Comparison of high and low-dose epinephrine & endoclip application in peptic ulcer bleeding
A case series analysis observational study

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Abstract

Peptic ulcer disease accounts for 50% to 70% of acute upper gastrointestinal bleeding cases. There is no consensus on the treatment of peptic ulcer bleeding (PUB) using endoscopic techniques. This study aimed to compare endoscopic techniques for PUB.

Patients with PUB who were hospitalized between January 2014 and June 2020 were included in this study. They were divided into 3 groups: endoclip and low-dose epinephrine injection (0–2 mg, Group 1, n = 62), endoclip and high-dose epinephrine injection (2–4 mg, Group 2, n = 54), and endoclip only (Group 3, n = 64).

Early bleeding and permanent hemostasis were higher in Group 2 (P = .014, .035). When evaluated in terms of late hemostasis and urgent surgical need, there was no significant difference between the groups (P > .05). Group 2 received a higher amount of blood. Thirty-day mortality occurred in 16.5%, 22.2%, and 9.4% of patients in Groups 1, 2, and 3, respectively. Group 2 had a longer hospital stay than Groups 1 and 3 (P = .008). The endoscopic success rates were 80.6%, 72.2%, and 90.6% in Groups 1, 2, and 3, respectively.

In PUB, if the patient's Rockall score is high and the ulcer size is larger than 2 cm, endoclip application can be used as the main treatment. Addition of epinephrine may be considered when necessary.

Abbreviations: PUB = peptic ulcer bleeding, SD = standard deviation.

Keywords: clips, endoscopy, epinephrine, peptic ulcer

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1. Introduction

Peptic ulcer disease accounts for 50% to 70% of acute upper gastrointestinal bleeding cases. Other causes include acute erosive gastritis, Cameron erosions, Dieulafoy lesions, malignancy, portal hypertensive gastropathy, esophagitis, gastric antral vascular ectasia, angiodysplasia, Mallory-Weiss syndrome, and esophageal or gastric varicose bleeding.[1] Endoscopic therapy significantly reduces re-bleeding rates, need for surgery, and mortality in patients with peptic ulcer bleeding (PUB), and guidelines recommend endoscopic treatment within 24 hours in most patients with upper gastrointestinal bleeding.[2] The most common endoscopic hemostatic interventions include epinephrine injection, thermal coagulation, argon plasma coagulation, sclerotherapy, and endoscopic clipping, which narrow the ulcer site, and compress the bleeding vessel.[3] There is no consensus on a common endoscopic treatment technique for PUB.

In terms of initial hemostatic efficacy, 80% to 100% success has been achieved with many endoscopic treatment methods. However, the re-bleeding risk is 90% in patients with PUB with high-risk active bleeding stigmata, 50% in those with no active bleeding but visible blood vessels, and 25% to 30% in ulcer bleeding with adherent clots. Despite the high hemostatic rate achieved, re-bleeding with an increased risk of death, can occur in approximately 10% to 30% of patients, usually within 3 days of treatment.[4]

Epinephrine is effective for initial hemostasis, but appears to be less effective than other monotherapies in preventing bleeding. Mechanical compression of the hemorrhaging vessel in peptic ulcer is the key factor for achieving initial hemostasis. In addition,

if the patient is receiving antiplatelet agents or has coagulopathy, endoclips are safer than thermal coagulation because they cause less tissue damage.[5] Several recent studies have demonstrated that large amounts of epinephrine injections are superior to small amounts of injections in recurrent bleeding in peptic ulcers. These studies suggest that local tamponade has the greatest effect on continuous hemostasis, and that larger volumes of epinephrine injection may prevent re-bleeding.[6] The purpose of this study was to compare bleeding and complication rates in peptic ulcer patients with bleeding after endoclip placement with 2 different doses of epinephrine injection (1–2 mg and 2–4 mg) and to evaluate the factors that affect treatment methods.

2. Materials and methods

2.1. Patients' criteria

The patients were hospitalized with suspicion of PUB due to hemodynamic irregularities such as hematemesis, melena, and shock. Endoscopic intervention was performed after erythrocyte suspension transfusion in patients with hemoglobin <7 to 8 mg/dL without severe comorbidities and in those with severe comorbidities and hemoglobin level <10 mg/dL.[6] The medication of patients on anticoagulant or antiaggregant drugs was discontinued, and low molecular weight heparin was added to their treatment.[7] All patients underwent upper gastrointestinal endoscopy within the first 24 hours after their hospitalization. The exclusion criteria were as follows: age ≤18 years, inability to tolerate sedation anesthesia due to major comorbid or terminal disease making endoscopy dangerous, not consenting to endoscopy, patients with diffuse oozing bleeding throughout the stomach, and non-PUB.

2.2. Selection of treatment modalities in the study

Endoscopy was performed with single-channel endoscopes (EPX-3500 HD, Fujifilm, Singapore; EPK-i5000, Pentax, Japan) by endoscopists with 5 years of experience treating patients with PUB. In the selection of treatment methods, ulcer size was considered a criterion in accordance with the current guidelines.[8] Endoclips were placed at the ulcer sites in all patients. In patients with active bleeding despite the application of endoclips, 0 to 2 mg epinephrine was injected if the ulcer size was less than 2 cm, while 2 to 4 mg epinephrine was injected if the ulcer size was larger than or equal to 2 cm. Treatment modalities included endoclip and low-dose epinephrine injection (0–2 mg injection group, Group 1) (Fig. 1), endoclip and high-dose epinephrine injection (2–4 mg injection group, Group 2) (Fig. 2), and endoclip placement only (Group 3) (Fig. 3).

2.3. Application of treatment modalities

Since the mechanical compression effect of the endoclips would decrease with epinephrine injection, endoclips were placed first, and epinephrine was administered later. In the low-dose epinephrine group (Group 1), 0 to 20 mL 1:10,000 epinephrine solution was injected circularly around the vein in the visible ulcer bed, while 21 to 40 mL 1:10,000 epinephrine solution was used in the high-dose epinephrine group (Group 2). Mechanically applied endoclips (Olympus Corp, HX5U, Tokyo, Japan) comprised stainless steel alloys. After achieving hemostasis, the bleeding site was observed for 10 minutes, and initial hemostasis

Figure 1. Application of endoclips to prepyloric ulcer bleeding followed by low-dose epinephrine injection.

was evaluated by irrigation with isotonic fluids. If bleeding occurred immediately after irrigation, initial hemostasis was unsuccessful. In patients without re-bleeding, a second control endoscopy was performed 1 week after initial hemostasis to exclude malignancy.

Endoscopy was performed in cases of re-bleeding, which was defined as early recurrence. Bleeding between the 24th hour and the first week of the procedure was considered a late recurrence. The procedure to be used in repeat endoscopy was decided after discussing it with the patient, regardless of the first treatment method. Patients who failed endoscopic treatment or repeat endoscopy underwent emergency surgery.
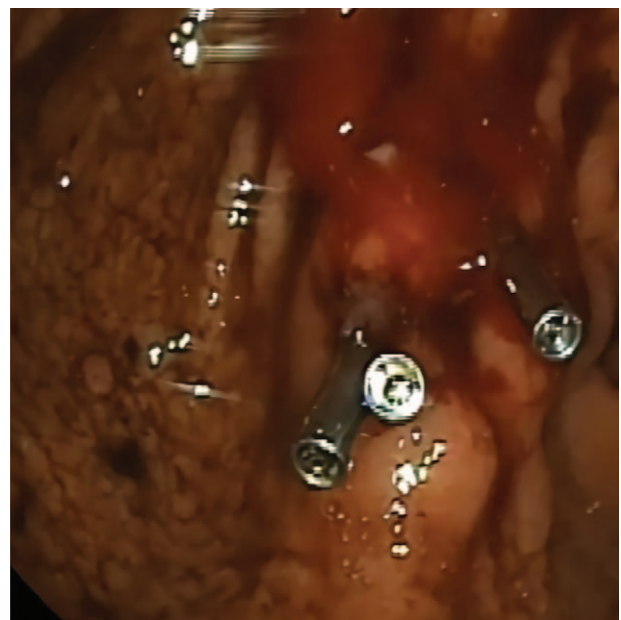

Figure 2. Application of endoclips to ulcer bleeding in incisura angularis followed by high-dose epinephrine injection.

Figure 3. Applying only endoclips to ulcer bleeding in the corpus.

2.4. Follow-up of patients

After the initial endoscopic hemostasis, the patients' vital signs and hemograms were followed regularly for the first 72 hours. All patients received acid suppressive therapy, and initial medical treatment was administered with a bolus dose of 80 mg pantoprazole plus 8 mg/hour infusion. After the third day, the dose was reduced to 40 mg administered intravenously twice a day, and after the seventh day, 40 mg was administered orally once per day.[9] If surgical intervention was needed, patients were not fed enterally within the first 24 hours of the procedure. Ulcer diets were administered to patients who were followed up uneventfully after this period.

2.5. Informed consent and ethics committee decision

Endoscopic treatment and possible complications of the procedure were explained to all patients included in the study, and written informed consent forms were obtained before endoscopy. Ethics committee approval was received from Istanbul Medeniyet University Göztepe Training and Research Hospital Ethics Committee with the code 2013-KAEK-64 on September 2, 2020. The study was conducted in accordance with the Declaration of Helsinki.

2.6. Statistical analysis

Continuous data were tested for significance at a 95% confidence interval. One-way ANOVA and Pearson chi-square tests were used to analyze continuous and categorical variables, respectively. Patient characteristics and outcomes were compared. All analyses were performed using SPSS software (version 20, SPSS Inc., Chicago). Statistical significance was set at $P < .05$.

3. Results

The files of 180 consecutive patients with PUB who were admitted to a tertiary referral hospital for acute PUB between January 2014 and June 2020 were reviewed from the hospital registry. A total of 1128 acute upper gastrointestinal bleeding was encountered. Of these, 43.4% had PUB, 47.8% had non-ulcer lesions, 5.2% had varicose bleeding, and 3.6% had no bleeding.

The mean ages of the patients in Groups 1, 2 and 3 were 62.45 (standard deviation [SD]11.86) years, 68.48 (SD12.50) years, and 62.22 (SD10.93) years, respectively. The male/female ratios of the patients were 38/24 in Group 1, 41/13 in Group 2, and 51/13 in Group 3. In Group 1, 45.2% were Forrest I, 21% were Forrest II-A, and 33.8% were Forrest II-B. In Group 2, Forrest I was detected in 38.9%, Forrest II-A in 25.9%, and Forrest II-B in 35.2%. In Group 3, 33.8%, 35.2%, and 42.2% had Forrest I, Forrest II-A, and Forrest II-B. The distribution of ulcer locations according to the Forrest classification is shown in Figure 4.

Helicobacter pylori was detected in 40 patients (64.5%) in Group 1, alcohol use was detected in 9 patients (16.7%) in Group 2, and 5 patients (9.3%) had a history of PUB in Group 2.

Before the endoscopic procedure, 9 patients in Group 1, 16 patients in Group 2, and 6 patients in Group 3 were admitted with hypovolemic shock. The mean Rockall risk classification scores of Groups 1, 2, and 3 were 4.38 (SD1.64), 5.14 (SD2.00), and 4.14 (SD1.95), respectively. As revealed by the one-way ANOVA test, the Rockall scores were significantly higher in Group 2 than in the other groups ($P = .012$). Age, sex, ulcer location, Forrest type, Helicobacter pylori status, use of non-steroidal anti-inflammatory drugs or alcohol, previous history of PUB, systolic blood pressure, comorbidities, laboratory test results (x, SD) (hemoglobin, hematocrit, platelets, urea, creatinine, bilirubin, alanine amino transferase, aspartate amino transferase), hypovolemic shock status, and Rockall risk scores are summarized in Table 1.

The mean amount of epinephrine used in endoscopic treatment was 1.50 (SD0.316) mg in Group 1 and 2.37 (SD0.294) mg in Group 2. The mean number of clips used in endoscopic treatment was 1.81 (SD0.43) in Group 1, 2.20 (SD0.74) in Group 2, and 1.54 (SD0.35) in Group 3. Early bleeding occurred in 4 patients (6.5%) in Group 1, 7 patients (12.9%) in Group 3, and none of the patients in Group 2. The highest rate of permanent hemostasis was achieved (96.87%) in Group 3. Rates of late hemostasis were similar to the rate of permanent hemostasis. Emergency surgery was required in 5 patients (8.1%) in Group 1, 8 patients (14.8%) in Group 2, and 2 patients (3.1%) in Group 3. Thirty-day mortality occurred in 9 patients (16.5%) in Group 1, 12 patients (22.2%) in Group 2, and 6 patients (9.4%) in Group 3. The mean amount of erythrocyte suspension transfusion was found to be higher in Group 2 than in Groups 1 and 3. The duration of hospital stay was 11.88 (SD6.38) days, 14.96 (SD5.18) days, and 11.19 (SD5.93) days in Groups 1, 2, and 3, respectively. The endoscopic success rate was 80.6% in Group 1, 72.2% in Group 2, and 90.6% in Group 3. The mean epinephrine dose, mean number of clips, early bleeding rates, permanent hemostasis rates, late hemostasis rates, emergency need for surgery, thirty-day mortality rates, hospital stay, mean blood transfusion levels, and endoscopic success rates are summarized in Table 2.

As revealed by one-way ANOVA test, the transfusion amount of erythrocyte suspension to the endoclip and high-dose epinephrine injection group was significantly higher than that in the other groups ($P < .001$). The length of hospital stay was higher in the endoclip and high-dose epinephrine groups ($P = .008$). The endoscopy success rate did not differ between the Forrest groups ($P = .119$). The duration of hospital stay did not differ with regard to the type of treatment method ($P = .559$).

Early bleeding and permanent hemostasis rates in the endoclip and high-dose epinephrine injection groups were significantly
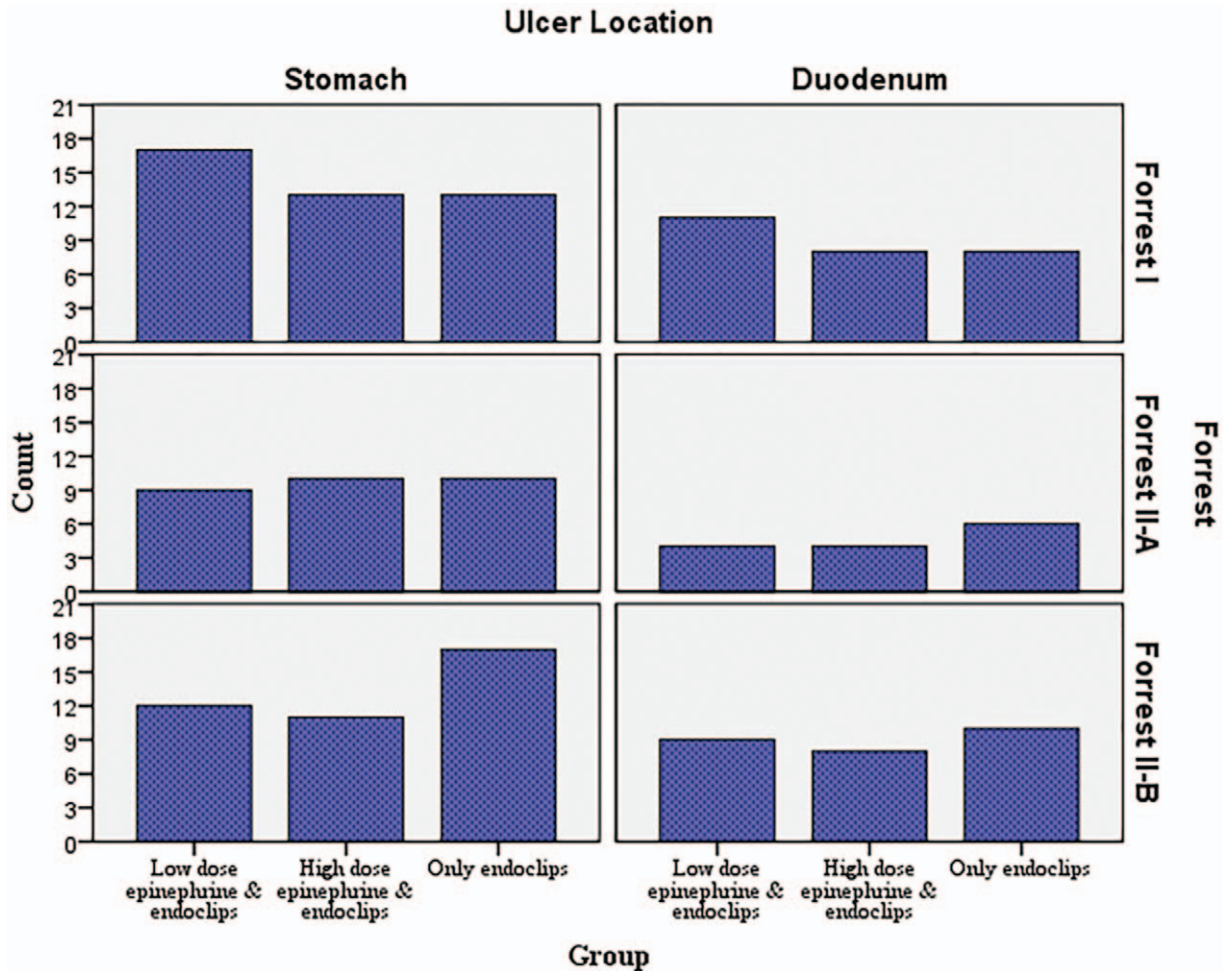
Ulcer Location

Figure 4. The distribution of ulcer locations according to Forrest classes.

higher than those in the other groups according to Pearson chi-square test ($P < .05$). When evaluated in terms of late hemostasis, urgent surgical need, and mortality, there was no significant difference between the groups ($P > .05$). The clinical results for treatment efficacy are summarized in Table 3.

The treatment effectiveness of the groups was compared, and the effect of treatment on mortality rate was investigated. In the comparison between Groups 1 and 2, Groups 1 and 3, and Groups 2 and 3, the net risk reductions (absolute risk reduction) were 4%, 8.16%, and 4%, respectively. The relative risk reduction value was also calculated to determine which patients would benefit from treatment, which was 52% between Groups 1 and 2, 72% between Groups 1, 3, and 58% between Groups 2 and 3. The numbers needed to treat were 25, 12.24, and 23.39 when Groups 1 and 2, 1 and 3, and 2 and 3 are compared. Table 4 summarizes the therapeutic efficacy (95% confidence interval) of treatment modalities in groups 1, 2, and 3 in reducing bleeding.

4. Discussion

Our study was based on the use of endoclips and accompanying epinephrine, with the idea that endoclip placement leads to hemostasis due to mechanical effects and compression of the ulcer vein, which may be prolonged by epinephrine injection around the ulcer bed. In a similar study, only epinephrine injection and

endoclip application were compared, and it was found that the mechanical effect and compression applied to the ulcer vessel in Forrest II-A lesions seriously affected the study results.[10] In a Cochrane review of 18 studies with 1868 patients with PUB, additional endoscopic therapy after epinephrine injection reduced re-bleeding rates from 18.5% to 10% and mortality rates from 4.7% to 2.5%.[11] Therefore, epinephrine injection is usually followed by a second method, such as thermocoagulation or endoclips.[12] On the other hand, studies have shown that high-dose epinephrine injection is superior to low-dose epinephrine injection in re-bleeding. In these studies, early re-bleeding rates in the low and high doses of epinephrine injection were 30% (15/50) and 16% (8/50), respectively, which were significantly different.[13] In our study, early bleeding and persistent hemostasis rates were significantly higher in the high-dose epinephrine injection group.

In most patients with upper gastrointestinal bleeding, early upper endoscopy is recommended for diagnosis and targeted endoscopic therapy, resulting in reduced morbidity, hospital stay, re-bleeding risk, and the need for surgery.[14] Endoscopic treatments include epinephrine injection, thermocoagulation, application of clips, and banding, all of which are similarly effective.[15] In a prospective randomized controlled trial, the efficacy of epinephrine and endoclip versus epinephrine injection therapy alone was compared. Re-bleeding occurred in 2 (3.8%)

Table 1

Clinical and endoscopic characteristics of the patients.

	Group 1 (n = 62)	Group 2 (n = 54)	Group 3 (n = 64)
Age (yrs)	62.45 (SD11.86)	68.48 (SD12.50)	62.22 (SD10.93)
(min-max)	(41–86)	(43–88)	(44–85)
Sex (gentleman/lady)	38/24	41/13	51/13
Forrest group, n (%)			
Forrest I	28 (45.2)	21 (38.9)	21 (32.8)
Forrest II-A	13 (21.0)	14 (25.9)	16 (25.0)
Forrest II-B	21 (33.8)	19 (35.2)	27 (42.2)
Ulcer location			
Stomach	45	102	48
Duodenum	31	60	26
Helicobacter pylori (+), n (%)	40 (64.5)	37 (68.5)	38 (59.4)
Non-steroidal anti-inflammatory drug use, n (%)	27 (43.5)	22 (40.7)	17 (26.6)
Alcohol use, n (%)	7 (11.3)	9 (16.7)	5 (7.8)
History of bleeding, n (%)	2 (3.2)	5 (9.3)	3 (4.7)
Comorbidities, n (%)			
Heart	4 (6.5)	11 (20.4)	12 (18.8)
Kidneys	4 (6.5)	1 (1.9)	1 (1.6)
Central nervous system	3 (4.8)	4 (7.4)	2 (3.1)
Liver	4 (6.5)	3 (5.6)	5 (7.8)
Lung	4 (6.5)	4 (7.4)	6 (9.4)
Gastro malignancy	1 (1.6)	1 (1.9)	1 (1.6)
Non-gastro malignancy	3 (4.8)	1 (1.9)	0 (0)
Systolic blood pressure	102.31 (SD15.36)	100.56 (SD15.31)	103.59 (SD15.39)
Laboratory test results (x, SD)			
Hemoglobin (g/dL)	8.84 (SD2.05)	7.65 (SD1.60)	9.08 (SD1.87)
Hematocrit (%)	26.52 (SD6.16)	22.95 (SD4.80)	27.25 (SD5.61)
Platelet ($\times 10^3/\mu$L)	266.76 (SD97.61)	250.33 (SD106.80)	254.95 (SD105.87)
Urea (mg/dL)	85.58 (SD32.80)	76.56 (SD29.54)	87.50 (SD32.65)
Creatinine (mg/dL)	1.07 (SD0.41)	0.95 (SD0.41)	1.06 (SD0.44)
Bilirubin (mg/dL)	0.81 (SD0.44)	1.08 (SD0.37)	0.76 (SD0.43)
Alanine amino transferase (U/L)	75.89 (SD38.26)	80.70 (SD36.13)	71.36 (SD35.47)
Aspartate amino transferase (U/L)	82.48 (SD37.93)	95.19 (SD36.81)	74.98 (SD35.49)
Hypovolemic shocks	9	16	6
Rockall risk score	4.38 (SD1.64)	5.14 (SD2.00)	4.14 (SD1.95)[*]

SD = standard deviation.

[*] One-way ANOVA $P = .012$.

patients in combination therapy and in 11 (21%) patients who received epinephrine injection only ($P = .008$), thus demonstrating that combination therapy is more effective than epinephrine injection alone in high-risk bleeding ulcers.[16] In a study comparing the efficacy of epinephrine injection with combined endoclip application, epinephrine injection, and bipolar electrocoagulation, endoscopic treatment was effective in terms of hemostasis during hospitalization in 96.3% (n = 103) of the patients, while the mean number of transfused blood units and hospitalization duration were similar between the groups. One of

Table 2

Endoscopic treatment procedures and clinical results of endoscopic therapy, n (%).

	Group 1 (n = 62)	Group 2 (n = 54)	Group 3 (n = 64)
Epinephrine use (mg)	1.50 (SD0.316)	2.37 (SD0.294)	–
(min-max)	(0–2 mg)	(2–4 mg)	
Number of clips	1.81 (SD0.43)	2.20 (SD0.74)	1.54 (SD0.35)
(min-max)	(1–3)	(1–4)	(1–2)
Early bleeding, n (%)	4 (6.5)	7 (12.9)	–
Permanent hemostasis, n (%)	56 (90.32)	45 (83.33)	62 (96.87)
Late hemostasis, n (%)	53 (85.48)	42 (77.77)	59 (92.18)
Emergency surgery, n (%)	5 (8.1)	8 (14.8)	2 (3.1)
30 days mortality, n (%)	9 (16.5)	12 (22.2)	6 (9.4)
Erythrocyte suspension transfusion amount (mL)	1192.87 (SD633.45)	1530.24 (SD565.18)	1100.57 (SD611.46)[*]
Hospital stay (day)	11.88 (SD6.38)	14.96 (SD5.18)	11.19 (SD5.93)[†]
Rate of successful Endoscopic treatment	50 (%80.6)	39 (%72.2)	58 (%90.6)

SD = standard deviation.

[*] One-way ANOVA $P < .001$.

[†] Pearson chi square $P < .01$.

Table 3

Clinical results of treatment effectiveness.

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	X^2 (*P*)
Early bleeding	4 (36.4)	7 (63.6)	0 (0)	8.597 (.014)[*]
Permanent hemostasis	6 (35.3)	9 (52.9)	2 (11.8)	6.286 (.035)[*]
Late hemostasis	9 (34.6)	12 (46.2)	5 (19.2)	4.921 (.085)[†]
Emergency surgery	5 (33.3)	8 (53.3)	2 (13.3)	5.248 (0.073)[†]
Mortality	9 (17.30)	12 (22.22)	6 (9.38)	3.809 (0.149)[†]

[*] Pearson chi square $P < .05$.

[†] Pearson chi square $P > .05$.

Table 4

Therapeutic efficacy (95% CI) of patients treated with clips only and patients treated with small and large volumes of epinephrine and clips in reducing bleeding.

	Absolute risk reduction	Relative risk reduction	Number needs to treat	Relative risk	Odds ratio
Group 1 [*] Group 2	%4	%52	25	1.53	1.59
Group 1 [*] Group 3	%8.16	%72	12.24	0.27	0.25
Group 2 [*] Group 3	%4	%58	23.39	0.42	0.41

CI = confidence interval.

the disadvantages of thermal methods and sclerosing agent injection is the risk of necrosis, leading to perforation.[17]

In a meta-analysis, acute bleeding recurred in 10% to 30% of cases, regardless of the treatment modality.[18] Bleeding recurrence has been identified as an important prognostic factor for mortality. Mortality still ranges from 3% to 14%, despite significant recent advances.[19] In our study, the total mortality rate due to bleeding was 15%, and there was no significant difference between the groups in terms of mortality.

Surgical treatment is recommended if bleeding cannot be controlled by endoscopy and embolization/arteriography, or if there is no interventional radiologist after a failed endoscopic procedure.[20] It is indicated in patients with re-bleeding or hemodynamic instability despite fluid therapy and blood transfusion.[21] Emergency surgery is currently only suitable for perforations, patients who fail non-surgical therapy, and those who remain hemodynamically unstable despite aggressive resuscitation.[22] In our study, emergency surgical intervention was performed in patients whose bleeding could not be controlled by endoscopic intervention and those who did not accept endoscopic intervention. Since interventional radiology is only available in certain centers, surgical intervention is more prominent in our hospital.

One of the fundamental limitations of this study is its single-center, observational design. The absence of therapeutic dual-channel endoscope in our endoscopy unit also poses a limitation because its use could affect the study results.

One of the strengths of this study is that it was conducted in a referral hospital with a large number of patients. In addition, patients from all Forrest groups were included, giving us a chance to evaluate the therapeutic effects on an extended population.

5. Conclusion

All procedures were effective in preventing acute PUB, and our study demonstrated that endoclip therapy may be the first-line treatment for uncomplicated PUB. However, if the patient has hypovolemic shock, the Rockall score is high and the ulcer size is larger than 2 cm, epinephrine injection may be considered if necessary.

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