A prospective, randomized trial of large- versus small-volume endoscopic injection of epinephrine for peptic ulcer bleeding

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Background: Endoscopic injection of epinephrine in the treatment of bleeding peptic ulcer is considered highly effective, safe, inexpensive, and easy to use. However, bleeding recurs in 6% to 36% of patients. The aim of this study was to determine the optimal dose of epinephrine for endoscopic injection in the treatment of patients with bleeding peptic ulcer.

Methods: One hundred fifty-six patients with active bleeding or nonbleeding visible vessels were randomized to receive small- (5-10 mL) or large-volume (13-20 mL) injections of a 1:10,000 solution of epinephrine.

Results: The mean volume of epinephrine injected was 16.5 mL (95% CI [15.7, 17.3 mL]) in the large-volume group and 8.0 mL (95% CI [7.5, 8.4 mL]) in the small-volume group. Initial hemostasis was achieved in all patients studied. The number of episodes of recurrent bleeding was smaller in the large-volume group (12/78, 15.4%) compared with the small-volume group (24/78, 30.8%, p = 0.037). The volume of blood transfused after entry into the study, duration of hospital stay, numbers of patients requiring urgent surgery, and mortality rates were not statistically different between the 2 groups.

Conclusions: Injection of a large volume (>13 mL) of epinephrine can reduce the rate of recurrent bleeding in patients with high-risk peptic ulcer and is superior to injection of lesser volumes of epinephrine when used to achieve sustained hemostasis. (Gastrointest Endosc 2002;55:615-9.)

Although peptic ulcer bleeding ceases spontaneously in 70% to 80% of patients, it can be catastrophic in the remainder. The mortality rate associated with such bleeding has been reduced to 2% to 6% through the endoscopic use of various methods of therapy. Endoscopic hemostatic techniques are thus a major advance in the treatment of these patients. By reducing both morbidity and mortality, endoscopic therapy has become the treatment of first choice for ulcer hemorrhage. Of the various possible techniques, the efficacy and safety of heat probe coagulation and multipolar probe electrocoagulation are well established. Hemostatic rates of 80% to 95% can be achieved with these modalities. However, bleeding recurs in 10% to 30% of patients.

Injection therapy is also effective, safe, relatively inexpensive, and easy to use. Impressive rates of hemostasis have been obtained by using solutions of various agents such as epinephrine, absolute alcohol, hypertonic saline solution, 50% glucose/water, thrombin, and fibrin sealants. Of these, epinephrine is the most commonly used agent for endoscopic injection. There is a wide range in the volume (2-25 mL) of epinephrine injected in various studies to achieve hemostasis. The reported rates of initial hemostasis obtained with epinephrine injection range from 80% to 100%. However, bleeding recurs in 6% to 36% of patients. The reason for this wide variation in rates of recurrent bleeding is unknown. Additionally, the optimal volume of epinephrine needed to obtain hemostasis has not been established.

The mechanisms that underlie hemostasis in response to endoscopic injection of epinephrine are vasoconstriction, vessel compression, and platelet aggregation. Among these, the immediate mechanical compression of the bleeding vessel is thought to be the most important for the initial control of bleeding. Therefore, initial endoscopic injection of a larger volume of epinephrine is theoretically better than injection of a smaller volume in patients at high risk for ulcer hemorrhage. The aim of this study was to compare the rates of recurrent
bleeding after injection of 2 different volumes of epinephrine in patients with ulcer bleeding. In addition, transfusion requirements, need for surgery, mortality, and lengths of hospital stay were compared between large- and small-volume injection groups of patients.

PATIENTS AND METHODS

Patients hospitalized with hematemesis or melena underwent endoscopy within 24 hours of admission. Those between the ages of 18 and 80 years were eligible for inclusion in the study if they had an ulcer with spurring hemorrhage, an oozing visible vessel, or a non-bleeding visible vessel. For inclusion, patients with a nonbleeding visible vessel had to have one of the following signs of recent bleeding: "coffee ground" material or blood in the stomach and/or duodenum; shock; or an initial hemoglobin level of less than 10 g/dL (normal: 14-16 g/dL). By history, no patient had chronic blood loss before study entry. Exclusion criteria were inability or unwillingness to give written informed consent, bleeding tendency (platelet count <50,000/mm³, prothrombin time <30% taking anticoagulant medication), bleeding gastric malignancy, pregnancy, or more than one bleeding source. Possible complications of endoscopic treatment were discussed with the patients and their relatives, and written informed consent was obtained before entry into the trial. The protocol was approved by the Clinical Research Committee of our hospital.

This study was a prospective, single-blind, randomized comparative trial. Patients were randomized by using numbered envelopes to 1 of 2 treatment groups according to a randomization table: small-volume epinephrine group or large-volume epinephrine group. The randomization methodology balanced the number of patients in each group and was prepared by a statistician who was not directly involved in the study. Patients were cared for by the investigators and other physicians not involved in the study.

A single, experienced gastroenterologist performed all hemostatic treatments. A commercially available endoscope (GIF-XQ240, Olympus Optical Co., Ltd., Tokyo, Japan) and a 4 mm, 23 G injector needle (NM-8L, Olympus) were used. In the small-volume injection group, 5 to 10 mL of a 1:10,000 solution of epinephrine were injected around the bleeding site (1 mL/injection at 2 to 3 mm from the point of bleeding). In the large-volume epinephrine group, 13 to 20 mL of a 1:10,000 solution of epinephrine were injected around the bleeding site. During injection, electrocardiographic monitoring was used to detect arrhythmias. Initial hemostasis was defined as cessation of hemorrhage for 5 minutes after endoscopic treatment. The injection treatment was considered to have failed if hemostasis was not obtained after injection of 10 mL of the epinephrine solution in the small-injection group and after injection of 20 mL in the large-volume group. These patients underwent alternative endoscopic treatments or surgery.

Recurrent bleeding was suspected if fresh blood was found in the stomach 6 hours after entry into the study; if vital signs were unstable; or if there was continued melena or bloody stools, or hematemesis. When there was a suspicion of recurrent bleeding, the patient underwent emergency endoscopy. If there was active bleeding or a fresh blood clot was found at the ulcer base, recurrence of bleeding was regarded as confirmed.

For ethical reasons, treatment regimens were discussed with patients in whom initial hemostasis was not achieved or who had evidence of recurrent bleeding. The therapeutic options included a second injection of epinephrine, heat probe thermoagulation, and surgery. One biopsy from the gastric antrum and one from the gastric body were obtained after cessation of bleeding, and the presence or absence of *Helicobacter pylori* infection was determined by means of a rapid urease test.

Vital signs were monitored hourly for the first 12 hours, every 2 hours for the second 12 hours, every 4 hours for the following 24 hours until they became stable, and then 4 times daily. A nasogastric tube was inserted and maintained for 24 hours after treatment. Hemoglobin level and hematocrit were determined at least once daily, and blood transfusions were given to maintain the hemoglobin concentration at greater than 10 g/L. Omeprazole (40 mg) was given intravenously every 6 hours for 3 days, then orally (20 mg/day) for 2 months. If the rapid urease test was positive, treatment for 1 week with triple drug therapy (omeprazole + clarithromycin + amoxicillin) was initiated within 24 hours of enrollment. Endoscopy was performed 72 hours after cessation of bleeding by the same endoscopist who performed the initial treatment. If there was no evidence of hemorrhage and no clot in the ulcer base, the patient was discharged and followed up with an endoscopy 2 to 3 months later.

Shock was defined as systolic pressure less than 100 mm Hg and pulse rate greater than 100 beats/min accompanied by cold skin, sweating, pallor, and oliguria. Ultimate hemostasis was defined as the lack of recurrent bleeding for 14 days after treatment.

The outcomes assessed were initial recurrence of bleeding, blood transfusion requirement, surgery, length of hospital stay, and mortality. Outcomes were assessed within 14 days after enrollment in the study.

Statistical analysis

The sample size was calculated based on previous experience with injection of a small volume of epinephrine, which had a rate of recurrent bleeding of 36%. If the rate of recurrent bleeding with injection of the larger volume of epinephrine was taken as 14.5%, a sample size of 76 was required for each group to achieve a statistical power of 90% at 10% type I error.

The Mann-Whitney rank sum test was used for the analysis of nonparametric quantitative data (age, volume of blood transfusion, volume of epinephrine injection, ulcer size, hemoglobin, and length of hospital stay). Unless otherwise indicated, values are expressed as mean (SD). The chi-square test, with or without Yates correction, and the Fisher exact test were used when appropriate to compare the location of bleeding, endoscopic findings, gastric contents, number of patients with *H pylori* infection, shock, comorbid illness, hemostasis, emergency
Peptic ulcer bleeding: large- vs. small-volume endoscopic injection of epinephrine


Table 1. Clinical variables of patients at study entry

<table>
<thead>
<tr>
<th></th>
<th>Small-volume epinephrine n = 78</th>
<th>Large-volume epinephrine n = 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, y)</td>
<td>68.7</td>
<td>65.6</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>64/14</td>
<td>66/12</td>
</tr>
<tr>
<td>Locations of bleeding ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>33 (42.3%)</td>
<td>43 (55.1%)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>43 (55.1%)</td>
<td>31 (38.8%)</td>
</tr>
<tr>
<td>Stoma</td>
<td>2 (2.6%)</td>
<td>4 (5.1%)</td>
</tr>
<tr>
<td>Endoscopic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spurting</td>
<td>9 (11.5%)</td>
<td>11 (14.1%)</td>
</tr>
<tr>
<td>Oozing visible vessel</td>
<td>23 (29.5%)</td>
<td>27 (34.6%)</td>
</tr>
<tr>
<td>Nonbleeding visible vessel</td>
<td></td>
<td>46 (59%)</td>
</tr>
<tr>
<td>Gastric contents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>25 (32.1%)</td>
<td>38 (48.7%)</td>
</tr>
<tr>
<td>Coffee grounds</td>
<td>28 (35.8%)</td>
<td>23 (29.5%)</td>
</tr>
<tr>
<td>Clear</td>
<td>25 (32.1%)</td>
<td>17 (21.8%)</td>
</tr>
<tr>
<td>Positive H pylori</td>
<td>53 (68%)</td>
<td>50 (64.1%)</td>
</tr>
<tr>
<td>Shock</td>
<td>29 (37.2%)</td>
<td>30 (38.5%)</td>
</tr>
<tr>
<td>Medical illness</td>
<td>53 (68%)</td>
<td>56 (71.8%)</td>
</tr>
<tr>
<td>Mean hemoglobin (g/L)</td>
<td>9.4</td>
<td>9.7</td>
</tr>
<tr>
<td>Mean ulcer size (cm)</td>
<td>1.0</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*p > 0.05 for all variables between the 2 groups.

operation, and mortality between the 2 groups. A p value of <0.05 was considered significant.

RESULTS

A total of 944 patients whose main symptoms were hematemesis, melena, or both, presented to the emergency department between September 1999 and June 2000. A total of 840 patients underwent endoscopy within 12 hours of arrival at the emergency department; 720 had peptic ulcers. Peptic ulcers with spurting hemorrhage, oozing visible vessel, or nonbleeding visible vessel were found in 168 patients. Twelve patients were excluded for the following reasons: no informed consent (n = 6), bleeding diathesis (n = 2), gastric malignancy (n = 2), and lack of cooperation (n = 2). There were 156 patients enrolled in the study, 78 in each group. The 2 groups were well matched for factors that could potentially affect outcome (Table 1). The numbers of patients with comorbid illness were similar between the groups (including 6 with cirrhosis in the small-volume group and 5 with cirrhosis in the large-volume group). By history, no patient had chronic blood loss before entry into the study.

The clinical outcomes for the patients studied are shown in Table 2. The volume of epinephrine injected was higher in the large-volume group (mean 16.5 mL, range 15.7-17.3 mL; vs. 8.0 mL, 95% CI [7.5, 8.4 mL]). Initial hemostasis was achieved in all patients in both groups. There were fewer episodes of recurrent bleeding in the large-volume group (12/78, 15.4%) than in the small-volume group (24/78, 30.8%; p = 0.037). The mean interval from initial hemostasis to an episode of recurrent bleeding was 3.5 days (3.7) in the small-volume group and 3 days (3.7) in the large-volume group (p = 0.68).

Of the 24 patients in the small-volume injection group who had recurrent bleeding, 8 were treated a second time by injection of epinephrine (ultimate hemostasis achieved in 6 whereas 2 required heat probe coagulation); 12 underwent heat probe coagulation (ultimate hemostasis achieved in 12); 2 were treated with supportive measures (ultimate hemostasis achieved in both); and, 2 underwent surgery and recovered uneventfully.

Of the 12 patients in the large-volume injection group in whom bleeding recurred, 9 underwent heat probe coagulation (ultimate hemostasis achieved in 9); 1 was treated with supportive measures alone (with ultimate hemostasis); and 2 had surgery and recovered uneventfully.

There was no death from peptic ulcer bleeding in either group. However, 4 patients died of unrelated illness in the large-volume group (2 pneumonia, 1 terminal lung cancer, 1 urinary tract infection with sepsis) and 6 died in the small-volume epinephrine group (3 decompensated liver cirrhosis, 1 urinary tract infection with sepsis, 1 uremia, 1 biliary tract infection with sepsis). The volume of blood transfused, duration of hospital stay, number of operations, and number of deaths were not statistically different between the 2 groups (Table 2). At 1 week after endoscopic treatment, there were no complications in either group including perforation of a peptic ulcer, aspiration pneumonia, cardiac complications, and fever.

DISCUSSION

Patients with actively bleeding peptic ulcer or peptic ulcer with nonbleeding vessel were enrolled in this
prospective study. Previous studies have confirmed that conservative management of patients with these stigmata is associated with a high risk of uncontrolled bleeding and recurrent bleeding.\(^1\) Consequently, it was unethical to include a control in the current study. Endoscopic findings were interpreted and endoscopic treatment performed by an experienced specialist endoscopist to minimize bias, although the determination of recurrent bleeding by endoscopic criteria was subjective. The mortality rate for peptic ulcer hemorrhage can be decreased with better hospital care including combined medical and surgical approaches and aggressive endoscopic treatment.\(^1,2\)

Recurrence of bleeding in patients with peptic ulcer hemorrhage has been consistently described as the most important prognostic factor.\(^16,19\) If it can be prevented, the mortality rate can potentially be reduced. Although a high rate of initial hemostasis can be achieved with endoscopic injection of epinephrine, a wide range of rates of recurrent bleeding after therapy are reported.\(^3-12\) Thus far, there is no proven explanation for this phenomenon. Mechanical compression of the bleeding vessel is the most important factor in the initial control of bleeding.\(^16,17\) However, the hemostatic effect may be prolonged by a combination of tamponade and vasoconstriction,\(^20\) and thus injection of a larger volume of epinephrine may be beneficial in preventing recurrent bleeding through these same mechanisms. In the present study, the rate of recurrent bleeding was significantly lower when a larger volume (>13 mL) of epinephrine was injected (12/78 patients, 15.4%; vs. 24/78 patients, 30.8%; \(p < 0.05\)).

Because submucosally injected epinephrine does not damage tissue or have appreciable systemic effects, large volumes can be used with a low risk of complication.\(^21\) To date, only a single case of hypertension and ventricular tachycardia after epinephrine injection of a Mallory-Weiss tear has been reported.\(^22\) Sung et al.\(^23\) confirm that although the plasma level of epinephrine rises 4 to 5 times above basal level immediately after injection, cardiovascular complications are not commonly observed. It has been confirmed that endoscopic injection of epinephrine is safe.\(^3-12\)

An intragastric pH of greater than 6 has been shown to lower the risk of recurrent bleeding in patients with bleeding peptic ulcers.\(^24\) Therefore, a high dose infusion of omeprazole reduces the risk of recurrent bleeding after successful endoscopic therapy.\(^25,26\) In the current study, the same intravenous dose of omeprazole was used as in a prior study,\(^26\) but higher rates of recurrent bleeding were noted. Differences in the therapeutic modalities applied for bleeding may explain the differences in rates of recurrent bleeding in these studies; heat probe coagulation or multipolar electrocoagulation were used in the previous studies.\(^25,26\) In addition, thermocoagulation was successful in controlling recurrent bleeding when epinephrine injection failed to do so in patients in the current study.

Combination therapy (injection with contact thermocoagulation, electrocoagulation, or laser photocoagulation) has been shown to be superior to injection therapy alone.\(^8,11,27\) However, it is often difficult to achieve hemostasis with contact devices or the application of laser emergency when visualization of the bleeding site is unsatisfactory (e.g., massive bleeding in a deformed duodenal bulb). In addition, these methods may not be available in rural hospitals. Therefore, epinephrine injection is frequently used as the first therapeutic modality for peptic ulcer bleeding. The aim of this study was to determine the volume of injected epinephrine that is optimal for arresting peptic ulcer bleeding. Consequently, use of a contact probe was not included.

The distribution of comorbid illness (number and severity) was similar in the 2 treatment groups in the current study. Therefore, the differences in outcome after endoscopic therapy are unlikely to have been influenced by the presence of comorbid illness. Some factors (e.g., ulcer size, active bleeding, shock, ulcer location) can be linked to the failure of injection therapy.\(^28,29\) These were also similar between the 2 groups in the present study. Length of hospital stay, numbers of patients who underwent surgery, and mortality were similar for the 2 groups. This may be due to the early detection of recurrent bleeding and the aggressive endoscopic therapy for such bleeding, thus minimizing the difference with respect to these outcomes between the 2 groups.

In conclusion, injection of a large volume (>13 mL) of a 1:10,000 solution of epinephrine can reduce the rate of recurrent bleeding in patients with peptic ulcers at high risk of bleeding, and is superior to injection of lesser volumes when used to achieve sustained hemostasis.

REFERENCES


