Pharmacotherapy & Endotherapy

GI BLEEDINGS AND ADVANCES IN THE ENDOSCOPIC THERAPIES

Upper GI bleeding is a common medical presentation in gastroenterology practice and approximately 90% of gastrointestinal bleeds are from the upper digestive tract. It is estimated that greater than 350,000 hospital admissions for UGI bleeding occurs annually with an overall mortality rate of 10%.

The causes of upper GI bleeding could be classified as follows:

• Duodenal ulcer (30-37%)
• Gastric ulcer (19-24%)
• Esophageal varices (6-10%)
• Gastritis or duodenitis (5-10%)
• Esophagitis or esophageal ulcer (5-10%)
• Mallory Weiss tear (3-7%)
• Gastrointestinal malignancy (1-4%)
• Dieulafoy’s lesion (1%)
• Arteriovenous malformation
• Angiodysplasia of the stomach or duodenum

During the past decade endoscopic hemostatic therapy has simplified management of upper GI bleeding. In fact endoscopy is considered a primary and pivotal early intervention in establishing the source and cause of bleeding. It also allows estimation of an individual's risk for recurrent bleeding and therapeutic intervention accordingly.

On the other hand, nearly one third of patients rebleed even after appropriate endoscopic intervention. This causes increased morbidity and mortality and thereby adds significantly to the cost of treatment.

Proton pump inhibitors (PPIs) have now been established as the standard treatment for prevention of ulcer bleeding after endotherapy replacing the earlier H2 receptor blockers. The adjuvant use of PPIs also decreases the rate of surgical intervention including transfusion requirements and hospital stay. This has been confirmed consistently by different studies and meta-analyses.

This chapter attempts to discuss the recent advances and consensus on management of upper GI bleeding.

Management of upper GI bleed has been classified primarily into:

1. Pharmacotherapy
2. Endoscopic management

Endoscopic management strategies again differ based on the cause of bleed and can be classified into two primary divisions:

• Variceal Bleeding
• Non variceal bleed
1. Pharmacotherapy:

Pharmacotherapy has focused on the use of profound acid suppression with proton-pump inhibitors in the treatment of patients with nonvariceal upper gastrointestinal hemorrhage. Experimental data have shown that gastric acid impairs clot formation, promotes platelet disaggregation, and favors fibrinolysis. The pharmacologic goal post haemostasis is therefore to achieve an intragastric pH>6.0 at which optimal clot formation and stabilization is achieved.

The efficacy of IV PPIs post endoscopic haemostasis to reduce rates of rebleeding, and the need for surgery in peptic ulcer bleeding has been clearly demonstrated. A few individual trials have now shown that high dose oral PPIs also reduce the rate of rebleeding. The recent introduction of immediate release preparations with rapid onset of action could provide an oral alternative for GI bleed.

A meta-analysis on the use of PPIs for peptic ulcer bleeding by Leontiadis et al. included 23 randomized controlled trials with 4308 patients. PPIs significantly reduced the rebleeding rate (OR 0.49) and surgery rate (OR 0.62), with no apparent effect on the mortality (OR 1.01). A significant effect on
mortality (OR 0.53) was observed when the analysis was restricted to only 2102 patients with high-risk stigmata (active bleeding or non-bleeding visible vessel).

The use of IV proton pump inhibitors (PPI) before endoscopy has been shown to reduce the need of endoscopic therapy and shorten hospital stay.

In a randomized, placebo-controlled study, Lau et al. showed that early administration (before endoscopy) of high-dose PPIs (80 mg i.v. bolus, followed by 8 mg/h omeprazole) speeds up the resolution of stigmata of bleeding and reduces the need for endoscopic hemostasis. Out of 369 randomized patients, 222 (110 with omeprazole, 112 with a placebo) were documented as having bleeding ulcers. The incidence of significant stigmata of bleeding, the presence of active bleeding with Forrest Ia and Ib, and the need for endoscopic hemostasis were significantly reduced in patients receiving omeprazole in comparison with the placebo.

However, the efficacy of PPIs to reduce all-cause mortality has not been demonstrated. Trials conducted in Asia demonstrated that adjuvant PPI treatment reduced all-cause mortality among all patients irrespective of the dose and mode of PPI usage. The magnitude of benefit of PPI therapy however differs across geographical locations and is significantly higher in the Asia-Pacific region compared to North America, Europe and South Africa. This has been attributed to enhanced pharmacodynamic effect of the proton pump inhibitors among Asians. The postulated reasons have included a lower parietal cell mass and a higher prevalence of H. Pylori infection. The genetic polymorphism for cytochrome 2C19 resulting in a “slow metabolizer” phenotype could also play a role in higher effectiveness.

It remains unclear if mortality in patients with peptic ulcer bleeding can really be improved by adjuvant PPI therapy. Future trials need to include a substantial number of patients, and mortality as a primary end point is required.

ENDOSCOPIC MANAGEMENT OF VARICEAL BLEEDING

**Epidemiology:**

Bleeding from esophagogastric varices is a major complication of portal hypertension. Varices are identified in about 30% of patients with well compensated cirrhosis and 60% of patients with decompensated cirrhosis. Small varices are at low risk of hemorrhage compared to bigger ones. Varices increase in size from small to large at the rate of 10-20% per year. Variceal bleeding takes place at the rate of 10-20% per year but rises to 20-30% per year in patients with large varices. The statistics are important because bleeding from varices is responsible for more than a quarter of deaths in patients with cirrhosis.

**Therapeutic endoscopy for variceal bleeding**

The goal of therapeutic endoscopy is to stop acute variceal bleeding by creating an intravariceal thrombus. Repeated procedures may induce variceal obliteration. Two techniques are now standardized:

A. **Endoscopic sclerotherapy:**

Sclerotherapy involves injecting an irritant solution (e.g., sodium morrhuate, ethanolamine or polidocanol) or a dehydrating chemical (sodium tetradecyl sulphate) into the esophageal varix or its adjacent supporting tissues. This results in acute induction of vascular spasm, with subsequent development of intravariceal thrombosis, intimal thickening and perivenous thrombosis.

Although sclerotherapy was introduced as early as 1939, it was only with the advent of fibre optic endoscopy in the mid 1970's that sclerotherapy was accepted as an effective mode of management of esophageal varices. It is now recognized that sclerotherapy can achieve early hemostasis in up to 95% of patients suffering from variceal bleeding.

However sclerotherapy has a number of drawbacks. These are summarized as follows:

1. It usually takes 3-6 ES sessions to obliterate esophageal varices.
2. ES has no role in the control of bleeding from portal hypertensive gastropathy.
3. It is rarely successful in the emergent control of bleeding from large gastric varices.
4. Complication rates have ranged from 10% to 20% and associated mortality rates as much as 1%-2%. Post sclerotherapy esophageal ulcers is the commonest complication of ES. These ulcers may be further complicated by esophageal dysmotility and esophageal stricturing which is seen in 1.6%-3% of patients.

Other complications including esophageal perforation (0.5%), systemic infections, pleural effusion, mediastinitis, portal and mesenteric vein thrombosis and adult respiratory distress syndrome has been reported.

6. Sclerotherapy is known to worsen portal hypertensive gastropathy and increase the size of gastric varices seen at sites above the level of variceal obstruction.

**Endoscopic variceal ligation (EVL)**

EVL is a promising alternative to sclerotherapy. The basic principle of this procedure is similar to and derived from a hemorrhoid banding procedure. A special ligating chamber is fitted to a standard endoscope. The varix is suctioned into the ligating chamber and an elastic O ring released around the neck of the varix creating a polyp. This results in the coagulative necrosis of the ensnared polyp, with eventual sloughing. Varices in the adjacent submucosa subsequently thrombose. Additionally, acute inflammation of the superficial mucosa leads to shallow ulcers followed by healing, granulation tissue and resultant obliteration of variceal channels.
The original band ligation device could employ only one “O” ring at a time. Technical problems were encountered with this system including a limited field of view and the need to reload bands. Multi-band ligation devices are now available. The multiband ligator has obviated the need of passing an overtube prior to starting an EVL and only one passage of the endoscope is needed. This has in turn reduced the risks of esophageal laceration and perforation and increased the safety of the procedure.

**Endoloop ligation** with detachable endoloops is the latest modification to overcome drawbacks associated with the use of band ligators. This is the only method that can stop bleeding from vessels 3-5mm in diameter because it exerts a greater compressive force on tissue compared to elastic bands. Also, because endoloops attach more tightly to tissue, it could be the treatment of choice for junctional varices in the cardia of the stomach where the tissues are thicker compared to the esophageal mucosa.

**EVL vs. ES vs. Endoloop**

The first randomized trial comparing EVL with ES was reported in 1992. By 1995 at least seven randomized trials underwent meta-analysis. Other long term data have subsequently been published comparing the two.

Compared to ES, EVL significantly reduced the rebleeding rate, the mortality rate, and the death rate due to rebleeding. On an average it took lesser number of EVL sessions to obliterate the mortality rate, and the death rate due to rebleeding. On comparing the two.

In fact, only 1.0% of EVL procedures were associated with fatal complications compared to 3.3% with ES. Some studies have however reported higher frequency of variceal recurrence (48%) compared with EVL. Comparative studies between EVL and Endoloop ligation have shown both to be equally effective in achieving hemostasis. There are no statistically significant difference in recurrent bleeding between the two groups. However variceal eradication after the initial treatment appears to be higher in the endoloop group compared to the band group. Also, technically the chances of damage to the endoscope are lesser with the endoloop as the connecting thread between the cap and trigger in the multiband ligation device exerts a strain on the endoscope throughout the procedure.

**Alternative endoscopic approaches and the future**

Endoscopic management of gastric varices is the current focus of research. One approach uses sclerotherapy technique to inject the tissue adhesive N-butyl-2-cyanoacrylate. Cyanoacrylate injections with simultaneous sclerotherapy have shown promising results. Other recent advances include the use of endoscope to deploy detachable clips and detachable snares in an effort to entrap esophageal varices and induce thrombosis.

Ligation therapy is considered the endoscopic treatment of choice for esophageal variceal bleeding. However ligation may be technically difficult in patients with a large amount of blood in the esophagus and treatment of active bleeding at initial endoscopy is more easily accomplished by sclerotherapy. Sclerotherapy is also useful near the end of a course of treatment when only small varices remain and proper degree of aspiration of the varices into the ligation chamber is not possible. Additional clinical experience with detachable endoscopic clips, snares and the newer techniques are required to standardize endotherapy of varices.

**ENDOSCOPIC MANAGEMENT OF NON VARICEAL UPPER GI BLEED**

**Epidemiology**

Peptic ulcer accounts for about 50-70% of all cases of upper GI hemorrhage as diagnosed on upper GI endoscopy. A Dieulafoy lesion accounts for up to 5% of cases of GI hemorrhage and is another important cause of upper GI bleeding. Upper GI vascular ectasias including gastric antral vascular ectasias (GAVE) and angiodysplasia are also being recognized as increasingly important sources of GI bleeding.

Bleeding from peptic ulcer stops spontaneously in 70-80% of cases. However mortality from peptic ulcer bleed ranges from 5-10% and could be as high as 50% in case of rebleed. Clinical and endoscopic stratification of patients into low and high risk categories is thus crucial to decide the line of management. The Rockall score is an accepted clinical scoring system for predicting outcome (Table Below).

<table>
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<th>Rockall numerical risk scoring system</th>
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<td>Age(years)</td>
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*SRH: Stigmata of recent hemorrhage
**Source: Rockall et al (23)
**Risk of rebleeding and mortality respectively were 4.3% and 0 when the score was <2; 14% and 4.6% when it was 3-5 and 37% and 22% when >6

The modified Forrest criteria are internationally accepted for endoscopic risk stratification of peptic ulcer and are as follows:

**Type 1: Actively bleeding ulcer**

1a. Spurring
1b. Oozing

**Type 2: Non actively bleeding ulcer**

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be classified as follows: (Table 1). 

Type 3: Ulcer with clean base

Type 2c & 3 require no endotherapy as risk of rebleed is only 5-10%.

Type 1 & 2 require endotherapy with a rebleed risk of 43-55%

Endoscopic haemostasis is thus the key therapeutic tool for management of all high-risk cases of non variceal bleed. In two meta-analyses comprising over 30 randomized trials involving over 2400 patients, endoscopic therapy significantly reduced rebleeding, need for emergency surgery, and mortality (24, 25).

In parallel these improved health outcomes are associated with significant cost benefit both to the patient and the healthcare system (26). The role of endotherapy for adherent clots is still not established.

Hemostatic techniques available at the time of endoscopy could be classified as follows: (Table 1).

### Endoscopic modalities available for management of UGI bleed

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<th>Injection</th>
<th>Thermal</th>
<th>Mechanical</th>
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<td>Adrenaline</td>
<td>Heater probe</td>
<td>Haemoclip</td>
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<td>Fibrin glue</td>
<td>Bicap probe</td>
<td>Banding</td>
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<td>Human thrombin</td>
<td>Gold probe</td>
<td>Endoloops</td>
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<td>Sclerosants</td>
<td>Argon plasma coagulation</td>
<td>Staples</td>
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<td>Alcohol</td>
<td>Laser therapy</td>
<td>Sutures</td>
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Selection of the optimal hemostatic device would depend primarily on the characteristics of the lesion, local expertise, equipment availability and of course cost of the procedure.

#### Thermal hemostatic devices:

All thermal devices generate heat either directly (heater probe) or indirectly by tissue absorption of light energy (laser) or passage of electric current through tissue (multipolar probes, argon plasma coagulator). Heating leads to edema, coagulation of tissue protein and contraction of vessels resulting in a haemostatic bond.

The conventional gold probe is reasonably effective, cheaper and widely available. Laser therapy is the precise, effective albeit expensive alternative. Laser systems may additionally be cumbersome requiring 220V power source and with limited portability. Both these methods however have the potential to cause unintentional injury to the adjacent as well as deeper tissues. The rate of perforation following treatment of GI bleeding ranges from 1.8-3% and precipitation of bleeding has been reported in up to 5% (27). Complications may be related to power setting, duration of application, and distance of the probe tip from the tissue.

Argon plasma coagulation has an inherent advantage in that it produces superficial tissue coagulation with a penetration depth of only 1 to 2 mm. Also, it is easier to use particularly in the duodenum and is cheaper than the laser.

At the Asian institute of gastroenterology we have recently used the “spray coagulation” system endoscopically with encouraging results. This method is normally used in surgery to control bleeding e.g., from the gallbladder fossa after cholecystectomy. It may be an useful alternative in that it involves no new equipment and thus is very cost effective.

#### Injection needles

Injection needles are devices passed through the working channel of an endoscope that allow the injection of liquid agents into target tissue. They consist of an outer sheath (plastic, Teflon or stainless steel) and an inner hollow—core needle and are available in lengths of 200 to 240cm. Solutions administered via these needles achieve haemostasis by mechanical tamponade, induction of vasospasm and thrombosis of vessels.

Injection therapy is simple to perform and is the cheapest available diagnostic modality. A large range of injection materials has been used including dilute adrenaline (1 in 10000), fibrin glue; thrombin, alcohol and a variety of sclerosants have been used. Current evidence suggests that dilute adrenaline is effective and safe for active hemorrhage. Rebleeding rates are reduced by the addition of agents such as thrombin or a thrombin—fibrinogen mixture. Sclerosants and alcohol should be used only sparingly because of the risk of serious complications including rebleeding, sclerotherapy ulcers and perforation.

#### Mechanical devices

These arrest bleeding by applying a direct pressure in case of minor injuries or by applying ligature when a larger vessel is involved. A range of metallic clips (haemoclips), bands and loops are now available.

Endoscopic haemoclips have achieved hemostasis in 84 to 100% of patients with a variety of upper GI bleeding sources peptic ulcers, Mallory Weiss tears, Dieulafoy lesions, gastric angiectasias, gastric tumors and following polypectomy, sphincterotomy and biopsy. The advantages of haemoclips are that they cause no tissue injury, do not impair tissue healing and can be applied relatively quickly and safely using improved applicators. Clips are particularly well suited for the treatment of arterial bleeding and visible vessels and appear to be the treatment of choice in such situations.

Other mechanical methods like band ligation and endoloops are usually used for small focal bleeds like Dieulafoy’s lesions. Newer mechanical suture devices are now being introduced but further clinical experience is needed to prove its practicability and long term results.

#### Combined modalities

There is trend towards combined use of two endoscopic modalities using injection and mechanical or injection and thermal probe therapy in actively bleeding peptic ulcer. Adrenaline injection and thermodocoagulation combined have shown lesser rebleed rates than injection alone in some studies whereas others have not
been as conclusive. Larger comparative trials are necessary for a
definite answer.

Consensus Recommendations for Endoscopic Management of Non-
variceal upper GI bleed

- Early endoscopy (within the first 24 hours) with risk clas-
sification by clinical and endoscopic criteria allows for safe
and prompt discharge of patients classified as low risk; im-
proves outcomes for patients classified as high risk; reduces
resource utilization for patients classified as either low or
high risk.

- A finding of low – risk endoscopic stigmata is not an indica-
  tion for endoscopic haemostatic therapy. A finding of a clot
  in an ulcer bed warrants targeted irrigation in an attempt at
  dislodgement, with appropriate treatment of the underlying
  lesion.

- No single solution for endoscopic therapy is superior to
  another for haemostasis.

- No single method of thermal coaptive therapy is superior
to another.

- Monotherapy with injection or thermal coagulation, is an
effective endoscopic haemostatic technique for high risk
stigmata; the combination is superior to either alone.

- The placement of clips is a promising endoscopic hemo-
  static therapy.

- Routine second look endoscopy is not recommended.

- In cases of rebleeding, a second attempt at endoscopic ther-
  apy is generally recommended.

As it stands today, optimal use of endoscopic therapeutic
modalities in combination with pharmacotherapy shall continue
to play a pivotal role in the management of UGI bleed in the
years ahead.

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