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Acid inhibition and peptic ulcer bleeding

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Key Words

Peptic ulcer bleeding – Proton-pump inhibitors (PPIs) – Combined endoscopic therapy – Transarterial embolisation (TAE)

Abstract

Peptic ulcer bleeding is one of the most common emergency situations in medicine. The combined pharmacological and endoscopic therapy together with emerging interventional radiological procedures are successfully treating peptic ulcer disease, reserving surgical procedures for only a small portion of patients unresponsive to 'conventional' therapy. Technological advancement has seen a great improvement in the field of endoscopic treatment in the form of various methods of hemostasis. However, pharmacological therapy with proton-pump inhibitors (PPIs) still plays the central role in the peptic ulcer bleeding treatment algorithm.

Introduction

Peptic ulcer disease (PUD) is the most common cause of upper gastrointestinal bleeding (UGIB), accounting for almost 50% of UGIB cases. The importance of treating peptic ulcer bleeding is even greater when we take into account that UGIB is one of the commonest medical emergencies. Today, the use of so many potent anti-clotting medications in treating numerous medical conditions increases the risk of UGIB even more. However, medical breakthroughs have changed the way PUD and peptic ulcer bleedings are handled, thwarting the threat of peptic ulcer bleeding at its source.

Epidemiology of Peptic Ulcer Bleeding

When speaking of peptic ulcer bleeding, we are practically describing UGIB. Over 45% of cases of UGIB are caused by peptic ulcer bleeding, localization being almost equally distributed between the stomach and the duodenum. Other important causes include gastric erosions (around 20%), varices (10%), Mallory-Weiss tears (7%) [1]. The mortality rate equals 7-10% [2].

The incidence of peptic ulcer bleeding varies proportionally with the incidence of UGIB, the latter varying from 50-100 patients/100,000 population/year of which 20-50 patients/100,000 population/year are attributed to peptic ulcer bleeding [3].

Etiology of PUD

Non-steroid anti-inflammatory drugs (NSAIDs) and *H. pylori* infection are the two most important causes of PUD, accounting for more than 90% of PUD occurrences [4]. The discovery of *H. pylori* and its relation to PUD during the 80's was one of the greatest discoveries in the second half of the 20th century [5]. The use of antibiotics led to a dramatic fall in the *H. pylori*-related PUD (causing 70-80% PUD cases during the 80's) and a relative rise of NSAIDs-induced PUD. The number of cases of PUD caused by *H. pylori* nowadays is only a few percent lower than the number of cases of PUD caused by NSAIDs, reflecting the decreasing incidence of *H. pylori* in the population and the increasing tendency of NSAIDs use [6].

Pathophysiology

The mechanism by which NSAIDs and *H. pylori* cause the peptic ulcer disease has been revealed in its rudimentary form. Specific molecular mechanisms responsible for the disease are being discovered every year. There are small differences in the pathophysiology of gastric and duodenal ulcer, but the basic mechanisms are the same. Present knowledge has established that PUD is caused by an imbalance between the aggressive and protective factors. The main aggressive factors are hydrochloric acid and pepsin [7]. The protective

factors, on the other hand, consist of several gastric and duodenal mucosa layers of defense. The first layer, which sheathes the luminal side of the epithelial cells, consists of mucus and of bicarbonate ions. The second layer is created from epithelial cells and tight intercellular junctions, while the third line of defense consists of adequate blood supply and local hormones (e.g. prostaglandins) [8]. The increase in acid and pepsin load (aggressive factors) or the decrease of the protective factors will eventually lead to the destruction of the epithelial lining and the formation of a peptic ulcer. The pathophysiological momentum is somewhat different in gastric ulcers where weakening of the protective factors is more pronounced, as opposed to duodenal ulcers, where increased intensity of aggressive factors prevails. In time, as the disease progresses and the aggressive factors are able to penetrate blood vessel walls, the peptic ulcer will start bleeding.

NSAIDs tip the balance in favor of ulcerogenic factors by decreasing the blood flow to the gastric mucosa (by inhibiting prostaglandine synthesis which in turn relax the musculature of the blood vessels) [9], while *H. pylori* infection at first induces intensified acid production and later destroys the mucus layer lining the epithelium [10].

Diagnosis

Diagnosing peptic ulcer bleeding is made in several steps. The first step is taking patient's history and performing a physical exam. As with every UGIB, there will be signs of blood exiting the organism either through mouth (hematemesis) or anus (melena, hematochesia). Tenderness in the epigastrium and skin paleness can be present when examining the patient. Laboratory tests are indicative of blood loss (low levels of hematocrite, hemoglobin, high levels of urea, etc.) The definite diagnosis is made by an expert endoscopist performing esophagogastroduodenoscopy (EGDS). It is the method by which the examiner directly visualizes intestinal mucosa and the site of bleeding. The advantage of EGDS is that it is also a therapeutic instrument which will be explained later in the text [11].

Various scoring systems have been developed in the attempt to distinguish between patients who have high and those who have low rebleeding risk, therefore reducing the number of unnecessary endoscopic procedures (e.g. Glasgow-Blatchford, clinical Rockall score) [12]. There are many pros and cons for this approach, but unreliability is the main reason why the scoring systems have not entered clinical practice guidelines.

EGDS, therefore, remains the gold standard in UGIB. It is used as a diagnostic, prognostic and therapeutic tool. Prognosis is especially important as it is directly related to the signs of bleeding from the bleeding site. Prognostic systems have been developed to standardize findings. Generally, they divide the bleeding activity into active bleeding, into signs of recent

hemorrhage and into ulcers that are in the process of healing (Forrest classification, the risk of rebleeding with every subtype is shown in Table 1 [13].

Therapy

Current therapeutic approaches in managing peptic ulcer bleeding and UGIB include endoscopic and radiological procedures, pharmacotherapy and surgery.

Endoscopic and radiological methods

The advantage of endoscopy over other methods is that it allows the examiner to make diagnosis, prognosis and apply therapy, all at the same time.

Endoscopic therapy is the field of many innovations. Currently, all endoscopic treatment procedures can be divided into three distinct treatment categories: injection, thermal and mechanical therapy. Injection therapy is the most commonly used endoscopic treatment where different substances are injected directly into the bleeding blood vessels or the surrounding tissue: diluted adrenaline, sclerosing agents, thrombin, fibrin glues, etc. Thermal therapy is based on coagulation. It is achieved by either non-contact (Nd-YAG laser, argon plasma coagulation) or contact (BICAP) methods. Finally, mechanical therapy is based on mechanical blood vessel compression using metal clipses [11]. As with every method, there is always a risk of failure and subsequent rebleeding. Recent studies have shown that combined endoscopic treatment (adrenaline + second method) results in a lower incidence of rebleeding, emergency surgical procedures and death [14].

Radiological procedures in PUD offer a new way to treat refractory bleeding ulcers and an alternative to surgery in patients in whom endoscopic procedures are unable to achieve hemostasis. This has become increasingly important in treating duodenal bulbar hemorrhages, especially of the posterior wall. Although the choice of the best embolization material is still being debated (coils, cyanaocrylate glue, gelatin sponge or calibrated particles), the data collected from recent studies imply that transarterial embolization (TAE) is a safe procedure with low incidence of complications and a high rate of success [15]. Endoscopic procedure still remains the therapy of choice.

Pharmacotherapy

Proton pump inhibitors (PPIs) are the cornerstone of peptic ulcer bleeding and UGIB therapy. The usefulness of PPIs in UGIB has been proven many times [16, 17]. The reasons underlying PPI use is that the gastric acid decreases platelet aggregation, increases clot lysis and decreases fibrinolytic activity. The target pH level needed to neutralize these effects is above 6 and PPIs have been proven to achieve and sustain the pH target level [18, 19].

The controversial topics haunting gastroenterologists today are not whether PPIs should be used, but rather when should they be used and in what form. The question of timing PPIs is related to the timing of endoscopic procedure and can be given either before or after the procedure. Studies assessing this problem have remained inconclusive, some stating that pre-endoscopic PPI use is a cost-effective strategy [20], others claiming there is no difference between the two [21]. The main issue is probably more related to the timing of EGDS (emergency or delayed) than of the PPIs. The second problem is the form in which PPIs should be administered (intravenously or orally). In the studies frequent administration of high-dose oral PPIs had similar effectiveness compared to the continuous administration of intravenous PPIs [22]. However, continuous administration of intravenous PPIs achieved target pH more rapidly, which is an important advantage in the setting of acute hemorrhagic condition.

Surgery

Bleeding ulcers that are refractory to endoscopic therapy (approximately 5-10% of cases) and TAE must be treated surgically [23, 24]. Unfortunately, surgery carries a certain risk of complications which is usually higher due to the patient's hemodynamic instability and coagulation disorder (as a result of recurrent bleeding). Luckily, technical advancements and the use of endoscopy in everyday practice have significantly reduced the number of surgical procedures needed to treat bleeding ulcers. The preferred method used to stop bleeding ulcers is applying hemostatic sutures at the site of bleeding. Vagotomy and pyloroplasty or partial gastrectomy (Billroth II, very rarely) is performed, if sutures cannot stop the bleeding [25].

Conclusion

The year 2010 has been important for proclaiming the new International Consensus Recommendations on UGIB (Table 2) [26, 27]. The main statement (C3) which has level of recommedation IA reflects the 100-years old idea *no acid equals no ulcer*. The role of PPIs in UGIB treatment is even more emphasized by statements C1 [28] and C2.

Statement A2 introduces prognostic scales into the UGIB treatment. However, prognostic scales cannot be used as a replacement for endoscopy, but rather as a guide to intensify the treatment when endoscopic findings are consistent with a low chance of rebleeding or to back up the decision to discharge the patient when the risk for rebleeding using both methods is low. Statement B3 solidifies the central position of endoscopy in UGIB treatment, while in statement B11 the role of endoscopy in ulcer follow-up has been diminished.

As in every emergency medical condition, treatment algorithms are being compiled and that is the case for UGIB as well. A unified view is still needed, but a common approach is shown in

Figure 1. When suspecting UGIB, esophagogastroduodenoscopy (EGDS) must be performed in order to confirm the diagnosis. Active bleeding sites (Forrest I) or sites with high-risk stigmata (Forrest IIa & b) should be treated endoscopically, followed by an intensive IV PPI treatment (bolus dose of 80 mg intravenous PPI combined with a 72-hours infusion of PPI 8 mg/h). Sites with low risk stigmata should be treated with oral PPIs. This is the framework upon which future modifications will be made; PPIs before or after EGDS, oral or intravenous PPIs, EGDS or scoring systems; future studies will give us the answers – components for a new and better treatment algorithm.

Peptic ulcer bleeding is a medical condition which has been haunting mankind throughout history, reaching its peak in the 20th century. Technological advancements have made it possible to treat the condition at its source; by determining etiology and pathophysiology of the disease we are now able to prevent it.

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Table 1 Risk of rebleeding according to Forrest classification [13]

Forrest classification		Definition		Risk of rebleeding
I	a	active bleeding	arterial	55%
	b		venous	
II	a	signs of recent hemorrhage	visible vessel	43%
	b		clot	22%
	c		hematin base	10%
III		ulcer in the process of healing	clean-base ulcer	5%

Table 2 Selected statements from the International Consensus Recommendations 2010 [27]

A.	**Resuscitation, risk assessment, and preendoscopy management**
A2	*Prognostic scales are recommended for early stratification of patients into low- and high-risk categories for rebleeding and mortality.*
B.	**Endoscopic management**
B3	*Early endoscopy within 24 hours of presentation is recommended for most patients with acute gastrointestinal bleeding.*
B11	*Routine second-look endoscopy is not recommended.*
C.	**Pharmacologic management**
C1	*Histamine-2 receptor antagonists are not recommended for patients with acute ulcer bleeding.*
C2	*Somatostatin and octreotide are not routinely recommended for patients with acute ulcer bleeding.*
C3	*Intravenous bolus followed by continuous-infusion proton-pump inhibitor can effectively decrease rebleeding in patients who have had successful endoscopic therapy.*

Figure 1 Treatment algorithm for non-variceal UGIB, modified from [29]