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• *BRIEF REPORTS* •

Epinephrine injection therapy versus a combination of epinephrine injection and endoscopic hemoclip in the treatment of bleeding ulcers

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Abstract

AIM: To assess the efficacy of hemoclip application in combination with epinephrine injection in the treatment of bleeding peptic ulcers and to compare the clinical outcomes between patients treated with such a combination therapy and those treated with epinephrine injection alone.

METHODS: A total of 293 patients (211 males, 82 females) underwent endoscopic therapy for bleeding peptic ulcers. Of these, 202 patients (152 males, 50 females) received epinephrine injection therapy while 91 patients (59 males, 32 females) received combination therapy. The choice of endoscopic therapy was made by the endoscopist. Hemostatic rates, rebleeding rates, need for emergency surgery and 30-d mortality were the outcome measures studied.

RESULTS: Patients who received combination therapy were significantly older (mean age 66±16 years, range 24-90 years) and more suffered from chronic renal failure compared to those who received epinephrine injection therapy alone (mean age 61±17 years, range 21-89 years). Failure to achieve permanent hemostasis was 4% in the group who received epinephrine injection alone and 11% in the group who received combination therapy. When the differences in age and renal function between the two treatment groups were taken into account by multivariate analysis, the rates of initial hemostasis, rebleeding rates, need for surgery and 30-d mortality for both treatment options were not significantly different.

CONCLUSION: Combination therapy of epinephrine injection with endoscopic hemoclip application is an effective method of achieving hemostasis in bleeding peptic ulcer diseases. However, superiority of combination therapy over epinephrine injection alone, could not be demonstrated.

Key words: Bleeding peptic ulcer; Epinephrine; Endoscopic hemoclip; Combination therapy

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INTRODUCTION

Gastrointestinal hemorrhage is a common complication of peptic ulcer disease. Despite advances in the clinical diagnosis of patients with gastrointestinal hemorrhage, the development of new pharmacological agents and endoscopic interventions, the mortality rate due to gastrointestinal hemorrhage has remained relatively unchanged at 6-10% for the past three decades[1-4]. This could be attributed to the increasing age and comorbidity of patients who present with gastrointestinal hemorrhage. About 80% of patients with gastrointestinal hemorrhage due to peptic ulcer disease stop bleeding with only supportive measures[2,5-7]. The remaining 20% who would continue to bleed or have recurrence of bleeding account for most of the mortality from gastrointestinal hemorrhage. This group of patients is a high-risk group who can be targeted for aggressive hemostatic therapy.

Hemostatic therapies include endoscopic, angiographic and surgical methods. Upper gastrointestinal endoscopy is the most effective diagnostic technique for peptic ulcer diseases. A skilled endoscopist is able to diagnose the bleeding source in over 95% of cases[8,9]. Endoscopic therapy is the acknowledged method of choice for controlling active peptic ulcer hemorrhage, reducing the risk of rebleeding as well as the need for surgical intervention[10,11]. For patients who fail endoscopic therapy, angiographic and surgical alternatives have to be considered.

A variety of methods may be used to achieve hemostasis of bleeding peptic ulcers endoscopically. These include contact thermal therapy, non-contact thermal therapy, injection therapy, and mechanical hemostasis. Epinephrine injection therapy has been shown to be effective in the treatment of bleeding peptic ulcers with reported initial hemostasis rates ranging from 80% to 100% and rebleeding

rates ranging from 9% to 36%[12-18]. In many centers, epinephrine injection has become standard endoscopic therapy for hemostasis. The use of metallic clips to achieve hemostasis endoscopically was first described by Hayashi *et al*[19] in 1975 but the technique was abandoned because of its technical complexity. In 1988, Hachisu[20] reported a permanent hemostasis rate of 84% in patients treated with endoscopic application of hemoclips. Uncontrolled studies by Binmoeller *et al*[21], Scapa[22] and Lai *et al*[23] reported initial hemostasis rates of 100%, 100% and 95% respectively with low rebleeding rates.

Epinephrine injection has been shown to achieve hemostasis by local tamponade, prolonged vasoconstriction and platelet aggregation[24]. The immediate compression of bleeding vessels is thought to be the most important for initial hemostasis. However, rebleeding may occur after the local tamponade effects of epinephrine wear off. Moreover, the vasoconstricting effect of epinephrine may be diminished in atherosclerotic vessels. The application of direct mechanical tamponade with a metallic hemoclip on the bleeding blood vessels may be more effective in preventing rebleeding. It may be possible that a combination of epinephrine injection followed by hemoclip application will be more effective in preventing rebleeding from peptic ulcers. We therefore compared the hemostatic efficacy of combined epinephrine injection and endoscopic hemoclip application with that of epinephrine injection alone in 293 patients with bleeding peptic ulcer disease.

MATERIALS AND METHODS

Over a 6-year period between September 1993 and September 1999, 293 patients (>18 years of age) with bleeding gastroduodenal ulcers were admitted to the Division of Gastroenterology at Toa Payoh Hospital, Singapore (subsequently Changi General Hospital, Singapore). These patients were included in the study if emergency endoscopy demonstrated a gastric or duodenal ulcer with major stigmata of recent hemorrhage (SRH): there an actively bleeding vessel, a non-bleeding visible vessel or an adherent clot resistant to washing. Adherent clots were removed to expose the underlying ulcer base. All the 293 patients received endoscopic therapeutic intervention with either epinephrine injection alone or with a combination of epinephine injection and hemoclip application. The choice of endoscopic therapy was decided by the endoscopist. Patients taking non-steroidal anti-inflammatory drugs (NSAIDs), aspirin or anticoagulants were not excluded but these drugs were stopped at the time of hospital admission. Concomitant medical conditions were recorded and all patients were classified according to the American Society of Anaesthesiologists (ASA) classification of physical status.

Endoscopic epinephrine injection therapy was performed using 1:10 000 epinephrine injected via a disposable needle (KeyMed Ltd, Southend-on-Sea). Multiple injections were performed around the bleeding point until hemostasis was secured. In the patients who received combination therapy, endoscopic hemoclip application was carried out using a clipping device (Olympus HX-5LR, Tokyo, Japan) after epinephrine injection had been performed.

After the index therapeutic endoscopy, all patients received oral acid suppressant therapy (either histamine receptor antagonists or proton pump inhibitors). The following outcome measures were recorded: *initial hemostasis* which was defined as the absence of bleeding when observed for 5 min after therapeutic endoscopic intervention, *rebleeding*, *need for emergency surgery*, and 30-d *mortality*. Criteria for rebleeding included the recurrence of haemetemesis and/or melena, a drop in hemoglobin of more than 2 g/dL over a 3-d period or the development of shock as defined by a systolic blood pressure below 100 mmHg, pulse rate greater than 100/min with peripheral vasoconstriction. If rebleeding was suspected, an emergency endoscopy was performed to confirm the re-bleeding and endoscopic treatment was repeated with either epinephrine injection alone or with combination therapy. The endoscopic therapy used for treatment of rebleeding was the same as that used in the initial endoscopy. The decision for emergency surgery would be made if initial hemostasis could not be achieved at the index endoscopy or if 2 consecutive endoscopic therapeutic interventions were unsuccessful.

Statistical analysis

Statistical analysis was performed using SPSS 9.01 for Windows. Differences in outcomes were compared using the chi-square test. Multivariate analysis was performed using binary logistic regression methods. Statistical significance was defined as a P value of less than 0.05.

RESULTS

Two hundred and ninety-three patients (82 females, 211 males; mean age 62 years), who presented with hemetemesis and/or melena, were found - at upper gastrointestinal endoscopy to have peptic ulcer diseases with active bleeding, a non-bleeding visible vessel or an adherent clot resistant to washing. Of these, 202 patients received epinephrine injection therapy alone while 91 patients received combination therapy of epinephrine injection with hemoclip application.

The characteristics of patients studied are shown in Table 1. There was no significant difference in gender, type of stigmata of hemorrhage, smoking habit, and lowest hemoglobin value between the two treatment groups. The patients were also classified according to the ASA classification of physical status. There was no significant difference in the number of patients of each ASA grade between the two treatment groups. The patients who received combination therapy were significantly older (66±16 years) compared to those who received epinephrine injection only (61±17 years). The two treatment groups were also compared with regard to the presence of common comorbid conditions (Table 2). Moderate chronic renal failure, defined as a plasma creatinine level of more than 300 μmol/L, was present in more patients who received combination therapy compared to those who received epinephrine injection alone. There were no other significant differences in the frequency of major comorbid conditions between the two groups. The patients who received combination therapy also tended to have more concomitant

Table 1 Clinical characteristics of patients in the two treatment groups

	Epinephrine injection alone (n = 202)	Combination therapy (n = 91)	P value
Gender (male:female)	152:50	59:32	0.066
Age (yr)	61±17	66±16	0.016
(range in years)	(21–89)	(24–90)	
Smoking, n (%)	61 (30.2)	30 (33.0)	0.674
Alcohol, n (%)	42 (20.8)	12 (13.2)	0.108
Recent NSAID usage, n (%)	70 (34.7)	37 (40.7)	0.338
Past history of peptic ulcer, n (%)	64 (31.7)	25 (27.5)	0.453
Past history of UGIB, n (%)	35 (17.3)	15 (16.5)	0.845
Lowest Hb	9.1±2.5	8.7±2.5	0.162
(range in g/dL)	(4.1-16.4)	(4.3-17.9)	
Ulcer type (GU:DU)	76:126	40:51	0.305
Endoscopic major SRH, n (%)			
- active bleeding	82 (40.6)	46 (50.5)	
- visible vessel	102 (50.5)	42 (46.2)	0.185
- adherent clot	18 (8.9)	3 (3.3)	
ASA physical status, n (%)			
- P1 (Healthy; no medical problems)	78 (38.6)	25 (27.5)	
- P2 (Mild systemic disease)	51 (25.2)	23 (25.3)	0.124
- P3 (Severe systemic disease)	73 (36.1)	43 (47.3)	

Table 2 Frequency of comorbid conditions of patients in the two treatment groups

	Epinephrine injection alone (n = 202), n (%)	Combination therapy (n = 91), n (%)	P value
Ischemic heart disease	50 (24.8)	28 (30.8)	0.281
Hypertension	69 (34.2)	40 (44.0)	0.108
Diabetes mellitus	44 (21.8)	25 (27.5)	0.288
Stroke	19 (9.4)	12 (13.2)	0.330
Chronic renal failure	9 (4.5)	10 (11.0)	0.036
Liver cirrhosis	9 (4.5)	1 (1.1)	0.143
Osteoarthritis	20 (6.8)	8 (2.7)	0.755
Malignancy	7 (3.5)	4 (4.4)	0.698
At least 1 comorbid illness	124 (61.4)	66 (72.5)	0.065

Table 3 Clinical outcome measures of the patients in the two treatment groups

	Epinephrine injection (n = 202), n (%)	Combination therapy (n = 91), n (%)	P value[1]
Initial hemostasis	199 (98.5)	91 (100)	0.637
Rebleeding	8 (4.0)	10 (11.0)	0.108
Emergency surgery	3 (1.5)	1 (1.1)	0.412
30-d mortality	11 (5.4)	6 (6.6)	0.754

[1]P value calculated using multivariate analysis to account for the increased age and increased frequency of chronic renal failure in the group receiving combination therapy.

illnesses with 72.5% having at least one other chronic illness compared to 61.4% of those who received epinephrine injection alone.

Table 3 shows the clinical outcome measures of the patients in the two treatment groups. Of the 202 patients who received epinephrine injection alone, initial hemostasis was achieved in 199 patients. The 3 patients in whom initial hemostasis could not be achieved endoscopically underwent surgery but died within 30 d of their initial presentation. Five patients re-bled during their hospital admission, necessitating further endoscopic therapy. Hemostasis was achieved on the second therapeutic endoscopy in 4 patients. One patient required surgery to achieve hemostasis. None of the patients who re-bled, died. However, 8 patients, in the patient group who received epinephrine injection only, died as a result of worsening of their pre-existing comorbid conditions following gastrointestinal bleeding. Thus the overall failure rate in the group who received epinephrine injection alone was 4% (8 of 202 patients, 3 primary failure, 5 recurrent bleeding).

Of the 91 patients who received combination therapy using epinephrine injection followed by hemoclip application, initial hemostasis was achieved in all the patients. Ten patients re-bled during their hospital admission, necessitating further endoscopic therapy. Hemostasis was achieved on the second therapeutic endoscopy in 9 patients. One patient required surgery to achieve hemostasis. None of the patients who re-bled died. However, there were 6 deaths in the patient group who received combination therapy as a result of worsening of their pre-existing comorbid conditions following the gastrointestinal hemorrhage. Thus the overall failure rate in the group who received combination therapy was 11% (10 of 91 patients, all from recurrent bleeding).

DISCUSSION

Gastrointestinal bleeding due to peptic ulcers is a serious and potentially life-threatening condition. Endoscopic haemostatic therapy has been shown to improve the outcomes in upper gastrointestinal hemorrhage. These therapies may be divided into four main groups: contact thermal therapy, non-contact thermal therapy, injection therapy, and mechanical hemostasis. Each method has advantages and disadvantages related to the technical aspects of the procedure as well as the mechanism by which hemostasis is achieved.

Following initial studies which showed that endoscopic hemoclip application was associated with a low rate of recurrent bleeding, more recent studies have focused on comparing the hemostatic efficacy of hemoclip application with that of other modalities. A retrospective study by Buffoli *et al* compared the efficacy of epinephrine injection alone versus a combined method of epinephrine injection with hemoclip application in the treatment of 99 patients with peptic ulcer bleeding. Re-bleeding occurred in 16.6% of those who received epinephrine injection alone and in 4.4% of those who received combination therapy, suggesting that a combined approach may be more efficacious than a single modality. However, this difference did not reach statistical significance, possibly because of the small number of patients. Prospective studies by Chung *et al*, and Gevers *et al* compared the hemostatic efficacy of the endoscopic hemoclip technique with that of epinephrine injection and a combined method in the management of bleeding peptic ulcers. In both studies, no significant benefit was shown with the combined method of epinephrine injection with hemoclip application over epinephrine injection alone. Again, both studies involved a relatively small number of patients (32-42 patients in each treatment arm). In the study by Gevers *et al*, sample sizes were calculated based on a rate

of failure in initial hemostasis of 30% for the group treated with epinephrine-polidocanol injection only, and 5% for the group treated with a combination of epinephrine-polidocanol injection and hemoclip application. However, in that study, the actual initial failure rate in the injection only group was 15% (the overall failure rate being 6%) while that in the combined therapy group was 25% (the overall failure rate being 25%). In the study by Chung *et al*, the overall failure rate in the injection only group was 14.6% while that in the combined group was 9.5%. In our study, which included 293 patients (202 treated with epinephrine injection only, 91 with combined epinephrine injection-hemoclip application), the overall failure in hemostasis occurred in 4% of the patients who received epinephrine injection only and in 11% of those who were treated with a combined method of epinephrine injection and hemoclip application. The fact that epinephrine injection therapy was very effective in achieving hemostasis and associated with a low rebleeding rate made it difficult to demonstrate any improvement, if any, in those treated by the combined epinephrine-hemoclip technique.

In our study, the patients who received combination therapy were significantly older and a significantly greater number had moderate chronic renal failure with plasma creatinine levels exceeding 300 μmol/L. Abnormal hemostasis is common in chronic renal impairment due to a variety of factors such as prolongation of bleeding time, decreased activity of platelet factor 3, abnormal platelet aggregation and adhesiveness, and impaired prothrombin consumption. A greater proportion of the patients who received combination therapy had a poorer physical status, with 47.3% having an ASA grade of P3 compared to 36.1% in those who were treated with epinephrine injection only, though this did not reach a statistical significance. When the differences in age and renal function between the two treatment groups were taken into account by multivariate analysis, the rebleeding rates for both treatment options were not significantly different.

Treatment of bleeding peptic ulcers with epinephrine injection or with hemoclip application has been shown to be safe and effective. The results of our study showed that the combination of epinephrine injection and hemoclip application was equally efficacious and could be employed in the treatment of bleeding peptic ulcers. The possibility that a combination of both methods will be even more efficacious is certainly appealing and logical. However, despite a greater number of patients compared to previous studies, we have not managed to demonstrate the superiority of combination therapy over epinephrine injection alone. The difference in efficacy may not be as great as previously perceived and future comparative studies would require even greater sample sizes.

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