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ORIGINAL ARTICLE

Retrospective Cohort Study

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

Saad Saffo, Anil Nagar

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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

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	*n* (%)	mean ± SD	Medications	*n* (%)	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)				
Systolic BP (mmHg)		112 ± 22	Endoscopic findings		
Diastolic BP (mmHg)		63 ± 14	Time to endoscopy (h)		29 ± 29
Heart rate (BPM)		95 ± 19	Ulcer location (gastric)	54 (41)	
Hemoglobin (g/dL)		8 ± 2	Forrest classification		
Platelets (10^3/μL)		275 ± 129	Ia	13 (10)	
BUN (mg/dL)		51 ± 29	Ib	47 (36)	
Creatinine (mg/dL)		1.6 ± 1	IIa	72 (55)	
Glasgow-Blatchford score		15 ± 3	Size (mm)		13 ± 9
Medical history			Endoscopic interventions		
Cardiovascular disease	55 (42)		Additional modality		
Congestive heart failure	37 (28)		Thermal therapy	60 (45)	
Active malignancy	18 (14)		Clipping	53 (40)	
Chronic renal dysfunction	59 (45)		Both thermal therapy and clipping	19 (14)	
Dialysis use	22 (17)		Epinephrine volume (mL)		5.5 ± 3
Cirrhosis	11 (8)		Large-volume epinephrine use (≥10 mL)	18 (14)	

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,

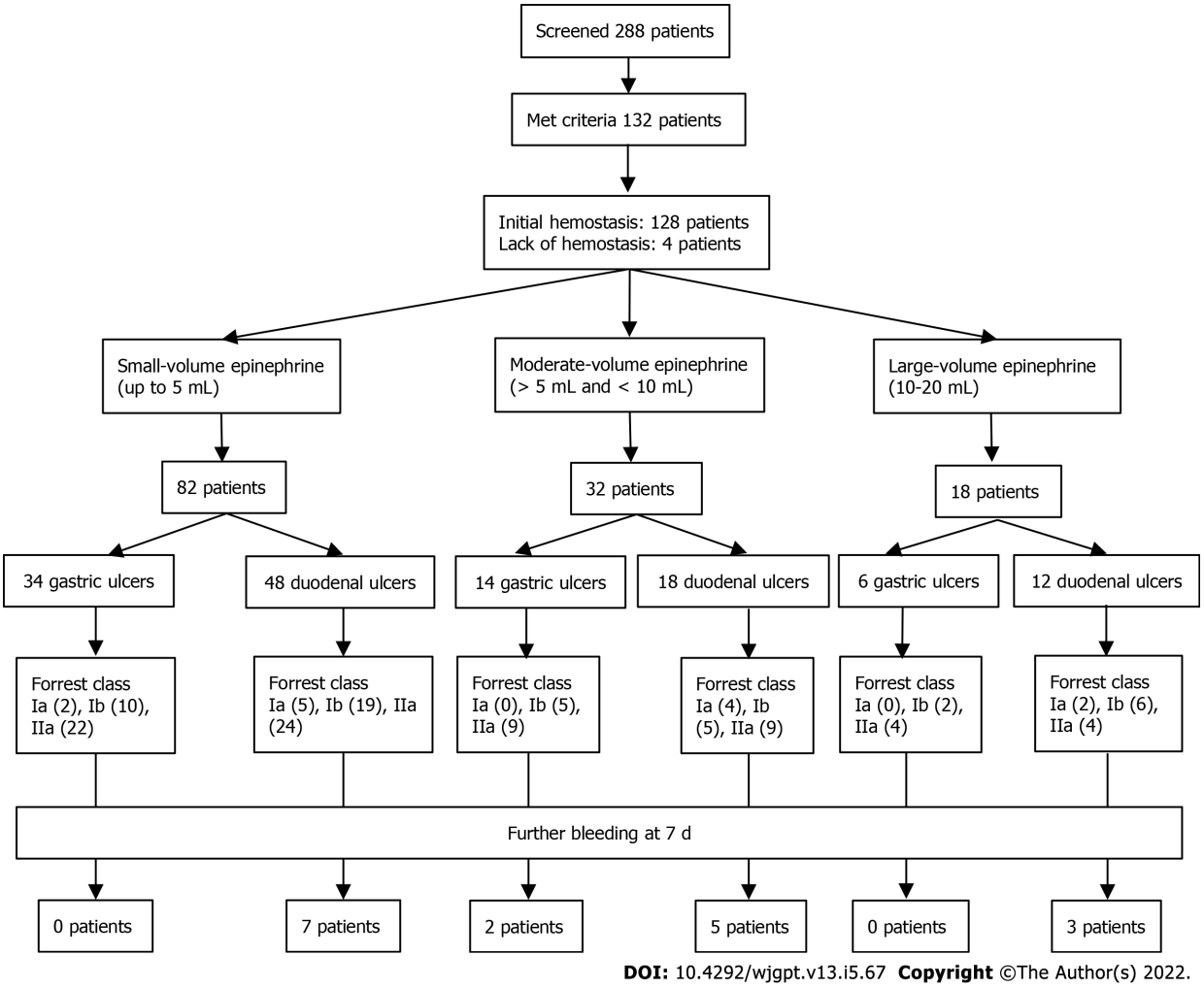

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Figure 1 Flow diagram for the study cohort detailing endoscopic findings, management, and outcomes.

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 (≥ 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
Further bleeding at 30 d[1]:			
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
Need for additional therapeutic interventions[1]:			
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
Mortality at 30 d[2]:			
Creatinine (mg/dL)	1.77	1.36-2.30	< 0.001
Hypotension requiring vasopressors	4.09	1.39-12.09	0.01

[1]Logistic regression analysis.
[2]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 *et al*[14], 2011	Thermal	6	Yes	1a and 1b	78[a]	4	5%	4 wk
Kim *et al*[12], 2015	Thermal	6	Yes	1a, 1b, 2a	151	12	8%	30 d
Lin *et al*[20], 1999	Thermal	7	Yes	1a, 1b, 2a	30	2	7%	14 d
Tekant *et al*[22], 1995	Thermal	7	No	1b and 2a	48[b]	3	6%	5 d
Chau *et al*[18], 2003	Thermal	8	Yes	1a, 1b, 2a	164[c]	34	21%	10 d
Chung *et al*[19], 1999	Thermal	10	No	1a, 1b, 2a	41	4	10%	7 d
Lin *et al*[17], 2003	Thermal and Clipping	10	Yes	1a, 1b, 2a	86	7	8%	14 d
Chung *et al*[21], 1997	Thermal	10	Some	1a and 1b	135	5	4%	4 wk
Grgov *et al*[13], 2013	Clipping	11	Yes	1a, 1b, 2a	35	2	6%	8 wk
Bianco *et al*[16], 2004	Thermal	12	Yes	1a, 1b, 2a	58	5	9%	30 d
Taghavi *et al*[15], 2009	Thermal and Clipping	21	Yes	1a, 1b, 2a	147[c]	13	9%	30 d
Total		10			973	91	9%	

[a]All patients received between 5 and 6 mL of epinephrine.
[b]Patients who received endoscopic therapy for pigmented spots or adherent clots were excluded.
[c]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.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Timing of percutaneous endoscopic gastrostomy tube placement in post-stroke patients does not impact mortality, complications, or outcomes

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Abstract

BACKGROUND

Percutaneous Endoscopic Gastrostomy (PEG) tubes are often placed for dysphagia following a stroke in order to maintain sufficient caloric intake. The 2011 ASGE guidelines recommend delaying PEG tube placement for two weeks, as half of patients with dysphagia improve within 2 wk. There are few studies comparing outcomes based on timing of PEG tube placement, and there is increasing demand for early PEG tube placement to meet requirements for timely discharge to rehab and skilled nursing facilities.

AIM

To assess the safety of early (≤ 7 d post stroke) *vs* late (> 7 d post stroke) PEG tube placement and evaluate whether pre-procedural risk factors could predict mortality or complications.

METHODS

We performed a retrospective study of patients undergoing PEG tube placement for dysphagia following a stroke at two hospitals in Saint Louis, MO between January 2011 and December 2017. Patients were identified by keyword search of endoscopy reports. Mortality, peri-procedural complication rates, and post-procedural complication rates were compared in both groups. Predictors of morbidity and mortality such as protein-calorie malnutrition, presence of an independent cardiovascular risk equivalent, and presence of Systemic inflammatory response syndrome (SIRS) criteria or documented infection were evaluated by multivariate logistic regression.

RESULTS

154 patients had a PEG tube placed for dysphagia following a stroke, 92 in the late group and 62 in the early group. There were 32 observed deaths, with 8 occurring within 30 d of the procedure. There was an increase in peri-procedural and post-procedural complications with delayed PEG placement which was not statistically significant. Hospital length of stay was significantly less in patients with early PEG tube placement (12.9 *vs* 22.34 d, $P < 0.001$). Protein calorie malnutrition, presence of SIRS criteria and/or documented infection prior to procedure or having a cardiovascular disease risk equivalent did not significantly predict mortality or complications.

CONCLUSION

Early PEG tube placement following a stroke did not result in a higher rate of mortality or complications and significantly decreased hospital length of stay. Given similar safety outcomes in both groups, early PEG tube placement should be considered in the appropriate patient to potentially reduce length of hospital stay and incurred costs.

Key Words: Percutaneous endoscopic gastrostomy tube; Dysphagia; Stroke; Enteral nutrition; Gastrostomy/adverse effect

Core Tip: Percutaneous Endoscopic Gastrotomy (PEG) tubes are often placed for nutrition for dysphagia following a stroke. The 2011 ASGE guidelines recommend delaying PEG tube placement for two weeks, although this guideline is based on weak evidence. There is increasing demand for early PEG tube placement to meet requirements for timely discharge to rehab facilities. This is the first study to compare outcomes such as mortality or complications of PEG tubes based on timing of placement in stroke patients. Early PEG tube placement did not result in a higher rate of mortality or complications and significantly decreased hospital length of stay.

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INTRODUCTION

Enteral nutrition is the recommended method for providing sufficient nutrition and calories to patients who are unable to tolerate oral feeding[1]. Stroke patients commonly require enteral nutrition. Post stroke oropharyngeal dysphagia occurs in over 65% of cases[2]. While most post-stroke dysphagia will improve within the first four weeks, 20% of patients may require short-term enteral tube feeding, and 8% require tube feeding for more than six months[3,4]. Malnutrition will occur after an acute stroke in 8% to 34% of cases[5].

Methods to provide enteral feeding include nasogastric (NG) tubes, percutaneous endoscopic gastrostomy (PEG) tubes, and percutaneous gastrostomy tubes placed by interventional radiology or surgery. Nasoenteral tubes are recommended for short-term use in patients who are expected to resume oral nutrition within 30 d [1]. According to the 2011 ASGE guidelines, if a patient is unable to resume oral feeding after 2-3 wk with a nasoenteric tube, then PEG tube placement is recommended[1]. This recommendation is graded as low quality and the authors suggest that further research is needed to strengthen the evidence supporting a 2-3 wk waiting period[1]. This study aims to evaluate the safety of

early *vs* delayed placement of PEG tubes in patients after an acute stroke.

The original recommendation for delayed PEG tube placement for two weeks seems to be derived from the observation that about half of patients with dysphagia improve within 2 wk, whereas only 15% of patients have persistent dysphagia after 1 mo[2]. Two of the earliest studies assessing safety of PEG tube placement after a stroke were published in the 1990s. Both studies found PEG feeding to be safe and effective when placed at least 2 wk after a stroke, however neither of these studies addressed early (< 2 wk post stroke) PEG tube placement[6,7]. In 2005, Dennis and colleagues were the first to evaluate outcomes of early PEG tube placement in 321 patients who were randomized to early PEG *vs* NG tube placement after an acute stroke, and found no major differences in survival, but non-statistically significant improvement in functional outcomes if NG feeding was used in the first 2-3 wk, followed by PEG if needed[8,9]. Since the publication of the 2011 ASGE guidelines, there has been one additional retrospective chart review study looking at timing of PEG tubes in 34623 stroke patients, in which early PEG placement (< 7 d post stroke) was associated with a significant decrease in length of hospital stay (10.4 *vs* 20.5 d)[10]. Furthermore, there was no significant difference in inpatient mortality rates and other complications, however overall mortality was not evaluated.

The primary objective of our study was to assess the safety of early PEG tube placement in stroke patients by evaluating mortality and complications in patients who underwent PEG tube placement within 7 d *vs* after 7 d of an acute stroke. Our secondary objectives included the identification of predictors of morbidity and mortality such as malnutrition, pre-procedural infections, and independent cardiovascular risk equivalents. We hypothesized that there would be no difference in outcomes, mortality, or complications with early PEG tube placement unless independent risk factors for complications were present. We hope our study will contribute to evidence-based decision making regarding the timing of PEG tube placement following a stroke.

MATERIALS AND METHODS

This is a bi-center retrospective study of all adult patients who underwent PEG tube placement for dysphagia following an acute stroke between January 2011 and December 2017 at Saint Louis University Hospital and Saint Mary's Hospital in Saint Louis, Missouri. This study was approved by the institutional review board at Saint Louis University School of Medicine. Patients were identified by performing a keyword search of upper endoscopy reports on the ProVation (ProVation Medical, Minneapolis, MN) database using the keywords "gastrostomy" and "PEG." Individual patient records and endoscopy reports were then reviewed to confirm that the indication for placement was dysphagia following an acute stroke, and that endoscopic tube placement was performed *via* the standard "pull through" technique as described by Ponsky and Gauderer[11]. Exclusion criteria included PEG tubes placed for indications other than dysphagia from acute stroke, using a nonstandard endoscopic tube placement method, or tubes placed by surgery or interventional radiology.

At both hospitals, standard dysphagia management following a stroke required assessment of dysphagia by both the neurology service and a speech therapist. Enteral nutrition with a nasogastric tube was initiated immediately after determination of dysphagia was made and if PEG tube placement would be delayed. If it was determined that prolonged PEG tube placement would be required, the gastroenterology service was consulted. Active infection delayed placement of PEG tube but pre-procedure malnutrition, defined as albumin < 3.2, did not delay the procedure. All anti-platelet and anti-coagulant agents were held prior to PEG placement, according to ASGE guidelines[12]. Patients with early PEG tube placement, defined as within 7 d from the stroke event, were compared to those with later interventions. A dose of antibiotics was given prior to all procedures. The PEG site was examined for infection and bleeding 24 h after tube placement, and tube feeds were initiated once the tube was deemed safe to use by the inpatient gastroenterology team.

Retrospective data was collected from review of the patients' electronic medical records available at the two study centers, including inpatient and outpatient follow up data. Baseline characteristics including age, gender, and comorbidities were compared for both groups. Outcomes evaluated included the rate of peri-procedural complications, the rate of post-procedural complications, and 90-d all-cause mortality after PEG placement. Peri-procedural complications were defined as those occurring during or within 24 h of PEG placement and included cardiovascular and cerebrovascular events, aspiration, bleeding, organ injury, perforation, or infection. Post-procedural complications were defined as those occurring after 24 hours and within 3 mo from PEG placement and included cardiovascular and cerebrovascular events, aspiration, bleeding, infection, and PEG tube site complications. Complication and mortality rates were calculated for both groups. Patients were censored at death or 90-d follow-up from date of PEG placement. The Kaplan-Meier Method was used to perform a time to event analysis. Predictors of morbidity and mortality were evaluated by multivariate logistic regression and included documentation of pre-procedure protein-calorie malnutrition (defined as albumin ≤ 3.2), having an independent cardiovascular risk equivalent outside of the current stroke (type 2 diabetes, prior stroke, abdominal aortic aneurysm, peripheral vascular disease, or Framingham risk score > 20%), and presence of Systemic inflammatory response syndrome (SIRS) criteria or documented infection (positive

urine or blood culture). All statistical analyses were performed using SAS 9.4 (SAS, Cary, NC) and results were considered significant with a P value ≤ 0.05. Statistical Review of the study was performed by a biomedical statistician.

RESULTS

Initial keyword search identified 482 cases on the ProVation endoscopy report database. 154 patients were included in the study after manually reviewing charts to exclude patients that did not meet the inclusion criteria. Among these, 62 patients underwent early PEG placement, while the remaining 92 patients had PEG tube placement after 7 d (See Figure 1). Baseline patient demographics (Table 1) and clinical comorbidities are listed (Table 2). There was a statistically significant difference in age between patient's undergoing early *vs* late PEG placement (74.7 *vs* 66.2 years, P = 0.0005). There was otherwise no significant difference in sex or the total number of comorbidities as described below. Among specific comorbidities however, there was a statistically significant difference in chronic kidney disease (3.2% *vs* 13.0%) and peripheral arterial disease (8.1% *vs* 1.1%) between patients undergoing early and late interventions.

Complications

Peri-procedural and post-procedural complications were compared between patients undergoing early *vs* late PEG placement (See Table 3). There were 3 peri-procedural complication events in the early group, compared to 8 in the late PEG placement group. There were 19 post-procedural complications in the early group, compared to 35 in the late PEG placement group. These differences, however, were not statistically significant. Similarly, there were no statistical differences in the type of peri-procedural or post-procedural complications based on timing of PEG tube placement (See Table 4).

Mortality

There were 32 total observed deaths, however only 8 occurred within 30 d from PEG placement, including 3 deaths in the early group *vs* 5 deaths in the late PEG placement group. The Kaplan-Meier Method was used to perform a time to event (death) analysis. As seen in Figure 2, there was no statistical difference in survival between both groups (log rank P = 0.593).

Predictors of Morbidity and Mortality

Pre-procedural risk factors for complications and mortality, such as protein calorie malnutrition, presence of SIRS or documented infection, and cardiovascular disease risk equivalents independent of current stroke, were evaluated by multivariate regression analysis. None of the risk factors studied significantly impacted 30- or 90-d mortality. Protein-calorie malnutrition [OR 1.31, (0.37-4.7)] and presence of infection or SIRS criteria [OR 1.55, (0.38-6.28)] were associated with an increase in peri-procedural and post-procedural complications, however these did not reach statistical significance (See Table 5).

Length of Stay

Total hospital length of stay was significantly lower in patients undergoing early PEG tube placement (12.9 *vs* 22.3 d, P < 0.001).

DISCUSSION

This study compared mortality, complications, and risk factors for morbidity in 154 patients with dysphagia following an acute stroke undergoing PEG tube placement within 7 d *vs* after 7 d of acute stroke. We had hypothesized that there would be no difference in outcomes, mortality, or complications with early PEG tube placement unless independent risk factors for complications were present. Our results support our hypothesis. There were no differences in mortality or rates of peri-procedural and post-procedural complication. Patients undergoing early PEG placement had no worse outcomes and had a shorter length of hospital stay.

The only other study to directly compare early PEG placement to later PEG placement was an observational study of the US Nationwide Inpatient Sample by George *et al*[10], which identified 34623 stroke patients undergoing PEG placement and found no difference in inpatient mortality. Our study results match its findings. Our study, which directly reviewed patients' charts rather than nationwide hospital data, extends its conclusions by additionally finding no difference in mortality at 30 and 90 d after hospitalization. Finally, both studies found a significant decrease in length of hospital stay associated with early PEG placement.

Our study defined "early" *vs* "late" PEG placement using a cutoff of 7 d after the acute stroke. This cutoff was defined prior to our data collection and was not the result of a "post-hoc" analysis. We chose

Table 1 Patient demographics

	All (*N* = 154)		PEG ≤ 7 d (*N* = 62, 40.26%)		PEG > 7 d (*N* = 92, 59.74%)		*P* value
	N	SD	*N*	SD	*N*	SD	
Age	69.62	15.02	74.65	13.89	66.24	14.87	**0.0005**[1]
Sex							0.0658
Female	78	50.65	37	59.68	41	44.57	
Male	76	49.35	25	40.32	51	55.43	
Any comorbidity	147	95.45	59	95.16	88	95.65	1.0000[2]
Number of comorbidities							0.4339[3]
0	7	4.55	3	4.84	4	4.35	
1	26	16.88	12	19.35	14	15.22	
2	37	24.03	13	20.97	24	26.09	
3	41	26.62	17	27.42	24	26.09	
4	26	16.88	12	19.35	14	15.22	
5	8	5.19	4	6.45	4	4.35	
6	5	3.25	0	0.00	5	5.43	
7	3	1.95	1	1.61	2	2.17	
8	0	0.00	0	0.00	0	0.00	
9	1	0.65	0	0.00	1	1.09	

[1]Obtained by Student's *t*-test;
[2]Obtained by Fisher's exact test;
[3]Obtained by Poisson regression, PEG: Percutaneous endoscopic gastrostomy, Significant *P* values are in bold.

this cutoff for several reasons. First, our clinical experience suggested that we were consulted by neurology for PEG placement earlier than 2 wk in the patients' hospital course, usually around 7 d. Second, using the same cutoff as the study by George *et al*[10] would allow for a direct comparison with their results. Finally, using an earlier cutoff than the guideline-based 2 wk, would allow us to better answer our hypothesis, which was that PEG placement earlier than 2 wk does not lead to worsened outcomes.

As previously discussed in our introduction, this 7 d interval is earlier than the 2 wk interval recommended in the 2011 ASGE guidelines[1]. Most recently, the 2019 guidelines for early management of acute ischemic stroke by the American Heart Association and the American Stroke Association also recommend the use of nasogastric tubes for feeding "in the early phase of stroke" and to place PEG tubes "in patients with longer anticipated persistent inability to swallow safely (> 2 to 3 wk)"[13]. The strength of this recommendation is graded as moderate, and the level of evidence is based on expert opinion and clinical experience[13].

Despite these recommendations to delay PEG placement for 2 wk, there is a high demand to initiate early placement. Stroke patients often require intensive inpatient or outpatient rehab and skilled nursing facility care; both of which require patients to resume oral nutrition or have a PEG tube given the high risk of nasoenteric tube displacement or blockage[6,7]. Delayed PEG placement could limit how quickly stroke patients can begin intensive rehabilitation and jeopardize their neurologic recovery. For this reason, determining the optimal timing of PEG placement is clinically important, but few studies have examined this directly. The 2005 "FOOD" randomized controlled trial comparing PEG tube *vs* nasoenteric tube feeding appeared to show the former was associated with a small increase in absolute risk of death or poor outcomes[8,9]. A later 2012 Cochrane review found that although there was insufficient data to offer definitive answers, PEG and NG tube feeding did not differ in terms of death or functional outcomes in patients with dysphagia following an acute or subacute stroke. Instead, PEG tubes were associated with improved food delivery, less treatment failures, and less GI bleeding[14]. However, neither of these studies specifically looked at the timing of placement. Our study, and the study by George *et al*[10], introduce new evidence for this discussion.

Our study had several limitations, most notably the relatively small population size, which likely contributed to an underpowered study and inability to identify significant differences in mortality, complication rates, or risk factors for these adverse outcomes. We attempted to account for any comorbidities contributing to the patients' clinical status and outcomes, and our demographic and

Table 2 Patient comorbidities

Types of comorbidities	All (*N* = 154)		PEG ≤ 7 d (*N* = 62, 40.26%)		PEG > 7 d (*N* = 92, 59.74%)		*P* value
	N	%	*N*	%	*N*	%	
Acute respiratory distress syndrome	1	0.65	0	0.00	1	1.09	1.0000[1]
Acute kidney injury	2	1.30	0	0.00	2	2.17	0.5158
Alcohol abuse	5	3.25	2	3.23	3	3.26	1.0000[1]
Amyotrophic lateral sclerosis	1	0.65	0	0.00	1	1.09	1.0000[1]
Anemia	4	2.60	2	3.23	2	2.17	1.0000[1]
Aortic dissection	1	0.65	0	0.00	1	1.09	1.0000[1]
Aortic stenosis	1	0.65	0	0.00	1	1.09	1.0000[1]
Arrhythmias	7	4.55	4	6.45	3	3.26	0.4403[1]
Atrial fibrillation	32	20.78	17	27.42	15	16.30	0.0955
Breast cancer	3	1.95	2	3.23	1	1.09	0.5652[1]
Coronary artery disease	29	18.83	9	14.52	20	21.74	0.2609
Cirrhosis	1	0.65	1	1.61	0	0.00	0.4026[1]
Chronic kidney disease	14	9.09	2	3.23	12	13.04	**0.0377**
Colon cancer	2	1.30	2	3.23	0	0.00	0.1605[1]
Chronic obstructive pulmonary disease	9	5.84	1	1.61	8	8.70	0.0853[1]
Dementia	15	9.74	5	8.06	10	10.87	0.5648
Diabetes mellitus	52	33.77	19	30.65	33	35.87	0.5014
Deep vein thrombosis	1	0.65	1	1.61	0	0.00	0.4026[1]
Heart failure	24	15.58	11	17.74	13	14.13	0.5445
Hyperlipidemia	45	29.22	20	32.26	25	27.17	0.4963
Hypertension	121	78.57	45	72.58	76	82.61	0.1369
Lung cancer	1	0.65	0	0.00	1	1.09	1.0000[1]
Nonalcoholic steatohepatitis	1	0.65	0	0.00	1	1.09	1.0000[1]
Obstructive sleep apnea	3	1.95	1	1.61	2	2.17	1.0000[1]
Peripheral artery disease	6	3.90	5	8.06	1	1.09	**0.0391**[1]
Parkinson's disease	2	1.30	0	0.00	2	2.17	0.5158[1]
Patent Foramen Ovale	1	0.65	1	1.61	0	0.00	0.4026[1]
Prostate cancer	2	1.30	0	0.00	2	2.17	0.5158[1]
Pulmonary hypertension	1	0.65	1	1.61	0	0.00	0.4026[1]
Seizure disorder	4	2.60	2	3.23	2	2.17	1.0000[1]
Stroke	38	24.68	14	22.58	24	26.09	0.6206[1]
Substance abuse	1	0.65	0	0.00	1	1.09	1.0000[1]
Thrombocytopenia	2	1.30	1	1.61	1	1.09	1.0000[1]
Thyroid cancer	1	0.65	1	1.61	0	0.00	0.4026[1]

[1]Obtained by Fisher's Exact Test, PEG: Percutaneous endoscopic gastrostomy, Significant *P* values are in bold.

comorbidity data were broadly similar for both patient groups. Nevertheless, there remains the possibility of confounding bias when assessing the mortality and hospital length of stay. It is possible that sicker patients required longer recovery before they could undergo PEG placement, affecting length of stay.

Table 3 Mortality and complications in percutaneous endoscopic gastrostomy tubes placed ≤ 7 d *vs* > 7 d post stroke

	Early PEG group (≤ 7 d)	Late PEG group (> 7 d)	Analysis value (*P*)
30-d mortality (Number of events)	3	5	1.00[1]
Peri-procedural complications (number of events)	3	8	0.53[1]
Post-procedural complications (number of events)	20	34	0.551
Hospital length of stay (d)	12.9	22.34	**< 0.001**[2]

[1]Obtained by Fisher's exact test;
[2]Obtained by Student's *t*-test; PEG: Percutaneous endoscopic gastrostomy, Significant *P* values are in bold.

Table 4 Types of peri-procedural and post procedural complications

	Early PEG group	Late PEG group	Analysis value (*P*) Fisher's exact
Peri procedural complication			
Pulled PEG tube	0	1	1
Pulmonary edema	0	1	1
NSTEMI	0	1	1
Bleeding	0	4	0.15
Pneumonia	1	1	1
Evolving stroke/herniation	1	0	0.4
Post procedural complications			
Aspiration	8	14	0.69
Pneumonia	10	16	0.84
Bleeding	2	2	1
Buried bumper	1	0	0.4
Cardiac arrest	2	1	0.57
Death	7	8	0.59
Ileus	0	1	1
Infection	5	4	0.49
Necrotizing pancreatitis	0	1	1
Pulled PEG tube	3	9	0.36
Pulmonary embolism	0	3	0.27
Respiratory failure	1	3	0.65
Seroma	1	0	0.4
Stroke	1	2	1

PEG: Percutaneous endoscopic gastrostomy; NSTEMI: Non-ST elevation myocardial infarction, Significant *P* values are in bold.

Another limitation of our study was its retrospective design, as all health care events for a given patient may not have been captured (*i.e.*, patients presenting to an outside hospital for PEG tube related complications). Additionally, pre-procedural platelet count and antiplatelet, anticoagulant, or immunosuppressant use were not examined.

Our study did assess age, which is a risk factor for prolonged dysphagia and poorer outcomes. There was a significant age difference between the early and late PEG placement groups, with the early group trending older (74.65 *vs* 66.24). If this were to affect results, it should have favored the late placement group. However, this study did not evaluate other identified risk factors for prolonged dysphagia and therefore need for enteral feeding, including National Institutes of Health Stroke Scale (NIHSS), presence of a bilateral infarction, pre-procedural clinical signs of aspiration, or stroke location in the frontal operculum or insular cortex[15]. These risk factors would have been assessed by the neurology

Table 5 Predictors of mortality: Multivariate logistic regression analysis

	Death in 30 d, OR [95%CI]	Death in 90 d, OR [95%CI]	Peri-procedural complication, OR [95%CI]	Post-procedural complications, OR [95%CI]
Protein calorie malnutrition (albumin ≤ 3.2)	0.757 [0.179-3.21]	0.854 [0.289-2.527]	1.31 [0.37-4.7]	1.07 [0.54-2.11]
Documented SIRS criteria or infection pre-procedure	0.524 [0.06-4.52]	0.56 [0.12-2.67]	1.55 [0.38-6.28]	1.92 [0.85-4.35]
Presence of cardiovascular risk equivalent independent of this stroke	0.24 [0.05-1.24]	0.35 [0.11-1.09]	0.65 [0.19-2.23]	1.63 [0.82-3.24]

SIRS: Systemic inflammatory response syndrome; OR: Odds ratio; PEG: Percutaneous endoscopic gastrostomy, Significant *P* values are in bold.

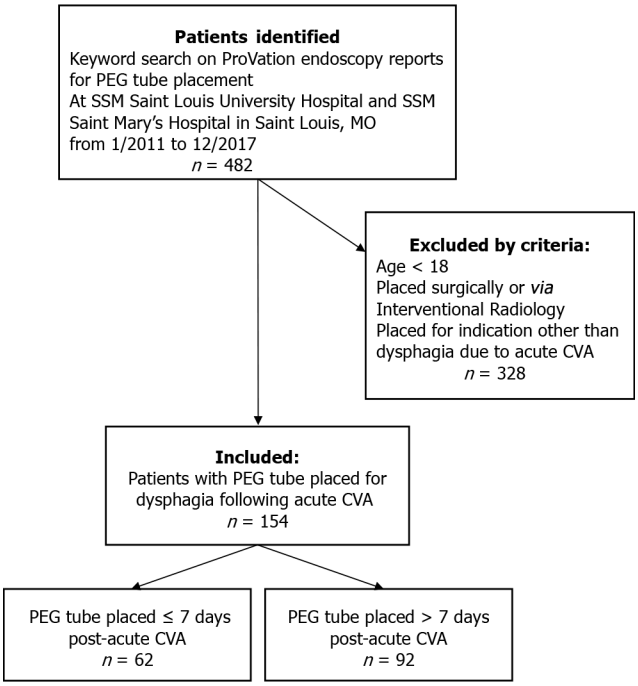

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Figure 1 Assembly of study cohort based on exclusion and inclusion criteria and manual chart review. PEG: Percutaneous endoscopic gastrostomy; SSM: Sisters of Saint Mary's; CVA: Cerebrovascular accident.

service who evaluated the stroke patients prior to consulting the gastroenterology service for gastrostomy tube placement. Unassessed differences in these risk factors for persistent dysphagia could contribute to differences in our study populations' outcomes.

A study published in Annals of Gastroenterology identified low albumin and positive urine cultures as predictors of mortality in patients who underwent PEG placement[16]. Other studies have found that patients with abnormal leukocyte counts were four times more likely to experience early and late complications[17] and that 30-d mortality was significantly higher in patients with a platelet count < 100000/μL[18]. Although our study did see an increase in peri-procedural complications in patients with protein-calorie malnutrition and pre-procedural SIRS or infection; as well as an increase in post-procedural complications in patients with protein-calorie malnutrition, pre-procedural SIRS or infection, or pre-existing cardiovascular risk equivalents, the findings were not statistically significant. The observed differences may have reached statistical significance with a larger population size.

Overall, our outcomes are comparable to those seen in the FOOD trial, which showed around a 40% incidence of any adverse outcome (*e.g.*, pulmonary embolism, infection, *etc.*) over an 8 month follow up period, a 10% mortality rate for non-malnourished patients at 3 mo, and nearly a 30% mortality rate for malnourished patients.

In conclusion, our study shows that early PEG tube placement, less than 7 d following an acute stroke, was not associated with increased mortality or complications when compared to delayed PEG placement. Although not statistically significant, there were fewer deaths and complications in patients undergoing early PEG tube placement. While the risk factors studied showed no statistically significant difference in complication rates or mortality, a large-scale study may favor delayed PEG tube placement

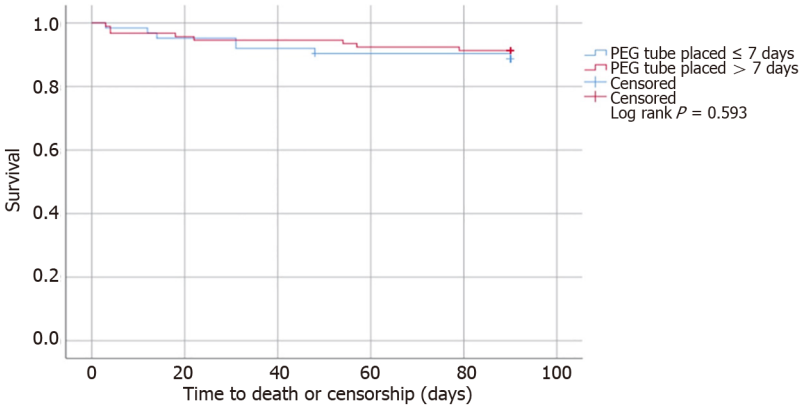

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Figure 2 Kaplan Meier Curve showing time to event (death) analysis in early versus late percutaneous endoscopic gastrostomy tube placement groups.

in patients with significant protein-calorie malnutrition, concurrent SIRS, or infection. As expected, hospital length of stay was significantly reduced in patients with early PEG tube placement. Given similar safety outcomes in both groups, early PEG tube placement should be considered in appropriate candidates. Prospective studies and cost analyses are warranted.

CONCLUSION

In conclusion, our study shows that early PEG tube placement, within 7 d of an acute stroke, was not associated with increased mortality or complications when compared to delayed PEG placement. Although not statistically significant, there were fewer deaths and complications in patients undergoing early PEG tube placement. While the risk factors studied showed no statistically significant difference in complication rates or mortality, a large-scale study may favor delayed PEG tube placement in patients with significant protein-calorie malnutrition, concurrent SIRS, or infection. As expected, hospital length of stay was significantly reduced in patients with early PEG tube placement. Given similar safety outcomes in both groups, early PEG tube placement should be considered in appropriate candidates. Prospective studies and cost analyses are warranted.

ARTICLE HIGHLIGHTS

Research background

Stroke patients commonly require enteral nutrition for dysphagia. Percutaneous endoscopic gastrostomy (PEG) tubes and nasogastric tubes are options for enteral feeding, but the optimal timing determining when PEG tubes should be placed is uncertain. The 2011 ASGE guidelines recommend waiting 2 wk for assessment of resolution of dysphagia prior to placing a PEG tube, but the recommendation is based on low quality evidence.

Research motivation

There is a demand for earlier placement of PEG tubes to facilitate earlier patient discharge to intensive rehab for neurologic recovery. An observational study using the Nationwide Patient Survey data found no difference in inpatient mortality or complication rates following early (within 7 d) PEG placement compared to delayed PEG placement after 7 d. This study was based on hospital data and could not provide longer term post-hospitalization outcomes or mortality. Further studies looking at the safety of early PEG placement are warranted.

Research objectives

This study aims to evaluate the safety of early (within 7 d) *vs* delayed (after 7 d) placement of PEG tubes in patients for dysphagia after acute stroke. Primary objectives were evaluation of 30- and 90-d mortality and rates of peri- and post-procedural complication. Secondary objectives included identification of predictors of morbidity and mortality in multivariate analysis.

Research methods

This bi-center, retrospective chart review identified 482 patients undergoing PEG placement based on endoscopy reports. After excluding patients with age < 18, PEG placed by surgery or interventional radiology, and indications other than dysphagia from acute stroke, 154 patients were identified for review, including 62 PEGs placed within 7 d of stroke and 92 placed after 7 d. Retrospective data was collected, and outcomes evaluated included rate of peri-procedural complications, rate of post-procedural complications, and 90-d all-cause mortality. Demographics and predictors of morbidity and mortality were also collected and evaluated in multivariate logistic regression.

Research results

Demographics and comorbidities were similar between groups, except for age (early 74.7 *vs* delayed 66.2 years, $P = 0.0005$). There was no statistically significant difference in peri- or post-procedural complication rate or mortality between groups. None of the proposed risk factors studies significantly impacted 30- or 90-d mortality, although protein-calorie malnutrition and presence of infection or SIRS criteria were non-significantly associated with an increase in complication rate. Finally, hospital length of stay was significantly lower in patients undergoing PEG tube placement (12.9 *vs* 22.3 d, $P < 0.001$).

Research conclusions

Early PEG placement was not associated with an increase in mortality or complications compared to delayed PEG placement in this retrospective chart review. This suggests early PEG placement is safe.

Research perspectives

Further prospective study to evaluate the safety of early PEG placement and reconsideration of the 2-wk delay in PEG placement is warranted.

FOOTNOTES

Author contributions: Reddy KM and Taylor J contributed equally to this work and wrote the paper, collected data, and designed the research; Westrich DJ also contributed to data gathering, writing portions of the paper and critically revised the paper; Lee P and Gor PJ collected data and contributed to revisions of the manuscript; Cheesman A contributed to revisions of the manuscript; Al-Hammadi N performed all statistical analysis.

Institutional review board statement: The study was reviewed and approved by the Saint Louis University Institutional Review Board (Approval No. 29062).

Informed consent statement: Informed consent was waived by the Saint Louis University Institutional Review Board for this retrospective chart review.

Conflict-of-interest statement: None of the authors have any conflicts of interest.

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