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Role of Endoscopy in Peptic Ulcer Bleeding

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ABSTRACT

Upper gastrointestinal endoscopy is fundamental in peptic ulcer bleeding for diagnosis, risk stratification and treatment. Endoscopy should be made within 24 hours of patient admission. Depending on endoscopic finding of peptic ulcer, rebleeding risk of ulcer and therapeutic options are defined. In ulcers with high risk stigmata such as oozing or spurting bleeding, endoscopic therapy is indicated. Different endoscopic hemostasis techniques are available including injection, thermal, and mechanical therapies and, more recently, hemostatic powders. Besides standard endoscopic hemostatic techniques, new modalities are emerged such as over the scope clips, endoscopic suturing, endosonography guided sclerotherapy. Complications of endoscopic therapy are perforation, inducing bleeding and wall necrosis associated with the treatment options.

Keywords: Peptic ulcer bleeding; Forest classification; Upper gastrointestinal endoscopy.

INTRODUCTION

Peptic Ulcers (PU) are the most common cause of upper gastrointestinal bleeding (UGIB) [1]. One-third to half of all acute UGIB is due to PU [1-2]. Upper gastrointestinal endoscopy has an important role in the diagnosis, treatment, and prognostication of PU bleeding. In this chapter, role of endoscopy in PU bleeding including pre-endoscopic consideration, risk stratification, available hemostatic treatments, need for second look endoscopy, complications and innovative techniques are reviewed.

PRE-ENDOSCOPIC CONSIDERATIONS

Timing of Endoscopy

Early endoscopic procedure within 24 hours of admission allows earlier discharge of patients with low-risk [3] and improves outcomes in patients with high risk [4]. Lower costs are also associated with early discharge after endoscopy of low-risk patients [5].

Several RCTs and retrospective cohort studies have showed that faster time to endoscopy is associated with higher rates of hemostasis, significant decreased length of stay in hospital, decreased rebleeding and need for surgery [6-11]. However a significant proportion of patients from 50% to 87% have a delay greater than 24 hours before undergoing upper endoscopy [12,13]. An important cause of cause of delays in endoscopic management is “weekend effect” that patients presenting on weekends are less likely to undergo early endoscopy, and have higher mortality [14-16].

Current guidelines on UGIB support that endoscopy within 24 hours of patient admission should be targeted as a stand-alone quality indicator in managing patients with UGIB [17-19].

Patients with Coagulopathy

PU bleeding is common in patients with coagulopathy, especially of that using vitamin K antagonists. Vitamin K antagonist should be discontinued in UGIB and present coagulopathy should be corrected by administrating fresh frozen plasma or prothrombin complex concentrate. Endoscopic management should not be delayed [4]. Limited observational data also suggest that endoscopic hemostasis can be safely performed in patients with an elevated INR less than 2.5 [20].

Improving Visibly

The quality of endoscopy can be adversely affected by poor visibility in patients requiring urgent endoscopy with UGIB due to obscuring blood in the gastric lumen. In 3% to 19% of the cases, no apparent cause of UGIB can be identified [21]. Use of water-jet pikes for irrigation and adequate suction power applied to the endoscope. The patient may need to be rolled over to positions different from the initial left lateral decubitus position to dislocate the blood pool and make the lesion visible. In the case of a large uncleared fundal pool, consider inserting a large-

bore nasogastric tube to empty the stomach and repeat the examination shortly thereafter [22]. Although the routine use of a nasogastric tube before endoscopy is not recommended, it may offer important prognostic information in selected patients, Prokinetic agents such as erythromycin and metoclopramide can be given before endoscopy to improve endoscopic visibility in patients with active bleeding and/or evidence of blood in the stomach [23,24]. Erythromycin, a motilin agonist, can be given at a dose of 250 mg intravenously, and metoclopramide 10 mg intravenously 30 to 60 minutes before endoscopy. The use of erythromycin is favored based on current data. However, the QT-interval–prolonging effect of erythromycin should be taken into consideration, and an electrocardiogram first performed [4].

RISK STRATIFICATION

The endoscopic findings of a bleeding ulcer have prognostic implications in terms of rebleeding, need for surgery, and mortality. As a result, they are integrated in risk assessment scores such as the complete Rock all score, and are further used to determine the need for endoscopic hemostasis. The stigmata of recent bleeding are used to characterize the endoscopic appearance at the base of the bleeding ulcer, and are commonly categorized according to the Forrest classification into high-risk stigmata (HRS) and Low-Risk Stigmata (LRS) (Table 1) [25]. Significant interobserver variability has been reported in the identification of endoscopic stigmata [26].

Table 1: Forrest classification of stigmata of recent bleeding.

Risk Statification	Stigmata of RecentHemorrhage	Forrest Classification	Rebleedingrates
High Risk Stigmata	Active spurtingbleeding	IA	55% (17%–100%)
	Active oozingbleeding	IB	
	Nonbleedingvisiblevessel	IIA	43% (0%–81%)
	Adherentclot	IIB	22% (14%–36%)
Low risk stigmata	Flatpigmented spot	IIC	10% (0%–13%)
	Cleanbase	III	5% (0%–10%)

Endoscopic hemostasis is indicated in all patients with active bleeding and non bleeding visible vessel and it has been well established to decrease continued or recurrent bleeding, surgery, and mortality [27-30]. In patients with LRS ulcers, endoscopic hemostasis has not been shown to alter outcomes [27,28]. The treatment of patients with pigmented spots or clean base ulcers therefore consists of oral acid suppressive pharmacotherapy alone.

The lesions with adherent clots are some what controversial. The recommended approach to ulcers with an overlying clot is to irrigate the lesion for dislodging the blood clot and reveal the underlying stigma. Removing the clot is achieved by washing in about 40% of lesions [31]. Ulcers with clots resistant to such manipulation are defined as adherent clots (Forrest IIB). These lesion scan be further managed by mechanical clot removal without disrupting the pedicle to expose the ulcer base (after preliminary dilute epinephrine injection around the ulcer), followed

by endoscopic therapy according to the stigmata of recent bleeding [4]. Studies have shown that endoscopic therapy decreases rebleeding in adherent clots [32-34]. However, a recent meta-analysis failed to show significant benefits of endoscopic therapy over medical therapy for adherent clots in terms of rebleeding, need for surgery, or mortality [30]. Consensus guidelines state that endoscopic therapy can be considered while acknowledging that intensive PPI therapy alone may be adequate [4].

ENDOSCOPIC HEMOSTASIS

Endoscopic management of NVUGIB has been shown to improve clinical outcomes, with significant reduction of recurrent bleeding, need for surgery, and mortality [4]. There are several endoscopic modalities including injection, thermal, and mechanical therapies and, more recently, hemostatic powders. Standard endoscopic therapies and innovations are overviewed below.

Injection Therapy

Different injectates including epinephrine, hypertonic saline, sclerosants (polidocanol, ethanolamine, absolute alcohol, sodium tetradecyl sulfate), and tissue adhesives (cyanoacrylate, thrombin, fibrin) can be used in endoscopic hemostasis. Injection therapy has been widely performed because of its ease of use and availability. Injections are delivered through a 25-gauge retractable catheter. Pooled data for injection therapies (including trials on epinephrine monotherapy, alcohol monotherapy, and a combination of other injectates) reveals a reduction in rebleeding compared with pharmacotherapy [29] in patients with HRS.

Epinephrine (1:10,000 or 1:20,000 dilution) is the most common injectate used in the control of NVUGIB. 0.5 to 1.5 mL of epinephrine should be administered in all 4 quadrants around the ulcer base with or without injections into the center of the ulcerated lesion itself [35].

The main mechanism responsible in hemostasis is tamponade effect of the volume of the injected material rather than the vasoconstrictive mechanism of the epinephrine or resulting platelet aggregation [25]. Furthermore, it has been suggested that higher total volumes (13–45 mL) per bleeding lesion may decrease rebleeding rates, presumably because of the greater tamponade effect [36-38]. However, higher doses of injected epinephrine are more likely to cause cardiovascular side effects, particularly when injected around the region of gastroesophageal junction and the distal esophagus; the use of more diluted solution (1: 100,000) should be used to avoid complications in case of injecting higher volume of epinephrine [39].

The application of epinephrine is the initial agent of choice in most ulcer bleeding. In the obscured views, it can be administred easily and safely. However injection therapies have been shown to be inferior to other monotherapies (thermal, fibrin glue, and clip), and combination therapies. It is also associated with a higher incidence of rebleeding and surgery when used alone comparing the other endoscopic therapies [4,30,40]. A meta analysis demonstrated that epinephrine injection, followed by a second modality, provides additional benefits with regard

to reducing rebleeding, surgery and mortality comparing with epinephrine monotherapy [40]. Mortality benefits were not reproduced in more recent analyses [29-30,41]. In conclusion, it should better to use epinephrine injection in combination with other endoscopic hemostatic in treatment of ulcer bleeding with HRS.

Sclerosants include polidocanol, ethanolamine, absolute alcohol, and sodium tetradecyl sulfate. These agents induce local inflammation and subsequent fibrosis, obliterating the lumen of the vessel. The technique is similar to that used for epinephrine, but volumes are much smaller (usually a maximum of 1 mL, divided in 0.1–0.3 mL aliquots per injection at 3–4 sites around or into the visible vessel) due to the potential risk of ulceration, necrosis, and perforation [43-46]. Nevertheless, sclerosant therapy has been associated with significant benefits in reducing rebleeding, surgery, and mortality in comparison with no therapy [30], and can be considered in the management of NVUGIB [4].

N-butyl-2-cyanoacrylate is a tissue adhesive. It polymerizes into a firm clot on contact with water. The glue can be used either undiluted or as a mixture of cyanoacrylate and lipiodol, an oily contrast agent to delay polymerization. The injection technique is not as user friendly as an epinephrine injection because the glue hardens quickly and there is the potential risk of damaging the endoscope, the operator, and patient if the glue is accidentally dispersed.

If the glue sticks to the lens, the endoscope should be withdrawn and cleaned with ethanol or nail polish remover immediately. Care must be taken to protect the eyes of the patient and the clinical personnel. Acryl ate glue should be slowly injected directly into the bleeding point (the glue is sticky with a considerable resistance to injection). To minimize the risk of embolization, not more than 1 or 2 mL glue is injected. At the end of the injection procedure, the glue spills with formation of a hard plug obliterating the bleeding point. In a randomized trial comparing cyanoacrylate with hypertonic saline-epinephrine injection in patients with high-risk bleeding PU, there were no differences in outcomes between the 2 groups, but 2 cases (1 fatal) of arterial embolization occurred in the cyanoacrylate group [47]. These agents are rarely used in the routine hemostasis of PU bleeding because of their high costs and lack of availability.

Fibrin glue is a 2-component system in which concentrated fibrinogen and factor XIII are combined with thrombin and calcium to simulate the final stage of the clotting cascade. Components are injected either as a subsequent injection in a standard 23-G injector needle or as a mixture of the 2 trough, a special dual-channel needle, to mix and activate the clotting cascade only when injected. Although, an early study with fibrine glue has found that it was associated with less recurrent bleeding compared with polidocanol in patients pretreated with epinephrine [48]. Other studies did not confirm any advantage in adding the fibrin glue to epinephrine injection alone [49]. Moreover, because the substance is relatively expensive and its use can be associated with the potential transmission of infectious diseases today, the use of fibrin glue is discouraged as a primary treatment modality.

Sodium hyaluronate is a natural polysaccharide with peculiar viscoelastic characteristics. Because of its ability to create a persistent sub mucosal cushion it is candidate for endoscopic sub mucosal dissection. In 2 case reports, sodium hyaluronate has been used to successfully achieve endoscopic hemostatic in bleeding ulcers [50-51]; however, clinical trials are needed.

Thermal Therapy

Thermal therapy means that applying heat or electric current to bleeding lesions, which can lead to coagulation of vessels and achieving hemostasis. Thermal treatment can be classified into two categories as contact (electro coagulation or heater probe) and noncontact electro coagulation.

Contact electro Coagulation

Monopolar, bipolar (BEC), ormultipolar (MEC) electro cauterization techniques are available for endoscopic contact electro coagulation.

A monopolar grasping forceps is designed for grasping, tenting, and sealing of readily accessible vessels, with suggested settings of 50 to 60 W, depending on the electrosurgical unit being used, using a soft coagulation mode. Although the device may also be suitable for other non variceal bleeding lesions, care regarding its use for the treatment of a visible vessel in an ulcer is warranted because grasping the vessel from an indurated base may result in vascular tearing and bleeding [52]. Clinical experience and data for endoscopic hemostasis with monopolar cautery devices are limited in management of PU bleeding.

In BEC or MEC, the electric circuit terminates locally at the tip of the probe and decreases the intensity of current providing limitation of penetration depth and decreasing the risk for perforation [53]. However, MEC/BEC may be difficult to use in the tangential position given that electric current occurs at the tip of the catheter. For optimal BEC/MEC, using a large-diameter (10F, 3.2 mm) probe is the best by providing constant pressure on the high risk lesion. Application of low energy (15 W) electro coagulation is done for 10 to 12 seconds until flattening of vessels or adequate coagulation of the stigmata [54]. The method aims effective physical occlusion and tamponade of the vessels followed by thermal coagulation. Long-duration (10–12 seconds) and low-energy (15 W) electro coagulation are preferred to achieve coaptive coagulation [55-56].

Contact Heater Probe

The heater probe radiates heat to tip and sides of the probe. The method is similar with contact electro coagulation, in terms of the using a large-diameter probe (10F, 3.2 mm) with firm constant pressure; however, coagulation is provided via heat energy (25–30 J) and is delivered in a pulsatile mode (4–5 pulses) [56-57]. The main advantage of the heater or gold probe over BEC/MEC is its ability to provide coagulation through the tip and sides of the probe, therefore allowing for ease of application in both the tangential and en-face position. The heater probe also.

The use of contact thermal therapy, namely heater probe and electro coagulation, is easy to use, allows simultaneous water irrigation, and is effective in both bleeding and non bleeding

lesions with HRS [29]. Effect of thermal coagulation in achieving hemostasis in patients with high-risk lesions has been showed by reducing rebleeding and mortality rates when compared with no endoscopic treatment [30]. However, studies on the comparison of contact thermal therapy with other modalities, alone or in combination, have not provided consistent results about superiority of one approach over another [29,58]. Nevertheless, thermo coagulation can be used either alone or in combination with injection therapy [4].

Noncontact Thermal Therapy

Noncontact devices (namely, argon plasma coagulation [APC]) deliver high-frequency monopolar current to the tissue through an ionized gas. The use of neodymium: YAG laser, a noncontact thermal method, is rarely used today for hemostatic endoscopic purpose because of the excessive depth of coagulation resulting in high rates of perforation as well as the excessive maintenance costs.

In APC application, direct contact between the probe and the target lesion should be avoided to prevent sub mucosal dissection and sub mucosal argon gas insufflations, which causes significant pain, pneumatosis, and risk of perforation [59]. The optimal distance between probe and target tissue is estimated to be 2 to 8 mm. superficial coagulation prevents further tissue damage.

APC is ideal for tangential bleeding lesions such as angiodysplasia, radiation telangiectasia, and gastric antral vascular ectasia, also known as watermelon stomach [60-61].

In terms of ulcer bleeding, several comparative trials showed that there was no significant difference in patient outcomes with APC treatment comparing with heater probe [62], sclerotherapy [63], epinephrine in combination with heater probe [64], endoclips [65] or polidocanol treatments [30]. Nevertheless, decreased rebleeding was reported in a study that compared APC with distilled water injection [66]. In addition, in a single small randomized trial, epinephrine plus APC treatment has been shown to led improved initial hemostasis comparing with heater probe treatment in patients with high-risk ulcer bleeding [67].

MECHANICAL THERAPIES

Through-The-Scope Clips

Endoclips is the most extensively applied and widely available technique among hemostatic mechanical therapies in the management of NVUGIB. It provides hemostasis via direct compression or tamponade of vessels. Moreover, endoclips application is usually associated with minimal to no tissue damage, therefore leading potentially to faster ulcer healing [68]. However, its use requires precision, en-face positioning and may be inadequate in fibrotic ulcer beds given its weak tensile strength [68]. Endoclips can be in many different sizes, lengths, and shapes, grasping and rotational abilities, and deployment mechanisms. Therefore, it is important to work with a conventional endoclips in emergency situations.

The use of endoclips is shown to be effective for ulcer bleeding. Several RCTs have demonstrated a benefit of endoclips over epinephrine injection [30] or thermal therapy [29] for rebleeding. However, it has been recently suggested that thermal or combination therapy may be favored over endoclips or sclerosants when managing actively bleeding lesions [1], and that thermal therapy should be used with epinephrine [69] based on lower-quality evidence.

Endoclips can be used alone or in combination with epinephrine, or as an alternative to thermal coagulation [4]. Ulcer location can guide the decision to use endoclips or other hemostatic modalities, as higher endoclip failure is seen for ulcers located in the posterior wall of the duodenum and gastric body, and along the lesser gastric curvature [70].

Endoscopic Band Ligation (EBL)

In PU bleeding, when the angle of approach is too tangential for hemoclip application, EBL can be performed even if the bleeding site must be approached tangentially.

EBL cannot be done successfully for bleeding lesions with severe underlying fibrosis that cannot be aspirated into the hood of a ligation device. Therefore, it is advisable to exclude chronic ulcers and perform EBL only in small-sized, non fibrotic lesions. In such selected lesions, band ligation has proven highly successful in patients with major stigmata of acute peptic ulcer bleeding with hemostasis achieved in all patients in a single session, with no rebleeding episodes and with no bleeding related or procedure related deaths [38].

Endoscopic Hemostatic Powders

Endoscopic topical hemostatic powders such as the Ankaferd Blood Stopper (ABS), Endo Clot, and TC-325 have been recently adapted to endoscopic hemostatic techniques. ABS is a herbal extract derived from 5 different plants that provides hemostasis by performing protein network behaving as an mainstay for erythrocyte aggregation [71].

The Endoclot is another hemostatic powder containing a biocompatible, non pyogenic, starch-derived compound. Hemostasis is achieved by Endoclot through mechanical tamponade and water absorption from serum, leading to concentration of platelets and clotting factors and thereby accelerating the clotting cascade [72]. In the literature, it has been shown that Endoclot is a safe and effective in the treatment of GIB [73-74]. However, more data are needed with regard to PU bleeding.

TC-325 is composed of a proprietary inorganic biologically inert powder. The endoscopic powder is propelled from a canister under CO_2 pressure and is delivered through a catheter onto the bleeding lesion. The endoscopic powder aggregates rapidly when it comes into contact with moisture of GI tract; therefore. TC-325 catheter should be maintained 1 to 2 cm from the high-risk lesion in noncontact mode, and suctioning should be avoided while it is in use or while the powder is settling.

The endoscopic powder serves as a mechanical barrier for hemostasis [74]. Its mechanism has been suggested to provide a port for enhancing platelet aggregation and activating clotting factors [75]. The powder only adheres to actively bleeding lesions, so its use in HRS lesions without active spurting or oozing is likely ineffective in providing appropriate hemostasis.

Advantages associated with TC-325 use are easy application with a lack of need for precise targeting (although the powder needs to reach the actively bleeding site), noncontact and non traumatic hemostasis, and ability to cover large surfaces of bleeding. In terms of safety, no major complications, including intestinal obstruction or vascular embolization, have been observed in patients treated with TC-325 for GIB [76-77]. However, the accumulation of CO2 gas may become uncomfortable for the patient.

High effectiveness and low re-bleeding rates of TC-325 monotherapy have been demonstrated in several studies [78]. It provides immediate hemostasis [76]. In addition, the powder residency time on the bleeding lesions was demonstrated to be less than 24 hours. Therefore, the current thinking is that TC-325 should not be used as the sole modality in lesions at high risk of rebleeding following the first 24 hours, such as peptic ulcer bleeding with HRS; indeed other modalities, namely thermal or mechanical therapies, should be added to ensure sustained hemostasis [76-77].

Innovations

Several methods to improve endoscopic visibility, risk stratification of bleeding lesions, and hemostasis have been emerged. Cap-assisted hemostasis, over the scope clips, endoscopic suturing, improved clips models, specialized baloon compression, endosonography guided injection therapies are also endoscopic procedure for hemostasis of PU bleeding, but needed to further studies [79-80]. Doppler ultrasonography, magnification endoscopy, and chromo endoscopy have been developed for risk stratification [81].

FAILURE OF ENDOSCOPIC THERAPY

Rebleeding after endoscopic hemostasis occurs in approximately 10% to 15% patients of NVUGIB [82]. Data specific to ulcer bleeding ovary between 6.3% and 25.2% [83].

Several independent predictors of endoscopic failure have been identified based on both pre-endoscopic and endoscopic features. Among pre-endoscopic features, hemodynamic instability, transfusion requirement, and hemoglobin value less than 10 g/dL have been suggested to predict the endoscopic failure [83]. In endoscopic findings, active bleeding at endoscopy, the location of bleeding ulcer in either the posterior duodenal wall or gastric high lesser curvature, greater ulcer size, particularly larger than 2 cm contribute to higher rebleeding rates [83].

In patients with clinical evidence of rebleeding, a second endoscopy should be attempted to achieve hemostasis. Failure of repeat endoscopy should be treated with transcatheter arterial embolization or surgery [84].

Second Look Endoscopy

A second-look endoscopy refers to the performing a preplanned repeat endoscopy 16 to 24 hours following the initial endoscopy, aimed to assess the need for further endoscopic therapy directed toward any possible HRS. This management has been shown to decrease rebleeding rates [85-86] although many of the trials did not include concomitant PPI use and used epinephrine monotherapy. In fact, in the setting of high-dose intravenous PPI, second-look endoscopy did not provide added benefits [87]. Consensus guidelines have concluded that contemporary data do not favor second look endoscopy [4]. The additional cost of second look endoscopy is also needs to be considered [88]. A rebleeding rate exceeding 31% may be needed to offset the cost of a second endoscopy [89]. In settings where the primary hemostasis is uncertain, and where the initial evaluation was incomplete because of blood clots, repeat endoscopy may be warranted [90].

Limitations and Complications

Endoscopic therapy is limited by factors such as an unstable condition of patients, inadequate visualization due to blood, and areas difficult to reach such as the posterior wall of duodenum, junction between the first and second part of duodenum, and lesser curvature side.

Complications of endoscopic therapy are limited and include aspiration pneumonia, perforation, induced bleeding in a non bleeding lesion and parietal wall necrosis. A pooled analysis for all these modalities revealed a complication rate of 0.5%.

Clips and epinephrine injection had the lowest rates of perforation while the heater probe had the highest rate. Perforation is more frequent for duodenal ulcers. Perforation of the ulcer bed usually requires surgical repair, although in recent years endoscopic clipping, such as over-the-scope-clip system, was successfully used to treat iatrogenic perforations [91-92]. Induced bleeding is usually controllable with on-going hemostasis in most cases and exceptionally requires radiologic or surgical treatment. Parietal wall necrosis can mainly be related to the use of sclerosing agents.

SUMMARY

Upper gastrointestinal endoscopy is the mainstay in the management of PU bleeding. It should be performed within 24 hours of patient presentation, following hemodynamic resuscitation. Endoscopic risk stratification into HRS and LRS is important for management with the us endoscopic therapy. The choice between injection, thermal, and mechanical modalities, and the use of hemostatic powders, depends on individual preferences, availability, and ulcer characteristics. Although, epinephrine injection is effective and easy to use, it is not recommended as a monotherapy.

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