Best Practice & Research Clinical Gastroenterology 42-43 (2019) 101608

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

Endoscopic management of nonvariceal upper gastrointestinal bleeding

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ARTICLE INFO

Article history:
Received 13 March 2019
Accepted 15 April 2019

Keywords:
Upper gastrointestinal bleeding
Peptic ulcer
Endoscopic therapy
Ovesco
Hemospray®
Second-look
Doppler endoscopic ultrasound
Antiplatelet
Anticoagulants

ABSTRACT

Endoscopic therapy is the mainstay of treatment for nonvariceal upper gastrointestinal bleeding (NVUGIB). Injection plus mechanical or thermal therapy continues to be the most widely used option. New endoscopic devices such as the use of an inert powder or a new class of over-the-scope clip system have demonstrated encouraging results as a rescue therapy for difficult hemostasis. Emerging data suggest that Doppler ultrasound-guided endoscopic therapy may improve the outcome of peptic ulcer bleeding. This review sumarizes the recent advances in the management of NVUGIB. With increasing use of anti-platelet agents and anti-coagulants, the management of NVUGIB in patients on anti-thrombotic therapy is also discussed.

Introduction

Nonvariceal upper gastrointestinal bleeding (NVUGIB) is defined as the bleeding with origin above the ligament of Treitz that is not variceal in origin. The incidence NVUGIB is decreasing worldwide [1–6]. A systematic review in 2011 showed an incidence rate ranged from 19.4 cases to 57 cases per 100,000 [1], whereas one retrospective study in 2002 reported an incidence rate of 81 cases per 100,000 [2].

The most common cause of NVUGIB is peptic ulcer disease, accounting for 36% of all the cases according to a UK audit [5]. *Helicobacter pylori* infection and non-steriodal anti-inflammatory drugs (NSAIDs) including low-dose aspirin account for the vast majority of peptic ulcer disease [3,4]. Erosive esophagitis, Dieulafoy lesion, Mallory-Weiss syndrome, and gastric antral vascular ectasia, and neoplasms are other well recognized causes of NVUGIB. One study reported that up to 17% of patients with signs of upper GI bleeding had no abnormal findings on first gastroscopy [5].

Despite a decreasing incidence of NVUGIB, mortality still remains high, reportedly between 5 and 10% [4,7]. Concurrent medical conditions such as atherothrombotic diseases in our aging population probably account for the significant mortality despite advances in endoscopic and pharmacological therapy for NVUGIB [8,9]. Factors predicting mortality include old age (>80 years), renal failure, liver cirrosis, advanced malignancy, low hemoglobin (<7 g/dL) on admission, and failed endoscopic hemostasis [6].

Initial assessment

Patients presenting with symptoms of upper GI bleeding should be evaluated promptly. Volume depletion should be corrected with crystalloid solutions in the casulty department. Anemia increases the risk of ischemia especially in those with coronary artery disease. Current guidelines recommend a restrictive transfusion strategy to keep a hemoglobin level of 7 g/dl [10]. In a large-scale randomized trial of patients with acute upper GI bleeding who were randomized to receive liberal or restrictive transfusion, survival at 6 weeks in the restrictive transfusion group was higher (95% vs. 91%, P = 0.02). However, a significant difference in survival was seen only in patients with Child's A or B liver cirrhosis [11].

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https://doi.org/10.1016/j.bpg.2019.04.001
1521-6918/

More data are required on the optimal level of transfusion in patients with cardiovascular diseases.

Coagulopathy at presentation is associated with a significant increase in mortality according to the UK National Audit [5]. However, there is evidence that mild to moderate anticoagulation (INR 1.3–2.7) at endoscopy did not increase the risk of recurrent bleeding [12]. Current guidelines do not recommend aggressive correction of coagulation before emergency endoscopy [13].

There have been a number of validated risk scores for risk assessment. Among them, the Glasgow Blatchford score (GBS) displays the best accuracy in identifying patients who do not need hospitalization (GBS = 0). GBS was derived from clinical parameters to predict the need for transfusion or any intervention to control bleeding [14]. Although GBS score >1 is sensitive in predicting the need for therapeutic endoscopy, its specificity is low. Therefore, GBS has limited value in guiding off-office-hour emergency endoscopy.

Given the limitations of nasogastric aspiration in assessing upper GI bleeding, wireless video capsule endoscopy has been investigated as a potential diagnostic tool for risk stratification. In a prospective cohorty study, Gralnek et al. [15] found that capsule endoscopy was safer and more convenient than nasogastric aspiration in identifying the source of bleeding. More studies are needed to establish the role of video capsule endoscopy in upper GI bleeding to justify its cost. Currently, there is not sufficient evidence to recommend using capsule endoscopy as a triage tool for upper GI bleeding [10].

Pre endoscopy pharmacotherapy

A meta-analysis of controlled RCTs found a significant reduction in high risk stigmata of bleeding and the proportion of patients requiring endoscopic therapy with pre-endoscopic proton pump inhibitor (PPI) therapy. There was, however, no difference in mortality, transfusion requirement or surgery [16]. Prokinetic agents including erythromycin and metoclopramide improve gastric emptying and viewing at endoscopy. Their use has been shown to reduce the need for a second-look endoscopy but there was no improvement in other clinical outcomes [17].

Timing of endoscopy

The optimal timing for endoscopy in patients with acute upper GI bleeding remains controversial. Endoscopy is often recommended within the first 24 h of presentation. A meta-analysis of cohort studies found that early endoscopy to high risk patients reduced the risk of recurrent bleeding, the need for surgery and duration of hospital stay [18]. Three small prospective randomized trials compared urgent endoscopy (ranging from <6 h to unspecified timing) to endoscopy within 24 h in patients with acute upper GI bleeding. None showed any benefit of urgent endoscopy on major clinical outcomes [19–21].

Who needs endoscopic treatment?

Forrest's classification uses endosocpic appearance to predict the risk of recurrent ulcer bleeding (Forrest I: active bleeders, Forrest IIa: visible vessel, IIb: an adherent clot, IIc: a flat pigmented spot, and Forrest III: a clean base ulcer) [22]. Endoscopic treatment is indicated in active bleeding ulcers and ulcers with non-bleeding visible vessel [23]. The ESGE Guideline recommends removing the adherent clot to reveal any underlying protuberant blood vessel at the ulcer base that requires further endoscopic treatment [10]. Although this approach appears to reduce the rate of rebleeding, there was no reduction in surgery or mortality [24,25]. Using a doppler ultrasound endoscope (USE), it is possible to detect arterial blood flow at the ulcer base. Ulcer base showing a positive doppler signal may be at high risk of recurrent bleeding irrespective of endoscopic apperance since the latter may have substantial inter-observer variability. A randomized trial showed that patients receiving doppler USE-guided therapy had reduced risk of rebleeding, surgery and mortality [26]. However, another randomized trial reported that doppler USE-guided therapy failed to reduce surgery, hospital stay or mortality although there was a significant reduction in recurrent bleeding within 30 days [27].

Which endoscopic treatment?

There are four types of endoscopic treatment: injection (diluted epinephrine, sclerosing agents and cyanoacrylate), thermal coagulaton (monopolar, bipolar or multipolar or heater probe), mechanical (clips, band ligation and over-the-scope) and topical therapy (Hemospray®, Cook Medical Inc., USA; Endoclot, EndoClot Plus Inc., USA and Ankaferd Blood Stopper, Ankaferd Health Products Ltd, Turkey) [28]. Adding a second modality to adrenaline injection therapy improves the outcome of hemostasis. In a meta-analysis of RCTs that compared adrenaline injection alone versus adreanline injection followed by a second modality, combination therapy significantly reduced the rate of recurrent bleeding, surgery, and mortality [29]. In a recent systematic review with network meta-analysis of dual therapy for bleeding ulcers, it was found that the addition of mechanical therapy to adrenaline injection significantly reduced the risk of recurrent bleeding and surgery. Patients who received adrenaline plus thermal therapy showed a significant reduction in recurrent bleeding only [30]. However, there are situations where a thermal coagulation or endoscopic clips without pre-injection with adrenaline are preferred to combination therapy. In an updated meta-analysis of 28 randomized trials, it was found that combining hemoclip with an injection did not improve hemostatic efficacy above hemoclip alone [31].

The choice of hemostatic modality often depends on specific needs. For instance, endoscopic application of clips can be difficult for ulcers along the lesser curve of the stomach and in the posterior bulbar duodenum. Similarly, clips cannot firmly grip chronic ulcers with fibrotic bases. In such instances, a thermal device may be more efficacious. A meta-analysis found that both clipping and thermoscoagulation alone are similar in their hemostatic efficacies [32] Cyanocrylate glue is another rescue therapy that has been used in the management of NVUGIB with difficult hemostasis. One retrospective study reported an overall success rate of 78.8% with cyanooacrylate injection during the first or repeated endoscopy [33]. On the other hand, use of sclerosing agents should be avoided since it is associated with an increased risk of gastroduoenal wall necrosis and perforation [30].

New endoscopic hemostatic modalities are emerging as alternative therapies for refractory UGIB. Over-the-scope (OTSC; Ovesco, Tübingen, Germany) device has been used as a rescue therapy with a success rate of 80% [34]. Recently, a prospective randomized trial showed that OTSC is superior to standard therapy in achieving hemostasis and reducing recurrent bleeding [35]. Others reported that OTSC system is effective and safe for ulcers up to 5 cm in diameter [36]. Unlike over-the-scope devices, topical therapy is easy to use and produces promising results. Hemospray® is a topical therapy in which the main component is a mineral-based hemostatic powder. The latter achieves haemostasis by producing a mechanical barrier absorbing serum to concentrate clotting factors, and activating the clotting cascade. It is safe and is completely eliminated from the GI tract after 70 h [37]. Hemospray is particularly useful in diffuse bleeding, such as tumor bleeding. It can also

be used as a bridge therapy to buy time until definitive treatment becomes available [38]. In a prospective study of Hemospray for peptic ulcer bleeding [39], primary hemostasis was achieved in 95%, and only 10% of patients developed rebleeding. In another study, hemospray was found to be the most efficacious and the least expensive strategy was standard therapy followed by Hemospray if necessary [40]. However, randomized clinical trials directly comparing topical agents with traditional hemostatic therapies in UGIB are lacking [10].

Other causes of NVUGIB

Endoscopic treatment of NVUGIB other than peptic ulcer depends on the severity of bleeding and preference of endoscopists because of the low quality of evidence in this field [4]. Bleeding from Mallory-Weiss syndrome has a mortality similar to that of peptic ulcer bleeding [10]. It can be managed by injection, mechanical or thermal therapies, although some endoscopists prefer clips or band ligation to thermal therapy [4]. Dieulafoy lesions are easily missed because the protuberant blood vessel is typically small, the sorrounding mucosa usually appears normal, and the bleeding is often intermittent. In one study, less than 50% of Dieulafoy's lesions are identified during the first endoscopy [41]. A randomized trial of band ligation versus through-the-scope clips for gastric Dieulafoy's lesions did not find any difference between these two procedures [42]. Bleeding from erosive esophagitis is mostly mild and self-limiting. Endoscopic treatment is rarely needed [10]. The mainstay of treatment of esophagitis is PPI, which has been demonstrated to be superior to H2-receptor antagonists [43]. Gastric vascular ectasia (GAVE) is conventionally treated with argon plasma coagulation. Recently, a systematic review of 74 cases of refractory GAVE treated with radiofrequency ablation reported an overall short-term (from 2 to 11 months) success rate of 74% (i.e., no recurrent drop in hemoglobin) [44]. However, randomized trials of radiofrequency ablation for GAVE are lacking.

Failed endoscopic hemostasis

Patients with failed endoscopic hemostasis can be divided into two groups: 1) those who continue to bleed because primary failure in controlling bleeding with endoscopy and 2) those with recurrent bleeding after initial success in endoscopic hemostasis. Patients with primary failure in hemostasis are usually old and frail with large ulcers located in difficult positions such as posterior duodenal bulb or lesser curvature of the stomach. While emergency surgery is the conventional treatment, angiographic embolization is an altenative option in centers where expertise is available. To date, there are 6 retrospective comparisons of angiographic embolization to surgery in patients with failed primary endoscopic hemostasis [45–51]. Angiographic embolization was associated with lower treatment related complications than surgery (20–54% vs. 37–68%). However, recurrent bleeding was about 25%. Mortality was similar following either treatment (3–30% vs. 14–30.4%).

Among patients with initial successful control of bleeding, recurrent ulcer bleeding occurs in about 8–15% of cases [45], depending on the type of ulcer according to Forrest's classification. Mortality after a surgical salvage according to data from a UK audit was almost 30% [52]. Ulcers at certain locations such as the posterior bulbar duodenum and the lesser curvature of the stomach are technically more difficult to secure hemostasis. Furthermore, these ulcers can erode into large arteries such as the gastroduodenal artery and the left gastric artery, leading to massive bleeding and substantial increase in morbidity and mortality. In a randomized trial of surgery versus repeat endoscopy for patients with recurrent ulcer bleeding, 75% of patients achieved sustained hemostasis after repeat endoscopy whereas the surgical arm had significantly more complications [53]. A subgroup analysis showed that large ulcers more than 2 cm and hypotension are factors predicting an unsuccessful outcome in repeat endoscopy [53].

Recently, one randomized trial sought to investigate whether pre-emptive angiographic embolization after endoscopic hemostasis to high-risk patients (i.e., ulcers$\geq$20 mm in diameter, spurting bleeding, hypotensive shock or hemoglobin<9 g/dL) would reduce the risk of recurrent bleeding. Eligible patients were randomized to receive pre-emptive angiographic embolization or standard treatment. However, this trial found that pre-emptive angiographic embolization failed to reduce recurrent bleeding [54].

Pharmacotherapy after endoscopic hemostasis

One approach to prevent recurrent bleeding after endoscopic hemostasis is to raise intragastric pH to above 6. This is because low gastric pH inhibits platelet aggregation and activates pepsinogen to lyse blood clots [4]. High-dose intravenous omeprazole is superior to intravenous administration of ranitidine in maintaining gastric pH > 6 [55]. In a systematic review of randomized trials, PPI therapy reduces recurrent bleeding and the need for surgery. However, there was no difference in mortality rate in the PPI group compared to the control group. A reduction in mortality from PPI treatment was evident only in a subgroup analysis that included patients with active bleeding or non-bleeding visible vessels (1.78% vs. 3.3%, OR 0.53; 95% CI 0.31–0.91) [23,56].

The optimal dose of PPI after endoscopic hemostasis continues to be controversial. While there is good evidence that continuous high dose PPI infusion reduces recurrent bleeding after endoscopic hemostasis, two meta-analyses of RCTs that enrolled patients with Forrest IIc and III ulcers found that low-dose and high-dose PPI regimens are equally effective. The data suggested that a lower dose of PPI is sufficient for low-dose patients [57,58]. Another meta-analysis found that intermitent PPI was not inferior to the continuous one [59]. However, a large proportion of studies were from Asia. Asian patients have lower parietal cell mass and a higher prevalence of CYP2C19 genetic polymorphism than patients in western countries. It remains uncertain whether this finding can be extrapolated to patients outside Asia.

Tranexamic acid is an antifibrinolytic drug that has been used for prevention of different types of bleeding for several decades [60]. Although early trials and metaanalysis suggested that tranexamic acid prevents recurrent bleeding and reduces mortality [61], the quality of these studies were mostly suboptimal. A large randomized controlled trial of about 8000 patients to assess the efficacy of tranexamic acid in both upper and lower gastrointestinal bleeding is currently ogoing (NCT01658124) [62].

Second-look endoscopy

A second-look endoscopy is usually performed within 24 h following initial endoscopic hemostasis to detect any high-risk stigmata or endoscopic signs of recurrent bleeding [10]. A meta-analysis found that routine second look endoscopy significantly reduces the risk of recurrent bleeding and the need for emergency surgery but there is no reduction in mortality [63]. However, most of these studies were performed before adjuvant PPI therapy was available. Current evidence suggests that it is not cost-effective to do routine second-look endoscopy [10,64]. We recommend second-look endoscopy in selected high risk patients e.g. after temporary control of bleeding with topical therapy (Hemospray), bleeding ulcers located at posterior duodenal bulb or gastric lesser curvature, before early resumption of anti-platelet or anti-coagulant therapy.

Management of antithrombotic therapy in UGIB

Anti-thrombotic therapy, which consists of antiplatelet drugs and anticoagulants, is increasingly used due to aging population. Antiplatelet drugs include low-dose aspirin and non-aspirin antiplatelet drugs (P2Y12 receptor inhibitors: clopidogrel, ticagrelor, prasugrel; protease-activated receptor antagonist: vorapaxar). Anticoagulants include vitamin K antagonists (warfarin and aldocumarol) and direct oral anticoagulants (DOACs) (factor Xa inhibitors: apixaban, edoxaban and rivaroxaban; and thrombin inhibitor: dabigatran). To date, a number of guidelines have been developed by various professional societies to guide the use of antithrombotics in acute upper gastrointestinal bleeding [10,13,65,66]. While this topic is beyond the scope of this chapter, we would like to summarize the most important points as follows:

1. Antithrombotic drugs should be withheld before endoscopy particularly in patients presenting with serious or life-threatening GI bleeding.
2. For patients with high thrombtic risks receiving dual antiplatelet therapy, however, one should avoid discontinuing both drugs.
3. Platelet transfusion is not useful in patients on antiplaelet therapy.
4. Antiplatelet drugs should be resumed early, preferably within 3–5 days after endoscopic hemostasis.
5. For patients on warfarin with an INR above 2.5 and life-threatening bleeding, prothrombin complex concentrate plus low-dose vitamin K are recommended for life-threatening bleeding. However, one should not delay endoscopy for life-threatening bleeding until normalization of INR.
6. In patients with high thromboembolic risk, warfarin should be resumed once adequate hemostasis is achieved.
7. Bridging anticoagulation therapy should be avoided in patients on warfarin with low thromboembolic risk.
8. Activated charcoal for life-threatening bleeding may be considered in patients on DOACs if the last dose of DOAC is taken within 3 h.
9. Idarucizumab is reserved for the treatment of life-threatening bleeding in patients on dabigatran.
10. Monitoring INR and treatment with vitamin K are not useful for treatment of bleeding associated with DOACs.
11. DOACs should be resumed after adequate hemostasis is achieved.
12. Bridging therapy is not recommended in patients on DOACs.

Summary

Despite advances in endoscopic therapies in the treatment of NVUGIB, there is no corresponding reduction in mortality. Aging population with multiple comorbilities probably accounts for the poor outcomes. It remains to be proven whether new endoscopic modalities such as doppler-guided endoscopic ultrasound, over-ther-scope mechanical devices and topical agents can improve the management of difficult hemostasis and clinical outcomes. Transcatheter arterial embolization is a less invasive alternative to surgery but has not been shown to reduce mortality. Successful outcomes often depend on prompt evaluation of patient risk, indiviudalized managment to minimize the risk of early recurrent bleeding, and careful attention to comorbidities.

Research agenda

1. Randomized head-to-head comparison between topical therapy and conventional endoscopic hemostatic modalities are not available.
2. The role of capsule endoscopy as a triage tool for upper GI bleeding remains unclear.
3. Whether doppler ultrasound-guided endoscopic therapy will improve clinical outcomes has shown conflicting results.

Practice points

1. Early endoscopy (<24 hours) to high risk patients reduces the risk of recurrent bleeding, the need for surgery and duration of hospital stay.
2. Injection plus mechanical or thermal therapy is the standard endoscopic therapy for non-variceal upper gastrointestinal bleeding.
3. Topic therapy such as Hemospray can be used as a bridge therapy to buy time until definitive treatment becomes available.
4. Over-the-scope endoscopic devices are potential alternative therapies for refractory non-variceal upper GI bleeding.

Role of the founding source

None.

Conflicts of interest

Francis K.L. Chan has served as a consultant to Eisai, Pfizer, Takeda, and Otsuka. He has been paid lecture fees by Eisai, Pfizer, AstraZeneca, and Takeda.

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