Randomized clinical trial

Randomized controlled trial of standard *versus* high-dose intravenous omeprazole after endoscopic therapy in high-risk patients with acute peptic ulcer bleeding

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Background: **Rebleeding from peptic ulcers is a major contributor to death. This study compared standard (40-mg intravenous infusion of omeprazole once daily for 3 days) and high-dose (80-mg bolus of omeprazole followed by 8-mg/h infusion for 72 h) in reducing the rebleeding rate (primary endpoint), need for surgery, duration of hospital stay and mortality in patients with peptic ulcer bleeding after successful endoscopic therapy.**

Methods: **This was a single-institution prospective randomized controlled study based on a postulated therapeutic equivalence of the two treatments. All patients who had successful endoscopic haemostasis of a bleeding peptic ulcer (Forrest classification Ia, Ib, IIa or IIb) were recruited. Informed consent was obtained and patients were randomized to receive standard- or high-dose infusions of intravenous omeprazole.**

Results: **Two (3 per cent) of 61 patients in the high-dose group and ten (16 per cent) of 61 in the standard-dose group exhibited rebleeding, a difference of −13 (95 per cent confidence interval −25 to −2) per cent. The upper limit of the one-sided confidence interval exceeded a predefined equivalence absolute difference of 16 per cent. Equivalence of standard- and high-dose omeprazole in preventing rebleeding was not demonstrated.**

Conclusion: **Intravenous standard-dose omeprazole was inferior to high-dose omeprazole in preventing rebleeding after endoscopic haemostasis for peptic ulcer bleeding. Registration number: NCT00519519 (http://www.clinicaltrials.gov).**

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Introduction

Peptic ulcer bleeding is a potentially life-threatening condition. Endoscopic treatment is usually effective, but bleeding recurs in 15–20 per cent of patients[1]. The rationale for the use of acid-inhibitory drugs for ulcer bleeding is based on *in vitro* data[2] showing that haemostatic mechanisms are highly pH-dependent and that coagulation and stable platelet aggregation do not occur at pH levels below 6. Evidence of the effectiveness of histamine H_2-receptor antagonists in bleeding peptic ulcers is conflicting[3], probably because the H_2-receptor antagonist dosages used in most trials were too low to maintain high intragastric pH[4]. Clinical studies have shown that high doses of proton pump inhibitors (PPIs) are needed to maintain intragastric pH at nearly neutral levels[5,6]. Intravenous infusion of high-dose omeprazole (80-mg bolus followed by 8 mg/h for 72 h) after endoscopic therapy results in greater reductions in the duration and severity of bleeding, number of operations and need for further endoscopic treatment compared with placebo[7].

It is not clear whether high-dose PPI therapy differs from standard-dose treatment (intravenous omeprazole 40 mg once daily for 3 days) in terms of effect on gastric acidity. There is some evidence that after initial endoscopic

treatment both high and standard doses of PPIs are equally effective in the prevention of rebleeding[8]. This trial has, however, been criticized on the grounds that the study included patients with Forrest class IIc (pigmented spot) lesions, which are not considered as high-risk stigmata for rebleeding. In addition, not all patients underwent endoscopy and not all patients with Forrest class I ulcers had endoscopic therapy.

The aim of the present study was to determine the equivalence (non-inferiority) of standard- and high-dose omeprazole infusions in reducing the rebleeding rate (primary endpoint), need for surgery, duration of hospital stay and mortality in patients with bleeding peptic ulcers and high-risk stigmata of rebleeding (Forrest Ia, Ib, IIa and IIc) who had already undergone endoscopic therapy.

Methods

This was a single-institution prospective randomized controlled trial approved by the Singapore General Hospital Ethics Committee and Health Science Authority of the Republic of Singapore. All patients with suspected upper gastrointestinal bleeding underwent oesophagogastroduodenoscopy (OGD) performed by experienced endoscopists within 48 h of admission. Bleeding peptic ulcer was classified according to the Forrest classification (Ia, spurting bleeding; Ib, oozing bleeding; IIa, visible vessel; IIb, clot; IIc, black base; III, clear ulcer base)[9]. Indications for endoscopic treatment were Forrest classes Ia, Ib, IIa and IIb. Endoscopic treatment included adrenaline 1/10 000 injection and/or use of a heater probe (HeatProbe®, model HPY; Olympus Optical, Tokyo, Japan) and/or endoscopic clipping. Patients with ulcer bleeding that could not be controlled by endoscopic treatment underwent immediate surgery, and were not enrolled in the study.

After successful endoscopic haemostasis, patients who satisfied the selection criteria were recruited. Inclusion criteria were: age over 21 years, OGD within 48 h of admission, no upper gastrointestinal surgery within the last month, Forrest class Ia, Ib, IIa and IIb ulcer, and non-malignant ulcer. Exclusion criteria were: impaired hepatic function, pregnancy, lactation, concomitant medication known to interfere with PPI therapy (warfarin, diazepam, phenytoin, clarithromycin, cimetidine or digoxin) and known malignancy.

Informed consent was obtained and patients were randomized using numbered envelopes to one of two treatments according to a randomization table. They received omeprazole (Losec®; AstraZeneca, London, UK) in either a standard dose (40-mg bolus once a day followed by continuous saline infusion for 72 h, equivalent to 120 mg omeprazole in 72 h) or a high dose (80-mg bolus followed by 8 mg/h for 72 h, equivalent to 656 mg in 72 h). To maintain blinding in both patients and investigators, two bolus saline injections were administered on the second and third days in the high-dose group. The randomization methodology was prepared by a statistician not directly involved in the study, and balanced the number of patients in each group. When a patient fulfilled the entry criteria and informed consent had been obtained, the nurse at the endoscopy centre opened the lowest numbered envelope. Patients were monitored in the high-dependency unit and the omeprazole regimen was started within 1 h of completing endoscopic treatment. After the infusions, both groups of patients were given oral omeprazole 40 mg daily for 4 weeks. Patients who were *Helicobacter*-positive on the basis of rapid urea tests were given an additional 1 week of triple therapy. All patients were evaluated at the end of 4 weeks. All investigators remained unaware of the patients' treatment until the study had been completed. There was no patient stratification.

The primary endpoint was recurrent bleeding after successful endoscopic treatment. Rebleeding was defined by haematemesis, shock (defined as systolic blood pressure of 90 mmHg or less, or a pulse rate of 110 per min or above), or a drop in haemoglobin level of more than 2 g/dl after transfusion to a level of 10 g/dl. Repeat endoscopy was performed in patients with signs of rebleeding, which was confirmed if the ulcer was actively bleeding (Forrest class I) or there was either altered blood ('coffee grounds') or fresh blood in the stomach or duodenum. Secondary endpoints were need for surgery, duration of hospital stay and death.

Statistical analysis

An equivalence trial must show that the true absolute difference between two proportions is no greater than a prespecified, clinically meaningful value (Δ); any difference equal to or less than Δ is considered clinically unimportant. To demonstrate equivalence with $(1 - \alpha) \times 100$ per cent confidence, it is sufficient to produce a $(1 - \alpha) \times 100$ per cent confidence interval (c.i.) that is completely captured in the equivalence interval $(-\Delta, \Delta)$. A sample size of 61 per group was calculated such that, for a value of $\Delta = 0{\cdot}16$ and a true difference of zero, a 95 per cent c.i. would fall completely within the equivalence interval with a probability of 0·90. It was planned that 63 patients should be enrolled in each group to allow for violations of protocol and/or non-evaluable patients. The value of $\Delta = 0{\cdot}16$ was based on the difference in rebleeding rates between high-dose and placebo groups in an earlier study[7].

Statistical analysis was performed using the statistical software package SPSS® version 13.0 (SPSS, Chicago,

Illinois, USA). Patient profiles and outcome measures were compared using Student's *t* test for parametric data, the Mann–Whitney *U* test for non-parametric data, and Pearson's χ^2 test, log-likelihood ratio test or Fisher's exact test for proportions. $P < 0{\cdot}050$ was considered statistically significant. Relative risks were calculated. A 95 per cent c.i. on the difference in proportions was calculated using Wilson's method[10]. Continuous data were summarized as mean(s.d.). Depending on the direction of the difference, non-inferiority or superiority could be demonstrated if the confidence interval dose did not include zero.

Results

Between July 2004 and August 2007, a total of 1243 patients were admitted with peptic ulcer bleeds. Some 1117 patients were excluded from enrolment, of whom 1053 had Forrest class IIc or III ulcers. Of the remaining 64 patients who had endoscopic therapy for Forrest Ia, Ib, IIa or IIb ulcer bleeds, recruitment did not occur because endoscopic treatment was unsuccessful (10 patients), there was severe hepatic dysfunction (8), the patient was taking concomitant medication with significant interaction with PPIs (10), there was terminal-stage malignancy (12) or the patient did not give consent (24) (*Fig. 1*).

A total of 63 patients were randomly assigned to receive high-dose and 63 to receive standard-dose omeprazole. Four patients were excluded from analysis owing to protocol violations (*Fig. 1*). There were 61 patients in each treatment arm for the final per-protocol analysis. Demographic and clinical characteristics, including methods of endoscopic therapy and the locations, sizes and Forrest classification of the ulcers, were similar in the two groups (*Table 1*). The only significant difference was a lower proportion of women in the standard-dose group ($P = 0{\cdot}043$).

There were more rebleeding episodes in patients who received standard-dose omeprazole (10 of 61 patients, 16 per cent) than in patients receiving the high-dose regimen (2 of 61 patients, 3 per cent) within 30 days of endoscopic treatment. The difference in proportions was −13 (95 per cent exact c.i. −25 to −2) per cent. As the difference was negative and the c.i. did not include zero, an inference of inferiority of the standard dose could be made. Patients thought to have rebleeding underwent a second endoscopy. Endoscopic retreatment of recurrent bleeding was successful in six of the ten patients in the standard-dose group and in one of the two patients in the high-dose group. The five patients with failed endoscopic treatment underwent immediate surgery. There were no significant differences between standard- and high-dose PPI use in terms of death (2 *versus* 0 respectively; $P = 0{\cdot}496$), need for surgery (4 *versus* 1; $P = 0{\cdot}361$) or mean length of hospital stay (5·9(6·4) *versus* 5·2(2·1) days; $P = 0{\cdot}411$). There were

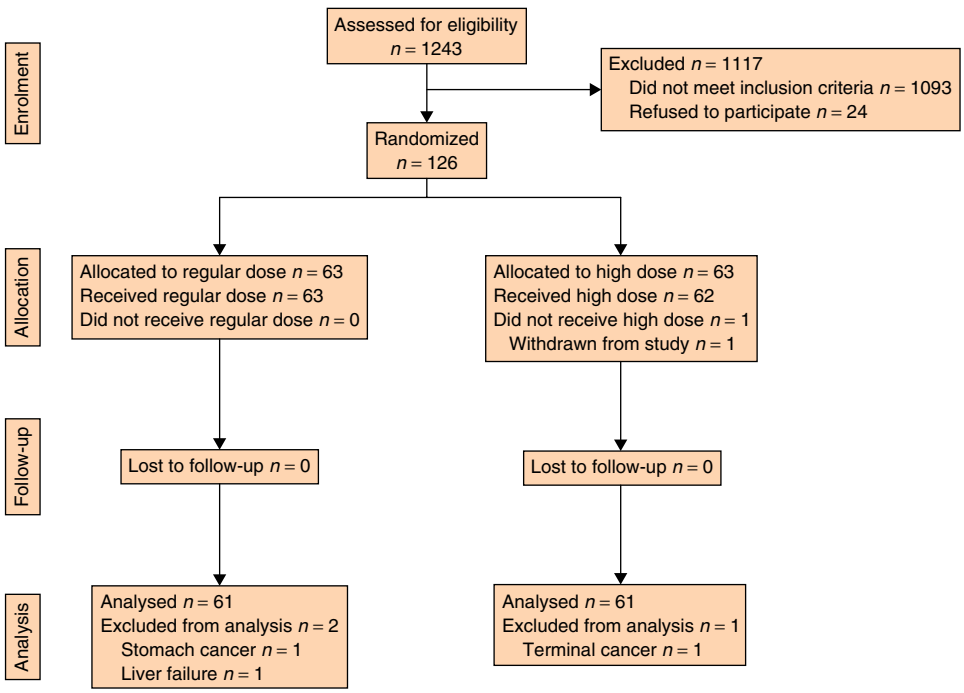

Fig. 1 CONSORT diagram for the trial

Table 1 Demographic and clinical details of patients in standard- and high-dose groups

	Standard dose ($n = 61$)	High dose ($n = 61$)	*P*
Age (years)*	64·2(13·1)	63·5(14·7)	0·780‡
Sex ratio (M : F)	49 : 12	39 : 22	0·043§
ASA score*	1·8(0·7)	2·0(0·8)	0·089‡
Hypotensive shock†	14	11	0·501§
Haemoglobin on admission (g/l)*	9·1(3·2)	9·2(2·7)	0·819‡
Site of ulcer			0·663¶
Proximal stomach	4	6	
Mid stomach	8	13	
Distal stomach	10	12	
D1	34	27	
D2	4	2	
Stoma	1	1	
Ulcer size (mm)*	7(4)	9(8)	0·163‡
Forrest classification			0·141¶
Ia (spurting vessel)	5	3	
Ib (oozing vessel)	22	24	
IIa (visible vessels)	24	15	
IIb (clot)	10	19	
Adrenaline injection (ml)*	8·8(4·4)	9·4(3·6)	0·425‡
Endoscopic therapy			0·434§
Unimodal (adrenaline only)	40	44	
Multimodal (adrenaline + others)	21	17	
Endoscopist (consultant grade and above)	22	25	0·577§
Blood transfusion (units)*	2·4(2·0)	2·1(1·7)	0·415‡

*Values are mean(s.d.). †Blood pressure less than 90/60 mmHg. ASA, American Society of Anesthesiologists. ‡Two independent samples *t* test; §χ^2 test; ¶log-likelihood ratio test.

no reported side-effects from the different omeprazole doses.

Discussion

In 2004, the American Society for Gastrointestinal Endoscopy recommended the use of PPIs in all patients with upper gastrointestinal bleeding[11]. The optimal dose has been the subject of debate. Although the study by Lau and colleagues[7] has become widely used as the benchmark upon which the practice of using high-dose PPIs in peptic ulcer bleeding is based, it has substantial limitations. Khuroo and co-workers[12] had already demonstrated conclusively that a standard dose of oral omeprazole was superior to placebo in preventing rebleeding and the need for surgery. The use of an inactive placebo as the comparator in the Lau *et al*. study is questionable, as high-dose intravenous PPIs would not be expected to be less effective than a standard dose.

A meta-analysis of PPI therapy in high-risk patients with acute peptic ulcer bleeding, published 1 year after the start of the present trial, showed that high-dose intravenous PPIs significantly decreased peptic ulcer rebleeding, need for surgery and mortality compared with placebo[13]. It also showed that non-high-dose PPI regimens improved outcomes, suggesting that dosages inferior to those used for high-dose intravenous PPI treatment might be effective. In the same meta-analysis, no analysis could be performed to compare high-dose PPIs with other PPI regimens because there was no head-to-head trial at that time.

Although a high-dose infusion regimen (80-mg bolus followed by 8 mg/h) has been used in most studies, the optimal dose of PPI to achieve almost complete cessation of gastric acid secretion for clot stabilization has not been determined. Two studies[8,14] suggested that reducing the infusion of intravenous omeprazole to the 'standard' dose of 20–80 mg per day might be feasible, although both were criticized for including patients with low-risk ulcers who did not require endoscopic therapy, excessively high rebleeding rates compared with those published in the literature in general, and relatively small sample sizes.

The present study was confined to patients with a high risk of further haemorrhage. The rebleeding rate of 16 per cent in the standard-dose group was not particularly high and was lower than the rebleeding rate (22 per cent) in the placebo arm of the Lau study[7]. It is more comparable to the 13·2 per cent probability of rebleeding reported in a pooled analysis of data from eight trials of high-dose PPI infusion[15]. The rebleeding rate for the high-dose group in the present study (3 per cent) is comparable to that of 6·7 per cent reported in the Lau study[7].

In the present study, standard-dose omeprazole was inferior to the high-dose regimen in preventing peptic ulcer rebleeding after endoscopic haemostasis. This finding is in contrast to that of a multicentre randomized trial conducted in Italy, where high-dose PPIs had no advantage in reducing the risk of recurrent bleeding after endoscopic therapy compared with the standard dose[16]. One explanation could be that rapid metabolism of PPIs in a non-Asian population contributes to the difficulty in maintaining intragastric pH above 6 for clot stabilization[6,17].

The present study did not show any differences in secondary outcomes in terms of death and surgery rates between the two groups. This was possibly due to the small number of events, and may be a type II statistical error. The findings are, however, consistent with those of other larger randomized trials[7,8,12,14,16].

Intravenous standard-dose omeprazole was inferior to a high-dose infusion in reducing the incidence of rebleeding after successful endoscopic haemostasis of bleeding peptic ulcers in a South-East Asian population.

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