Intravenous proton pump inhibitors before endoscopy in bleeding peptic ulcer with high-risk stigmata: A multicentre comparative study

Christopher N Andrews MD FRCPC[1], Adrian Levy PhD[2], Martin Fishman MD FRCPC[3], Michael Hahn MD FRCPC[4], Kenneth Atkinson MD FRCPC[5], Peter Kwan MD FRCPC[6], Robert Enns MD FRCPC[7]

CN Andrews, A Levy, M Fishman, et al. Intravenous proton pump inhibitors before endoscopy in bleeding peptic ulcer with high-risk stigmata: A multicentre comparative study. Can J Gastroenterol 2005;19(11):667-671.

BACKGROUND: It is not clear if starting intravenous proton pump inhibitors (IV PPI) before endoscopic therapy provides additional benefit over starting it afterward in patients with high-risk ulcer stigmata of peptic ulcer disease.

METHODS: All patients who received IV pantoprazole bolus and infusion and underwent endoscopy in six Canadian hospitals over 20 months were reviewed. Only patients with high-risk ulcer stigmata (arterial bleeding, oozing, nonbleeding visible vessel or adherent clot) were included. Patients receiving IV PPI before endoscopy (before group) were compared with those who received it after endoscopy (after group) with respect to endoscopic findings and, secondarily, to patient demographics and clinical outcomes.

RESULTS: The demographics and baseline characteristics of the before group (n=57) and the after group (n=109) were similar. The before group was more likely to have had IV PPI started outside of daytime hours, and median time to endoscopy in patients admitted with upper gastrointestinal bleeding was 24 h (interquartile range 9.5 to 35) in the before group and 11.3 h (interquartile range 3.7 to 17.2) in the after group (P<0.0001). At the time of endoscopy, 33% of patients in the before group had actively bleeding lesions (Forrest 1a or 1b) compared with 54% in the after group (P=0.01), but there were no significant differences in rebleeding, surgical rates, intensive care unit admission or death between the groups.

CONCLUSION: IV PPI infusions before endoscopy may lower the proportion of actively bleeding peptic ulcer lesions at endoscopy, but this finding does not appear to affect rates of rebleeding, surgery or death.

Key Words: *Gastrointestinal hemorrhage; Intravenous; Pantoprazole; Retrospective*

Des inhibiteurs de la pompe à proton par intraveineuse avant une endoscopie en cas d'ulcère gastroduodénal hémorragique à haut risque de stigmates : Une étude comparative multicentrique

HISTORIQUE : Il n'est pas établi clairement si l'administration d'inhibiteurs de la pompe à proton par intraveineuse (IPP IV) avant un traitement endoscopique s'associe à des bénéfices supplémentaires par rapport à l'administration après ce traitement chez les patients à haut risque de stigmates ulcéreux causés par un ulcère gastroduodénal.

MÉTHODOLOGIE : Tous les patients qui ont reçu un bolus et une infusion de pantoprazole IV et ont subi une endoscopie dans six hôpitaux canadiens au cours d'une période de 20 mois ont été analysés. Seuls les patients à haut risque de stigmates ulcéreux (hémorragie artérielle, suintements, vaisseau visible non hémorragique ou caillot adhérent) étaient inclus. Les patients recevant des IPP IV avant l'endoscopie (groupe avant) ont été comparés à ceux qui en ont reçu après l'endoscopie (groupe après) pour ce qui est des observations endoscopiques, puis de leur démographie et de leurs issues cliniques.

RÉSULTATS : Les caractéristiques démographiques et en début d'étude du groupe avant (n=57) et du groupe après (n=109) étaient similaires. Le groupe avant était plus susceptible d'avoir reçu des IPP IV entrepris hors des heures du jour. Le délai moyen jusqu'à l'endoscopie chez les patients hospitalisés par suite d'une hémorragie œsogastroduodénale était de 24 heures (écart interquartile de 9,5 à 35) au sein du groupe avant et de 11,3 heures (écart interquartile de 3,7 à 17,2) au sein du groupe après (P < 0,0001). Au moment de l'endoscopie, 33 % des patients du groupe avant présentaient des lésions en cours d'hémorragie (Forrest 1a ou 1b) par rapport à 54 % au sein du groupe après (P = 0,01), mais on ne remarquait aucune différence significative en matière de reprise de l'hémorragie, de taux de chirurgie, d'admission à l'unité de soins intensifs ou de décès entre les groupes.

CONCLUSION : Les infusions d'IPP IV avant l'endoscopie pourraient ralentir la proportion de lésions hémorragiques d'ulcères gastroduodénaux à l'endoscopie, mais cette observation ne semble pas influer sur le taux de reprises de l'hémorragie, d'opération ou de décès.

Intravenous forms of proton pump inhibitors (IV PPI) have been available for clinical use for over 10 years (1). Prospective randomized trials have shown efficacy in preventing rebleeding from high-risk peptic ulcers (defined as active bleeding or presence of a nonbleeding visible vessel) after endoscopic therapy using a bolus followed by continuous infusion of IV PPI (2-5). The optimal timing of administration of IV PPI is not known. In most studies, IV PPI was administered after endoscopic assessment with or without endoscopic therapy. It is not known if IV PPI administered before endoscopic therapy is beneficial, although a recent study (6) in abstract form suggests that this practice may reduce endoscopic signs of bleeding and the need for hemostatic therapy. A recent review of our usage patterns of IV PPI revealed that infusions

[1]*Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA;* [2]*Department of Health Care and Epidemiology, University of British Columbia;* [3]*Richmond General Hospital;* [4]*Lion's Gate Hospital;* [5]*Royal Columbian Hospital;* [6]*Vancouver General Hospital;* [7]*Division of Gastroenterology, Department of Medicine, St Paul's Hospital, University of British Columbia, Vancouver, British Columbia*

Correspondence and reprints: Dr Robert A Enns, Pacific Gastroenterology Associates, St Paul's Hospital, University of British Columbia, 770–1190 Hornby Street, Vancouver, British Columbia V6K 2A5. Telephone 604-688-6332 ext 222, fax 604-689-2004, e-mail renns@interchange.ubc.ca

of the drug were started in advance of endoscopy in over 50% of patients presenting with suspected upper gastrointestinal (UGI) bleeding (7). Bleeding peptic ulcers with high-risk stigmata are currently the only GI cause of hemorrhage for which strong evidence exists on the use of IV PPI. We therefore decided to compare outcomes of all patients with bleeding peptic ulcer disease (PUD) who received IV PPI infusion before endoscopy with those who received it after endoscopy.

This analysis was an exploratory one which was designed to be hypothesis-generating. It was a retrospective analysis of a large local database for which the primary goal was to determine if high risk ulcers were 'downstaged' by the use of IV PPI before endoscopy. Additionally, secondary objectives were to evaluate the clinical outcomes (rates of rebleeding, surgery and mortality) of patients receiving IV PPI before endoscopy with those receiving it following the endoscopy.

METHODS

Patients

All patients who received IV pantoprazole (PANTO IV; Altana Pharma Inc, Canada) and upper endoscopy for the indication of bleeding from high-risk peptic ulcer stigmata (defined below) between November 1999 and June 2001 (20 months) in six hospitals in the metropolitan Vancouver area were reviewed retrospectively. The present study forms a subanalysis of a comprehensive review of IV PPI usage for all indications in 854 patients during the same time period published previously (7). Three of the hospitals were academic teaching hospitals and three were nonacademic secondary or tertiary care hospitals. The institutional review boards of each hospital gave full approval for the study.

Every instance of IV PPI usage over the study time frame was identified from hospital pharmacy databases and correlated with patient charts. All other information, including timing of administration of IV PPI, was obtained from the patient's hospital chart. Endoscopic findings were gathered from dictated reports, endoscopic pictures and/or chart notes.

Drugs

The IV formulation of the PPI pantoprazole was approved in Canada in 1999. No other IV PPI were approved for use in Canada during the time period of the present study. All patients received a bolus dose of pantoprazole (80 mg in 95% of patients, with the remainder receiving 40 mg) followed by an 8 mg/h infusion (in 98% of patients, with higher infusion rates in the remainder). Because the goal of the present study was to analyze the effect of IV PPI in relation to endoscopic diagnosis and management of bleeding peptic ulcer, any patient who had IV PPI started more than 48 h before or after endoscopy was excluded.

Sources of information

Data were abstracted from charts by an investigator (CNA) and two research assistants using a standardized information template. Abstractors had ongoing supervision for maintenance of data quality. The template included information on timing, dose and duration of administration of IV PPI; indications for use; sociodemographic information (including age, sex, number and type of comorbid medical conditions; and risk factors for PUD including recent nonsteroidal anti-inflammatory use or a previous history of PUD); lowest pre-endoscopy hemoglobin; lowest pre-endoscopy systolic blood pressure; elapsed time between emergency department arrival and endoscopy; endoscopic findings and intervention; and outcomes including transfusion requirements, rebleeding, surgery, need for intensive care unit (ICU) admission and death.

Comorbidity was scored using the Charlson index (8), a well-validated score (9) which assigns points to 19 conditions, giving a predictive relative risk of one-year mortality from comorbid conditions. A higher score correlates with higher comorbidity. Because ulcer disease is one of the index comorbidities, the minimum score in this study was 1.

The Rockall score (10) (a validated predictor of mortality due to UGI hemorrhage) was calculated for each patient. The complete score uses data on age, presence of shock, comorbidity, cause of bleed and major stigmata of recent hemorrhage (using endoscopic findings) to predict mortality. The initial score (measured before endoscopy) uses data on age, presence of shock and comorbidity only. The range of possible scores is from 0 to 7 for the initial score and 0 to 11 for the complete score, with a higher score predictive of higher mortality.

Definitions

High-risk peptic ulcer stigmata were defined as arterial bleeding (corresponding to Forrest class 1a), active oozing (Forrest 1b), presence of a nonbleeding visible vessel (Forrest 2a) or adherent clot (Forrest 2b). Endoscopic therapy was defined as any injection therapy, heater probe, hemoclip or bipolar electrocautery undertaken at the bleeding ulcer site to control or prevent further bleeding.

Because UGI bleeding may not immediately be recognized on admission, may only be one of a list of admission diagnoses or may have been treated with IV PPI but did not have UGI hemorrhage coded, patients were considered to be admitted with UGI bleeding if IV PPI was started or endoscopy performed within 24 h of admission to hospital. The remainder of the patients had UGI bleeding while hospitalized for other reasons. Patients who had ceased to have acute medical issues but who were then waitlisted for extended care facilities on the same admission were deemed to be discharged on the date they were waitlisted for an alternate level of care.

Outcome definitions

Rebleed was defined as a postresuscitation drop in hemoglobin of 20 g/L or higher, a sudden drop in systolic blood pressure (more than 20 mmHg) unexplained by medications, or evidence of new hematemesis or melena stool. Only rebleeds that occurred during the same admission and within 30 days of initial bleed were included.

Surgery was defined as any laparotomy undertaken for control of UGI bleeding or perforation from any source after identification and/or resuscitation of the initial UGI bleed.

ICU admission was defined as admission to an ICU for monitoring or hemodynamic instability as a direct result of UGI hemorrhage. Patients who developed GI bleeding while admitted to an ICU for other reasons were not included in this measurement. Typically, in the Vancouver area, patients with routine UGI bleeding are not admitted to the ICU. Patients usually require multiorgan system failure to gain access to an ICU.

Death was defined as death from any cause during the same admission that occurred within 30 days of initial UGI bleeding. Becuase most deaths in the context of UGI bleeding are due to sequelae of bleeding or comorbidities as opposed to direct exsanguination, all deaths were included. Patients discharged alive in less than 30 days were not followed further.

Statistical analysis

This was a retrospective study of all patients meeting inclusion criteria over the study period; a statistical power calculation was not performed. Differences between the means of continuous variables with apparently normal distributions were assessed using Student's *t* test. Categorical and ordinal variables, and continuous variables with potentially skewed distributions, were compared using the Mann-Whitney U test. Differences in group proportions were analyzed with the Pearson χ^2 test, or the Fisher Exact Test if sample sizes were less than five. Two-tailed tests of significance at the P<0.05 level were used to determine statistical significance.

RESULTS

Population

One hundred sixty-six patients met the study criteria, with 57 receiving IV PPI before endoscopy (before group) and 109 receiving it after endoscopy (after group). There were no significant differences between the groups with respect to age, sex, length of stay, comorbidity index, initial Rockall score (data not shown), complete Rockall score, history of previous PUD or nonsteroidal anti-inflammatory drug use, lowest hemoglobin and lowest systolic blood pressure (Table 1). A similar proportion of patients received IV PPI before endoscopy in both academic teaching hospitals and community hospitals (data not shown).

Most patients had comorbidities with a median of 2 to 3 points on the Charlson comorbidity index. This sizable degree of comorbidity is due to the fact that nearly one-half of the patients did not present to hospital with UGI hemorrhage, but rather, developed the condition while hospitalized for another reason.

Timing of IV PPI administration and endoscopy

The group receiving IV PPI before endoscopy received a median of 14.3 h (interquartile range [IQR] 6.0 to 25.1, range 0 to 45) of IV PPI infusion by the time of endoscopy. In the other group, a median 3.5 h (IQR 1.9 to 6.7, range 0 to 37) elapsed after endoscopy before commencement of IV PPI therapy (Table 2).

The time from admission to endoscopy was significantly different in patients admitted with GI bleed (approximately one-half the patients in each arm), with a median of 24 h in the group receiving IV PPI before endoscopy and 11 h in those receiving IV PPI after endoscopy. The before group also had 70% of IV PPI infusions started outside of usual daytime hours (07:00 to 18:00), which was significantly higher than the after group (49%, P<0.01). Both groups had a similar proportion of endoscopies performed outside of usual daytime hours (approximately 25%). Both groups received a similar median duration of IV PPI infusion.

TABLE 1
Patient demographics, risk factors and baseline clinical values

Variable	IV PPI before endoscopy (n=57)	IV PPI after endoscopy (n=109)	P
Age, mean years (SD)	64.2 (17.7)	66.2 (16.1)	0.472
Female, n (%)	19 (33)	45 (41)	0.318
Length of stay, median days (IQR)	7 (5–15.5)	8 (5–20)	0.412
Charlson comorbidity index, median points (IQR)	2 (2–4)	3 (2–4)	0.891
Rockall score (complete), median points (IQR)	6 (4–7)	5 (4–7)	0.827
Previous PUD, n (%)	12 (21)	34 (31)	0.166
NSAID use, n (%)	19 (33)	32 (29)	0.598
Admitted with UGI bleeding, n (%)	29 (51)	59 (54)	0.690
Hemoglobin, mean g/L (SD)	76 (18.4)	71 (17.8)	0.144
Systolic blood pressure, mean mmHg (SD)	93 (18)	96 (20)	0.362

IQR Interquartile range; IV PPI Intravenous proton pump inhibitor, NSAID Nonsteroidal anti-inflammatory drug; PUD Peptic ulcer disease; UGI Upper gastrointestinal

Outcomes

At the time of endoscopy, significantly fewer patients in the before group (33%) had active ulcer bleeding (Forrest 1a or 1b lesions) than in the after group (54%) (P=0.011) (Table 3). A similar proportion of patients in both groups received endoscopic intervention (injection therapy, heater probe or bipolar electrocautery).

There were no significant differences in the rates of rebleeding, surgical intervention, need for ICU admission or death within 30 days between the two groups.

DISCUSSION

At the hospitals surveyed, many patients presenting with suspected UGI bleeding received IV PPI infusions before receiving endoscopy (7). In the present study, all patients with high-risk bleeding peptic ulcers who received IV PPI were analyzed. There were no significant baseline differences between those who received IV PPI before and those who received it after endoscopy.

At the time of endoscopy, significantly fewer patients in the group receiving IV PPI before endoscopy (33%) had active ulcer bleeding (defined as Forrest class 1a or 1b lesions) compared with the after group (54%). The patients in the before group received a median of 14.3 h of IV PPI infusion before endoscopy, whereas the patients in the after group had none.

TABLE 2
Timing of intravenous proton pump inhibitor (IV PPI) administration and endoscopy in study patients

Variable	IV PPI before endoscopy (n=57)	IV PPI after endoscopy (n=109)	P
Duration of IV PPI infusion until endoscopy, median hours (IQR)	14.3 (6.0–25.1)		
Time elapsed after endoscopy until IV PPI infusion started, median hours (IQR)		3.5 (1.9–6.7)	
IV PPI infusion started outside of daytime hours (07:00–18:00), n (%)	40 (70)	53 (49)	0.008
Endoscopy performed outside of daytime hours (07:00–18:00), n (%)	14 (25)	29 (27)	0.775
Time to endoscopy from admission, median hours (IQR)*	24 (9.5–35)	11.3 (3.7–17.2)	<0.0001
Total duration of IV PPI infusion, median hours (IQR)	72 (43–107)	67 (39–89)	0.183

**Based on patients admitted with upper gastrointestinal bleeding only (n=29 in before group, n=59 in after group). IQR Interquartile range*

TABLE 3
Endoscopic findings and patient outcomes

Variable	IV PPI before endoscopy (n=57)	IV PPI after endoscopy (n=109)	P
Endoscopic findings, n (%)			0.047
Arterial pumping	5 (9)	10 (9)	
Oozing	14 (25)	49 (45)	
Nonbleeding visible vessel	24 (42)	27 (25)	
Adherent clot	14 (25)	23 (21)	
Active bleeding on endoscopy, n (%)*	19 (33)	59 (54)	0.011
Endoscopic therapy, n (%)	39 (68)	73 (67)	0.850
Transfusion needs, median units PRBC (IQR)	4 (2–8)	4 (2–7)	0.381
Rebleed, n (%)	16 (28)	29 (27)	0.840
Surgery, n (%)	2 (4)	1 (1)	0.272
Intensive care unit admission, n (%)	4 (7)	5 (5)	0.495
Death, n (%)	6 (11)	16 (15)	0.454

**Active bleeding defined as arterial pumping or oozing (Forrest 1a or 1b). IQR Interquartile range; IV PPI Intravenous proton pump inhibitor; PRBC Packed red blood cells*

There are three possible explanations for this finding. First, in the majority of patients, the natural course of bleeding peptic ulcer is to spontaneously cease bleeding (11-13). The median time to endoscopy from admission was significantly longer in the group receiving IV PPI before endoscopy (24 h) than in the after group (11 h). Therefore, it is possible that the longer time to endoscopy would account for less actively bleeding lesions. For example, it could be hypothesized that those patients who could wait for endoscopy until a more convenient time simply had IV PPI infusions started in the interim. This idea is supported by the finding that the majority of patients who had IV PPI before endoscopy had it started outside of daytime hours. However, both groups had a similar prima facie assessment of the severity of GI bleeding based on the similar burden of comorbidity, hemodynamic status and initial Rockall scores at the time of presentation with bleeding. Although other unmeasured factors may have contributed to the timing of endoscopy, it appears the severity of bleed and comorbidity (at least in the variables measured in this analysis) did not appear to play a role in the decision-making process of when to start IV PPI infusions.

Alternatively, it is possible that IV PPI infusions may decrease the amount of active bleeding ('downstaging' the lesions) over time compared with no medical therapy at all, with the biological rationale that increasing intragastric pH allows improved blood clot formation and more rapid slowing of blood loss compared with volume resuscitation alone. This effect was seen in a prospective trial of oral PPI for bleeding peptic ulcer where a reduction in rebleeding was seen in the absence of endoscopic hemostatic therapy (14). This finding was also seen in a large double-blind randomized control study of 1147 UGI bleed patients randomly assigned to intermittent IV omeprazole boluses or placebo before endoscopy, where significantly fewer patients in the omeprazole group had endoscopic signs of UGI bleeding (33%) compared with the placebo group (45%) (15). More recently, a prospective randomized trial of IV omeprazole or placebo before endoscopy showed similar findings, with less hemostatic therapy required in the omeprazole group; however, this study has only been presented in abstract form (6).

A third contributing factor is the interobserver variability in endoscopic recognition of high-risk stigmata of bleeding. Although studies have shown wide interobserver variability for definition of high-risk stigmata (16), correlation is higher within institutions (13,17) and interobserver agreement is good for active bleeding (17,18).

Whichever explanation is correct is unclear. However, the present study suggests that it may be a safe practice to start IV PPI early and, if necessary, to delay endoscopy to address other medical issues. Thus, the use of early IV PPI may 'downstage' lesions without detracting from clinical outcomes. The clinician must keep in mind, however, that endoscopic assessment and hemostatic therapy is the definitive treatment and standard of care for bleeding peptic ulcer; IV PPI is not a substitute for this therapy.

In terms of the cost of this practice, a study by Enns et al (19) compared a strategy of empirically treating all patients presenting to the emergency department with IV PPI infusion and endoscopic treatment versus endoscopic treatment alone using a statistical model of a hypothetical cohort of 1000 patients. Based on the expected frequencies of endoscopically treatable ulcers and efficacy of IV PPI from the landmark IV PPI study by Lau et al (4), and using Canadian cost figures, results showed that sufficient rebleeds would be prevented to provide a net cost savings. The main caveat of this study requires stopping IV PPI infusions in patients who do not have high-risk ulcer stigmata on endoscopy. In our experience, this has not been the case, with the majority of patients with low-risk lesions having their infusions continued (7).

Individual physician practices and awareness, although not assessed in this study, could have also played a role in the decision process for starting IV PPI. The time period of this study began with the introduction of IV PPI into Canada, and before the landmark study by Lau et al (4), which clearly showed the benefit of IV PPI given as bolus followed by infusion after endoscopic therapy. Starting IV PPI before endoscopy was thus a reasonable practice, even though it was not evidence-based.

The high rebleeding rate may be a reflection of inadequate endoscopic treatment, which was only performed in approximately two-thirds of the patients in each group. Endoscopic hemostasis of active ulcer bleeding or visible vessels has been shown to significantly decrease rebleeding, surgery and mortality rates in two meta-analyses (20,21). Although most of the patients who did not receive endoscopic therapy in the present study had adherent clots (data not shown), recent research has suggested that aggressive treatment of clots reduces rebleed rates as well (22,23).

Mortality in the present study was high, with a rate of 11% in the group receiving IV PPI before endoscopy and 15% in the after group. This is higher than the average case-fatality rates reported in other studies, which generally range from 4% to 10% (12,24-27). However, the median complete Rockall scores of the groups of 5 and 6 (out of a possible 11), correlated with a mortality of 10.8% and 17.3%, respectively, in the original Rockall paper, with mortality for patients with rebleeding even higher than this (10). The mean lowest recorded hemoglobin (76 g/L in the before group and 71 g/L in the after group) and mean lowest systolic blood pressure in the mid-90s range suggested relatively severe peptic ulcer bleeding in the present study population. Factors that also affected the case-fatality rate were the significant comorbid illness of this group, as well as the older age of the patients

(average over 60 years); both have been shown to increase the mortality rate (28,29).

Starting IV PPI infusions in advance of endoscopic therapy did not affect the outcome measures of rebleeding, transfusion requirements, need for surgery or ICU admission or death. Although there was significantly lower active bleeding seen at the time of endoscopy in the group given IV PPI beforehand, the significance of this finding is not clear. The fact that the outcomes were similar in the group receiving IV PPI before endoscopy, even though the time to endoscopy was longer for these patients, suggests that IV PPI infusions may allow the clinician to delay endoscopy (to focus on more pressing patient comorbidities, for example, or until regular opening hours of the clinician's endoscopy suite) without jeopardizing the patient's ultimate outcome. The hypothesis that early administration of IV PPI 'downstages' lesions is supported by the present study; however, due to the retrospective nature of this database, inherent flaws are present that limit the strength of this inference. Results of prospective studies in the arena of early IV PPI administration are awaited and will no doubt raise further questions, such as the optimal duration of prior IV PPI and its relationship to timing of endoscopy.

REFERENCES

1. Brunner GH, Thiesemann C. The potential clinical role of intravenous omeprazole. Digestion 1992;51(Suppl 1):17-20.
2. Goletti O, Sidoti F, Lippolis PV, De Negri F, Cavina E. Omeprazole versus ranitidine plus somatostatin in the treatment of severe gastroduodenal bleeding: A prospective, randomized, controlled trial. Ital J Gastroenterol 1994;26:72-4.
3. Hasselgren G, Lind T, Lundell L, et al. Continuous intravenous infusion of omeprazole in elderly patients with peptic ulcer bleeding. Results of a placebo-controlled multicenter study. Scand J Gastroenterol 1997;32:328-33.
4. Lau JY, Sung JJ, Lee KK, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. N Engl J Med 2000;343:310-6.
5. Lin HJ, Lo WC, Lee FY, Perng CL, Tseng GY. A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. Arch Intern Med 1998;158:54-8.
6. Lau JY, Leung JW, Wu JC, et al. Early administration of high-dose intravenous omeprazole prior to endoscopy in patients with upper gastrointestinal bleeding; A double blind placebo controlled randomized trial. Gastroenterology 2005;128:A50. (Abst)
7. Enns RA, Andrews CN, Fishman M, et al. Description of prescribing practices in patients with upper gastrointestinal bleeding receiving intravenous proton pump inhibitors: A multicentre evaluation. Can J Gastroenterol 2004;18:567-71.
8. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373-83.
9. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. A critical review of available methods. J Clin Epidemiol 2003;56:221-9.
10. Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. Gut 1996;38:316-21.
11. Katschinski B, Logan R, Davies J, Faulkner G, Pearson J, Langman M. Prognostic factors in upper gastrointestinal bleeding. Dig Dis Sci 1994;39:706-12.
12. Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med 1994;331:717-27.
13. Lau JY, Chung SC, Leung JW, Lo KK, Yung MY, Li AK. The evolution of stigmata of hemorrhage in bleeding peptic ulcers: A sequential endoscopic study. Endoscopy 1998;30:513-8.
14. Khuroo MS, Yattoo GN, Javid G, et al. A comparison of omeprazole and placebo for bleeding peptic ulcer. N Engl J Med 1997;336:1054-8.
15. Daneshmend TK, Hawkey CJ, Langman MJ, Logan RF, Long RG, Walt RP. Omeprazole versus placebo for acute upper gastrointestinal bleeding: Randomised double blind controlled trial. BMJ 1992;304:143-7.
16. Freeman ML. Value of stigmata in decision-making in gastrointestinal haemorrhage. Best Pract Res Clin Gastroenterol 2000;14:411-25.
17. Mondardini A, Barletti C, Rocca G, et al. Non-variceal upper gastrointestinal bleeding and Forrest's classification: Diagnostic agreement between endoscopists from the same area. Endoscopy 1998;30:508-12.
18. Lau JY, Sung JJ, Chan AC, et al. Stigmata of hemorrhage in bleeding peptic ulcers: An interobserver agreement study among international experts. Gastrointest Endosc 1997;46:33-6.
19. Enns RA, Gagnon YM, Rioux KP, Levy AR. Cost-effectiveness in Canada of intravenous proton pump inhibitors for all patients presenting with acute upper gastrointestinal bleeding. Aliment Pharmacol Ther 2003;17:225-33.
20. Cook DJ, Guyatt GH, Salena BJ, Laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: A meta-analysis. Gastroenterology 1992;102:139-48.
21. Sacks HS, Chalmers TC, Blum AL, Berrier J, Pagano D. Endoscopic hemostasis. An effective therapy for bleeding peptic ulcers. JAMA 1990;264:494-9.
22. Bleau BL, Gostout CJ, Sherman KE, et al. Recurrent bleeding from peptic ulcer associated with adherent clot: A randomized study comparing endoscopic treatment with medical therapy. Gastrointest Endosc 2002;56:1-6.
23. Jensen DM, Kovacs TO, Jutabha R, et al. Randomized trial of medical or endoscopic therapy to prevent recurrent ulcer hemorrhage in patients with adherent clots. Gastroenterology 2002;123:407-13.
24. Zed PJ, Loewen PS, Slavik RS, Marra CA. Meta-analysis of proton pump inhibitors in treatment of bleeding peptic ulcers. Ann Pharmacother 2001;35:1528-34.
25. Blatchford O, Davidson LA, Murray WR, Blatchford M, Pell J. Acute upper gastrointestinal haemorrhage in west of Scotland: Case ascertainment study. BMJ 1997;315:510-4.
26. Jiranek GC, Kozarek RA. A cost-effective approach to the patient with peptic ulcer bleeding. Surg Clin North Am 1996;76:83-103.
27. Rockall TA, Logan RF, Devlin HB, Northfield TC. Influencing the practice and outcome in acute upper gastrointestinal haemorrhage. Steering Committee of the National Audit of Acute Upper Gastrointestinal Haemorrhage. Gut 1997;41:606-11.
28. Branicki FJ, Coleman SY, Fok PJ, et al. Bleeding peptic ulcer: A prospective evaluation of risk factors for rebleeding and mortality. World J Surg 1990;14:262-9; discussion 269-70.
29. Allan R, Dykes P. A study of the factors influencing mortality rates from gastrointestinal haemorrhage. Q J Med 1976;45:533-50.