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Current Opinions in Bleeding Peptic Ulcer Disease

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Abstract

Background: Peptic ulcer is the commonest cause of acute upper gastrointestinal bleeding accounting for the majority of cases of non-variceal haemorrhage. Its incidence is rising in the older population and accounts for a considerable clinical and economic burden.

Methods: A MEDLINE/EMBASE based search of the literature from 1985 to 2013 inclusive was performed using the medical subject terms peptic ulcer disease, duodenal ulcer, upper gastrointestinal non-variceal bleeding, endoscopic therapy, pharmacological therapy, haemostasis, surgery for bleeding peptic ulcer. Manual retrieval of relevant articles in the reference lists of the original papers was then performed. Conclusions were drawn from published evidence on the current opinions and treatment options available for bleeding peptic ulcer disease.

Results: The incidence of bleeding peptic ulcer disease and hospital admission rates has not changed significantly in the last two decades. Progress in the development and the use of endoscopic and pharmacological therapies has revolutionised the management of bleeding peptic ulcer disease. However, the improved survival accrued to these advances is offset by the mortality in the increasing elderly population with associated medical co-morbid factors. The operation for bleeding peptic ulcer disease is still being performed in small but significant number of patients who fail endoscopy.

Conclusion: The management of patients with bleeding peptic ulcer disease requires a multidisciplinary approach. Clinical presentation, patient's age, presence of co-morbidity and the endoscopic appearances of the ulcer including the presence of stigmata of recent haemorrhage are used to determine the subsequent level of care. Endoscopic therapy provides unique opportunities for early diagnosis and maintenance of primary haemostasis in bleeding peptic ulcer disease.

Keywords: Bleeding ulcer disease; Resuscitation; Endoscopy; Haemostasis; Drug therapy; Surgery

Introduction

Peptic ulcer is the commonest cause of acute upper gastrointestinal bleeding accounting for about 35-50% cases of non-variceal haemorrhage [1-4]. It is responsible for a considerable clinical and economic burden and it is estimated that 1 billion of dollars is spent annually in the United States [3,4]. The incidence of gastrointestinal bleeding secondary to peptic ulcer disease and hospital admissions for this acute complication have not changed significantly in the last two decades [5]. The incidence varies from 50-150 cases per 100 000 per year and accounts for about 15000 hospital admissions per year in the United Kingdom. Similar incidence of 48-160 cases per 100,000 adults per year has been reported in the United States [4]. The incidence is highest in areas of socioeconomic deprivation [1]. The incidence of peptic ulcer bleeding is rising in the elderly patients [6-8].

Despite recent advances in diagnosis and therapy, mortality rates for this life threatening entity remained essentially unchanged at 6-14% over the last two decades. This has been linked to the fact that patients are older and have associated multiple medical co-morbid factors that worsen the prognosis. Other reasons responsible for this poor outcome include the underuse of endoscopic haemostatic techniques and widespread use of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin [1,4,7,9-14]. Most deaths occur in the elderly and there seem to be a direct correlation between the number and severity of medical co-morbidities with the mortality [1,7,10,12]. Higham et al. [7] reported a decline in the admission and mortality rates among young individuals with significant increase rates among the elderly patients. Mortality however is reported to be lower in specialist units and this reduction probably may be related to strict adherence to protocols and guidelines [15].

Management strategies for bleeding peptic ulcer disease have changed dramatically over recent decades due to the introduction of acid suppressive therapy with especially proton pump inhibitors (PPIs)] and endoscopic therapy. The improvements in non-surgical modalities like pharmacotherapy with PPI and therapeutic endoscopy have revolutionised the management of bleeding peptic ulcer and surgical therapy is generally reserved for those patients in whom endsocopic therapy fails or is not available. The advent of endoscopic and pharmacological therapies has been shown to diminish the need for emergency surgery in bleeding peptic ulcer disease. However, when such therapies fail surgery is still indicated. The operation for peptic ulcer bleeding is still being performed on significant number of patients who fail endoscopic and pharmacological therapy [16,17]. There have been recent improvements in the management and outcome of bleeding peptic ulcer disease due to the readily available use of endoscopic and pharmacological therapy and the addition of intensive therapy unit (ITU) care.

This is a review of the published literature on the current opinions in the management of bleeding peptic ulcer disease. Various therapeutic methods are available and recommendations outlined based on current available evidence.

Methodology

A MEDLINE and EMBASE based search of the literature from 1985

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to 2013 inclusive was performed using the medical subject terms peptic ulcer disease, duodenal ulcer, bleeding upper gastrointestinal bleeding, non-variceal upper gastrointestinal bleeding, endoscopic therapy, haemostasis, surgery for bleeding peptic ulcer. Manual retrieval of relevant articles in the reference lists of the original papers was then performed. The pathophysiology, diagnosis, management and outcome were reviewed. Conclusions were drawn from published evidence on the current treatment options available for bleeding peptic ulcer disease.

Pathophysiology

Significant haemorrhage from peptic ulcer disease is due to erosion of an underlying artery and the severity of the bleeding relates to the size of the arterial defect and the diameter of the artery [13]. The natural history reflects the progressive erosion commonly of a large posterior duodenal ulcer into the gastroduodenal artery and to a lesser extent, high and lesser curve gastric ulcers involving branches of the left gastric artery. The main modifiable risk factors for acute peptic ulcer bleeding are active *Helicobacter pylori* (*H. pylori*) infection and the use of cyclo-oxygenase (COX) inhibitors and antiplatelet agents. The interaction of *H. pylori* with other risk factors in acute bleeding peptic ulcer is not fully understood. It is believed that in general, *H. pylori* infection and aspirin or non-steroidal anti-inflammatory agents (NSAIDs) have both independent and additive effects in increasing peptic ulcer bleeding [2,4,13]. The majority of bleeding peptic ulcers present with little or no history of dyspepsia, while a history of significant consumption of aspirin or non-steroidal anti-inflammatory drugs is common [13]. Kolkman and Meuwissen [18] have shown that the inhibition of continuing bleeding from peptic ulcer disease by gastric acid is mainly by two mechanisms: prevention of clot formation and promotion of clot lysis and then by ongoing chemical tissue damage.

Helicobacter pylori (*H. pylori*) infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) cause the vast majority of peptic ulcers and their complications. There is a close relationship observed between *H. pylori* and uncomplicated peptic ulcers [19]. However, the precise aetiopathogenetic role of H. pylori in bleeding peptic ulcer disease has not been fully studied [20]. Acute bleeding from duodenal and gastric ulcers usually stops spontaneously in about 70-80% of cases and supportive therapy is only required [14,18]. The remaining group of patients that failed to stop represents a high risk category requiring prompt identification and treatment to improve the outcome in this condition.

Risk Assessment and Stratification

The current standard of care in patients with upper gastrointestinal bleeding is early panendoscopy to establish a specific diagnosis, identify predictors of further recurrent bleeding and perform concurrent endoscopic haemostasis if high risk stigmata are present [21]. Risk assessment of these patients is based on both clinical and endoscopic characteristics. The clinical rationale for early endoscopic diagnosis and treatment rests on endoscopic classification of findings as high or low risk for recurrent bleeding. The stigmata of high risk bleeding include visible actively bleeding and non-bleeding vessels, adherent clot, spurting or oozing vessels [1,22-26]. Rockall scoring system [1,26] developed from a large prospective audit of patients with acute upper gastrointestinal bleeding in England identified age, shock state, comorbid factors and specific endoscopic findings as independent predictor of re-bleeding and death (Table 1). The scheme of risk assessment should aid in making clinical decisions as to both the need for urgent intervention and the prediction of continued or recurrent bleeding in the context of endoscopic therapy. The scoring system also aims to enable cost-effective use of the available resources. Rockall et al. [1,26] in their original reports demonstrated a good correlation of increasing score with re-bleeding and mortality.

Blatchford et al. [27] have developed an entirely clinically based scoring system in Glasgow which predicts outcome without the need to undertake endoscopy. Blatchford score was modelled on the clinical process and laboratory parameters rather than treatment outcome and the full score can be used to determine the required level of care on admission and to identify those patients who need urgent treatment. Rockall score is the most widely used method for risk assessment to date and it has been validated by independent studies [28-30]. Vreeburgh et al. [28] confirmed that Rockall score accurately predicts mortality but less so at predicting re-bleeding. Deaths are also almost entirely restricted to the elderly patients especially with significant associated general medical diseases. However, a recent study by Cheng et al. [31] showed that Blatchford scoring system outperformed Rockall scoring in predicting clinical outcomes in clinical setting and easier to use in everyday clinical practice.

Various factors associated with an increased risk of surgical intervention and mortality include the presence of shock on admission, re-bleeding, associated comorbid factors, transfusion more than 5 unit of blood, age over 60 years and endoscopic appearance of the ulcer [26,32,33]. Active bleeding from peptic ulcer in a shocked patient carried about 80% risk of continuing bleeding and/or death while a non-bleeding visible vessel at the base of the ulcer is associated with a 50% risk of re-bleeding in hospital [34,35]. Therefore, the independent predictors of outcome in patients with upper gastrointestinal bleeding at presentation are haemodynamic instability, concurrent medical illness and age [26,32,33] (Table 1).

Major SRH, major stigmata of recent haemorrhage (active bleeding or visible vessel); GI, gastrointestinal, BP, blood pressure (Table 2).

Treatment of Bleeding Peptic Ulcer Disease

The goals of therapy are haemodynamic stabilisation, determination of the cause, stopping the bleeding and prevent recurrence. Management of patients with acute upper gastrointestinal bleeding should be focused and dictated by the severity and cause of the bleeding and the presence

Variable & Score	0	1	2	3
Age (years)	<60	60-79	≥80	
Shock	"No shock": pulse <100 + systolic BP ≥ 100 mm Hg	"Tachycardia": pulse ≥ 100 + systolic BP ≥ 100 mm Hg	"Hypotension": systolic BP ≥ 100 mm Hg	
Comorbidity	"Hypotension": systolic BP ≥ 100 mm Hg	No major comorbidity	Cardiac failure, ischaemic heart disease, any major comorbidity	Renal failure, liver failure, disseminated malignancy
Diagnosis	Mallory Weiss tear, no lesion identified and no SRH/blood	All other diagnoses	Malignancy of upper GI tract	
Major SRH	None or dark spot only		Blood in upper GI tract, adherent clot, visible or spurting vessel	

Table 1: The Rockall Risk Scoring System [1,26].

Admission parameters	Score
Heart rate (beat/minute) ≥ 100	1
Systolic blood pressure (mmHg)	
100-109	1
90-99	2
<90	3
Blood urea (mg/dL)	
19-22.3	2
22.4-27.9	3
28.0-69.9	4
≥ 70.0	6
Haemoglobin g/dL (Men)	
≥ 12-13	1
10-11.9	3
<10	6
Haemoglobin g/dL (Women)	
≥10-12	1
<10	6
Clinical presentation	
Syncope	2
Melaena	1
Comorbidities	
Hepatic disease	2
Heart failure	2

Table 2: The Blatchford Risk Scoring System [27].

of associated comorbid diseases. A formal risk assessment should always be done to triage these patients into a high risk and a low risk groups. Bleeding from peptic ulcer disease will stop spontaneously in 70-80% of patients without recurrence [14,16,36,37]. Therefore, the main goal of management is to identify patients at high risk of continuing or recurrent bleeding with adverse outcome on the basis of clinical, laboratory and endoscopic variables [1,21,26,27,36,38,39].

The first priority in the management of acute upper gastrointestinal bleeding is active resuscitative efforts to maintain patent airway, breathing, and correct fluid losses and restore blood pressure and tissue perfusion. The patients must be adequately worked up and comorbid diseases must be promptly identified and appropriate supportive measures instituted often in the intensive care or high dependency care settings [38,39]. Central venous pressure monitoring is useful especially in the elderly with associated cardiac problem in order to guide fluid replacement volume. Adequate resuscitation is aimed at maintaining central venous pressure of 5-10 cm H_2O and a urine output of more than 30 ml/hr [38]. Blood transfusion is administered to patients who are shocked or actively bleeding and also if the haemoglobin concentration is less than 100g/L [13,38,39]. The evidence for this transfusion threshold is rather poor but it is known that the risk of significant adverse cardiac events is high in these patients when the haemoglobin concentration is less than 70g/L in the intensive care unit setting [13,38]. Baradarian et al. [40] in a cohort comparison study demonstrated that early intensive resuscitation in patients with acute upper gastrointestinal bleeding reduces the mortality with fewer myocardial infarctions in the intervention group.

Medical Therapy

The role of medical therapy for active, recurrent or recent bleeding peptic ulcer is unclear and controversial. There are three groups of agents that have been used in an attempt to reduce the risk of re-bleeding in these patients: (a) acid suppressing drugs, (b) somatostatin and its analogue octreotide and (c) antifibrinolytic agents. The use of acid suppressing agents is based on the observation that the stability of a blood clot is reduced in an acid environment probably by optimising platelets aggregation [1,41]. It is crucial that the gastric pH does not fall below 6 at which clot lysis occurs. Pepsin has been found to further inhibit coagulation in an acid environment since it has maximal proteolytic activity at pH 2 but negligible activity at a higher pH level [1,41].

Proton Pump Inhibitors (PPIs)

The discovery and the use of PPIs in the management of acute bleeding peptic ulcer disease have revolutionised the management of this clinical entity. The rationale for use of PPI and other potent acid inhibitors is to raise the intragastric pH of patients with recent bleeding and thereby prevent clot lysis [42]. The use of acid-suppressing agents in the management of bleeding peptic ulcer pre-endoscopy continues to be highly controversial. For example, a meta-analysis of 6 randomised controlled trials comparing PPIs with either placebo or histamine-2 receptor antagonists (H2RAs) found no evidence that pre-endoscopic use of PPIs led to a reduction in the most important outcome measures such as re-bleeding, overall mortality and the need for surgical intervention in acute upper GI bleeding [43]. Barkun [44] in fact submitted that the use of pre-endoscopic PPIs may offer false sense of security thereby delaying the need for early endoscopic intervention in acute bleeding peptic ulcer disease and may downstage high-risk ulcers into low risk on endoscopy. He therefore advised that the use of pre-endoscopic PPIs should not replace the appropriate initial resuscitation of the patients or delay the early performance of endoscopic interventions.

The optimal standard of care of the non-variceal upper bleeding is the performance of early endoscopy and aggressive gastric acid secretion suppression. The use of high dose intravenous PPIs are generally indicated after endoscopic therapy in high risk group with major stigmata and anticipated re-bleeding [13,45]. Several clinical trials have shown that a high dose intravenous regime of omeprazole, 80mg bolus followed by 8 mg/hr for the next 72 hrs after endoscopy significantly reduces the risk of re-bleeding and need for emergency surgery [32,42,46]. Leontiadis et al. [32] in a meta-analysis on the use of PPI treatment for acute peptic ulcer bleeding involving 21 randomized controlled trials and a total of 2915 patients showed that PPI therapy reduces re-bleeding and surgical intervention rates in studies comparing treatment with placebo or H2RA but there is no evidence of an effect on mortality rates. Leontiadis et al. [47] reported the analysis of some other clinically relevant end-points from the results of the Cochrane Collaboration on the effects of PPI therapy. They demonstrated that overall, PPIs therapy marginally reduced transfusion requirements (WMD=-0.6 units; 95% CI, -1.1 to 0; P=0.05) and length of hospital stay (WMD=-1.1 days; 95% CI, -1.5 to -0.7; P<0.0001). Another meta-analysis of 9 randomized controlled trials and 1829 patients demonstrated that PPIs are superior to H2RA and placebo in preventing re-bleeding and the need for surgery in patients with bleeding ulcers. PPIs however, did not seem to reduce mortality rate [48]. Kahi et al. [49] in a meta-analysis comparing endoscopy therapy with medical therapy for bleeding peptic ulcer with adherent clot involving six studies and 240 patients showed that endoscopic therapy is superior to medical therapy in preventing re-bleeding (8.2% versus 24.7%) but no difference in the need for surgery, length of hospital stay, transfusion requirement and mortality. Recent studies have shown the use of PPIs to be cost-effective especially when administered intravenously rather than orally in the treatment of bleeding peptic ulcer [44,50,51]. PPI does seem to be superior to H2RA in the management of acutely bleeding peptic ulcer by significantly reducing re-bleeding and surgical intervention rates but these agents have no effect on mortality rate.

There are various studies that investigated the role of PPIs on clinical outcome in acutely bleeding ulcer disease. Bardou et al. [52]

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did a meta-analysis involving 18 studies and 1855 patients assessing three treatment groups: high-dose bolus of PPIs followed by continuous intravenous infusion (40-80 mg and at least 6 mg/h), high-dose oral PPIs (at least twice the standard dosage), and non-high-dose PPIs. Mixed-effect models were used to determine rate difference between treatment and control groups. They showed that high-dose intravenous PPIs significantly reduced re-bleeding (-14.6%), the need for surgery (-5.4%), and mortality (-27%) compared with placebo, and re-bleeding (-20.6%) compared with H2RA. In this study, compared with placebo, high-dose oral PPIs significantly reduced only re-bleeding (-11.8%), while non-high-dose PPIs therapy significantly improved all three outcomes. However, Wang et al. [53] in a meta-analysis of RCTs involving 1157 patients concluded that the use of high-dose PPIs were equivalent to non-high-dose PPIs in reducing the rates of re-bleeding, surgical intervention, and mortality after the initial endoscopic therapy. However, one must quickly say that there were a number of methodological errors in some of the studies included in this meta-analysis including the mixed bag of patients with both high- and low-risk lesions.

The other meta-analysis by Leontiadis et al. [54] examined 21 randomized controlled studies with a total of 2915 patients comparing PPI therapy with placebo or H2RA in endoscopically proved bleeding peptic ulcer in relation to the impact on re-bleeding, surgical intervention and mortality. They reported that PPI therapy had no significant effect on mortality [OR, 1.22, 95% CI, 0.79-1.57; number needed to treat (NNT) incalculable] but reduced re-bleeding (OR, 0.46; 95% CI, 0.33-0.64; NNT, 12) and surgery (OR, 0.59; 95% CI, 0.46-0.76; NNT, 20). Results were similar when the meta-analysis were restricted to 10 trials with highest methodological quality (OR, 0.96; 95% CI, 0.46-2.01, for mortality; OR, 0.41; 95% CI, 0.25-0.68; NNT, 10, for re-bleeding; OR, 0.62; 95% CI, 0.46-0.83; NNT, 25, for surgery). Further subgroup analysis were performed to determine whether intravenous or oral PPIs had different effects and this showed that it did not matter whether PPIs were given intravenously or orally; there was no effect on mortality, but there was an effect on re-bleeding and surgical intervention. In fact, a more recent meta-analysis of comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding by Neumann et al. [55] concluded that there is insufficient evidence for suggesting superiority, inferiority or equivalence of high-dose PPI treatment over lower doses in peptic ulcer bleeding.

Various studies have evidently provided a strong support for the use of PPIs in bleeding peptic ulcer disease and agreed that they have significant effects on re-bleeding and surgical intervention compared with either placebo or H2RA but there is a disagreement on the effect on mortality rates. Therefore, based on the current evidence, the most conservative approach to the management of high-risk bleeding peptic ulcers is the use of intravenous PPI therapy post endoscopic therapeutic measures.

Histamine-2 Receptor Antagonists (H2RAs)

The role and efficacy of H2 receptor antagonists (H2RAs) have been previously studied with conflicting outcome. Collins and Langman [56] in a meta-analysis involving 27 randomized controlled trials of over 2500 patients of H2RA showed no real benefit in bleeding duodenal ulcers but marginal benefit in reducing the rates of re-bleeding, surgery and death in bleeding gastric ulcers. However, a more relatively recent meta-analysis by Levine et al. [57] comparing intravenous H2RA therapy with placebo in bleeding peptic ulcer disease failed to show any benefit on mortality but only a small significant reduction in re-bleeding and surgical intervention rates. Therefore, available published data do not support the use of H2RA in the treatment of bleeding peptic ulcer disease [4,58]. Selby et al. [46] in a meta-analysis of 21 randomized placebo-controlled trials of 3566 patients demonstrated a significant reduction in re-bleeding and surgery rates but no effect on mortality rate. However, when analysed separately for H2RA and PPIs, H2RA significantly reduced the need for surgery but not re-bleeding rate while PPIs showed superior effect by a significant reduction in re-bleeding rate and the need for surgery. Other studies [59,60] have convincingly demonstrated the superiority of intravenous pantoprazole when compared with H2RA, ranitidine in preventing re-bleeding after a successful endoscopic therapy for bleeding peptic ulcer. However, there was no statistically significant difference between the two with regard to the need for emergency surgery, transfusion requirements, length of hospital stay and mortality.

The effect of H2RA on bleeding peptic ulcers has therefore been disappointing, presumably because these agents do not provide optimal acid inhibition and reduction in intra-gastric pH.

Somatostatin and its analogue

Somatostatin and its analogue octreotide suppress acid secretion and reduce splanchnic blood flow but there is no sufficient evidence to advocate their routine use in the treatment of actively bleeding peptic ulcer. The use of somatostatin or its analogue octreotide is therefore not recommended by the international experts in the routine management of patients with acute non-variceal upper GI bleeding [4,11].

Eradication of Helicobacter pylori

Eradication of H pylori in patients with bleeding peptic ulcers has been shown to reduce the risk of recurrent bleeding in meta-analyses of selected patients, randomised control trials and prospective observational studies [19,61-65]. There is however no rationale for urgent intravenous eradication therapy and oral medication can be initiated either immediately or during the follow-up in patients found to be infected with H pylori [11]. There is suggestion that CLO test lacks sensitivity with a high false negative rate in patients undergoing endoscopy for actively bleeding peptic ulcers [11,66,67]. There may be a need to run a confirmatory test outside the acute context of bleeding if the initial result was negative. Therefore, the current international consensus guidelines support testing patients with bleeding peptic ulcers for *H. pylori*, and administering eradication therapy if the test is positive with confirmation of eradication thereafter [4].

Endoscopic Therapy Techniques

Endoscopy is the primary diagnostic and treatment modality which should be undertaken after adequate resuscitation has been achieved. In some cases, this could happen concurrently as the resuscitative efforts especially in patients with ongoing massive bleeding. Endoscopy has the roles of establishing an accurate diagnosis, risk stratification and / or prognostication and therapeutic intervention [1,6,26,45, 68]. Progress in endoscopic therapy has come to the point that it is expected to achieve primary haemostasis in about 80-95% of patients. Though its results are impressive, recurrent bleeding after this procedure is common occurring in 15-25% of patients usually within the first 24 hours [6,13,45]. The evidence of endoscopic therapy in maintaining haemostasis in bleeding peptic ulcer is based on various published data [4,11,25,69-71]. The trend is towards combination therapy using injection as well as thermal or mechanical therapy with each designed to seal the bleeding arterial defect created by the eroding ulcer. The rationale for the use of combination endoscopic therapy is based on their different modes of action on arterial haemostasis as well as on

randomised clinical trials that reported their effectiveness for active bleeding and for prevention of re-bleeding during clot treatment [4,11,25,26, 37,69-72]. These clinical trials and meta-analyses have shown a reduction in both the re-bleeding rate and the need for surgical intervention with the use of endoscopic therapy.

There are other studies that compared the results of endoscopic treatment with medical therapy and showed that the former was associated with a significant reduction in re-bleeding rate compared with medical therapy alone [25,71,73]. However, combination endoscopic therapy has not been shown to reduce significantly 30-day mortality rate. This may have been due to the increase in the incidence of bleeding peptic ulcer in the older population and associated increased medical comorbidity among these patients [6,7,9].

Diluted adrenaline is the most widely used injection endoscopic therapy in the management of actively bleeding peptic ulcer disease. Adrenaline injection activates coagulation cascade, causes vasoconstriction, tamponade artery and facilitates clotting by enhancing platelet aggregation [68]. The injection is generally delivered in 4 quadrants around the high-risk stigmata or active bleeding site and then in the middle of it [74]. The use of endoscopic adrenaline injection alone does not provide adequate and long lasting haemostasis and therefore must be used in combination with other endoscopic modalities [25,26,31,69,70,71,72,75,76].

Thermal probe achieves haemostasis by causing arterial tamponade, coaptively coagulates tissue and activates arterial coagulation and thrombosis. The tissue coagulation induces intravascular platelets aggregation leading to arterial thrombosis [74]. Argon plasma coagulation (APC) is a new device that induces controlled, noncontact electrocoagulation of the bleeding vessels [77,78]. Havanond and Havanond [79] in a meta-analysis of APC therapy for acute non-variceal upper gastrointestinal bleeding involving two randomized controlled trials and 121 participants showed no evidence to suggest that this new technique is superior to other endoscopic therapies. This finding may be due to non-availability of adequate data from these two studies. Therefore, further randomized controlled large studies are required to make any meaning conclusion. Church et al. [80] in a multicentre double-blind randomized controlled trial showed that combination of thrombin and the heater probe does not confer an additional benefit over heater probe and placebo as endoscopic treatment for bleeding peptic ulcer.

Endoclips or 'Haemoclips' have the role of mechanical obliteration of the defect in the artery especially those greater than 1mm who do not usually stop bleeding with injection or thermal coagulation. The clips in spite of improvements in their design can be difficult to apply especially in deformed duodenal cap or awkwardly placed ulcers with active bleeding [81]. Lai et al. [81] in an uncontrolled prospective study using endoscopic haemoclip treatment for bleeding peptic ulcer in 40 patients (20 with spurting and 20 with oozing ulcers) showed an initial haemostatic rate with this technique of 95% and re-bleeding rate of 8%. In patient with shock on admission, haemoclipping achieved ultimate haemostatic rates of 71% and 83% respectively in spurting and oozing ulcers. Haemostasis was achieved in 100% of patients without shock regardless of endoscopic haemorrhagic finding. They therefore concluded that endoscopic haemoclip placement is an effective and safe option and deserves further study in the treatment of bleeding peptic ulcers.

There is little evidence that addition of sclerosants reduces the rate of re-bleeding and the use of these agents may even cause life threatening necrosis and perforation [82,83]. Use of absolute alcohol injection into the bleeding point does not confer advantages over adrenaline and carries the risk of clinical perforation [82,83]. Injection of agents which directly stimulate clot formation like fibrin glue or thrombin have been shown to be effective in stopping the bleeding but are not readily available [84]. Two meta-analyses and other randomised clinical trials have shown evidence attesting to the efficacy, safety and improved outcomes in patients treated with endoscopic haemostasis compared with those on medical therapy alone followed by surgery if bleeding recurs [24,25,70,71,73].

Haemostatic powder or haemospray is emerging as the new addition to the endoscopic armamentariums in the treatment of bleeding peptic ulcer disease [85,86]. This can be directly applied via a catheter through the endoscope working channel. This nanopowder with clotting abilities has been shown to be highly effective for achieving hemostasis of arterial bleeding in a heparinized animal model. When sprayed on a bleeding site, the powder becomes cohesive and adhesive, and forms a stable mechanical barrier by covering the bleeding site. Giday [85] in a prospective pilot study of 20 patients with upper GI bleeding showed that the application of nanopowder, TC-325 was associated with a 95% initial haemostasis with no evidence of active bleeding seen on repeat gastroscopy at 72 hours. There was no mortality or adverse events reported during 30-day follow-up period.

Therefore, a carefully performed endoscopy provides an opportunity for an accurate diagnosis of the source of the upper gastrointestinal bleeding with identification of those high-risk subgroups that may benefit most from endoscopic therapeutic manoeuvres. Effective endoscopic therapy of bleeding peptic ulcer can significantly improve outcomes by reducing the risk of re-bleeding, transfusion requirements and need for surgery, as well as reducing the cost of medical care. Currently, the most widely used standard evidence-based combination endoscopic therapy in bleeding peptic ulcer is injection with diluted adrenaline, followed by thermocoagulation with heater probe.

The timing of endoscopy

The current international consensus guidelines and recommendation suggest that early endoscopy be performed within 24 hours of presentation for patients with acute upper gastrointestinal bleeding [4, 11]. However, a recent data from a nationwide UK survey of 6750 patients treated in 208 hospitals with upper GI bleeding showed that this recommendation is not widely followed [87]. The main reason for non-adherent to the guideline was the absence of a formal out of hour endoscopy services in about half of the hospitals surveyed. Bjorkman et al. [88] in a randomised controlled trial showed that an urgent endoscopy performed within the first 12 hours when compared with early endoscopy between 12 and 24 hours does not seem to confer an advantage in relation to re-bleeding, the need for surgery or mortality in unselected patients with non-variceal upper GI bleeding.

The concept of scheduled 'second-look' endoscopy

Re-bleeding is a major problem even after successful endoscopic therapeutic measures and has been reported in up to 15-25% of cases irrespective of the method of treatment [6,13,22,23,24,25,36,45,84, 89,90]. Re-bleeding is known to be an important and a significant risk factor in acute bleeding peptic ulcer related mortality. The use of a routine second look endoscopy has been one of the strategies targeted at prevention of re-bleeding and its objective is to treat persistent stigmata of recent hemorrhage before re-bleeding occurs. However, the benefit of a routine second-look endoscopy after the initial haemostasis in the absence of further bleeding or patient instability is disputed. There

are conflicting reports concerning scheduled second-look therapeutic endoscopy in bleeding peptic ulcer disease. Marmo et al. [91] in a meta-analysis of four studies comparing between scheduled second-look endoscopy with re-treatment and expectant treatment showed that the risk of re-bleeding with the former approach was reduced by 6.2%, but the risk reduction for surgery and mortality were insignificant. They therefore concluded that patients must be carefully and appropriately selected for a second-look endoscopy and re-treatment. The benefit of selective use of second-look endoscopy was reported from a single centre prospective randomised trial that included only Forrest I and IIa ulcers by Chiu et al. [92]. These patients were randomised into scheduled second-look endoscopy with further therapy as necessary and expectant group. They reported that scheduled second-look endoscopy with appropriate re-treatment reduced the recurrent bleeding (RR 0.33, 95% CI 0.1-0.96) and a trend towards a reduction in the number of operations performed for recurrent bleeding. In another meta-analysis looking at the effectiveness comparing routine with an as-needed second-look endoscopy, El Ouali et al. [93] concluded that in the absence of high-dose PPI and especially in patients at very high risk re-bleeding, routine second-look endoscopy appears effective in these selected patients with acute peptic ulcer bleeding. However, with the small of the included trials and patients in these studies, the application of these results in the era of high-dose PPI and to the unselected patients with high-risk stigmata of recent bleed is unclear.

While the international consensus and guidelines have not recommended routine second-look endoscopy, it may be indicated depending on the local endoscopic and surgical services if there is a clear clinical evidence of re-bleeding or if the initial therapeutic endoscopic procedure was unsuccessful [23,38]. Repeat endoscopic therapy has been shown with fewer complications in good hands with no increased mortality risk and at no additional cost compared with surgery [91,94]. However, in the light of the available evidence, routine second-look endoscopy cannot be recommended. Selected high-risk patients with stigmata of recent bleed or poor surgical candidates may benefit from second-look endoscopy, but overall the use of high-dose intravenous PPIs may obviate the need for this procedure.

Non-bleeding ulcers with adherent clots

The role of endoscopic therapy in patients with non-bleeding peptic ulcers with adherent clots is controversial and not clearly defined. One concern with endoscopic manipulation is the possibility of provoking bleeding while the clot is elevated from the ulcer base. Cook et al. [70] in a meta-analysis showed that endoscopic therapy is of significant benefit in patients with actively bleeding or a visible vessel but not in patients with non-bleeding adherent clots. The reported incidences of adherent clots in patients who have suffered from bleeding peptic ulcers vary widely from 0-50% [36]. This wide variability in the incidence of adherent clots from various studies may be due to inter-observer differences in the diagnosis and Jensen et al. [24] attempted to improve on the uniformity of diagnosis with a pre-study meeting of investigators in the conduct of their clinical trial. Two randomised controlled trials supported the lifting of the clots overlying an ulcer floor followed by endoscopic therapy [24,25]. Jensen et al. [24] in a study involving 32 patients (17 to medical therapy and 15 to endoscopic therapy) reported that endoscopic therapy completely abolished recurrent bleeding, whereas 35.3% of patients on medical therapy alone experienced re-bleeding. Bleau et al. [25] reported similar results in a study with 56 patients (35 to medical therapy and 21 to endoscopic therapy). The main drawback of these studies is small sample size. Bini and Cohen [95] in a retrospective study involving 244 patients with adherent clots confirmed the superiority of combined endoscopic therapy over medical treatment alone in reducing recurrent bleeding, median hospital stay and overall transfusion requirements.

The use of combined endoscopic therapy and the adjunctive use of PPI have also been compared in a prospectively randomised trial with the use of PPI infusion alone in the treatment of ulcers with non-bleeding visible vessels or clots [96]. The study clearly showed that combined endoscopic and PPI therapy was superior to PPI alone in preventing re-bleeding (1.4% versus 11%). The importance of proton pump inhibitor therapy in the management of patients with non-bleeding adherent clots has been noted and the benefit of such therapy is to promote clot formation and stability by sustaining intragastric pH at about 6-7. In another related randomised study of 101 patients, Jung et al. [97] compared the use of oral omeprazole alone (40 mg 12 hourly) with endoscopic ethanol injection therapy for prevention of recurrent bleeding from peptic ulcers with non-bleeding visible vessels or fresh adherent clots. They showed no difference in outcome between the two groups in relation to re-bleeding rate, the need for surgery, transfusion requirements and mortality. This view has been recently echoed in a meta-analysis of six randomised controlled trials between 2006 and 2011 involving a total of 615 patients by Tsoi et al. [98] who were randomly assigned to receive oral PPIs (n=302) or intravenous PPIs (n=313). Their result showed that there was no significant difference between oral and intravenous PPIs observed regarding recurrent bleeding (RR: 0.92, 95% CI: 0.56-1.50), mean volume of blood transfused (-0.02 unit, 95% CI: -0.29-0.24 unit), need for surgery (RR: 0.82, 95% CI: 0.19-3.61) and all-cause mortality (RR: 0.88, 95% CI: 0.29-2.71). However, the duration of hospital stay in days was significantly shortened in those receiving oral PPIs (-0.74 day, 95% CI: -1.10 day to -0.39 day) compared to the intravenous PPIs group.

Patients with non-bleeding adherent clots at the time of initial endoscopy have variable rates of re-bleeding. The group of the patients with high risk of re-bleeding must be carefully identified with targeted irrigation that may expose high risk stigmata of recent bleeding and these patients have been clearly shown to benefit from endoscopic therapy. The current recommendation therefore is to treat such patients with non-bleeding adherent clots but with other major stigmata of haemorrhage by combination endoscopic therapy and PPI for the initial bleeding episode. Patients with non-bleeding adherent clots that are resistant to irrigation at endoscopy have low re-bleeding rate and can be expectantly and safely treated with PPI alone [4].

Failure of endoscopic therapy and re-bleeding

The progress in endoscopic therapy for bleeding peptic ulcer disease has reached a point where it is expected to achieve primary haemostasis in about 95% of patients [23]. However, re-bleeding is a major problem even in the best of hands accounting for about 15-25% of cases, usually within the first 24 hours following the initial endoscopy [13,22,24,25,36,84,89,96]. One of the significant predictors of mortality following bleeding peptic ulcer is the re-bleeding rate. Lau et al. [99] in a clinical trial showed that patients whose re-bleeding was treated by further endoscopic therapy have similar outcome when compared with those subjected to surgery in relation to mortality and transfusion requirements. Wong et al. [100] and Chung et al. [101] analysed independent factors associated with endoscopic therapeutic failures in two separate studies and reported that ulcers greater than 2 cm in diameter and the presence of active bleeding at endoscopy were independent predictors of failure. The other significant factor identified for therapeutic endoscopic failure was the presence of hypotension [91,99]. In a more recent study by Maggio et al. [102] looking at the Canadian data from the national registry (the REASON Registry) of patients with upper gastrointestinal bleeding showed that patients who

present with haematemesis or bright red blood via the nasogastric tube aspirate were at particularly high risk for re-bleeding within the first 72 h of their admission to the hospital.

Surgical intervention is therefore recommended for failure of endoscopic therapy to achieve primary haemostasis or continued bleeding following a second endoscopic therapy in otherwise surgically fit candidates.

The Role of Surgery

Despite improvements in endoscopic and medical therapies for acute bleeding ulcer, operations for this complication of peptic ulcer disease is still being performed in a small but significant number of patients who have failed therapeutic endoscopy and medical therapy [12,13]. Surgery is most often necessary in the acute setting typically within 48 hrs of initial bleeding in the high risk group. There are specific indications for surgery including active bleeding that cannot be controlled by endoscopic therapy, re-bleeding after an initial successful endoscopic therapy and that failed to stop after a repeat endoscopic intervention, patients age 60 years and above, those with comorbid factors with predictive poor response to hypotension, transfusion requirement more than 5-8 units in 24 hrs and large (>3 cm in diameter) posterior duodenal ulcer or lesser curve gastric ulcer [5,38,103]. The type of surgery done depends upon the site of the ulcer and the severity of the bleeding. Bleeding duodenal ulcers are generally treated by under-running the ulcer with or without pyloroplasty. Continued bleeding from gastric ulcer may be treated by simple ulcer excision or by partial gastrectomy depending on their size and location [5,13,38,103].

The Role of Selective Arterial Embolisation

The use of interventional emergency transcatheter arterial embolization (IETAE) is gaining ground in the treatment of actively bleeding peptic ulcer disease. This technique is indicated in patients who have failed endoscopy control and are not fit for surgical intervention. It is minimally invasive, can be repeated, effective and safe even in unstable and elderly patients [104-108]. IETAE has been shown to be effective at controlling bleeding, equally effective as surgical intervention and reducing mortality [104-108]. Wang et al. [109] in a review of their experience with 29 patients who underwent emergency transcatheter arterial embolization for acute massive duodenal ulcer haemorrhage showed that this technique is effective, safe and can be performed quickly and especially suitable for frail elderly patients or those with multi-organ dysfunction with actively bleeding duodenal ulcer. Yap et al. [110] in a more recent review of 95 patients with gastrointestinal bleeding showed great technical success, safety and efficacy of this interventional procedure and suggested that it should be considered when endoscopic therapy is not feasible or unsuccessful.

Conclusion

The management of patients with bleeding peptic ulcer disease requires a multidisciplinary approach. The risk of death after admission for acute bleeding peptic ulcer depends on the age of the patient 60 years being critical cut off point, the presence of shock, comorbid factors, the presence of major stigmata of recent or recurrent bleeding [1,45]. Rockall scoring system is known to accurately predict mortality [1,13,26]. Clinical presentation, age of the patient, presence of co-morbidity and the endoscopic appearance of the ulcer such as the presence of stigmata of recent haemorrhage in patients with peptic ulcer bleeding are used to determine the subsequent level of care. Advances in endoscopic and pharmacological therapies have revolutionised the management of bleeding peptic ulcer disease and in fact acute bleeding from gastrointestinal tract as a whole. It provides unique opportunities for early diagnosis and maintenance of haemostasis by various techniques. However, improved survival from advances in resuscitation, endoscopic therapy and drug therapies has been offset by an increasing number of elderly high risk patients with multiple medical co-morbid factors who account for an increasing proportion of deaths from acutely bleeding peptic ulcer disease. An interesting potential future area of development in achieving better primary endoscopic haemostasis in the near future will be the possibility of the use of endoscopic suturing technique.

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