



Retrospective Cohort Study

# Impact of epinephrine volume on further bleeding due to high-risk peptic ulcer disease in the combination therapy era

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## Abstract

### BACKGROUND

In monotherapy studies for bleeding peptic ulcers, large volumes of epinephrine were associated with a reduction in rebleeding. However, the impact of epinephrine volume in patients treated with combination endoscopic therapy remains unclear.

### AIM

To assess whether epinephrine volume was associated with bleeding outcomes in individuals who also received endoscopic thermal therapy and/or clipping.

### METHODS

Data from 132 patients with Forrest class Ia, Ib, and IIa peptic ulcers were reviewed. The primary outcome was further bleeding at 7 d; secondary outcomes included further bleeding at 30 d, need for additional therapeutic interventions, post-endoscopy blood transfusions, and 30-day mortality. Logistic and linear regression and Cox proportional hazards analyses were performed.

### RESULTS

There was no association between epinephrine volume and all primary and secondary outcomes in multivariable analyses. Increased odds for further bleeding at 7 d occurred in patients with elevated creatinine values (aOR 1.96, 95% CI 1.30-3.20;  $P < 0.01$ ) or hypotension requiring vasopressors (aOR 6.34, 95% CI 1.87-25.52;  $P < 0.01$ ). Both factors were also associated with all secondary outcomes.

### CONCLUSION

Epinephrine maintains an important role in the management of bleeding ulcers, but large volumes up to a range of 10-20 mL are not associated with improved bleeding outcomes among individuals receiving combination endoscopic therapy. Further bleeding is primarily associated with patient factors that likely cannot be

overcome by increased volumes of epinephrine. However, in carefully-selected cases where ulcer location or size pose therapeutic challenges or when additional modalities are unavailable, it is conceivable that increased volumes of epinephrine may still be beneficial.

**Key Words:** Peptic ulcer disease; Gastrointestinal bleeding; Upper endoscopy; Endoscopic hemostasis; Epinephrine

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**Core Tip:** To our knowledge, this is the only study specifically aimed at clarifying the impact of epinephrine volume in patients treated with combination endoscopic therapy. Our findings suggest that larger volumes of epinephrine are unlikely to improve clinical outcomes among patients who also receive thermal therapy and/or clipping.

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## INTRODUCTION

Peptic ulcer disease (PUD) is the most common cause of upper gastrointestinal bleeding (UGIB), accounting for one-third to one-half of all cases[1-3]. Therapeutic endoscopic modalities are indicated for peptic ulcers with high-risk findings, including: (1) Spurting (Forrest class Ia); (2) Oozing (Forrest class Ib); or (3) Non-bleeding visible vessels (Forrest class IIa). Dilute epinephrine is a widely-available, safe, and effective therapy frequently used by endoscopists[4-6]. When it is injected circumferentially near an ulcer margin, epinephrine induces transient vasospasm and mechanical tamponade, often achieving rapid hemostasis. Clinical trials investigating this technique for monotherapy demonstrated that large volumes of epinephrine (up to 30-45 mL) are associated with a reduced risk for rebleeding[7-9].

In the last two decades, the combination of epinephrine with additional endoscopic modalities, including thermal therapy and/or clipping, for UGIB due to PUD has been shown to be more effective than epinephrine monotherapy in preventing rebleeding[10-11]. Guidelines have suggested that large volumes of epinephrine are not routinely necessary when additional endoscopic therapy is applied, and clinicians have anecdotally opted to use smaller quantities[5]. However, combination therapy studies have not assessed the impact of epinephrine volume on UGIB outcomes[12-22]. To address this question, we identified a contemporary cohort of patients at our tertiary center who received combination endoscopic therapy for high-risk PUD. We hypothesized that, while ulcer characteristics and other host factors may influence endoscopic therapy, patients who received larger volumes of epinephrine would have a reduction in further bleeding, need for additional therapeutic interventions, and post-endoscopy blood transfusions.

## MATERIALS AND METHODS

### Patient selection

The study was exempted by the Institutional Review Board at Yale-New Haven Hospital. Electronic endoscopy records were queried from June 2017 to October 2020; 288 patients who underwent upper endoscopy for PUD and received endoscopic injection of dilute epinephrine (1:10000) at any point during the procedure were identified. Patients were subsequently excluded if they: (1) Did not have symptoms of overt bleeding; (2) Were not treated with combination endoscopic therapy; (3) Received interventions only for Forrest class IIb, IIc, or III ulcers; (4) Had multiple high-risk ulcers in different locations that required endoscopic treatment and could account for UGIB; (5) Received hemostatic spray (Hemospray®; Cook Medical, Bloomington, Indiana, United States); (6) Had missing data; or (7) Were initially screened into the cohort due to findings from interval endoscopies but did not meet the inclusion criteria at the time of index endoscopy. All patients received proton pump inhibitors (PPIs), and our cohort included patients with both in-hospital and out-of-hospital UGIB.

**Table 1** Baseline characteristics (*n* = 132)

Demographics	<i>n</i> (%)	mean ± SD	Medications	<i>n</i> (%)	mean ± SD
Age (yr)		70 ± 16	Antiplatelet agents	64 (48)	
Sex (male)	86 (65)		Anticoagulants	36 (27)	
Race (White)	96 (73)		NSAIDs	28 (21)	
Presentation			Medical interventions		
In-hospital bleeding	64 (48)		ICU admission	66 (50)	
Hematemesis	25 (19)		Hypotension requiring vasopressors	39 (30)	
Melena	93 (70)		Blood transfusion (units)		4 ± 4
Hematochezia	29 (22)		Endoscopic findings		
Systolic BP (mmHg)		112 ± 22	Time to endoscopy (h)		29 ± 29
Diastolic BP (mmHg)		63 ± 14	Ulcer location (gastric)	54 (41)	
Heart rate (BPM)		95 ± 19	Forrest classification		
Hemoglobin (g/dL)		8 ± 2	Ia	13 (10)	
Platelets (10 <sup>3</sup> /μL)		275 ± 129	Ib	47 (36)	
BUN (mg/dL)		51 ± 29	IIa	72 (55)	
Creatinine (mg/dL)		1.6 ± 1	Size (mm)		13 ± 9
Glasgow-Blatchford score		15 ± 3	Endoscopic interventions		
Medical history			Additional modality		
Cardiovascular disease	55 (42)		Thermal therapy	60 (45)	
Congestive heart failure	37 (28)		Clipping	53 (40)	
Active malignancy	18 (14)		Both thermal therapy and clipping	19 (14)	
Chronic renal dysfunction	59 (45)		Epinephrine volume (mL)		5.5 ± 3
Dialysis use	22 (17)		Large-volume epinephrine use (≥10 mL)	18 (14)	
Cirrhosis	11 (8)				

BP: Blood pressure; BPM: Beats per minute; BUN: Blood urea nitrogen; ICU: Intensive care unit; NSAIDs: Non-steroidal anti-inflammatory drugs.

### Data collection

Clinical data were collected from the time of presentation up to a follow-up period of 30-days using electronic medical records (EMR). Presenting symptoms, vital signs, and labs were obtained from the initial emergency department or urgent care center evaluation for patients who experienced out-of-hospital bleeding. For patients who developed in-hospital bleeding, these variables were acquired at or near the time overt UGIB was documented. Medical history and medication data were attained from clinic, admission, and inpatient progress notes, nursing documentation, and medication administration records. Endoscopy records were reviewed for exam indications, findings, and interventions, including epinephrine volume and additional therapeutic maneuvers; endoscopic images were evaluated for clarification when deemed necessary. Epinephrine volume was categorized as follows: small (up to 5 mL), moderate (more than 5 mL but less than 10 mL), or large (10 mL or more).

### Outcomes

The primary outcome was further rebleeding, defined as the presence of either: (1) Persistent bleeding without successful hemostasis at the time of index endoscopy; or (2) Rebleeding from the index source within 7 d of initial hemostasis based on clinical assessment by a gastroenterologist. Secondary outcomes included: (1) Further bleeding within 30 d of index endoscopy; (2) Need for additional therapeutic interventions; including endoscopic therapies; vascular embolization, or surgery; (3) Post-endoscopy blood transfusions; measured as units of packed red blood cells (pRBCs) administered after the initial endoscopy; (4) All-cause mortality at 30 d; and (5) Serious adverse effects (AEs) attributed to epinephrine use; including ventricular arrhythmias or cardiac ischemia. The etiology of bleeding, occurrence of rebleeding or AEs, and cause of death were determined by the authors of this study by synthesizing assessments in the EMR from gastroenterology, internal medicine, critical care, surgery,

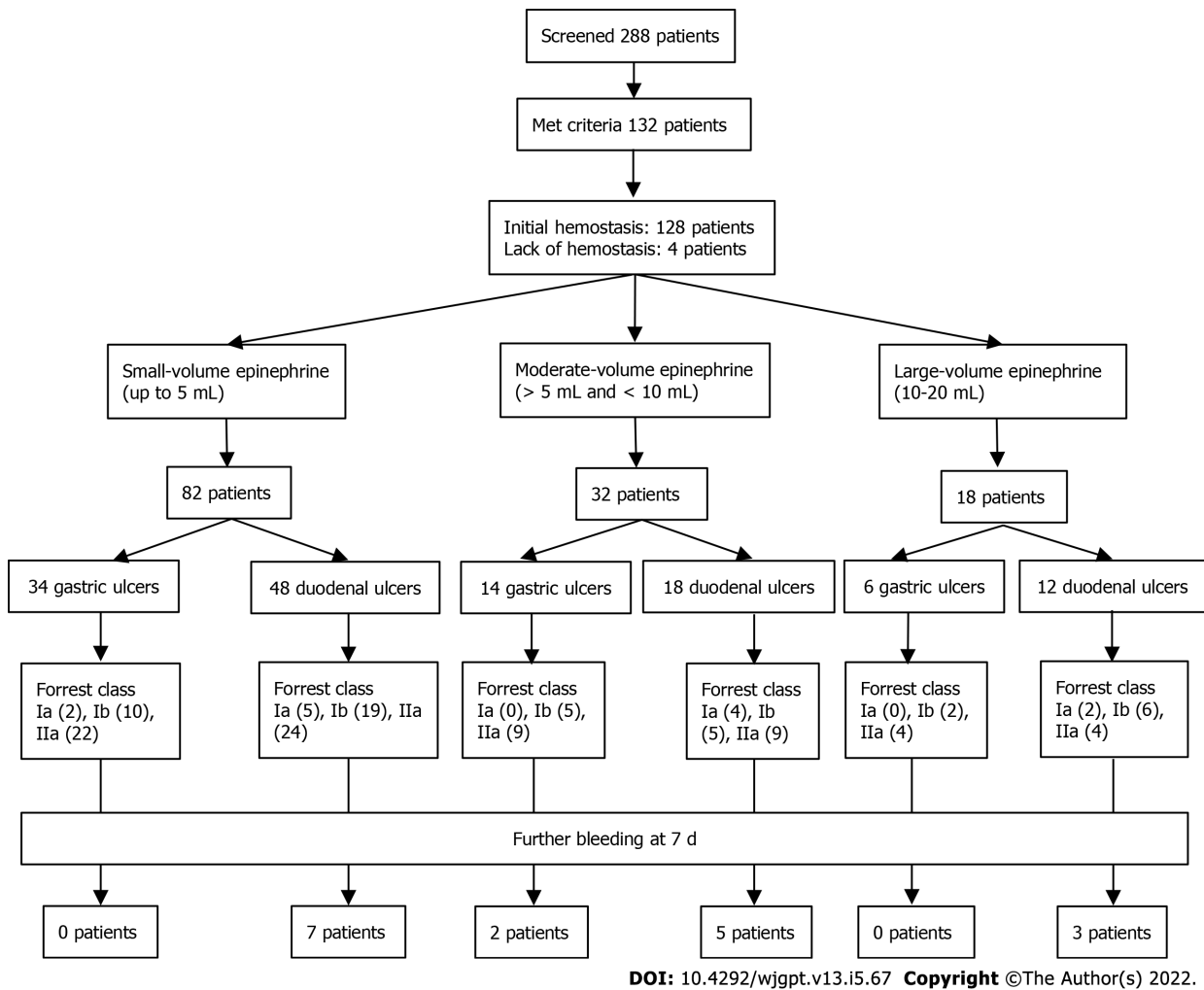


Figure 1 Flow diagram for the study cohort detailing endoscopic findings, management, and outcomes.

and/or interventional radiology (IR) providers.

### Statistical analysis

The impact of endoscopic findings, including ulcer location, absolute size, and Forrest classification (Ia/Ib *vs* IIa), on the absolute volume of epinephrine injected was examined using a multivariable linear regression model. For the main analyses, logistic and linear regression and Cox proportional hazards models were used to evaluate the impact of epinephrine volume on UGIB outcomes in relation to the effect of other relevant covariates, including age, presenting features (admission status, presence of hematochezia, creatinine levels, and hypotension requiring vasopressors), comorbidities [cardiovascular disease and congestive heart failure), medications (antiplatelet therapy, anticoagulant, and/or non-steroidal anti-inflammatory drugs (NSAIDs) use], and endoscopic factors (time to endoscopy, ulcer location, Forrest classification, and size). Epinephrine volume was assessed as a continuous variable; the remaining covariates were dichotomized with the exception of creatinine values, which were also maintained as continuous variables. Variables with *P* values less than 0.05 in univariable analyses were subsequently included in multivariable analyses. All analyses were performed in R (R Core Team, 2019); survival analysis was done using the *survival* package[23].

## RESULTS

### Characteristics of the study cohort

During a period of more than three years, 132 PPI-treated patients received combination endoscopic therapy that included epinephrine injection for Forrest class Ia, Ib, and IIa ulcers in the stomach or duodenum and met the remaining criteria for our study (Figure 1 and Table 1). Our cohort predominantly consisted of elderly individuals who had comorbid conditions such as cardiovascular disease (42%) or chronic renal dysfunction (45%) and used one or more antiplatelet agents, NSAIDs, and/or

**Table 2 Univariable and multivariable logistic regression analyses for factors associated with further bleeding at 7 d**

Variable	OR	95%CI	P value
Univariable logistic regression:			
Age ( $\geq 75$ yr)	2.47	0.88-7.60	0.09
Admission status (in-hospital)	2.91	1.01-9.63	0.06
Hematochezia	2.96	0.98-8.6	0.04
Creatinine (mg/dL)	1.86	1.31-2.78	< 0.001
Hypotension requiring vasopressors	5.70	1.98-17.88	< 0.01
Cardiovascular disease and/or congestive heart failure	2.71	0.94-8.98	0.08
Antiplatelet therapy, anticoagulants, and/or NSAIDs	0.57	0.20-1.70	0.30
Time to endoscopy (> 24 h)	0.71	0.23-2.00	0.53
Location of ulcer (duodenal)	6.19	1.65-40.43	0.02
Forrest class (Ia and Ib)	2.47	0.88-7.60	0.09
Size of ulcer (> 20 mm)	0.89	0.13-3.59	0.88
Epinephrine volume (mL)	1.06	0.92-1.22	0.38
Multivariable logistic regression:			
Hematochezia	1.48	0.41-5.05	0.54
Creatinine (mg/dL)	1.96	1.30-3.20	< 0.01
Hypotension requiring vasopressors	6.34	1.87-25.52	< 0.01
Location of ulcer (duodenal)	3.44	0.81-23.72	0.13

Variables with  $P < 0.05$  in univariable analysis were included in multivariable analysis. aOR: Adjusted odds ratio; BPM: Beats per minute; BUN: Blood urea nitrogen; CI: Confidence interval; NSAIDs: Non-steroidal anti-inflammatory drugs; OR: Odds ratio.

anticoagulants (70%). In-hospital bleeding was common (48%); half were either already in the intensive care unit (ICU) or required admission to the ICU and 30% needed vasopressors for hypotension. Endoscopy occurred at a mean time of 29 h (standard deviation 29 h, range 1-199 h). Ulcers were present in the following locations: 8 (6%) in the gastric cardia, 7 (5%) in the gastric fundus, 23 (17%) in the gastric body, 1 (1%) in the gastric incisura, 15 (11%) in the gastric antrum, 57 (43%) in the first portion of the duodenum, 20 (15%) in the second portion of the duodenum, and 1 (1%) in the third portion of the duodenum. Ulcer size ranged from 2 to 50 mm, and actively bleeding ulcers (Forrest class Ia or Ib) were encountered in 45% of cases. The mean volume of epinephrine was 5.5 mL (standard deviation 3 mL, range 1-20 mL), and 18 patients (14%) received 10 or more mL. There was no association between the volume used and ulcer location ( $P = 0.50$ ), ulcer size ( $P = 0.15$ ), or Forrest classification ( $P = 0.92$ ).

### Overall outcomes

Initial endoscopic hemostasis was achieved in 128 patients (97%), and vascular embolization was performed by IR for the remaining 4 individuals. Among patients who had successful endoscopic hemostasis, rebleeding within 7 d occurred in 13 (10%) and rebleeding within 30 d occurred in 21 (16%); of those who had failure of initial endoscopic hemostasis, one experienced rebleeding less than 48 h after endoscopy and embolization. Among all 22 (17%) patients who experienced rebleeding within 30 d, 19 (14%) required at least one additional endoscopic or endovascular intervention, including 10 (8%) who required endoscopic hemostasis, 3 (2%) who required vascular embolization, and 6 (5%) who required both; none required surgery. Among the entire cohort, 15 (11%) died within 30 d, and 5 deaths were due to probable refractory UGIB. No serious AEs attributed to epinephrine injection were reported.

### Further bleeding

In univariable logistic regression analysis, epinephrine volume did not correlate with further bleeding at 7 d (OR 1.06, 95%CI 0.92-1.22;  $P = 0.38$ ); however, 4 other variables with  $P$  values < 0.05 were included in multivariable logistic regression analysis (Table 2). Increased odds for further bleeding were observed in patients who had elevated creatinine values (aOR 1.96, 95%CI 1.30-3.20;  $P < 0.01$ ) or hypotension requiring vasopressors (aOR 6.34, 95%CI 1.87-25.52;  $P < 0.01$ ). This analysis was repeated using a follow-up period of 30 d. There was a positive association between increased epinephrine volume and further

**Table 3** Multivariable logistic regression and cox proportional hazards analyses for factors associated with further bleeding at 30 d, need for additional therapeutic interventions, and mortality at 30 d

Variable	aOR or aHR	95%CI	P value
<b>Further bleeding at 30 d<sup>1</sup>:</b>			
Hematochezia	2.83	0.95-8.44	0.06
Creatinine (mg/dL)	1.73	1.18-2.64	< 0.01
Hypotension requiring vasopressors	7.68	2.69-24.38	< 0.001
Epinephrine volume (mL)	1.07	0.93-1.24	0.31
<b>Need for additional therapeutic interventions<sup>1</sup>:</b>			
Admission status (in-hospital)	1.36	0.37-5.18	0.64
Hematochezia	1.49	0.43-4.90	0.52
Creatinine (mg/dL)	1.60	1.06-2.47	0.03
Hypotension requiring vasopressors	8.53	2.51-34.72	< 0.01
Epinephrine volume (mL)	1.09	0.93-1.26	0.27
<b>Mortality at 30 d<sup>2</sup>:</b>			
Creatinine (mg/dL)	1.77	1.36-2.30	< 0.001
Hypotension requiring vasopressors	4.09	1.39-12.09	0.01

<sup>1</sup>Logistic regression analysis.

<sup>2</sup>Cox proportional hazards analysis. Variables with  $P < 0.05$  in univariable analysis were included in multivariable analysis. aHR: Adjusted hazard ratio; aOR: Adjusted odds ratio; BUN: Blood urea nitrogen; CI: Confidence interval.

bleeding at 30 d in univariable analysis (OR 1.14, 95%CI 1.01-1.30;  $P = 0.03$ ) but not in multivariable analysis (aOR 1.07; 95%CI 0.93-1.24;  $P = 0.31$ ). Increased odds for further bleeding at 30 d were observed in those with elevated creatinine values (aOR 1.73, 95%CI 1.18-2.64;  $P < 0.01$ ) or hypotension requiring vasopressors (aOR 7.68, 95%CI 2.69-24.38;  $P < 0.001$ ) in multivariable analysis (Table 3).

#### **Need for additional therapeutic interventions**

There was a positive association between increased epinephrine volume and the need for additional endoscopic or endovascular interventions in univariable logistic regression analysis (OR 1.14, 95%CI 1.00-1.30;  $P < 0.05$ ) but not in multivariable logistic regression analysis (aOR 1.09; 95%CI 0.93-1.26;  $P = 0.27$ ). Only elevated creatinine values (aOR 1.60, 95%CI 1.06-2.47;  $P = 0.03$ ) and hypotension requiring vasopressors (aOR 8.53, 95%CI 2.51-34.72;  $P < 0.01$ ) were associated with additional therapeutic interventions in multivariable analysis (Table 3).

#### **Post-endoscopy blood transfusions**

A mean of 2 units of pRBCs were transfused after the initial endoscopy (standard deviation 3 units; range 0 to 14 units); 49 patients required no transfusions, 32 required 1 unit, and 51 required 2 or more units. In a univariable linear regression model, there was no correlation between epinephrine volume and the units of pRBCs transfused after initial endoscopy ( $P = 0.28$ ). However, 6 other variables (admission status, presence of hematochezia, creatinine values, hypotension requiring vasopressors, time to endoscopy, and ulcer location) with  $P$  values  $< 0.05$  in univariable linear regression models were included in a multivariable model (analysis not shown); increased post-endoscopy blood transfusions were only observed among patients with elevated creatinine values ( $P < 0.01$ ) or hypotension requiring vasopressors ( $P < 0.001$ ).

#### **Mortality**

In a univariable Cox proportional hazards model, there was no association between epinephrine volume and death up to a follow-up of 30 d (HR 1.11, 95%CI 0.98-1.26;  $P > 0.10$ ). In multivariable analysis (Table 3), elevated creatinine values (aHR 1.77, 95%CI 1.36-2.30;  $P < 0.001$ ) and hypotension requiring vasopressors (aHR 4.09, 95%CI 1.39-12.09;  $P = 0.01$ ) were associated with increased mortality.

**Table 4** Prospective combination therapy studies incorporating epinephrine for peptic ulcer disease

Ref.	Additional therapy	Mean volume (mL)	PPI	Forrest class	Number	Rebleeding	Follow-up
Karaman <i>et al</i> [14], 2011	Thermal	6	Yes	1a and 1b	78 <sup>a</sup>	4 5%	4 wk
Kim <i>et al</i> [12], 2015	Thermal	6	Yes	1a, 1b, 2a	151	12 8%	30 d
Lin <i>et al</i> [20], 1999	Thermal	7	Yes	1a, 1b, 2a	30	2 7%	14 d
Tekant <i>et al</i> [22], 1995	Thermal	7	No	1b and 2a	48 <sup>b</sup>	3 6%	5 d
Chau <i>et al</i> [18], 2003	Thermal	8	Yes	1a, 1b, 2a	164 <sup>c</sup>	34 21%	10 d
Chung <i>et al</i> [19], 1999	Thermal	10	No	1a, 1b, 2a	41	4 10%	7 d
Lin <i>et al</i> [17], 2003	Thermal and Clipping	10	Yes	1a, 1b, 2a	86	7 8%	14 d
Chung <i>et al</i> [21], 1997	Thermal	10	Some	1a and 1b	135	5 4%	4 wk
Grgov <i>et al</i> [13], 2013	Clipping	11	Yes	1a, 1b, 2a	35	2 6%	8 wk
Bianco <i>et al</i> [16], 2004	Thermal	12	Yes	1a, 1b, 2a	58	5 9%	30 d
Taghavi <i>et al</i> [15], 2009	Thermal and Clipping	21	Yes	1a, 1b, 2a	147 <sup>c</sup>	13 9%	30 d
Total		10			973	91 9%	

<sup>a</sup>All patients received between 5 and 6 mL of epinephrine.

<sup>b</sup>Patients who received endoscopic therapy for pigmented spots or adherent clots were excluded.

<sup>c</sup>Patients who received endoscopic therapy for adherent clots were excluded. PPI: Proton pump inhibitor.

## DISCUSSION

Our study suggests that larger volumes of epinephrine up to a range of 10 to 20 mL for Forrest class Ia, Ib, and IIa PUD are unlikely to be associated with improved UGIB outcomes in the combination therapy era. In the context of improvements in standard medical therapy, including widespread PPI use, and the incorporation of additional endoscopic modalities such as thermal therapy and clipping, further bleeding due to therapeutic failure has become less common, and the relative impact of epinephrine volume is likely limited in most cases[24].

Our findings support the notion that adverse UGIB outcomes such as further bleeding, additional therapeutic interventions, excess transfusions, and death are more likely to occur as a result of general host factors rather than endoscopic factors among individuals receiving combination therapy. Patients with comorbidities such as renal dysfunction and hypotension requiring vasopressors may be less likely to have a favorable response to conventional medical and endoscopic therapies. The application of increased volumes of epinephrine up to the modest range evaluated in our study will likely not have a meaningful impact on outcomes.

Our study has some methodologic constraints, including a limited sample size, retrospective design, and data from one tertiary center. The majority of the patients in our cohort also received epinephrine injections of 1 to 5 mL, which is markedly less than the average volume (6 to 21 mL) reported in prior prospective combination therapy studies that included Forrest class Ia, Ib, and IIa ulcers[12-22]. In most cases included in our study, epinephrine was primarily used to improve visualization and limit bleeding as additional endoscopic hemostasis interventions were being applied. Ulcer characteristics, including location, size, and Forrest classification did not influence decisions relating to the volume of epinephrine use, indicating that providers were often only willing to use modest volumes, regardless of the technical aspects of the case. Only 18 patients received 10 or more mL of epinephrine, and the maximum volume used was 20 mL (one individual). Therefore, the impact of volumes greater than 10-20 mL in patients treated with combination therapy remains unclear.

The rates of rebleeding and further bleeding at 30 d among our cohort were 16% and 19%, respectively. These values were higher than anticipated for patients receiving combination therapy and may suggest that our study included an increased proportion of patients with risk factors for persistent bleeding or rebleeding, which is supported by the high rate of individuals requiring ICU admission among our cohort[11]. Although we attempted to address relevant covariates in our analyses, there may have been other unmeasured confounding variables that had some impact on outcomes, including the presence of coagulopathy, use of mechanical ventilation, or administration of other medications that may increase the risk for ulcer-related bleeding. Of the previously-cited prospective combination therapy studies that reported epinephrine volume, 10 of 11 reported rebleeding rates between 4% and 10% with no clear relationship to epinephrine volume (Table 4)[12-22].

## CONCLUSION

Because of its availability, safety, and efficacy, epinephrine will continue to maintain an important role in the management of UGIB from PUD. However, in light of the other medical and endoscopic therapies that have emerged over the past 20 years, there is likely a limited role for the use of increased volumes of epinephrine for patients who require endoscopic therapy for high-risk PUD. Endoscopists should decide on the appropriate volume on a case-by-case basis depending on a combination of technical factors, including the magnitude of active bleeding encountered and ulcer location and size. Based on the findings of initial prospective monotherapy studies, there is minimal harm associated with the use of volumes up to 30-45 mL in most individuals[7-8]. Therefore, providers should not be reluctant to use large volumes if deemed necessary, and in cases where ulcer location or size pose therapeutic challenges or when additional modalities cannot be utilized, it is conceivable that this strategy may still be beneficial. However, large volumes of epinephrine will likely not overcome patient factors that are not readily modifiable and predispose to further bleeding.

## ARTICLE HIGHLIGHTS

### **Research background**

In monotherapy studies for bleeding peptic ulcers, the volume of epinephrine injected had an impact on clinical outcomes. Large volumes up to a range of 30-45 mL were associated with a reduction in rebleeding. However, the impact of epinephrine volume on patients treated with combination endoscopic therapy remains unclear.

### **Research motivation**

Understanding whether epinephrine volume can impact clinical outcomes among patients treated with combination endoscopic therapy can help inform clinical practice for the management of bleeding ulcers, a condition commonly encountered by endoscopists.

### **Research objectives**

To examine whether epinephrine volume could impact the risk for further bleeding, need for additional medical or procedural interventions, and survival while accounting for other important clinical and endoscopic factors.

### **Research methods**

Comprehensive clinical and endoscopic data from 132 patients with Forrest class Ia, Ib, and IIa peptic ulcers treated at our tertiary care center were reviewed. We assessed for relevant clinical outcomes such as rebleeding within 7 and 30 d, need for additional intervention, post-endoscopy blood transfusions, and mortality. We used logistic regression analysis to determine the impact of clinical and endoscopic factors.

### **Research results**

There was no association between epinephrine volume and rebleeding, need for additional intervention, post-endoscopy blood transfusions, or mortality. Increased odds for further bleeding at 7 d occurred in patients with elevated creatinine values (aOR 1.96, 95%CI 1.30-3.20;  $P < 0.01$ ) or hypotension requiring vasopressors (aOR 6.34, 95%CI 1.87-25.52;  $P < 0.01$ ). Both factors were also associated with all secondary outcomes.

### **Research conclusions**

Volumes of epinephrine up to a range of 10-20 mL are not associated with improved bleeding outcomes among individuals receiving combination endoscopic therapy. Further bleeding is primarily associated with patient factors that likely cannot be overcome by increased volumes of epinephrine, including the presence of shock and renal failure.

### **Research perspectives**

It is unlikely that large volumes of epinephrine are routinely necessary for the management of high-risk peptic ulcer disease. However, in select cases where ulcer characteristics pose therapeutic challenges or additional modalities are unavailable, it is conceivable that large volumes of epinephrine may still be beneficial.



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## FOOTNOTES

**Author contributions:** Saffo S and Nagar A designed the study, interpreted the data and revised the manuscript; Saffo S collected and analyzed the data and wrote the initial draft of the manuscript; Nagar A is the guarantor of the study.

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