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Original Article

Hypertonic dextrose spray as topical endoscopic hemostasis for non-variceal upper gastrointestinal bleeding

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A B S T R A C T

Background: Endoscopic hemostasis is the primary therapeutic method for gastrointestinal bleeding. Hemoclips and thermocoagulation are the most commonly used methods of endoscopic hemostasis to control non-variceal upper gastrointestinal bleeding (NVUGIB). Recent findings have proven that hypertonic saline has the ability to act as a topical hemostatic agent in gastrointestinal bleeding and has the advantages of being inexpensive and readily available. This study aimed to compare the efficacy of hypertonic dextrose solution spray as an endoscopic hemostasis method for NVUGIB to that of standard therapy (hemoclips and thermocoagulation).
Methods: This experimental prospective study included patients with NVUGIB in Cipto Mangunkusumo National Central General Hospital between February 2020 and December 2021. There were 32 patients each in the control and intervention groups. Patients in the control group were treated with epinephrine only or with hemoclips/thermocoagulation, while the intervention group received hypertonic dextrose solution (40%) spray with or without epinephrine as an endoscopic hemostatic method.
Results: In the 64 patients with NVUGIB, peptic ulcers were the most common cause of bleeding (39.2%). The Rockall scores varied greatly from 0–6, with the most frequent Rockall score being 2 (31.3%). Nearly half of patients (43.8%) had Forrest IB bleeding. Initial hemostasis was successful in 100% of the control group and 96.9% of the intervention group. There were no complications after endoscopic hemostasis in both groups. The occurrence of re-bleeding was the same in both groups (25.0%). Eleven patients (17.2%) died during the study period. No significant differences were found in the success rate of initial hemostasis and the re-bleeding rate of NVUGIB between the control and intervention groups.
Conclusion: This study showed that hypertonic dextrose solution (40%) spray had a hemostatic effect. Hence, we recommend hypertonic dextrose solution spray as an alternative to endoscopic hemostasis for NVUGIB.

Keywords: Hemostasis, endoscopic; Hypertonic dextrose solution; Non-variceal upper gastrointestinal bleeding

Introduction

Despite recent advances in treatment, non-variceal upper gastrointestinal bleeding (NVUGIB), which is a medical emergency in gastroenterology, remains a problem with an annual incidence of about 90 to 108 per 100,000 and a mortality rate ranging from 3% to 14%.[1] Patients with NVUGIB often come to the emergency room with hematemesis, melena, or hematochezia.[1,2] The most common cause of NVUGIB is peptic ulceration, which refers to a disruption of the mucosal barrier that results in exposure of the submucosal layer to acid and pepsin present in the gastroduodenal lumen.[3] *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drug (NSAID) use may cause peptic ulceration. Other possible causes of NVUGIB are gastroduodenal erosion, esophageal-peptic and vascular lesions, vascular ectasia, Mallory-Weiss tears, and neoplasms.[4,5] Endoscopy remains the first-line modality to diagnose and treat NVUGIB, and it should be done within 24 hours.[1,6] Previous studies have shown that urgent endoscopy within < 12 hours reduced the risk of mortality and surgical intervention, with an overall success rate of 85% to 95%.[6–8]

Endoscopic hemostasis is the main therapeutic method in gastrointestinal bleeding. Several methods of endoscopic hemo-

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stasis have been used in daily practice, such as injections of epinephrine, sclerosing agents, thermal devices (unipolar and bipolar electrocoagulation and argon plasma coagulation), mechanical devices (clipping and ligation), and topical hemostatic agents.[9,10] Epinephrine can be used as the primary hemostatic agent or in combination with other hemostasis methods.[11] The usage of epinephrine combined with clips or thermal therapy has shown better outcomes than the injection of epinephrine alone. However, no significant difference was found between monotherapy with clips and thermal therapy.[11] A multicenter study reported a 92.4% hemostasis rate of over-the-scope clip use as monotherapy in treating NVUGIB.[12] Thermal therapy using argon plasma coagulation and heater probe coagulation showed initial hemostasis rates of 97.7% and 81%, respectively, in ulcer bleeding.[13] Some of these methods have limitations since they may be difficult to apply in some cases and require expertise.[14] The usage of Hemospray, a topical hemostatic agent, had success rates of 89.5% for acute hemostasis and 89% at 72 hours after the initial hemostasis procedure.[8] Another topical hemostatic agent, polysaccharide hemostatic powder (known as EndoClot) showed no significant difference in effectiveness compared to conventional endoscopic therapy when used as monotherapy or combined with conventional hemostatic methods.[14]

In recent years, hypertonic dextrose spray has been successfully used as a topical hemostatic agent in other types of gastrointestinal bleeding (radiation enteritis, colorectal anastomosis bleeding, and diversion pouchitis). It has been proposed that hypertonic dextrose solution could establish hemostasis through osmotic dehydration.[15–18] This study aimed to compare the efficacy of hypertonic dextrose solution spray as an endoscopic hemostasis method for NVUGIB to standard therapy (hemoclips and thermocoagulation). Hypertonic dextrose should be considered as an alternative hemostatic topical agent for NVUGIB, since it is affordable and quite abundant at health facilities.

Methods

The study protocol was approved by the Ethics Committee of Faculty of Medicine, University of Indonesia (IRB No. 20-02-0130). This prospective experimental study was conducted at Cipto Mangunkusumo National Central General Hospital from February 2020 to December 2021. Between February 2020 and December 2021, there were 135 patients who presented to the hospital with suspected upper gastrointestinal bleeding and underwent endoscopy within 24 hours. Patients with variceal bleeding were excluded. The sample calculation in this study used a population proportion hypothesis test (two-tailed test) for a prospective experimental study. Sixty-six patients with NVUGIB were included, and cluster randomization was carried out (Fig. 1). After randomization, two patients dropped out due to deteriorating conditions. The inclusion criteria were age above 18-year-old, NVUGIB confirmed through an examination with esophagogastroduodenoscopy, and resuscitation until hemodynamic stability prior to treatment. Patients with blood clotting disorders (platelet level < 50.000 µL, prolongation of bleeding and clotting time) and those who declined to participate in this study were excluded.

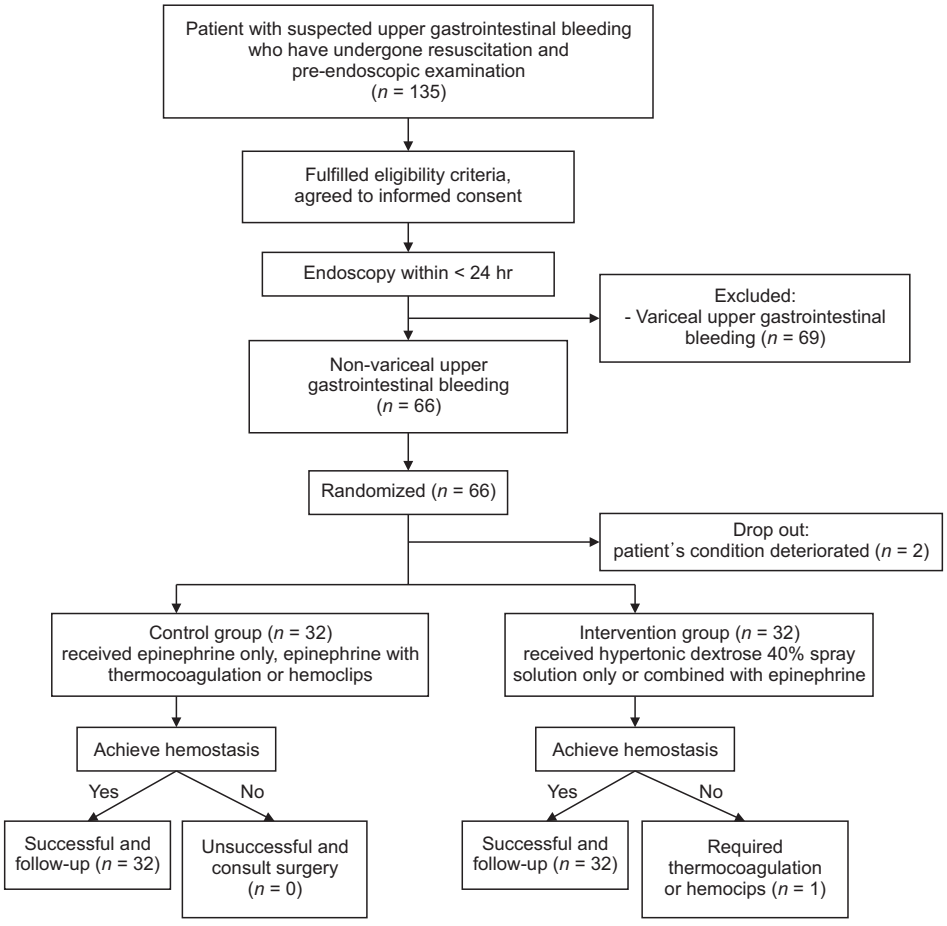

Fig. 1. Flowchart of study.

Written informed consent was obtained from all patients. Eligible patients were divided into the control and intervention groups. In total, 64 patients with NVUGIB received initial proton pump inhibitor (PPI) therapy (40 mg intravenous 2 times a day or an 8-mg/h PPI drip). The control group consisted of 32 NVUGIB patients treated with epinephrine only or epinephrine combined with clipping/thermocoagulation. The intervention group consisted of 32 NVUGIB patients treated with 100 mL of a hypertonic dextrose solution (40%) spray with or without epinephrine (Fig. 2). The amount of epinephrine used in the lesions was 3 mL of 1 : 10,000 epinephrine, and we used hypertonic dextrose solution (40%) in this study because it is commercially available at our hospital and in Indonesia more generally.

If the bleeding stopped for more than 5 minutes after treatment, initial hemostasis was considered successful. Follow-up was done 7 days after treatment to observe re-bleeding and mortality. Re-bleeding was defined as the presence of hematochezia or melena, hemodynamic instability, or a decrease in hemoglobin > 1 g/dL.

Statistical analysis was performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The chi-squared test was used to compare outcomes of endoscopic hemostasis between the two groups. The threshold for statistical significance was at $P < 0.05$.

Results

Table 1 shows patients' demographic characteristics. The median age was 55.5 years, and male patients predominated (70.3%). The majority of patients (65.6%) had minor comorbidities. Previous anticoagulant and NSAID consumption was recorded. A history of anticoagulant consumption was found in 4.7% of patients, while NSAID use was significantly more common in the control group than in the intervention group (12.5% vs. 0%; $P = 0.033$). Hemorrhagic shock occurred in 43.8% of patients. A hemoglobin level < 7 g/dL was found in 29.7% of patients. The Rockall scores ranged from 0 to 6 points, with the most common score being 2 (31.3%).

As shown in Table 2, the etiology of NVUGIB varied greatly, encompassing erosive gastritis, esophageal ulcer, gastric ulcer, duodenal ulceration, bleeding due to a neoplasm, and bleeding due to sphincterotomy and ampullectomy. The most common cause of bleeding was peptic ulcers (39.2%), which included esophageal, gastric, and duodenal ulcers, followed by neoplasms (34.3%), and sphincterotomy (20.3%).

According to the Forrest classification (Table 3), out of 64 NVUGIB patients who underwent endoscopic hemostasis, the most common lesion categorization was Forrest IB (46.9% in the control group and 40.6% in the intervention group), followed by Forrest IIB (25.0% in the control group and 28.1% in the intervention group), Forrest IIA (21.9% in the control group and 28.1% in

Table 1 Demographic Characteristics of NVUGIB Patients

Characteristic	Control (n = 32)	Intervention (n = 32)	Total (n = 64)	P-value
Age				0.056
Mean (SD)			53.4 (14.3)	
Median			55.5	
<40	7 (21.9)	6 (18.8)	13 (20.3)	
40–<60	9 (28.1)	18 (56.3)	27 (42.2)	
60–<80	16 (50.0)	8 (25.0)	24 (37.5)	
Sex				0.412
Male	21 (65.6)	24 (75.0)	45 (70.3)	
Female	11 (34.4)	8 (25.0)	19 (29.7)	
Comorbidities†				0.095
No comorbidities	3 (9.4)	1 (3.1)	4 (6.3)	
Minor	23 (71.9)	19 (59.4)	42 (65.6)	
Major	6 (18.8)	12 (37.5)	18 (28.1)	
Anticoagulant use				0.516
(–)	30 (93.8)	31 (96.9)	61 (95.3)	
(+)	2 (6.3)	1 (3.1)	3 (4.7)	
NSAID use				0.033*
(–)	28 (87.5)	32 (100.0)	60 (93.8)	
(+)	4 (12.5)	0 (0.0)	4 (6.2)	
Hemorrhagic shock				0.076
(–)	22 (68.8)	14 (43.8)	36 (56.2)	
(+)	10 (31.3)	18 (56.3)	28 (43.8)	
Hemoglobin pre-hemostasis				0.633
< 7 g/dL	10 (31.3)	9 (28.1)	19 (29.7)	
≥ 7 g/dL	22 (68.8)	23 (71.9)	45 (70.3)	
Rockall score				0.312
0	2 (6.3)	1 (3.1)	3 (4.7)	
1	0 (0.0)	0 (0.0)	0 (0.0)	
2	11 (34.4)	9 (28.6)	20 (31.3)	
3	9 (28.1)	5 (15.6)	14 (21.9)	
4	3 (9.4)	6 (18.8)	9 (14.1)	
5	6 (18.8)	10 (31.3)	16 (25.0)	
6	1 (3.1)	1 (3.1)	2 (3.1)	

Values are presented as number (%).
NVUGIB, non-variceal upper gastrointestinal tract bleeding; SD, standard deviation; NSAID, nonsteroidal anti-inflammatory drug.
*Statistically significant ($P < 0.05$).
†Major comorbidities included renal failure, liver malignancy, and disseminated malignancy. Minor comorbidities includes hypertension, diabetes mellitus, gastrointestinal and non-gastrointestinal neoplasms, and pancreato-biliary disorders.

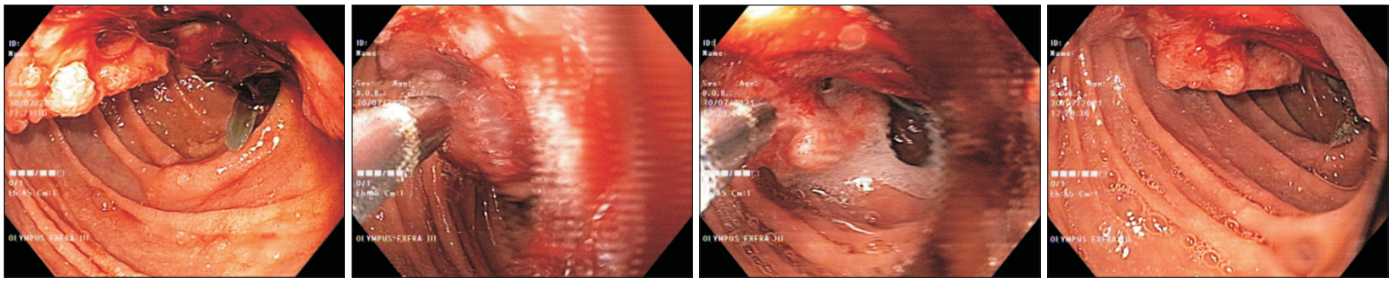

Fig. 2. Bleeding caused by an ampullary mass treated with hypertonic 40% dextrose spray.

Table 2 Etiologies of Non-Variceal Upper Gastrointestinal Bleeding (NVUGIB)

Etiology	Control (n = 32)	Intervention (n = 32)	Total (n = 64)
Erosive gastritis	2 (6.3)	1 (3.1)	3 (4.7)
Esophageal ulcer	1 (3.1)	0 (0.0)	1 (1.6)
Gastric ulcer	1 (3.1)	4 (12.5)	5 (7.8)
Duodenal ulcer	12 (37.5)	7 (21.9)	19 (29.7)
Neoplasm bleeding	8 (25.0)	14 (43.8)	22 (34.4)
Post-sphinterectomy bleeding	7 (21.9)	6 (18.8)	13 (20.3)
Post-ampulectomy bleeding	1 (3.1)	0 (0.0)	1 (1.6)

Values are presented as number (%).
P-value = 0.306.

Table 3 Forrest Classification of Non-Variceal Upper Gastrointestinal Bleeding

Forrest classification	Control (n = 32)	Intervention (n = 32)	Total (n = 64)
IA	2 (6.3)	1 (3.1)	3 (4.7)
IB	15 (46.9)	13 (40.6)	28 (43.8)
IIA	7 (21.9)	9 (28.1)	16 (25.0)
IIB	8 (25.0)	9 (28.1)	17 (26.6)
IIC	0 (0.0)	0 (0.0)	0 (0.0)
III	0 (0.0)	0 (0.0)	0 (0.0)

Values are presented as number (%).
P-value = 0.835.

the intervention group and Forrest IA (6.3% in the control group and 3.1% in the intervention group). In both groups there were no lesions belonging to the low-risk categories of Forrest IIC and III. No significant difference was found between the control and intervention groups in the Forrest classification (P = 0.835).

In the control group, four patients (12.5%) were treated with epinephrine alone, while 14 patients (43.8%) received epinephrine combined with hemoclips and 14 patients (43.8%) received epinephrine combined with thermocoagulation. In the intervention group, 14 patients (43.8%) were given 40% dextrose spray only and 18 patients (56.3%) were given 40% dextrose spray combined with epinephrine (Table 4).

Successful initial endoscopic hemostasis was achieved in 100% of patients in the control group and 96.9% of the intervention group. Hemostasis using 40% dextrose solution combined with epinephrine failed in one patient, who then underwent thermocoagulation to achieve hemostasis. There were no complications in either the control or intervention group. Both the control and intervention groups had the same number of re-bleeding cases (25.0% in each). Mortality occurred in 21.9% of the intervention group and 12.5% of the control group (Table 5). No statistically significant difference was found between the control and intervention groups in the success rate of initial hemostasis or the re-bleeding rate (P = 0.313 and > 0.999, respectively).

Discussion

The most common age group in patients enrolled in this study was 40 to 60 years, followed by > 60 years. The higher risk of NVUGIB in older age groups is related to higher exposure to drugs such as NSAIDs and aspirin. These drugs increase the risk of ulcers and bleeding since they cause gastric erosion and inhibition

Table 4 Hemostatic Agents Used for Non-Variceal Upper Gastrointestinal Bleeding

Hemostatic agent	Control (n = 32)	Intervention (n = 32)
Dextrose 40%	0 (0.0)	14 (43.8)
Dextrose 40% + epinephrine	0 (0.0)	18 (56.3)
Epinephrine	4 (12.5)	0 (0.0)
Epinephrine + hemoclips	14 (43.8)	0 (0.0)
Epinephrine + thermocoagulation	14 (43.8)	0 (0.0)

Values are presented as number (%).
P-value < 0.001.

Table 5 Post-Hemostatic Characteristics of NVUGIB Patients

	Control (n = 32)	Intervention (n = 32)	Total (n = 64)	P-value
Successful initial hemostasis				0.313
Yes	32 (100.0)	31 (96.9)	63 (98.4)	
No	0 (0.0)	1 (3.1)	1 (1.6)	
Complications				< 0.001
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
No	32 (100.0)	32 (100.0)	64 (100.0)	
Re-bleeding				> 0.999
Yes	8 (25.0)	8 (25.0)	16 (25.0)	
No	24 (75.0)	24 (75.0)	48 (75.0)	
Mortality				0.320
Yes	4 (12.5)	7 (21.9)	11 (17.2)	
No	28 (87.5)	25 (78.1)	53 (82.8)	

Values are presented as number (%).
NVUGIB, non-variceal upper gastrointestinal tract bleeding.

of platelet aggregation.[19] The observed male predominance was similar to what has been observed in some previous studies.[19–21] A possible explanation is gender-related differences in lifestyle, since cigarette smoking and alcohol consumption are more common in men.[22] Both major and minor comorbidities were found in this study. In cases of NVUGIB, assessing comorbidities is useful to predict patients' outcomes, since patients with coexisting comorbidities exhibit higher mortality rates after NVUGIB.[23]

Anticoagulant and long-term NSAID consumption are risk factors related to NVUGIB. NSAIDs and anticoagulants induce damage to the gastroduodenal mucosa through both local and systemic mechanisms.[19,24] NSAIDs and anticoagulants reduce the hydrophobicity of the mucous layer, causing the underlying epithelium to be more exposed to luminal acid and pepsin and prone to mucosal disruption.[24] However, prior histories of anticoagulant and long-term NSAID consumption were found in only a few patients in this study (4.7% and 6.2%, respectively). Other well-known risk factors, such as *H. pylori* infection, alcohol consumption, cigarette smoking, and consumption of herbal drinks (which commonly contain NSAIDs), were not recorded in this study.

Hemorrhagic shock due to bleeding was documented in 43.8% of patients. NVUGIB patients with shock were resuscitated adequately before endoscopy. Aside from resuscitation, NVUGIB patients were also treated with a PPI, tranexamic acid, vitamin K, and sucralfate acid to stop ongoing bleeding. Patients underwent endoscopy after they were considered to have reached a hemo-

dynamically stable condition. Therefore, it was more common to find non-active bleeding ulcers (healing ulcers). The higher proportion of patients with hemoglobin levels ≥ 7 g/dL was also related to the stabilization process done before the intervention. Ensuring patients are in a stable condition before endoscopy is important, since hemodynamic instability leads to worse outcomes.[25]

The initial Rockall score was calculated to predict the re-bleeding and mortality rate in patients with upper gastrointestinal bleeding. The Rockall score combines clinical parameters such as patient's age, the occurrence of shock (based on heart rate and blood pressure measurements), comorbidities, diagnosis, and endoscopic findings.[26,27] In this study, the most common Rockall score was 2 (31.3% of patients), without a significant difference between the control and intervention groups (P = 0.312). This finding is consistent with a study conducted by Bozkurt et al,[26] where the most common Rockall score was also 2 (22.9% of patients).

Peptic ulcer bleeding was the most common cause of NVUGIB (39.2%) in this study, followed by neoplasms (34.4%). In recent years, NVUGIB caused by neoplasms has become more frequent, whereas cases of NVUGIB related to peptic ulcer bleeding have decreased. These changes are related to a decreasing prevalence of *H. pylori* infection and an increase in the consumption of gastric acid-suppressing drugs.[2,28]

The administration of a 40% dextrose spray resulted in successful hemostasis in 31 of 32 patients (96.9%). These results are consistent with a previous study conducted by Katsinelos et al,[15] in which hemostasis was achieved by administering a 50% dextrose spray combined with epinephrine in 41 of 44 patients (93.18%). These dextrose sprays with different concentrations of dextrose could both provide successful hemostasis. This study also showed that providing the 40% dextrose spray alone (i.e., not combined with epinephrine) gave good results, achieving hemostasis in 14 patients (100% of the patients who received the dextrose spray alone).

In the control group, 43.8% of patients each used epinephrine combined with hemoclips or thermocoagulation, while epinephrine alone was used to achieve hemostasis in the remaining 12.5%. All three methods were successful. This is in accordance with a previous study conducted by Karaman et al,[13] which found that the use of epinephrine combined with thermocoagulation achieved 97.7% success in treating acute upper gastrointestinal bleeding caused by gastric or duodenal ulcers. In addition, the results for using epinephrine combined with hemoclips are also in line with a study conducted by Mangiafico et al,[29] which achieved hemostasis in 93% of patients.

No significant difference was found between the control and intervention groups in the success rate of initial hemostasis (100% in control group and 96.9% in intervention group; P = 0.313). The re-bleeding rate in the control and intervention groups also showed no significant difference (P > 0.999). Re-bleeding occurred in 8 patients (25.0%) in both the control and intervention groups.

The mortality rate in this study was 17.2%. Based on previous studies, the mortality rate could be influenced by delays in performing endoscopy (i.e., > 24 hours), the presence of comorbidities, and the presence of lesions that are classified as high risk for peptic ulcer bleeding (Forrest Ia-IIb).[30]

Several theories on how hypertonic dextrose acts as a hemostatic agent have been proposed. Hypertonic dextrose causes osmotic dehydration, which then induces mural necrosis of blood vessels, resulting in their obliteration, as well as inflammation and fibrosis in the perivascular space. Aside from controlling bleeding, this mechanism also helps the process of tissue merging, thereby promoting mucosal healing.[17] Another mechanism proposed is that high levels of glucose in a hypertonic solution might cause an increase in endothelin-1 mRNA levels. Endothelin-1 is a strong vasoconstrictor that might further enhance the hemostatic effect of hypertonic dextrose.[15]

As a commonly used hemostatic agent, epinephrine has the ability to constrict bleeding vessels and aggregate platelets, resulting in hemostasis. The effect of epinephrine lasts for 5 to 10 minutes, while the addition of hypertonic dextrose prolongs swelling and extends the effects of epinephrine.[15,31] No previous reports have described using hypertonic 40% dextrose spray as a method for endoscopic hemostasis. However, several reports have shown successful initial hemostasis with different concentrations of hypertonic dextrose spray (e.g., 50%) as an endoscopic hemostasis method for bleeding caused by colorectal anastomosis,[17] radiation enteritis,[16] and diversion pouchitis.[18]

Using a topical hemostatic agent in the form of a spray has the advantage of being able to reach lesions in difficult locations. If the ulcer is difficult to access, other endoscopic modalities that need direct and stable contact with the tissue might be difficult to use, with an increased risk of perforation.[23]

Hypertonic dextrose is considered safe, as previous studies showed it does not cause severe necrosis or bleeding.[32] However, there are some concerns regarding the possible effects of hypertonic dextrose spray, such as an increase in the blood glucose level. However, since there is no direct injection of hypertonic dextrose into the blood vessels, the risk of hyperglycemia should not be a concern. Further research is needed regarding this matter.

In conclusion, we concluded that hypertonic 40% dextrose solution spray is as effective as other commonly used endoscopic hemostatic agents (hemoclips and thermocoagulation) in treating NVUGIB. Therefore, hypertonic 40% dextrose solution spray can be used as an alternative therapy for NVUGIB, considering that it is inexpensive and readily available.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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