Therapeutic options for patients bleeding with peptic ulcers

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ABR THOMSON. Therapeutic options for patients bleeding with peptic ulcers. Can J Gastroenterol 1994;8(4):269-274. It is likely that the best outcome for the patient with an acute upper gastrointestinal bleed (GIB) includes early diagnosis: for a bleeding lesion with a high risk of rebleeding, in an older patient with systolic hypotension or in a person with multiple medical problems. Early therapeutic endoscopy with meticulous control of intragastric pH will likely achieve the best outcome. The ideal pH criterion to stop bleeding or to prevent recurrence is unknown. An algorithm is presented to guide the clinical management of patients with GIB, and to focus on important questions for future therapeutic studies.

Key Words: *Acute hemorrhagic gastritis, Duodenal ulcers, Gastric ulcers, Intragastric pH, Therapeutic endoscopy, Upper gastrointestinal bleeding*

Options thérapeutiques pour les patients porteurs d'ulcères gastroduodénaux qui saignent

RÉSUMÉ : Le pronostic a de meilleures chances d'être favorable chez les patients qui souffrent d'une hémorragie gastro-intestinale supérieure aiguë si le diagnostic est fait précocement : chez les sujets âgés qui ont une lésion hémorragique accompagnée d'un risque élevé de nouveaux saignements qui ont une hypotension systolique ou qui présentent de nombreux problèmes de santé. L'endoscopie thérapeutique précoce, accompagnée d'un contrôle méticuleux du pH gastrique, est le plus susceptible d'amener un meilleur pronostic. Le critère quant au pH idéal pour cesser l'hémorragie ou prévenir sa récidive reste à définir. Un algorithme est présenté afin de guider le traitement clinique des patients qui manifestent une hémorragie gastro-intestinale haute et d'insister sur les questions importantes relatives aux études thérapeutiques à venir.

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UPPER GASTROINTESTINAL TRACT bleed (GIB) is a common medical emergency which constitutes approximately 15% of the workload of major Canadian teaching universities (1). About 30% of these patients rebleed, 20% require emergency surgery and 5% die (2,3). Surgery is usually indicated for severe, persistent or recurrent bleeding. Any treatment that might delay surgery to optimize the opportunity to stabilize patients, or prevent its need in the first place, would be useful. Any medical therapy that could reduce the risk of rebleeding or death would be of even greater value.

The therapeutic options for patients with bleeding peptic ulcers include surgery, therapeutic endoscopy (Table 1) and drugs. After appropriate resuscitation, current medical therapy includes mechanical compression of the bleeding vessel using the various forms of therapeutic endoscopy. The choice of drugs that might improve the clinical outcome of patients with GIB includes antifibrinolytic therapy, reduction in splanchnic pressure with somatostatin (or a long acting analogue such as octreotide) or acid-lowering measures using H_2 receptor antagonists or proton pump inhibitors.

TABLE 1
Endoscopic therapy of bleeding ulcer

Injection sclerotherapy
Saline + adrenaline
Sclerosant
Heater probe
Laser

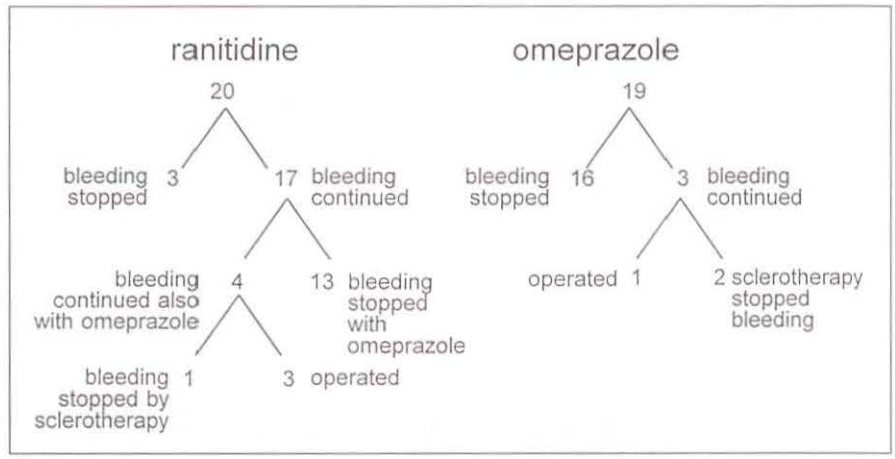

Figure 1) *Omeprazole/ranitidine in patients with bleeding peptic ulcers. Reproduced with permission from reference 32*

THERAPEUTIC ENDOSCOPY

Diagnostic endoscopy has assumed an important role in the management of patients with GIB because of its accuracy in establishing a diagnosis, in determining which patient is likely to continue bleeding and in identifying which patient may benefit from a therapeutic intervention (4). From the reported results of controlled clinical trials (5,6), participants of the 1989 United States National Institute of Health Consensus Conference (7) recommended that therapeutic endoscopy be the hemostatic procedure of first choice for patients with ulcers at risk of rebleeding. Numerous forms of endoscopy therapy are available (Table 1). Sacks and colleagues (6) performed a meta-analysis that demonstrated that therapeutic endoscopy reduces the need for emergency surgery by nearly two-thirds, and reduces the mortality rate of patients with GIB by nearly one-third. Injection therapy is equal to that of thermal methods such as YAG laser (8) or multipolar electrocoagulation (9), while equal or inferior results are achieved with heat probes (10,11).

Let us consider an important study that strongly emphasizes the importance of therapeutic endoscopy in GIB. In a series of 1880 patients admitted consecutively to a single hospital in Barcelona with a bleeding peptic ulcer, 341 had a high risk of further hemorrhage as assessed by the presence of active arterial bleeding or a nonbleeding visible vessel (12). These were older patients with a mean age of 64.9±15 years. The location of the ulcers was: 58% duodenal, 32.3% gastric, 5% stomal and 4.7% pyloric. A nonbleeding visible vessel was seen in 65.1%, oozing in 31.4% and spurting in 3.5%. Adrenaline was injected (1 per 10,000, aliquots of 1.0 to 2.0 mL first around and then into the visible vessel or over and around the bleeding area up to a total of 10 to 15 mL) with or without added thrombin or 1% polidocanol (13). Initial hemostasis was achieved in 111 of 119 actively bleeding patients (93%). Permanent hemostasis was defined as cessation of bleeding and absence of recurrence during hospitalization. Rebleeding occurred in 75 of the 341 patients (22%), at a mean internal of 53 h. A second emergency injection was attempted in 36 therapeutic failures, with hemostasis in 55%. Surgery was required in 52 of the 341 patients (15%) and overall mortality rate was 4.9%. The major complications from injection therapy were few, and included two persons with perforations and two with aspiration pneumonia (1.2%). As reported by others (14-16), therapeutic failure was more frequent in patients with ulcers at the posterior wall of the duodenal bulb, close to the gastroduodenal artery. Thus, endoscopy has gone from being challenged as having any benefit for the patient with GIB to being the management of choice.

ANTIFIBRINOLYTIC AGENTS

The antifibrinolytic drug tranexamic acid was first studied in a randomized clinical trial for GIB 20 years ago. Henry and O'Connell (17) have performed a meta-analysis of six randomized double-blind placebo controlled trials of fibrinolytic inhibitors in 1267 patients with GIB from Britain, Sweden and Australia. In five of the six trials there was a high proportion of older persons. The prevalence of bleeding sites ranged from 43 to 88% peptic ulcers and 4 to 23% gastric erosions. Tranexamic acid 3 to 6 g/day was given in four trials and 4.5 to 12 g/day for a further two to seven days in two trials. Treatment with tranexamic acid was associated with a 20 to 30% reduction in the rate of rebleeding, a 30 to 40% reduction in the need for surgery and a 40% reduction in mortality. This beneficial effect – reduction in complications – was supported, for example, by a large single centre study from Nottingham (18) of 775 patients presenting with hematemesis or melena or both. In those treated, 1 g tranexamic acid was given intravenously q6h for 48 h and then 1 g by mouth q6h, or treatment was intravenous cimetidine 400 mg q6h for 48 h, followed by 400 mg by mouth q6h, compared with placebo. Mortality was reduced in patients receiving tranexamic acid (6.3%, P=0.0092 versus placebo) or cimetidine (7.7%, P=0.045), compared with placebo (13.5%). These differences persisted for tranexamic acid but not for cimetidine when excluding patients withdrawn from the study. Interestingly, treatment with tranexamic acid was not associated with any decrease in the rate of bleeding or the need for operation.

Unfortunately, the use of tranexamic acid is complicated by an increased incidence of thrombophlebitis

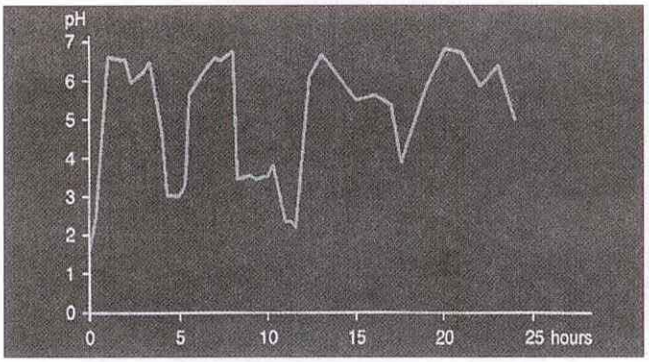

Figure 2A) *Median pH in gastric juice after ranitidine bolus doses 50 mg q6h (n=9). Reproduced with permission from reference 41*

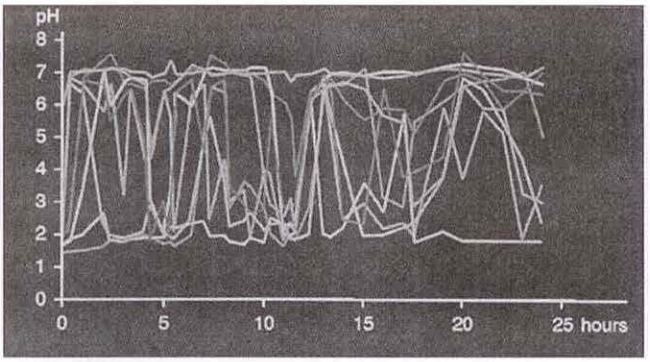

Figure 2B) *Individual curves for pH in gastric juice after ranitidine bolus doses 50 mg q6h (n=9). Reproduced with permission from reference 41*

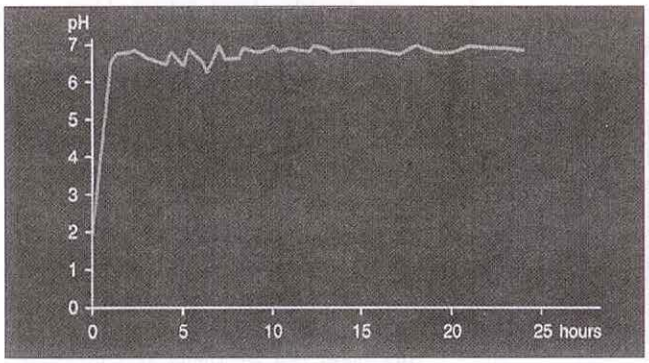

Figure 3A) *Median pH in gastric juice after omeprazole continuous infusion (80 mg + 8 mg/h) (n=9). Reproduced with permission from reference 41*

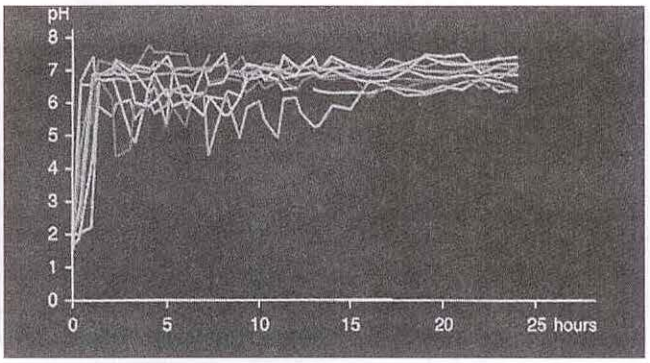

Figure 3B) *Individual curves for pH in gastric juice after omeprazole continuous infusion (80 mg bolus + 8 mg/h) (n=9). Reproduced with permission from reference 41*

(19). Despite this, it remains unclear why this form of therapy has not gained wider acceptance. The potential mechanism of benefit from this therapeutic agent is also uncertain.

SOMATOSTATIN AND OCTREOTIDE

Agents reducing splanchnic bloodflow have been studied in the treatment of patients presenting with hematemesis and melena. The hormone somatostatin reduces gastric acid secretion (20), pepsin (21) and gastrin secretion (22), and in noncirrhotics it reduces splanchnic bloodflow (23). A large double-blind controlled single centre study was performed in 630 unselected patients admitted to the Nottingham hospitals with hematemesis and melena (24). Placebo or somatostatin 250 μg was given in an initial intravenous bolus followed by a 72 h intravenous saline infusion providing 250 μg of somatostatin or placebo hourly. No difference was noted between somatostatin versus placebo in terms of rebleeding – 70 of 315 (22%) with somatostatin versus 89 of 315 (28%) with placebo – or operation rates – 35 of 315 (11%) with somatostatin versus 25 of 315 (8%) with placebo. None of these differences was statistically significant. However, it should be noted that 'all comers' were accepted and it could be argued that the inclusion criteria should be limited to those groups of patients in whom a low placebo-response rate can be expected to allow the trial drug a chance to show its potential efficacy.

In the study of somatostatin performed by Langman and colleagues (25), a generous dose of somatostatin was used, yet the study was negative. The somatostatin was given by infusion after a loading dose, so that the short half-life of about 3 mins is not a consideration. The somatostatin analogue octreotide (SMS 201-995, Sandoz, Basel, Switzerland) has a half-life of about 100 mins. In a second study, patients were included with GIB from bleeding gastric or duodenal ulcers requiring blood transfusion or plasma expanders. Christiansen et al (26) conducted a controlled 23 multicentre study in Denmark and Germany, with 123 patients on placebo and 115 on octreotide. There was no difference in the rates of stopping bleeding and preventing rebleeding between placebo (70.6%) and octreotide (69.6%), nor any difference between the two groups in surgery rates, blood transfusion requirements and time required before bleeding stopped.

Vasopressin has been used to treat patients with nonvariceal upper GIB, but there may be serious complications in those with cardiovascular or renal disease, and efficacy is marginal (27-29).

HISTAMINE H_2 ANTAGONISTS

Until September 1985 there were 27 reported randomized controlled clinical trials including about 2500 patients treated with histamine H_2 antagonists, with no single study sufficiently large to stand alone and to provide clear-cut

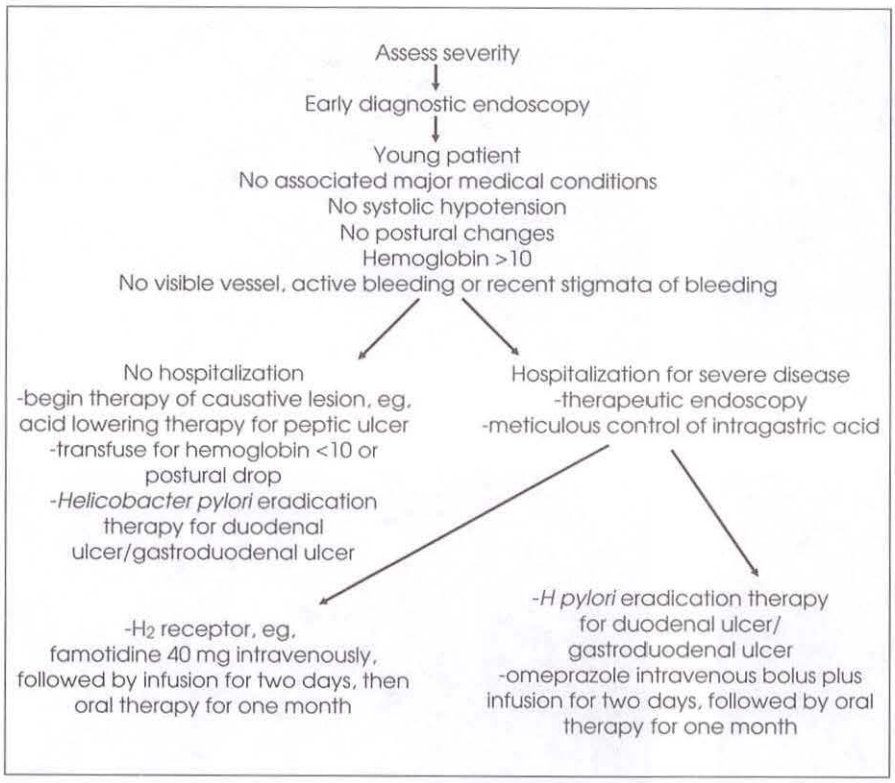

Figure 4) *Suggested algorithm for patients with upper gastrointestinal bleeding*

evidence of efficacy. In the absence of definitive studies, meta-analysis (which reviews critically the available clinical trials) assesses the homogeneity of any treatment such as H_2 antagonists and pools the data to obtain an overall measure of benefit. The rates of persistent or recurrent bleeding was examined in 25 studies, the need for surgery in 22 studies or death in 24 studies (30). The proportion of patients in whom bleeding was judged to have been persistent or recurrent ranged from 10 to 45%. Continued bleeding occurred somewhat less frequently in the treated patients than in the controls in 14 of the 24 studies. A statistically significant result ($P<0.05$) was noted in only one study (31). The odds ratio comparing the treated with the control groups was 0.89, which was not a statistically significant beneficial effect. The need for surgery ranged from 0 to 35% in 22 studies, and there was a typical odds ratio of 0.78 in the patients treated with cimetidine or ranitidine. This is a statistically significant reduction, suggesting that treatment with H_2 receptor antagonists reduces the operation rate by about 22%. Fortunately the number of deaths in the trials was low and the combined mortality results from all studies indicate an odds rate of 0.70, suggesting that treatment reduces mortality by about 30% ($P=0.02$). For patients with bleeding from gastric ulcers, the combined data suggest that treatment significantly reduced these three major complications, whereas no differences were noted for patients with duodenal ulcers. It is therefore important to reconsider the routine use of systemic H_2 receptor antagonists in all patients who present with GIB.

PROTON PUMP INHIBITORS

A single centre, double-blind placebo controlled study of 1147 unselected patients presenting with upper GIB to the Nottingham hospitals over a 42-month interval was performed to compare placebo with 80 mg omeprazole given intravenously immediately after admission to hospital and before endoscopic confirmation of bleeding or its site. The loading dose of omeprazole was followed by three doses of omeprazole 40 mg intravenously by bolus at eight hourly intervals, then 40 mg orally at 12 h intervals. Treatment was started within 12 h of admission and given for four days or until surgery, discharge or death. No significant differences were found between the placebo and omeprazole groups for rates of transfusion (301 of 569 [53%] for placebo versus 289 of 578 [52%] for omeprazole), rebleeding (100 [18%] versus 85 [15%]), operation (63 [11%] versus 62 [11%]) and death (30 [5.3%] versus 40 [6.9%]). The only difference was a significant reduction in endoscopic signs of bleeding in patients treated with omeprazole compared with those treated with placebo (236 [45%] for placebo versus 176 [33%] for omeprazole, $P<0.0001$). Despite early reductions in signs of bleeding with omeprazole, mortality was not reduced. Logistic regression was used to analyze the combined effects of age, initial systolic blood pressure and bleeding site; for rates of rebleeding (overt hemorrhage), operation and death, increasing age and low initial systolic blood pressure were the strongest and most significant prognostic factors, and the presence of a gastric or duodenal ulcer was a significant factor for rebleeding and operation but not for death. No stratification was done for site or initial activity of bleeding lesions.

In contrast to this negative placebo-controlled study with 'all comers', Brunner and Chang (32) performed a smaller open randomized controlled trial (Figure 1) comparing intravenous therapy with ranitidine or omeprazole (omeprazole by bolus, 80 mg initially followed by 40 mg every 12 h for five days versus ranitidine 50 mg followed by continuous infusion of 400 mg ranitidine per day). Patients were critically ill with actively bleeding peptic ulceration. Successful treatment was proven by follow-up endoscopy on day 6, unless there was earlier treatment failure. Of 20 patients in the ranitidine group, 17 were treatment failures with more than 2.5 L of blood necessary to maintain a hemoglobin level above 10 g/L (Figure 1). Bleeding could be controlled subsequently in 13 of 17 patients after changing to omeprazole (76%), and 16 of 19 patients started on omeprazole were successfully treated (84%).

This open study success has been

accompanied by a number of brief reports of the beneficial use of omeprazole to control hemorrhage from acute hemorrhagic gastritis (33), in five critically ill patients with life-threatening nonvariceal upper GIB who had failed to respond to conventional therapy (34) and in 11 older patients not responding to ranitidine or somatostatin, with persistence of clinical or endoscopic signs of bleeding due to erosive gastritis or acute peptic ulcer (the hemoglobin concentration was not raised despite four units of blood) (35).

The positive results of the study of Bruner and Chang (32) may have been due to the inclusion of patients with bleeding (36). The presence of active arterial bleeding at emergency endoscopy is associated with further hemorrhage in 95% of cases (4), while a nonbleeding visible vessel on the ulcer floor results in a rebleeding rate of 33 to 55%. Stigmata of bleeding also provides a target to which endoscopic therapy must be addressed to obliterate the underlying artery (14,37).

What is the rationale for using acid lowering therapy to treat patients with GIB? Humoral- and thrombocyte-induced hemostasis only occurs at pH values above 6.0 (38). Thrombocyte aggregation and clot formation are inhibited in the presence of even small amounts of acid, and newly formed clots are subject to rapid digestion by gastric juice at pH values below 5.0 (39). Pepsin further enhances platelet disaggregation. This argues for meticulous intragastric pH control in patients with upper gastrointestinal bleeding.

The various therapeutic regimens used in these studies include H_2 receptor antagonists given by bolus, infusion or bolus plus infusion, and omeprazole given by bolus. The extent of acid control (pH greater than 5.0) is better with cimetidine by infusion versus by bolus (40) and a loading dose of famotidine achieves superior acid control when given before infusion, compared with infusion alone (unpublished data). A loading dose of ranitidine does not add to the acid inhibiting effect of an infusion or ranitidine (unpublished data). The infusion of ranitidine results in considerable diurnal rhythm of intragastric values of pH, with great variation between subjects (Figure 2). An intravenous bolus of omeprazole followed by infusion of proton pump inhibitor maintains the median intragastric pH consistently above 6 with little fluctuation and nontachyphylaxis (41, 42) (Figure 3). It now becomes appropriate to test this new and apparently ideal regimen in a clinical setting.

Three trials reported in abstract form have suggested that there may be a lower rate of rebleeding in patients with peptic lesions not due to nonsteroidal anti-inflammatory drugs, in whom anti-helicobacter therapy was initiated at the time of diagnosis of a bleeding peptic ulcer. Increasing evidence is accumulating to buttress the appropriateness of eradicating *Helicobacter pylori* to reduce the frequency of ulcer relapse, and this eradication therapy appears to be appropriate in patients presenting with a bleeding peptic lesion.

In summary, the patient who presents with acute upper GIB needs prompt clinical assessment and resuscitation (Figure 4). Early endoscopy is required for diagnosis therapy. Only patients with active bleeding or high risk of rebleeding, or medically endangered patients require admission to hospital. The role of routine use of systemic infusions of H_2 receptor antagonists is not proven, and the promising role for meticulous control of intragastric pH using proton pump inhibitors needs to be established.

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