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## **The Role of Endoscopic Ultrasound in Non-variceal Upper Gastrointestinal Bleeding Management**

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### **Abstract**

Non-variceal upper gastrointestinal bleeding (NVUGIB) is one of the challenging situations in clinical practice. Despite gastric ulcer and duodenal ulcer are still the main cause of acute NVUGIB, there are other causes of bleeding which might not always can be detected through the standard endoscopic evaluation. Endoscopic standard UGIB management consists of injection, thermal coagulation, hemoclips, and combination therapy. However, these methods are not always successful for rebleeding prevention. Endoscopic ultrasound (EUS) has been used recently for portal hypertension management, especially in managing acute variceal bleeding. EUS has been considered as a better visualization tool to visualize the bleeding vessel in gastroesophageal variceal bleeding. There have been studies looking at the role of EUS for managing NVUGIB, however, most of studies are case reports. Therefore, it is important it review back to see the evolution and innovation of endoscopic treatment for NVUGIB and the role of EUS for possibility to replace the endoscopic standard haemostasis management in daily practice.

### **INTRODUCTION**

Upper gastrointestinal bleeding (UGIB) is one of the challenging situations in clinical practice due to its etiology, location, types of bleeding, and its severity. It comprises of

non-variceal and variceal bleeding.<sup>[1,2]</sup> In the past, there has been no significant change from time to time regarding the etiology of non-variceal upper gastrointestinal bleeding (NVUGIB). Gastric ulcer (GU) and duodenal ulcer (DU) are still the main cause of acute NVUGIB, where hemorrhage and perforation are the major causes for mortality.<sup>[3,4]</sup> A recent large multicenter study showed that the bleeding etiology for NVUGIB were dominated by DU, followed by GU, whereas neoplasia was ranked as the fourth common cause of NVUGIB when compared to other non-malignant causes, such as Mallory-Weiss, esophagitis, and Dieulafoy's lesion. Recurrent bleeding was found in 3.2% of patients, with 4.5% mortality rate in 30 days. Endoscopic standard treatment which consists of injection, thermal coagulation, hemoclips, and combination therapy have shown better bleeding control rate. However, endoscopic treatment failure was still found to be higher in patients with several predictors, such as in-hospital bleeding, hematemesis, renal failure, neoplasia, and liver cirrhosis.<sup>[5]</sup> Recently, there has been innovation management using endoscopic ultrasound (EUS) for managing variceal bleeding as it can target the bleeding vessel much better than conventional endoscopic management.<sup>[6]</sup> Therefore, in this review, the role of EUS would be discussed further.

## **METHODS**

We collected all articles which have been published on standard endoscopic management as well as endoscopic ultrasound guided management in UGIB through the Medline/PubMed databases. The keywords used were EUS-guided vascular therapy, upper gastrointestinal bleeding, and non-variceal upper gastrointestinal bleeding. The purpose of this review was to elaborate the standard endoscopic management, limitations, new development or technique innovation, bleeding causes, and patient's outcome.

## **ENDOSCOPIC MANAGEMENT FOR NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING**

Standard endoscopic hemostasis treatment for managing NVUGIB consists of drug injection (epinephrine, cyanoacrylate, and other sclerosing agents), thermal coagulation, mechanical method, as well as topical treatment.<sup>[7]</sup> Endoscopic findings and bleeding ulcers stratification based on Forrest class have been routinely used as a standard parameter for endoscopic treatment options' decision. Based on the Forrest classification, active bleeding (class IA and B) has 55% rebleeding rate with 11% mortality rate, followed by visible vessel (class IIA) with 43% rebleeding and 11% mortality rates, adherent clot (class IIB) with 22% rebleeding and 7% mortality rates, flat spot (class IIC) with 10% rebleeding and 3% mortality rates, and clean base ulcer (class III) with 5% rebleeding and 2% mortality rates.<sup>[8]</sup> A randomized controlled trial by Chau *et al* looking at the role of epinephrine injection combined with heat probe coagulation therapy *vs* epinephrine injection combined with argon plasma coagulation treatment in patients with bleeding peptic ulcers showed no significant difference between both combined methods in achieving successful hemostasis (95.9% *vs* 97.7%). This study mostly included patients with Forrest class IB and IIA. However, the rebleeding rate from both of groups were still high (21.6% and 17.0%), and the hospital mortality was 6.2% and 5.7%.<sup>[9]</sup> Another randomized controlled trial by Lo *et al* has showed that combined therapy using epinephrine injection with hemoclip therapy *vs* epinephrine injection alone was more effective in controlling the rebleeding rate (100% *vs* 33%,  $p=.02$ ). In fact, no surgery was even required in the combination treatment group when compared to the single treatment group ( $p=.023$ ).<sup>[10]</sup> The use of clip in NVUGIB might be less mucosal injury when compared to thermal therapy.<sup>[11]</sup> In 2010, a novel electrocautery forceps alone or with combined method in Japan based on a retrospective multicenter data in nonmalignant gastroduodenal ulcer bleeding showed that the rate of successful bleeding control was achieved in 96.8% peptic ulcer patients, and 100% artificial ulcer patients. However, there were 12 patients with rebleeding, which was consists of seven (11.5%) peptic ulcer patients, and five (7.6%) artificial ulcer patients. In the rebleeding management, only one patient needed repeat endoscopic hemostasis treatment, and one patient required surgery after underwent combination

treatment method. However, this study has been limited by the patient's selection bias as well as the endoscopist's procedure skill.<sup>[12]</sup> Another innovation on endoscopic management on UGIB using a novel hemostatic powder (the "GRAPHE" registry), TC-325, showed that the immediate bleeding control effect was achieved by 96.5% of the patients, however, recurrent bleeding was found in 26.7% of patients at day 8 and 33.5% at day 30. Melena and pulsatile bleeding are the two most important factors for recurrent bleeding.<sup>[13]</sup> A large multicenter prospective study by Kawaguchi *et al* showed that the most frequent cause of NVUGIB were gastric ulcer (GU) which was 69%, followed by duodenal ulcer (DU) which was 27% and gastroduodenal ulcer (4%). The in-hospital four-week mortality rate was 5%, where 2 patients who died were associated with the bleeding itself. Patients who were presented with DU had significantly higher mortality rate when compared to patients with GU (16% *vs* 4%,  $p=.014$ ). In this study, 20 patients (8%) had unsuccessful endoscopic treatment. Other factors were comorbidities, the use of antithrombotic agent, and in-hospital onset.<sup>[14]</sup> Based on the guideline recommendations from the international consensus group for NVUGIB management, it has been suggested that TC-325 can become a temporary treatment option with low evidence. This is due to its high rebleeding rates after 72 h and one week. Endoscopic treatment, such as epinephrine injection, thermal coagulation, and clip are still considered as the main treatment. However, there was no significant difference in term of mortality rate even with combination therapy.<sup>[15]</sup>

#### **ENDOSCOPIC ULTRASOUND EVOLUTION AND INNOVATION IN MANAGING NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING**

In the evolution of therapeutic endoscopic ultrasound (EUS) development, a pioneer study by Boustiere *et al* performed EUS in liver cirrhotic patients, where gastric varices could be identified and stratified much better than esophageal varices. All cases suspected with the presence of GV was confirmed by EUS examination.<sup>[16]</sup> In 2000, Lee *et al* published a study on EUS-guided cyanoacrylate injection for bleeding GV showed that repeated injection under EUS guidance might improve patient's survival as the

recurrent bleeding incidence was decreased significantly when compared to on-demand treatment.<sup>[17]</sup> Another small case series study by Romero-Castro *et al* showed successful EUS-guided cyanoacrylate injection for the perforating veins related to GV.<sup>[18]</sup> These innovation studies also has been supported by a recent acute variceal bleeding case series study.<sup>[19]</sup> This study concluded that EUS can give accurate approach in varices treatment. **[Figure 1]** In 2011, a study by Binmoeller *et al* showed that EUS-guided transesophageal combined treatment using coil and cyanoacrylate for GV management was successfully achieved in all cases. The rebleeding was noted to be not associated with the variceal bleeding.<sup>[20]</sup> This was followed and supported by a recent study published by Bick *et al*, where they showed that by using EUS, the GV can be covered in a larger number when compared to the standard endoscopic injection.<sup>[21]</sup> In fact, the use of EUS for NVUGIB management also has been studied in the past, however, most of it were only case report studies.<sup>[22]</sup> The first well-known case series study was published in 1996, which described the use of EUS examination for Dieulafoy's lesion evaluation and management. Three patients underwent sclerotherapy injection using polidocanol 1% under EUS guidance successfully without any adverse events.<sup>[23]</sup> This study was supported by other two case reports in patients who experienced bleeding due to Dieulafoy's lesion. One case report described the treatment using thermal contact with 7F Bicap probe (Boston Scientific). This probe was passed through the EUS channel combined with 2.5 mL absolute alcohol; which resulted into deep mucosal thermal burn; thus, reducing the amplitude of arterial wave form. Another case underwent endoscopic band ligation after EUS evaluation. Both cases reported that there was no rebleeding after the first procedure.<sup>[24,25]</sup> In 2008, Levy *et al* published a study on EUS-guided angiotherapy for refractory NVUGIB, which consists of **bleeding due to hemosuccus pancreaticus, Dieulafoy's lesion, duodenal ulcer (DU), gastrointestinal stromal tumor (GIST), and occult GI bleeding**. In this case series study, absolute alcohol injection was performed for hemosuccus pancreaticus bleeding and Dieulafoy's lesion, and cyanoacrylate injection for DU and GIST patients. All patients in this study did not have any rebleeding episodes, even after more than 12 mo.<sup>[26]</sup> A larger case series study

by Law *et al* <sup>1</sup> on the use of EUS-guided hemostasis treatment in patients with resistant non-variceal bleeding (GIST, colorectal vascular malformations, duodenal masses, or polyps, Dieulafoy's lesions, DUs, and rectally invasive prostate cancer), showed that the complete vascular cessation was achieved in 63% of patients and the flow decrease in 37% of patients. There were no adverse events observed after the procedure. No patients had rebleeding within 12 mo follow-up after the procedure.<sup>[27]</sup> Two studies reported only bleeding due to pancreatic pseudoaneurysm. One study was a case of a patient with chronic pancreatitis and splenic vein thrombosis with portal hypertension, who underwent EUS-guided pancreatic pseudocyst drainage, endoscopic retrograde cholangiopancreatography (ERCP), followed by laparoscopic cholecystectomy for the biliary tract stones. The late bleeding was due to the presence of pseudoaneurysm close to the pancreatic pseudocyst drainage area. The bleeding was controlled with n-butyl cyanoacrylate injection through EUS guidance. No recurrent bleeding was observed after the hemostatic procedure. The other case was a patient experienced pseudoaneurysm that was induced by hemosuccus pancreaticus which has been confirmed by computed tomography angiography (CTA). This patient underwent EUS-guided coil embolization. No bleeding was recorded after more than a year.<sup>[28,29]</sup> The role of EUS-guided vascular therapy also has been reported in visceral pseudoaneurysm. The first case reported by Lameris *et al* where a thrombin-collagen compound was injected into pseudoaneurysm and the doppler study revealed complete obliteration. No rebleeding after 10 mo follow-up.<sup>[30]</sup> Sharma *et al* reported the bleeding from visceral pseudoaneurysm due to acute pancreatitis, and it was successfully controlled by human thrombin injection.<sup>[31]</sup> A recent single-blind study by Jensen *et al* in 148 patients with severe NVUGIB who underwent endoscopic hemostasis with Doppler guidance showed that the rebleeding rate was significantly lower when compared to the control group (11.1% vs 26.3%,  $p=.0214$ ).<sup>[32]</sup> However, the use of EUS image with doppler ability would give more accuracy and advantage to detect the bleeding source and manage severe NVUGIB due to possible poor visualization during standard endoscopic hemostasis procedure. **[Figure 2]**

## **CONCLUSION**

NVUGIB is still a challenging situation where there are variety of causes which sometimes cannot be detected through standard endoscopic examination. EUS has shown that it had an important role in managing UGIB, especially in NVUGIB. However, it would still need larger study before it can be recommended as the first-line approach in managing NVUGIB.



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PRIMARY SOURCES

1	"Gastrointestinal Interventional Endoscopy", Springer Science and Business Media LLC, 2020 <small>Crossref</small>	14 words — 1 %
2	<a href="http://www.ncbi.nlm.nih.gov">www.ncbi.nlm.nih.gov</a> <small>Internet</small>	14 words — 1 %

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