assessment for methodological biases was done by using the Joanna Briggs institute meta-analysis of statistics assessment and review instrument. PRISMA (12)(preferred reporting items for systematic reviews and meta-analyses) tool was used to minimize reporting bias upon write-up of this study.
Data collected included Author name, year of publication, country of study, study design, what comparison groups involved, varicose lesion location, study sample size, definitive diagnoses, number/ proportion of rebleeding events among followed up patients, the name of tissue adhesive utilized and follow-up duration. This was independently performed by two authors, namely; ZH and DZ with SL to resolve discrepancies. The current study had on outcome, the risk of rebleeding.

**Analysis**

The risk of rebleeding among gastric and esophageal varices patients were analyzed separately. Moreover, the risk of rebleeding in gastric or esophageal varices groups were analyzed separately depending on whether the cyanoacrylate was utilized alone or in combination with other treatments. This gave rise to five separate analyses on which quantitative analysis was conducted: (1) Analyzing pooled risk of rebleeding in gastric varices treated with cyanoacrylate alone; (2) analyzing pooled risk of rebleeding in esophageal varices treated with cyanoacrylate alone; (3) analyzing pooled risk of rebleeding in gastric varices treated with cyanoacrylate with ethanolamine; (4) analyzing pooled risk of rebleeding in gastric varices treated with cyanoacrylate with endoscopic ultrasound guided coils; and (5) analyzing a pooled risk of rebleeding in esophageal varices treated with cyanoacrylate with percutaneous transhepatic variceal embolization. A qualitative narrative (i.e. descriptive) approach was utilized in assessing the risk of rebleeding in gastroesophageal varices treated with cyanoacrylate with sclerotherapy as the eligible studies involved different participants.

The risk of rebleeding was calculated dividing the number of patients rebleeding during the follow-up period after endoscopic hemostasis by the total number of patients that initially underwent the endoscopic hemostasis procedure. The denominator did not include patients lost during the follow up. Standard error, upper and lower confidence intervals (at 95% confidence interval) for the risk, were obtained from the “generate command” in computer software *STATA Version 15* which was also used to generate forest plots for pooled analysis. The software was customized to random or fixed effect model depending on the heterogeneity ($I^2$) of the studies when analyzing the outcomes. Fixed effect model was used when $I^2$ was less than 50% and random effect model was used when $I^2$ was more than 50% indicating significant heterogeneity.

**Assumptions**

Participants were considered to have been correctly diagnosed with upper gastrointestinal bleeding due to gastric or esophageal varices, and not due to other causes such as Mallory-Weiss tear or gastritis. Despite the country under which treatment was given, all patients were considered to have received standard care.

**Results**

A total of sixty (60) studies that seemed to be relevant to our study basing on screening titles and abstract, were sought for full texts. Five of these were eliminated after thorough full-text reading. *Webb et al (1981)*(8) did not report our outcome of interest; *Datta et al. (2003)*(13) and *Smith et al. (2014)*(14) utilized fibrin glue; *Noh et al. (2004)*(15) and *Zhang et al. (2007)* (16) used Korean and Chinese language, respectively. A total of 55 studies were included in the systematic review while 39 studies were pooled for statistical analysis.

**Characteristics of included studies**

*Table 1* illustrates characteristics of all included studies in our pooled analysis. These were published between the year 1989 and 2019 from countries in Africa, Europe, Asia, and North America. Eleven studies were retrospective observational; sixteen were prospective observational; two were case series; and ten were randomized clinical trials. Thirteen studies were comparative, one arm of which was cyanoacrylate. Eleven studies were non-comparative involving only cyanoacrylate outcome assessment while of the two studies, one involved comparing different doses of cyanoacrylate (i.e. 0.5mls versus 1.0mls) while another compared diluted versus undiluted cyanoacrylate. Follow-up duration after treatment with cyanoacrylate ranged from six weeks to fifteen years in another study. One study did not report duration of follow-up.
A total of 39 studies reported 3630 who had either gastric or esophageal variceal and underwent hemostasis with cyanoacrylate alone or in combination with other treatments. A total of 497 had gastric or esophageal recurrent bleeding episodes during the follow-up period.

Table 1. Study characteristics
| Author     | Country of study | Study design          | Comparison groups | Lesion location (Sample size) | Diagnoses                                      | Participants rebleed | Type of tissue adhesive utilized | Follow-up duration |
|------------|------------------|-----------------------|-------------------|-----------------------------|-----------------------------------------------|----------------------|----------------------------------|-------------------|
| Ramond     | France           | Case series           | butyl cyanoacrylate versus Sclerosant | Gastric 27                  | Cirrhosis; Portal vein thrombosis             | 10 out of 27 followed up | butyl cyanoacrylate             | 1-38 Months (Mean: 14.7 ±11.0) |
| Oho        | Japan            | Randomized trial      | ethanolamine oleate (n = 24) or butyl cyanoacrylate (n = 29) | Gastric                      | Gastric varices                                | 9 out of 29 in the cyanoacrylate group | cyanoacrylate       | 14 months                      |
| D’Imperio  | Italy            | Prospective trial     | N-butyl-2-cyanoacrylate       | Esophageal 24; Gastric 54; Duodenal 2 | Upper gastrointestinal tract varices           | 2 from gastric varices; 0 from duodenal varices; Esophageal not reported | N-butyl-2-cyanoacrylate | 6 Months                       |
| Omar       | Egypt            | Prospective trial     | Polidocanol, Ethanolamine, Cyanoacrylate | Esophageal 60                  | Schistosoma hepatic fibrosis                   | 0                    | Cyanoacrylate                   | Not accessed       |
| Kind       | Italy            | Retrospective         | One arm study: Bucrylate | Gastric 174                  | Gastric varices                                | 27 (Occurred during the first 30 days) | Bucrylate           | 12 years                        |
| Evrad      | Belgium          | Retrospective         | N-butyl-2-cyanoacrylate versus Proprenolol | Esophageal 16; Gastric 5       | Esophagogastric varices                        | Esophageal 4; Gastric 2 | N-butyl-2-cyanoacrylate         | 6 weeks            |
| Noophun    | Thailand         | Prospective           | One arm study: cyanocrylate | Gastric 24                    | Gastric varices                                | 10                   | N-butyl-2-cyanoacrylate         | Minimum of 4 weeks  |
| Tan        | Taiwan           | Prospective           | Band ligation Versus N-butyl-2-cyanoacrylate | 49                            | Liver cirrhosis                                | 11                   | N-butyl-2-cyanoacrylate         | 680.67 ±710.54 days |
| Cheng      | China            | Retrospective         | One arm study: N-            | Gastric 635                   | Gastric varices                                | 44 out of 550 followed up | N-butyl-2-cyanoacrylate         | Up to 10 years     |
| Author | Country | Study Type | Intervention | Location | Outcome | Follow-up |
|--------|---------|------------|--------------|----------|---------|-----------|
| Kuo 2007(26) | China | Randomized trial | Histoacryl versus Histoacryl + hypertonic glucose solution | Gastric 67 | Gastric varices | 2 out of 34 who received Histoacryl alone | N-butyl-2-cyanoacrylate 37.9 ±18.5 months |
| Hong 2009(27) | Korea | Randomized trial | Endoscopic N-butyl-2-cyanoacrylate injection versus balloon-occluded retrograde transvenous obliteration | Gastric 27 | Gastric variceal hemorrhage | 10 out of 14 in the N-butyl-2-cyanoacrylate group | N-butyl-2-cyanoacrylate Up to 17 Months |
| Hou 2009(28) | Taiwan | Randomized trial | 0.5 mL Versus 1.0 mL of cyanoacrylate | Gastric 44 | Gastric variceal hemorrhage | 14 out of 47 in the 0.5mls group; 17 out of 44 in the 1ml group | N-butyl-2-cyanoacrylate Up to two years |
| Procaccini 2009(29) | USA | Retrospective | Cyanoacrylate versus TIPS | Gastric 105 | Gastric variceal hemorrhage | 13 out of 61 in the Cyanoacryl group (4/58 at 72hrs; 5/47 at 3 months; 4/40 at 1year) | Cyanoacrylate Up to one year |
| Rivet 2009(30) | France | Prospective | Cyanoacrylate versus Band ligation | Esophageal 8 | Portal hypertension due to portal vein thrombosis, biliary atresia and antitrypsin deficiency | 3 out of 8 in the cyanoacrylate group | Cyanoacrylate 12.5 10.6 weeks |
| Cheng 2010(31) | China | Retrospective | Butyl cyanoacrylate | Gastric varices 753 | Gastric varices due to viral | 33 | Butyl cyanoacrylate Up to 6 months after |
| Choudhuri 2010(32) | India | Prospective | N-butyl-2-cyanoacrylate | Gastric varices 170 | Gastric variceal hemorrhage | 23 out of 158 that were followed-up | N-butyl-2-cyanoacrylate | 30.7 + 17.2 months |
|------------------|------|-------------|-------------------------|-------------------|-----------------------------|-------------------------------------|-------------------------|-------------------|
| Mishra 2010(33)  | India | Prospective | Cyanoacrylate versus beta blocker | Gastric 33; Esophageal 26 | Gastric varices | 3 out of 33 | Cyanoacrylate | 26 Months |
| Soga 2010(34)    | Japan | Case report  | N-butyl-2-cyanoacrylate | Gastric 1; Duodenal 1 | Gastroduodenal varices | No rebleeding recorded | N-butyl-2-cyanoacrylate | 53 days |
| Binmoellar 2011(35) | USA | Retrospective | N-butyl-2-cyanoacrylate | Gastric 30 (24 variceal; 6 non variceal) | Gastric varices; Non variceal lesion | No bleeding recorded from 24 variceal group | N-butyl-2-cyanoacrylate | 193 (24-589) days |
| Kang 2011(36)    | Korea | Retrospective | N-butyl-2-cyanoacrylate | Gastric varices 127 | Gastric varices | 29 out of 127 | N-butyl-2-cyanoacrylate | One year |
| Liao 2013(37)    | Taiwan | Prospective | Cyanoacrylate | Gastric varices 69 | Gastric varices | 10 out of 69 | Cyanoacrylate | More than 30 months |
| Tantau 2013(38)  | Romania | Prospective | Cyanoacrylate versus Band ligation | Gastric 37 | Gastric varices | 6 out of 19 in the Cyanoacrylate group | Cyanoacrylate | 27.26 ± 214.16 days |
| Al-Bawardy 2016(39) | USA | Retrospective | 2-octyl cyanoacrylate | Gastric 95 | Gastric Variceal Hemorrhage | 8 out of 95 | 2-octyl cyanoacrylate | Up to 15 years |
| Singh 2016(10)   | India | Prospective | Diluted versus undiluted Cyanoacrylate | Gastric 30 | Gastric Variceal Hemorrhage | 5 out of 30 | Cyanoacrylate | Up to one year |
| Liu 2019(40)     | China | Prospective | Cyanoacrylate with Versus without antibiotic | Gastric varices 107 | Gastric varices | 106 out of 107 | Cyanoacrylate | 4.59 ± 1.63; 4.30 ± 1.48 Days |
| Xiaoqing 2019(2) | China | Prospective | Cyanoacrylate versus Cyanoacrylate | Gastric varices 130 | Gastric varices | 8 out of 62 in the Cyanoacrylate | Cyanoacrylate | 38.8 months for |
| Author   | Country | Study Type   | Intervention                                                                 | Main Outcomes                                                                                         | Control Group                                                                                     | Duration |
|----------|---------|--------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|----------|
| Thakeb   | Egypt   | Randomized trial | N-butyl-2-cyanoacrylate plus ethanolamine oleate 5% versus ethanolamine alone | Gastric varices 57; Esophageal varices 59                                                              | 3 out of 57 gastric varices; 1 out of 59 esophageal varices.                                      | Up to 32 months |
| Maruyama | Japan   | Retrospective | Cyanoacrylate plus ethanolamine                                               | Gastric varices 20                                                                                   | 10 out of 20 gastric varices                                                                    | Cyanoacrylate 28.1 months |
| Bhat     | United States of America | Retrospective | Cyanoacrylate and coils guided by endoscopic ultrasound                       | Gastric varices 125                                                                                 | 10 out of 125 gastric varices                                                                   | Cyanoacrylate Median: 436 days; |
| Robles-Medranda | Ecuador | Prospective | Cyanoacrylate and coils guided by endoscopic ultrasound                       | Gastric varices 30                                                                                   | 1 out of 27 gastric varices patients followed up                                                | Cyanoacrylate Up to 12 months |
| Zhang    | China   | Randomized trial | Cyanoacrylate with percutaneous transhepatic variceal embolization           | Esophageal varices 92                                                                               | 14 out of 86 esophageal varices patients followed up                                            | Cyanoacrylate Mean: 31.5 months |
| Zhang    | China   | Randomized trial | Cyanoacrylate with percutaneous transhepatic variceal embolization           | Esophageal varices 52                                                                               | 8 out of 52 esophageal varices patients followed up                                             | Cyanoacrylate Median: 25 months |
| Tian     | China   | Prospective  | Cyanoacrylate with percutaneous transhepatic                                 | Gastric varices 71                                                                                  | 7 out of 71 gastric varices                                                                     | Cyanoacrylate Mean: 24.2 ± 12.4 months |
| Study | Country | Study Design | Treatment | Control | Follow-up | Outcome |
|-------|---------|--------------|-----------|---------|-----------|---------|
| Feritis 1995(47) | Greece | Randomized trial | N-butyl-2-cyanoacrylate with sclerotherapy | Esophageal varices 126 | 8 out of 67 esophageal varices patients followed up | 30 days |
| Dhiman 2002(48) | India | Prospective | N-butyl-2-cyanoacrylate with sclerotherapy | Gastric varices 29 | 3 out of 29 esophageal varices patients followed up | Up to 6 months |
| Shi 2014(49) | China | Retrospective | Transjugular intrahepatic portosystemic shunt alone versus combined with Cyanoacrylate | Esophageal Variceal 53 | 3 out of 53 esophageal varices patients followed up | Cyanoacrylate 35.8 months |
| Ma 2018(50) | China | Prospective | Combined cyanoacrylate with balloon-occluded retrograde transvenous obliteration | Gastroesophageal varices 28 | 8 out of 26 cyanoacrylate | 90 days |
| Dai 2017(51) | China | Randomized trial | Band ligation alone versus in combination with cyanoacrylate | Gastroesophageal varices 97 | 7 out of 49 esophageal varices patients followed up | Cyanoacrylate 20 months |
| Zeng 2017(52) | China | Randomized trial | Cyanoacrylate plus Polidocanol versus cyanoacrylate plus lipiodol in | Gastric varices 96 | 11 out of 94 gastric varices patients followed up | Cyanoacrylate 6 months |
Pooled risk of rebleeding in gastric varices treated with cyanoacrylate alone

**Figure 2** illustrates a forest plot of pooled risk of rebleeding for gastric varices after cyanoacrylate treatment. A total of twenty-five studies reported 2590 gastric variceal patients, of whom 402 had had rebleeding after initial treatment with cyanoacrylate hemostasis. The risk ranged from the minimum of 0.04 (4%) to a maximum of 0.99 (99%) in another study. Two studies were excluded for not having rebleeding incidences during the follow up period. The pooled overall risk of rebleeding was 0.30 (confidence interval: 0.30-0.31).

There was a significant heterogeneity observed with $I^2$ of 99.7%, p-Value<0.05. This led us to conduct sensitivity analysis, eliminating peculiar studies from the analysis. **Figure 3** illustrates a sensitivity analysis forest plot of pooled risk of rebleeding for gastric varices after elimination of peculiar studies. Ramond et al (1989)(17) and Soga et al (2010)(34) were case series and case report respectively; D’Imperio et al. (1996)(19), Omar et al. (1998)(20), Noophun et al. (2005)(23), Rivet et al (2009)(30), Cheng et al (2010)(31), Binmoeller et al (2011)(35) and Tantau et al. (2013)(38) had less than one-year of follow-up; while Kind et al. (2000)(21), Tan et al. (2006)(24), Procaccini et al. (2009)(29), Choudhuri et al. (2010)(32), Mishra et al. (2010)(33), Liao et al. (2013)(37), Singh et al. (2016)(10), Cheng et al. (2007)(25), Kuo et al (2007)(26), Huo et al. (2009)(28), Kang et al. (2011)(36), Al-Baward et al. (2016)(39) and Xiaoqing et al. (2019)(2) were excluded by meta-regression. Evrad et al. (2003)(22), Hong et al. (2009)(27), Soga et al. (2010)(34) and Liu et al. (2019)(40) were excluded because their findings did not fulfill normality test criteria for calculation of confidence interval (i.e.N(1-Pe) ≥ 10). The resulting overall pooled risk was 0.16 (Confidence interval: 1.13-0.18) with no significant heterogeneity (i.e. $I^2=0.0\%$, p-Value=0.619).

Pooled risk of rebleeding in esophageal varices treated with cyanoacrylate alone

**Figure 4** illustrates a forest plot of pooled risk of rebleeding for esophageal varices after cyanoacrylate treatment. A total of five studies reported 134 esophageal variceal patients, 7 of whom had had rebleeding after initial treatment with cyanoacrylate hemostasis. The risk of rebleeding ranged from the minimum of 0.25 (25%) to a maximum of 0.38 (99%) in another study. Three studies were excluded for not having rebleeding incidences during the follow up period. The pooled overall risk of rebleeding was 0.29 (confidence interval: 0.11-0.47). There was no significant heterogeneity observed; $I^2$ of 0.0%, p-Value=0.537).

Pooled risk of rebleeding in gastric varices treated with cyanoacrylate with ethanolamine

Two studies illustrated treatment with a combination of cyanoacrylate and ethanolamine; Thakeeb et al. (1995)(41) and Maruyama et al. (2010)(42). Thakeeb reported 3 (i.e. risk= 0.052) rebleeding events among gastric variceal patients; and one (risk=0.017) rebleeding events among esophageal varices patients. Maruyama reported 10 (i.e. risk =0.5) rebleeding events among gastric varices patients. **Figure 5** illustrates a forest plot of pooled risk, 0.08(0.02-0.14) of rebleeding in gastric varices treated with a combination of cyanoacrylate with ethanolamine.

Pooled risk of rebleeding in gastric varices treated with cyanoacrylate with endoscopic ultrasound guided coils

Two studies illustrated treatment with a combination of cyanoacrylate and coils guided by endoscopic ultrasound; Bhat et al. (2016)(43) and Robles-medranda et al. (2019)(44). Bhat et al. (2016) reported 10 rebleeding events out of 125 gastric varices patients who were followed-up. This corresponds to the risk of 0.08 (Confidence interval: 0.03-0.13). Robles-medranda et al. (2019) reported 1 rebleeding event out of 27 gastric varices patients, which corresponds to the risk of 0.04(Confidence interval: -0.03-0.11). **Figure 6** illustrates a forest plot of pooled risk of rebleeding in gastric varices treated with cyanoacrylate with endoscopic ultrasound guided coils.
Pooled risk of rebleeding in esophageal varices treated with cyanoacrylate with percutaneous transhepatic variceal embolization

Three studies illustrated treatment with a combination of cyanoacrylate and percutaneous transhepatic variceal embolization in gastroesophageal varices; Zhang et al. (2007)(16) and Zhang et al. (2008)(45) involved esophageal varices patients, and reported rebleeding risks of 0.16 (confidence interval: 0.08-0.24) and 0.15 (confidence interval: 0.06-0.25), respectively. Tian et al. (2011)(46) involved gastric varices patients and reported rebleeding risk of 0.10 (confidence interval: 0.03-0.17). Figure 7 illustrates a forest plot of pooled risk of rebleeding in esophageal varices treated with cyanoacrylate with percutaneous transhepatic variceal embolization.

Risk of rebleeding in gastroesophageal varices treated with cyanoacrylate with sclerotherapy

Two studies assessed the efficacy of combination of cyanoacrylate and sclerotherapy in the treatment of gastroesophageal varices. In one study, Feretis et al. (1995)(47) compared the combination versus sclerotherapy alone in the treatment of esophageal varices and reported the risk for rebleeding in the combination group to be 0.12 (Confidence interval: 0.04-0.20). In another one arm study, Dhiman et al. (2002)(48) assessed the outcome of the combination therapy in the treatment of gastric varices and reported a risk of 0.10 (Confidence interval: 0.05-0.18). Forest plot was not constructed as the two studies involved different participants (i.e. gastric and esophageal varices).

Other combination treatments with cyanoacrylate

In their study Shi et al. (2014)(49) compared between transjugular intrahepatic portosystemic shunt alone versus combined with Cyanoacrylate for Esophageal Variceal Bleeding. The combination therapy reduced the rebleeding risk to a third of one observed in transjugular intrahepatic portosystemic shunt alone. That is from 0.19 to 0.06, p-Value of 0.04. In another study, Ma et al. (2018)(50) combined cyanoacrylate with balloon-occluded retrograde transvenous obliteration in 28 patients with gastroesophageal varices and reported a rebleeding risk of 0.31 (confidence interval: 0.13-0.49).

Dai et al. (2017)(51) compared band ligation alone versus in combination with cyanoacrylate in the treatment of gastroesophageal varices. The risk of rebleeding in the combination therapy was reduced to a quarter that recorded in band ligation alone. That is from 0.56 to 0.14, p-Value<0.01. Zeng et al. (2017)(52) compared two combinations; cyanoacrylate plus Polidocanol versus cyanoacrylate plus lipiodol in the treatment of gastric varices. The later showed the risk of rebleeding of 0.13 (Confidence Interval: 0.03-0.22) as compared to 0.10 (Confidence interval: 0.02-0.19) in the polidocanol combination.

Table 2 summarizes risks of rebleeding in gastric and esophageal varices when treated with cyanoacrylate alone or in combination with other treatments as discussed earlier.

Table 2 risks of rebleeding in gastric and esophageal varices when treated with cyanoacrylate alone or in combination with other treatments

Key: * Calculated from a single study (Not pooled); ** Gastric or esophageal varices not specified (Gastroesophageal)

Note: The values in the table are independently calculated and the table does not mean statistical comparison between them.

Discussion

Through decades-long progressive improvements in the treatment of gastroesophageal varices, cyanoacrylate has evolved to be one of favored first line of treatment. The current study was aimed at utilizing systematic review of literature and pooled analysis to assess the overall risk of gastroesophageal rebleeding after an initial treatment with cyanoacrylate alone and/or in combination with other treatments.
| Hemostasis treatment type                                      | Pooled risk of gastric varices rebleeding (Confidence interval) | Pooled risk of esophageal varices rebleeding (confidence interval) |
|---------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------|
| Cyanoacrylate alone                                          | 0.16 (0.13-0.18)                                                | 0.29 (0.11-0.47)                                               |
| Cyanoacrylate combined with ethanolamine                      | 0.08(0.02-0.14)                                                 | 0.02 (-0.02-0.05).                                            |
| Cyanoacrylate combined with endoscopic ultrasound guided coils | 0.07(0.03-0.11)                                                 | -                                                             |
| Cyanoacrylate combined with percutaneous transhepatic variceal embolization | 0.10(0.03-0.17) *                                               | 0.16(0.10-0.22)                                               |
| Cyanoacrylate combined with transjugular intrahepatic portosystemic shunt | -                                                             | 0.06(-0.01-0.12) *                                            |
| Cyanoacrylate combined with sclerotherapy                     | 0.10 (0.05-0.18) *                                              | 0.12 (0.04-0.20) *                                            |
| Cyanoacrylate combined with band ligation                      | 0.10(0.04-0.24) *                                               | 0.12(0.04-0.24) *                                              |
| Cyanoacrylate combined with polidocanol                        | 0.10 (0.02-0.19) *                                              | -                                                             |
| Cyanoacrylate combined with lipiodol                          | 0.13 (0.03-0.22) *                                              | -                                                             |
| Cyanoacrylate combined with balloon-occluded retrograde transvenous obliteration | -                                                             | 0.31 (0.13-0.49) **                                           |

Following treatment of gastric varices with cyanoacrylate alone, twenty-five studies demonstrated different risks of rebleeding from the minimum of 0.04 to a maximum of 0.99 in another study, with the overall pooled risk of 0.30 (confidence interval: 0.30–0.31). However, after getting rid of peculiar studies that increased heterogeneity, the resulting overall pooled risk was 0.16 (Confidence interval: 0.13–0.18). This risk of rebleeding coincides with that previously reported by Hou et al. (2009)(28) but differed from majority of other studies. Authors believe that the reason for the differences among studies to be technological advancement with time. This can be demonstrated majority of studies from the year 2010 forward having lower risk of rebleeding than studies before 2010. Different sample sizes and different study methodologies could also explain the differences.

Esophageal varices treated with cyanoacrylate alone showed the risk of rebleeding ranging from the 0.25 to 0.38 in different studies with the pooled overall risk of 0.29 (confidence interval: 0.11–0.47). Following a fewer number of studies, a meta regression could not be conducted. However, authors believe that the reason for the differences between studies to be due to different methodological approaches between the studies as Rivet et al. (2009)(30) followed up their patients for twice the duration used by Evrad et al. (2003)(22). Authors of this study hypothesize that; gastric varices respond better to cyanoacrylate as compared to esophageal varices in terms of lower risk of rebleeding. We call upon randomized clinical trials comparing the risk of rebleeding between gastric varices and esophageal varices treated with Cyanoacrylate alone.

When cyanoacrylate is combined with ethanolamine in the treatment of gastric varices the pooled risk of rebleeding after treatment is 0.08(Confidence interval: 0.02–0.14). The result aligns with that reported by Thakeb et al. (1995) but differs from Maruyama who reported higher risk of 0.5. The difference is accounted fewer sample size by Maruyama. On the other hand, when the combination is used to treat esophageal varices the risk of rebleeding is 0.017(confidence interval: -0.02-0.05). From an otherwise weak basis, we hypothesize that esophageal varices in contrast to gastric varices, respond better to the combination of cyanoacrylate and ethanolamine, in terms of lower risk of rebleeding. We call upon clinical randomized clinical trials to test this hypothesis.
From our findings, when cyanoacrylate is combined with endoscopic ultrasound guided coils to treat gastric varices the pooled risk of rebleeding is 0.07 (confidence interval: 0.03–0.11). This finding is more or less similar to that reported by Bhat et al. (2016)(43), but is higher than that reported by Robles-medranda et al. (2019)(44). The reason for the differences could be explained by different sample sizes among studies pooled. One study had nearly five times the sample size used by the other.

When esophageal varices are treated with a combination of cyanoacrylate and percutaneous transhepatic variceal embolization the pooled risk of rebleeding is 0.16 (confidence interval: 0.10–0.22). This is coinciding with findings previously reported by Zhang et al. (2007)(16). In another study by Tian et al. (2011)(46) when the combination is used to treat gastric varices, the risk of rebleeding is 0.10 (confidence interval: 0.03–0.17). We hypothesize that esophageal varices in contrast to gastric varices, respond better to the combination of cyanoacrylate and percutaneous transhepatic variceal embolization in terms of lower risk of rebleeding. Authors call upon randomized clinical trials to test this hypothesis.

The risk of rebleeding in gastric varices treated with cyanoacrylate with sclerotherapy was lower by 0.02 from that of esophageal varices treated with the same combination. The difference could partly be due to more or less same number of sample sizes among the two studies descriptively analyzed. In combination with other treatments such as transjugular intrahepatic portosystemic shunt and balloon-occluded retrograde transvenous obliteration, it is evident that, cyanoacrylate improves efficacy of the treatment of gastroesophageal varices in terms of lowering rebleeding risk.

**Study Limitation And Measures Taken**

Our study search was limited to English published literature; involved pooling of studies with different sample sizes, different study designs and different follow-up durations. These were thought to introduce heterogeneity in the pooled analysis. However, authors appraised eligible studies; performed sensitivity analyses, meta-regression and used random effect models to deal with high heterogeneity among pooled studies. We also utilized PRISMA tools to minimize reporting biases.

**Conclusion**

Conclusion: In treating both gastric and esophageal varices, cyanoacrylate produces better results in terms of lower risk of rebleeding when combined with other treatments than when used alone. The combination of cyanoacrylate with ethanolamine or with endoscopic ultrasound guided coils produces lowest risk of rebleeding in esophageal and gastric varices, respectively. We call upon randomized trials to test these hypotheses.

**Abbreviations**

PRISMA – preferred reporting items for systematic reviews and meta-analyses

MeSH – Medical Subject Headings

ZH - Zixuan Hu (Author)

DZ - Decai Zhang (Author)

JS - Joel Swai (Author)

TL - Tao Liu (Author)

SL - Shaojun Liu (Author)
Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: Authors declared no competing interests

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Author’s contributions: Study designing: JS; data search ZH, JS and TL; data extraction: ZH, DZ, and SL; data analysis and interpretation: JS and ZH; Manuscript drafting: JS; manuscript critical intellectual content revision: SL, TL and DZ. All authors read and approved the final version of the manuscript.

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**Figures**
Figure 1

PRISMA 2009 Flow Diagram
Figure 2

A forest plot of pooled risk of rebleeding for gastric varices after cyanoacrylate treatment.

Figure 3

A forest plot of pooled risk of rebleeding for gastric varices after cyanoacrylate treatment.
Forest plot after sensitivity analysis of pooled risk of rebleeding for gastric varices

| Study  | Year | Sample_size | Events | ES (95% CI) | Weight |
|--------|------|-------------|--------|-------------|--------|
| Evrad  | 2003 | 16          | 4      | 0.25 (0.04, 0.46) | 71.43  |
| Rivet  | 2009 | 8           | 3      | 0.38 (0.04, 0.71) | 28.57  |
| D'Imperio | 1996 | 24          | 0      | Excluded     | 0.00   |
| Omar   | 1998 | 60          | 0      | Excluded     | 0.00   |
| Mishra | 2010 | 26          | 0      | Excluded     | 0.00   |
| Overall |      |             |        | 0.29 (0.11, 0.47) | 100.00 |

Figure 4

A forest plot of pooled risk of rebleeding of esophageal varices after cyanoacrylate treatment.

| Study  | Year | Sample_size | Events | ES (95% CI) | Weight |
|--------|------|-------------|--------|-------------|--------|
| Thakeeb | 1995 | 58          | 3      | 0.05 (-0.01, 0.11) | 93.66  |
| Maruyama | 2010 | 20          | 10     | 0.50 (0.28, 0.72) | 6.34   |
| Overall |      |             |        | 0.08 (0.02, 0.14) | 100.00 |
Figure 5
Illustrates a forest plot of pooled risk of rebleeding in gastric varices treated with a combination of cyanoacrylate with ethanolamine.

![Forest plot for Figure 5]

Figure 6
A forest plot of pooled risk of rebleeding in gastric varices treated with cyanoacrylate with endoscopic ultrasound guided coils.

![Forest plot for Figure 6]
Figure 7

Illustrates a forest plot of pooled risk of rebleeding in esophageal varices treated with cyanoacrylate with percutaneous transhepatic variceal embolization.