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Improvement of Short-Term Outcomes for High-Risk Bleeding Peptic Ulcers With Addition of Argon Plasma Coagulation Following Endoscopic Injection Therapy

A Randomized Controlled Trial

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Abstract: A second endoscopic method together with injection therapy is recommended to treat high-risk bleeding peptic ulcers. This study investigated whether additional argon plasma coagulation (APC) treatment could influence hemostatic efficacy following endoscopic injection therapy to treat high-risk bleeding ulcers.

From October 2010 to January 2012, eligible patients with high-risk bleeding ulcers were admitted to our hospital. They prospectively randomly underwent either APC therapy along with distilled water injection or distilled water injection alone. Episodes of rebleeding were retreated with endoscopic combination therapy. Patients in whom retreatment was ineffective underwent emergency surgery or transarterial embolization (TAE).

A total of 116 enrolled patients were analyzed. The hemostatic efficacy in 58 patients treated with APC along with distilled water injection was compared with that in 58 patients treated with distilled water injection alone. The 2 treatment groups were similar with respect to all baseline characteristics. Initial hemostasis was accomplished in 56 patients treated with combined therapy, and 55 patients treated with distilled water injection therapy (97% vs 95%, $P = 0.648$). Bleeding recurred in 2 patients treated with combined therapy, and 9 patients treated with distilled water injection (3.6% vs 16%, $P = 0.029$). Treatment method was the only independent prognostic factor for recurrent bleeding (odds ratio 0.17; 95% confidence interval 0.03–0.84; $P = 0.029$). The 2 groups did not differ significantly in hospital stay, TAE, surgery, and mortality.

Endoscopic therapy with APC following distilled water injection is more effective than distilled water injection alone for preventing rebleeding of peptic ulcer.

Abbreviations: APC = argon plasma coagulation, AUGIB = acute upper gastrointestinal bleeding, CI = confidence interval, NBVV = nonbleeding visible vessel, NSAID = nonsteroidal anti-inflammatory drug, OR = odds ratio, PPI = proton pump inhibitor, TAE = transarterial embolization.

INTRODUCTION

Acute peptic ulcer bleeding is characterized by hematemesis, melena, or both, and remains the most common cause of nonvariceal bleeding, with significant associated mobility or mortality.[1,2] This medical emergency carries hospital mortality in excess of 10%[3] despite advances in pharmacologic and endoscopic therapies, probably because of the burden associated with the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) and existing comorbidities in elderly populations in numerous counties.[2]

During recent decades, endoscopic treatment for achieving hemostasis has served as the preferred treatment for bleeding peptic ulcer, providing better therapeutic outcomes than pharmacologic or surgical treatment.[1,4,5] Commonly used methods include injection therapy (eg, diluted epinephrine, various sclerosants, and distilled water), hemostatic clip placement, and thermocoagulation (eg, heat probe and argon plasma coagulation [APC]).[4–8]

Endoscopic therapy with diluted epinephrine has become a customary method for ceasing hemorrhage of peptic ulcers with high-risk stigmata because of its ease of handling and low cost. However, the plasma levels of epinephrine rise to 4 to 5 times baseline levels immediately after injection with a small volume (3 to 11 mL) of 1:10,000 epinephrine solution.[9] This phenomenon may increase the risk of cardiovascular events, either hypertensive crisis or arrhythmia. Our previous investigation showed that a local tamponade effect using distilled water is as effective as diluted epinephrine solution.[6] Consequently, a nontoxic injection solution (eg, distilled water) is preferred to agents with potential systemic side effects for endoscopic therapy. In addition, the international consensus recommended that injection with diluted epinephrine offers suboptimal hemostatic efficacy and should be combined with another method.[4] Combination therapies are already known to outperform single therapies for high-risk bleeding peptic ulcers.[5] For example,

application of heat probe or hemoclip following injection therapy achieves higher hemostastic efficacy than injection therapy alone.[5,8]

APC is a noncontact thermal method of hemostasis that transmits energy to the tissue via ionized and conductive argon gas produced by high-frequency monopolar electrosurgery.[10] Previous randomized trials have shown APC to possibly be as effective as heat probe or hemoclip therapy for peptic ulcer bleeding, whereas to date only a few small-scale studies have examined the APC method for treating peptic ulcer bleeding.[11] Given this background, this investigation aims to determine whether additional APC therapy following distilled water injection can improve outcomes for high-risk bleeding peptic ulcers.

PATIENTS AND METHODS

Study Population

In this study, we screened patients with acute upper gastrointestinal bleeding (AUGIB) who were admitted to the emergency department of Kaohsiung Veterans General Hospital between October 2010 and January 2012. Inclusion criteria were age >20 years and having high-risk peptic ulcer bleeding. Acute hemorrhage from upper gastrointestine was defined as the classical presentation with hematemesis, coffee-ground emesis, and/or melena. High-risk bleeding ulcers were defined as those accompanied by stigmata of a bleeding visible vessel (spurting or oozing), a nonbleeding visible vessel (NBVV), or an adherent clot.[4] NBVV at endoscopy was defined as a raised red, red-blue, or pale hemispheric vessel protruding from the ulcer bed, without active bleeding. Finally, an adherent clot was defined as an overlying blood clot that was resistant to vigorous irrigation.

Exclusion criteria included the following: the presence of another potential bleeding site (eg, gastroesophageal varix, gastric cancer, reflux esophagitis); coexistence of active and severe illnesses (eg, septic shock, stroke, myocardial infarction, surgical abdomen); treatment with an anticoagulant (eg, warfarin); pregnancy; history of stomach surgery; or refusal to participate in the study.

In the current study, baseline characteristics of both study groups were gathered at 24 hours after admission. Some definitions of events were expressed herein: smoking was defined as daily inhalation of tobacco smoke during the past 3 months; habitual consumption of alcohol was defined as imbibing alcohol twice or more per week during the past 3 months; shock was considered systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg, together with heart rate exceeding 100 beats/min; comorbid diseases included unresolved malignancy, diabetes mellitus, liver cirrhosis, uremia, congestive heart failure, chronic pulmonary obstructive disease, and pneumonia; and finally, coagulopathy was defined as prothrombin time >14 seconds and/or activated partial thromboplastin time >45 seconds.

Randomization

In this prospective, parallel-group, randomized controlled trial, eligible patients were randomized into 2 groups using opaque sealed envelopes numbered according to a table of random numbers before the first therapeutic endoscopy (index endoscopy): the Combined group and the Injection group. All participants provided informed consent. The Combined group patients received APC therapy following distilled water injection at index endoscopy. Meanwhile, the Injection group

patients online underwent distilled water injection at index endoscopy. Subsequently, both treatment groups were treated with intravenous pantoprazole (Pantoloc i.v.; Nycomed GmbH, Singen, Germany) at 40 mg every 12 hours during the first 3 days, followed by oral pantoprazole (Pantoloc; Takeda GmbH, Oranienburg, Germany) at 40 mg daily throughout the remainder of the 56-day study period. The primary end point was rebleeding, whereas the secondary end points included initial hemostasis, need for surgery/transarterial embolization (TAE), transfusion requirements, period of hospitalization, severe adverse event (stricture, obstruction, or perforation), and death at 30 days postrandomization.[8]

The study protocol accorded with the Declaration of Helsinki of the World Medical Association (October 2008). The study protocol was also approved by the Institutional Review Board at Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan (IRB No. VGHKS98-CT8-13).

Endoscopic and Pharmacological Therapies

All participants with AUGIB considered suitable for the trial received intravenous pantoprazole with an initial dose of 40 mg, followed by 40 mg every 12 hours until endoscopic examination, and underwent index endoscopy within 24 hours upon admission. Inserting a nasogastric or orogastric tube allowed the physicians access to the stomach and its contents. Gastric lavage was not performed routinely.[12] Intramuscular injection with hyoscrine methonitrate 20 mg and local pharyngeal anesthesia with 8% xylocaine spray were used for premedication.[7]

Therapeutic endoscopies were randomly performed by 4 experienced endoscopists with >5 years of experience, using Olympus GIF XQ230, GIF XQ260, GIF Q260J, or GIF H260Z endoscope (Olympus Corporation, Tokyo, Japan). High-risk ulcers were irrigated with normal saline and/or distilled water via the accessory channel of the endoscope or water pump. Distilled water was then applied in aliquots of 0.5 to 2.0 mL, both at and around the site of target bleeding, in volumes of up to 25.0 mL if necessary. Injection amount was determined by endoscopists based on ulcer or vessel size and location. The addition of a 3-prong device together with snare catheter following vigorous irrigation may exposure the underlying stigmata for ulcers with adherent clot. Ulcer size was estimated using biopsy forceps, with a 6-mm opened cup. *Helicobacter pylori* status was not tested routinely at index endoscopy owing to potential bleeding and/or lower sensitivity through endoscopic biopsy for *H. pylori* detection.[13] APC therapy in the Combined group followed distilled water injection once bleeding stopped or subsided. In addition, the risk statuses of all patients were assessed using the Rockall score system.[14]

APC therapy was realized by an Olympus electrosurgical unit/APC unit (PSD-60/Endoplasma; Olympus Corporation), and its catheters were 2.3 and 3.5 mm equipped with different endoscope channels.[7] APC treatment used a coagulation mode at gas flow/power settings of 1.5 L/min and 40 W for duodenal ulcers and 40 to 60 W for gastric ulcers.[10] The operative distance between the probe and target bleeding ranged from 2 to 8 mm. Frequent air sucking was warranted to decrease APC-induced smoke and gastric decompensation, with appropriate treatment of high-risk bleeding ulcers.

On achieving initial hemostasis, patients were admitted to the ward of the gastrointestinal department, and their vital signs and hemoglobin levels were closely monitored by the medical care team. Both study groups were treated with partial

parenteral nutrition as patients kept fasting. After 2 days of observation, the patients spent 2 to 3 days on a soft diet, followed by a regular diet. Continue pantoprazole infusion at 40 mg every 12 hours was administered to all participants during the first 3 days. To promote ulcer healing, oral pantoprazole was prescribed at 40 mg once daily, starting with the resumption of oral intake and continuing throughout the 56-day study period. After discharge, all participants were requested to undergo follow-up in our outpatient department on days 14, 18, and 56 postrandomization.

In patients who required an NSAID, the medicine was discontinued for 3 days following the therapeutic endoscopy and resumed on day 4. Similarly, for patients receiving antiplatelet therapy for cardiovascular and/or cerebrovascular diseases, the treatment was halted for 3 days following the index endoscopy. The antiplatelet therapy (eg, aspirin 100 mg/d, clopidogrel 75 mg/dy) was resumed on day 4.

Initial Hemostasis and Rebleeding

Initial hemostasis was defined as endoscopically verified bleeding stopping for at least 5 minutes after both scheduled treatments at index endoscopy.[7] If initial hemostasis failed owing to uncontrollable, abundant hemorrhage, patients underwent another endoscopic modality or emergency surgery, as determined by the responsible gastroenterologist.

Rebleeding was observed during the 30-day study period. One or more of the following criteria were considered as evidence of recurrent bleeding: aspiration of fresh blood from a nasogastric or orogastric tube; pulse rate exceeding 100 beats/min; a drop in systolic blood pressure exceeding 30 mm Hg; or continuation of coffee ground emesis or melena with a decline in hemoglobin of at least 2 g/dL. In the event of rebleeding, emergency endoscopy for the second hemostasis was performed. Rescue endoscopic therapy following injection therapy (distilled water or normal saline) included APC, hemoclip, and heater probe. When the rescue therapy failed to achieve hemostasis, emergency surgery or TAE was indicated.[4]

Sample Size Calculation and Statistical Analysis

According to recent clinical studies, the incidences of recurrent peptic bleeding following APC treatment[15–17] and injection therapy[8] were 4.7% and 22.3%, respectively. It is estimated that at least 58 patients in each group were required to achieve a statistical power of 80% with a type I error of 0.05, when using the MedCalc statistical package (MedCalc Software, Mariakerke, Belgium).

Qualitative variables were compared using the χ^2 test and Fisher exact test whenever considered appropriate. Quantitative data were expressed as mean $\pm$ standard deviation using the Student 2-tailed t test. The intension-to-treatment analysis included all enrolled subjects. Logistic regression univariate and multivariate analyses were applied to detect possible prognostic factors for recurrent bleeding and death. To identify the most valuable predictors, those variables significant at $P < 0.20$ in univariate models were subsequently subjected to multivariate analysis. Interim analysis of hemostatic efficacy was performed following enrollment of 50% of the subjects. A statistical boundary was established for deciding to stop the study ($P < 0.01$). All hypothesis tests were conducted against a 2-sided alternative where appropriate. The level of significance was set at $P < 0.05$. Analyses were performed using SPSS 12.0.1C (SPSS Inc, Chicago, IL).

RESULTS

Baseline Characteristics

Between October 2010 and January 2012, 143 consecutive patients with high-risk bleeding peptic ulcers were recruited via the Division of Gastroenterology, Kaohsiung Veterans General Hospital. Twenty-seven patients were excluded owing to bleeding gastric malignancy (n = 4), acute severe illness (n = 11), status as wafarin users (n = 5), pregnancy (n = 1), and refusal to participate (n = 6). Thus, the remaining 116 participants underwent either combination therapy (Combined group, n = 58) or injection therapy only (Injection group, n = 58) (Figure 1).

Most of the 116 enrolled patients were male (70%) and/or aged 60 years old and over (63%). Regarding location of high-risk ulcers, 57 cases (49%) involved the stomach (Combined group, n = 25; Injection group, n = 32) and 59 (51%) involved the duodenum (Combined group, n = 33; Injection group, n = 26). Bleeding types were divided into spurting (n = 2), oozing (n = 33), NBVV (n = 50), and adherent clot (n = 31). The average injection volume was 7.6 mL (range 2–25 mL). Table 1 shows patient characteristics and endoscopic demographics. Baseline characteristics at entry were comparable in terms of age, sex, history of peptic ulcers or ulcer bleeding, location and size of ulcers, type of bleeding, shock status, hemoglobin level, platelet count, coagulopathy, Rockall score, and use of NSAID, antiplatelet drugs, or steroids at presentation.

No participant was lost to follow up until the end of study period. However, 1 patient in the Combined group and 2 patients in the Injection group failed to adhere to the scheduled pantoprazole regimen postdischarge.

Initial Hemostasis

Initial hemostasis was achieved in 56 patients treated with APC following distilled water injection, and in 55 patients treated using distilled water injection alone (97% vs 95%, $P = 0.648$) (Table 2). Among the 5 patients in whom initial hemostasis was not successfully achieved, 2 patients in the Combined group and 1 patient in the Injection group underwent heater probe combined with distilled water injection for second hemostasis; the remaining 2 patients received hemoclipping along with distilled water injection in the Injection group. No subject subsequently required emergency surgery or TAE.

Rebleeding

The exact incidence of rebleeding was assessed by excluding the 5 patients with failed initial hemostasis. Significantly, peptic ulcer bleeding recurred more frequently in the Injection group (3.6% vs 16%, $P = 0.029$) (Table 2). Among the 11 patients with recurrent bleeding, 2 in the Combined group and 3 in the Injection group underwent heater probe combined with distilled water injection for second hemostasis; the remaining 5 patients received either hemoclipping (n = 3) or APC (n = 2) along with distilled water injection and 1 patient underwent emergency surgery in the Injection group. No patient arranged for TAE.

Variables such as age, sex, history of peptic ulcer or ulcer bleeding, ulcer location and size, bleeding type, shock status, hemoglobin level, platelet count, coagulopathy, and use of NSAID, antiplatelet drugs, or steroids at presentation and treatment method were analyzed to identify rebleeding predictors. The multivariate logistic regression model only identified treatment method as an independent factor predictive of first rebleeding (odds ratio [OR] 0.17; 95% confidence interval [CI]
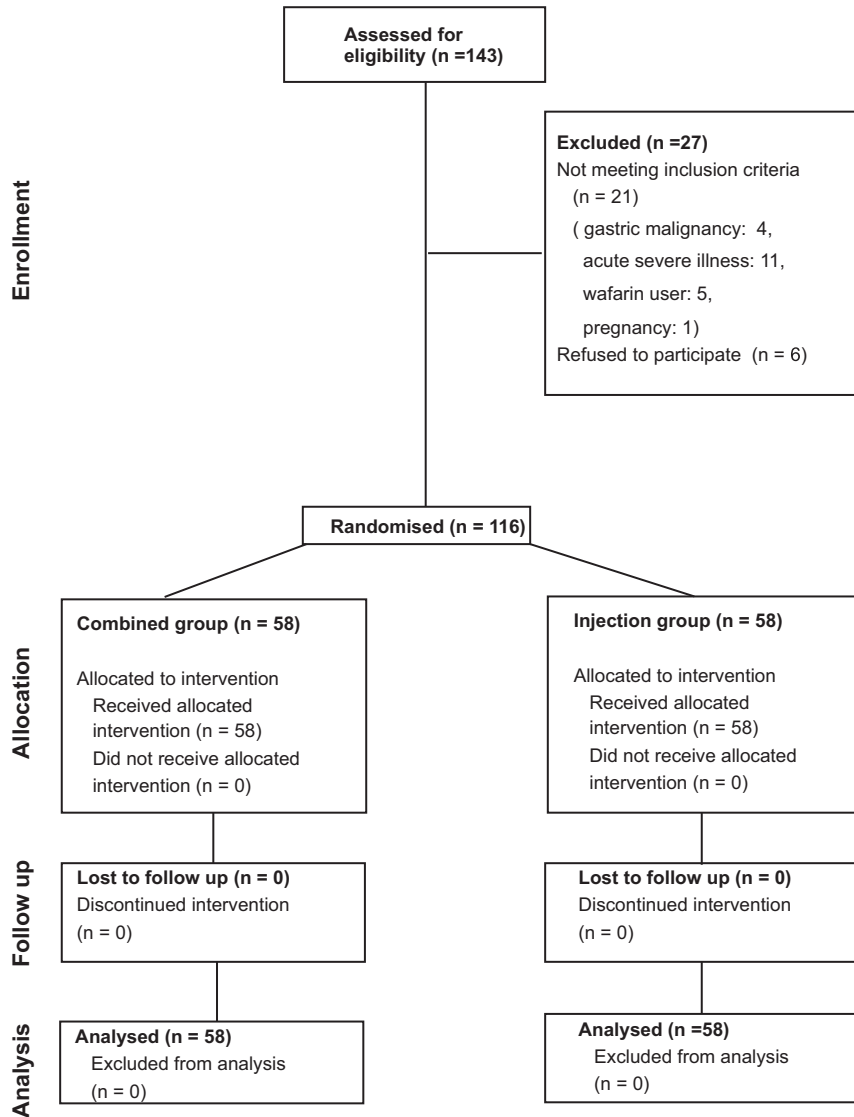
FIGURE 1. Flow chart of enrolment.

0.03–0.84; $P = 0.029$) (Table 3). Restated, the odds of rebleeding in the Combined group are 83% lower than in the Injection group, with the true population effect being between 3% and 84%. This result was statistically significant.

Hospital Stay, Blood Transfusion, Surgery, and TAE

Both treatment groups displayed no significant differences in hospital stay ($7.6 + 6.8$ vs $8.6 + 7.1$ days, $P = 0.462$) or transfusion requirements ($4.4 + 4.3$ vs $4.3 + 4.3$ units, $P = 0.941$) (Table 2). Only 1 patient, who initially presented with oozing from their ulcer, received emergency surgery in the Injection group because of profound, uncontrollable rebleeding following initial hemostasis. No participants needed to receive TAE during the 30-day follow-up.

Adverse Events and Mortality

No severe adverse procedure-related event (stricture, obstruction, or perforation) could be identified in either

treatment group (Table 2). In addition, no procedure-induced bleeding occurred at the therapeutic endoscopies.

Four deaths occurred in patients with uncontrolled rebleeding (Table 2). One of the 4 underwent emergency surgery in the Injection group, but died of hypovolemic shock. The remaining 3 (Combined group 2; Injection group 1) experienced profound rebleeding and died of hypovolemic shock, coexisting with multiple organ failure (n = 1), terminal lung cancer with sepsis (n = 1), and sudden cardiac death (n = 1). Furthermore, the all-cause mortalities were comparable between both treatment arms (3.4% vs 3.4%, $P = 1.000$).

DISCUSSION

This prospective randomized controlled study clearly showed that the hemostatic efficacy of APC treatment following injection therapy was superior to that of injection therapy alone in preventing rebleeding in patients with bleeding high-risk peptic ulcers, although combination therapy failed to prove

more effective in second end points (eg, death, need for surgery, transfusion requirements, and hospital stay). Neither treatment group in the current study exhibited adverse effects or procedure-induced bleeding.

Endoscopic therapy offers an advantage in maintaining permanent hemostasis, reducing the need for surgery/TAE and decreasing all-cause death when compared with pharmacologic therapy alone.[18] Recent practice guidelines recommended the application of thermocoagulation, hemoclip, or sclerosant injection in ulcers with high-risk stigmata, either alone or together with epinephrine injection therapy.[4,19] Guidelines did not mention whether clear evidence existed that APC, a noncontact thermocoagulation, could help treat high-risk bleeding ulcers. Furthermore, a systemic review of APC therapy compared with heater probe and sclerosant injection found no evidence of the superiority of APC to other endoscopic modalities.[11] Our previous study[7] compared APC with distilled water injection for ulcers with high-risk stigmata and revealed that ulcer bleeding recurred in 11% of cases in the APC arm and 27% of cases in the injection arm, demonstrating statistically significant recurrence rates. Therefore, it is reasonable to examine whether adding APC to injection therapy could outperform injection therapy alone. Indeed, the current study demonstrated that the combination of APC and distilled water injection

outperformed injection alone in preventing ulcer rebleeding (3.6% vs 16%, $P = 0.029$), although no significant difference existed with regard to the second end points. As we know, recurrent bleeding has been identified as the most important risk factor for death,[20] and controlling recurrent bleeding through adequate endoscopic tools can decrease mortality and mobility. Notably, the rate of recurrent bleeding was relatively low (3.6%) in the Combined group, though those participants did not receive high-dose pantoprazole infusion. This phenomenon may result from a lower incidence of high-risk bleeding ulcers or lower Rockall score than other clinical trials.[5,8,11]

The main clinical issue in combination therapy was the possible risk of gastroduodenal wall necrosis and/or perforation. A meta-analysis enrolling 2472 patients (20 controlled trials) demonstrated that the risk of bowel wall perforation was significantly increased in the combination therapy relative to monotherapy (7 vs 0, $P = 0.03$). Perforations occurred in 5 patients treated with thermal methods following injection therapy and 2 cases treated with dual injection therapy.[5] Thus, expertise and clinical judgment should be applied before recommending contact-type thermocoagulation combined with endoscopic injection as the gold standard for all ulcers with high-risk stigmata.[5] In contrast, no perforation was observed in either treatment group in the current study. Adding APC to injection therapy did not increase the rate of perforation, probably owing to superficial tissue injury by the noncontact thermal method. Another specific complication was procedure-induced bleeding (eg, hemorrhage precipitated in an ulcer with NBVV). In this study, no procedure-induced bleeding occurred at therapeutic endoscopies, whereas our previous study[16] identified that 3 patients with NBVV (3/23, 13%) suffered from procedure-induced bleeding in the APC arm. The authors presumed that APC alone permitted the unsealing of vessel thrombosis and then induced bleeding, but antecedent injection therapy followed by APC enabled physical compression of bleeding vessel before coagulation therapy and reduced the rate of induced bleeding.

APC method is an effective and safe for endoscopic hemostasis, which offers controlled, noncontact electrocoagulation.[10] Originally, Grund et al[21] reported a novel method for thermocoagulation using APC via a flexible endoscopy in 1994. APC is repeatable and can be easily learned by endoscopists.

TABLE 1. Baseline Characteristics of the Study Group

	Combined Group (n = 58)	Injection Group (n = 58)	P
Age, y (SD)	61.5 ± 12.3	65.9 ± 17.3	0.120
Male sex	40 (69%)	41 (71%)	0.840
Cigarette consumption	20 (35%)	13 (22%)	0.150
Alcohol consumption	14 (24%)	10 (17%)	0.359
Aspirin or clopidogrel use	5 (9%)	8 (14%)	0.377
NSAID use	25 (43%)	17 (29%)	0.122
Steroid use	0 (0%)	1 (2%)	1.000
Previous gastric surgery	0 (0%)	2 (3%)	0.496
Previous peptic ulcer	30 (52%)	27 (47%)	0.577
Previous ulcer bleeding	18 (31%)	24 (41%)	0.246
Shock status	4 (7%)	3 (5%)	0.697
Hemoglobin, g/dL (SD)	9.7 ± 2.6	9.5 ± 2.7	0.666
Platelet count, k/cumm (SD)	199.4 ± 89.0	214.1 ± 82.7	0.361
Coagulopathy	6 (10%)	5 (9%)	1.000
Comorbid disease	16 (28%)	17 (30%)	0.791
Ulcer size, mm (SD)	14.0 ± 7.6	13.5 ± 7.0	0.706
Ulcer >20 mm	17 (29%)	12 (21%)	0.284
Ulcer location			0.265
Gastric ulcer	25 (43%)	32 (55%)	
Duodenal ulcer	33 (57%)	26 (45%)	
Bleeding type			
Sputing	1 (2%)	1 (2%)	1.000
Oozing	17 (29%)	16 (28%)	0.837
NBVV	26 (45%)	24 (41%)	0.708
Adherent clot	14 (24%)	17 (29%)	0.529
Injection volume, mL (SD)	7.2 ± 4.5	7.8 ± 5.1	0.488
Rockall score	6.1 ± 1.8	5.9 ± 1.7	0.534

NBVV = nonbleeding visible vessel, NSAID = nonsteroidal anti-inflammatory drug, SD = standard deviation.

TABLE 2. Clinical Outcomes of the Study Population

	Combined Group (n = 58)	Injection Group (n = 58)	P
Initial hemostasis	56 (97%)	55 (95%)	0.648
Rebleeding	2 (3.6%)	9 (16%)	0.029
Spurting	0 (0%)	1 (1.8%)	
Oozing	1 (1.8%)	2 (3.6%)	
NBVV	1 (1.8%)	5 (9.1%)	
Adherent clot	0 (0%)	1 (1.8%)	
Surgery	0 (0%)	1 (1.7%)	1.000
Transarterial embolization	0 (0%)	0 (0%)	1.000
Blood transfusion, unit (SD)	4.4 + 4.3	4.3 + 4.3	0.941
Hospital stay, d (SD)	7.6 + 6.8	8.6 + 7.1	0.462
All-cause mortality	2 (3.4%)	2 (3.4%)	1.000

NBVV = nonbleeding visible vessel.

TABLE 3. Probable Effects of Variables on Recurrent Bleeding

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Aspirin or clopidogrel use	3.13 (0.73–13.50)	0.125	1.16 (0.18–7.34)	0.872
Comorbid disease	2.82 (0.84–9.48)	0.095	2.92 (0.64–13.31)	0.167
NBVV	2.95 (0.84–10.44)	0.093	3.30 (0.85–12.83)	0.084
Treatment method	0.17 (0.04–0.82)	0.027	0.17 (0.03–0.84)	0.029

CI = confidence interval, NBVV = nonbleeding visible vessel, OR = odds ratio.

APC has been successfully applied to hemostais or ablation, particularly for Barrett's esophagus, watermelon stomach, gastric antral vascular ectasia, and radiation proctitis.[10] The APC method has numerous theoretical advantages relative to contrast-type themocoagulation:[7] the burn depth can be preset to 0.5 to 3 mm, depending on different power/flow settings, and is especially appropriate for thin-wall bowls (eg, duodenum, colon); the arcing effect of the APC method can better approach the location of bleeding than can hemoclip or heater probe,[10] particularly those locations in the posterior wall or lesser curvature of the upper gastric body or posterior wall of the duodenal bulb; and APC is theoretically smokeless owing to the more desiccated and less carbonized effect of tissue destruction when involving hemorrhage from the digestive tract.[10] Conversely, unpredictable injury depth and shallow coagulation insufficient for hemostasis may be considered shortcomings of APC treatment.[10,21] In this study, APC was performed with an Olympus PSD/Endoplasma unit, which is equivalent to the predicate devices such as ERBE VIO APC2 and ERBE APC3000. Nevertheless, no head-to-head in vitro or human study has assessed the thermal effects associated with these devices from different companies (eg, ERBE, ConMed, Genii),[22] and thus far it remains unclear whether our investigation can be applied 1:1 on all APC generators. This point is key because the old and new APC generators may differ significantly, for example, the VIO system is 30% to 50% more effective than the ICC system with the same power/flow/operation time settings,[23] which hints at actual tissue injury being more aggressive.

The investigation suffers some limitations. First, it has some possible bias because of a nonblinded study design, despite the enrollment criteria and outcome measurements being defined as objectively as possible. Second, some patients could not undergo early endoscopic treatment during hospitalization owing to critical illness or anticoagulant therapy. Interpretation of these study results thus should be limited to the enrolled subpopulation with high-risk bleeding ulcers. Lastly, the current study applied a low-dose regiment of proton pump inhibitor (PPI), whereas international guidelines recommended high-dose PPI regiments. Actually, low-dose PPI reduced recurrent bleeding but was not shown to influence mortality rate.[4]

To summarize, this study indicates that patients with high-risk bleeding ulcers at endoscopy still encountered appreciably high rebleeding rates if treated with injection therapy alone. The combination of immediate APC treatment following injection therapy during endoscopy could considerably reduce rebleeding rate without increasing severe adverse events. Large-scale studies are warranted to clarify whether combination therapy has advantages in reducing the need for surgery/TAE or mortality.

REFERENCES

1. Lau JY, Barkun A, Fan DM, et al. Challenges in the management of acute peptic ulcer bleeding. *Lancet.* 2013;381:2033–2043.

2. Al Dhahab H, McNabb-Baltar J, Al-Taweel T, et al. State-of-the-art management of acute bleeding peptic ulcer disease. *Saudi J Gastroenterol.* 2013;19:195–204.

3. Palmer K. Management of haematemesis and melaena. *Postgrad Med J.* 2004;80:399–404.

4. Barkun AN, Bardou M, Kuipers EJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med.* 2010;152:101–113.

5. Marmo R, Rotondano G, Piscopo R, et al. Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials. *Am J Gastroenterol.* 2007;102:279–289.

6. Lai KH, Peng SN, Guo WS, et al. Endoscopic injection for the treatment of bleeding ulcers: local tamponade or drug effect? *Endoscopy.* 1994;26:338–341.

7. Wang HM, Hsu PI, Lo GH, et al. Comparison of hemostatic efficacy for argon plasma coagulation and distilled water injection in treating high-risk bleeding ulcers. *J Clin Gastroenterol.* 2009;43:941–945.

8. Vergara M, Bennett C, Calvet X, et al. Epinephrine injection versus epinephrine injection and a second endoscopic method in high-risk bleeding ulcers. *Cochrane Database Syst Rev.* 2014;10:CD005584.

9. Sung JY, Chung SC, Low JM, et al. Systemic absorption of epinephrine after endoscopic submucosal injection in patients with bleeding peptic ulcers. *Gastrointest Endosc.* 1993;39:20–22.

10. Vargo JJ. Clinical applications of the argon plasma coagulator. *Gastrointest Endosc.* 2004;59:81–88.

11. Havanond C, Havanond P. Argon plasma coagulation therapy for acute non-variceal upper gastrointestinal bleeding. *Cochrane Database Syst Rev.* 2005;2:CD003791.

12. Lu Y, Loffroy R, Lau JY, et al. Multidisciplinary management strategies for acute non-variceal upper gastrointestinal bleeding. *Br J Surg.* 2014;101:e34–e50.

13. Sánchez-Delgado J, Gené E, Suárez D, et al. Has H. pylori prevalence in bleeding peptic ulcer been underestimated? A meta-regression. *Am J Gastroenterol.* 2011;106:398–405.

14. Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut.* 1996;38:316–321.

15. Karaman A, Baskol M, Gursoy S, et al. Epinephrine plus argon plasma or heater probe coagulation in ulcer bleeding. *World J Gastroenterol.* 2011;17:4109–4112.

16. Li YR, Hsu PI, Wang HM, et al. Comparison of hemostatic efficacy of argon plasma coagulation with and without distilled water injection in treating high-risk bleeding ulcers. *Biomed Res Int.* 2014;2014:413095.

17. Kim JW, Jang JY, Lee CK, et al. Comparison of hemostatic forceps with soft coagulation versus argon plasma coagulation for bleeding peptic ulcer—a randomized trial. *Endoscopy.* 2015DOI http://dx.doi.org/10.1055s-0034-1391565 [in press].

18. Cook DJ, Guyatt GH, Salena BJ, et al. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Gastroenterology.* 1992;102:139–148.

19. Sung JJ, Chan FK, Chen M, et al. Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding. *Gut.* 2011;60:1170–1177.

20. Laursen SB. Treatment and prognosis in peptic ulcer bleeding. *Dan Med J.* 2014;61:B4797.

21. Grund KE, Storek D, Farin G. Endoscopic argon plasma coagulation (APC) first clinical experiences in flexible endoscopy. *Endosc Surg Allied Technol.* 1994;2:42–46.

22. Technology Committee ASGE, Tokar JL, Barth BA, et al. Electro-surgical generators. *Gastrointest Endosc.* 2013;78:197–208.

23. Manner H, May A, Faerber M, et al. The tissue effect of second generation argon plasma coagulation (VIO APC) in comparison to standard APC and Nd:YAG laser in vitro. *Acta Gastroenterol Belg.* 2007;70:352–356.