ORIGINAL ARTICLE

Endoscopic treatment for high-risk bleeding peptic ulcers: A randomized, controlled trial of epinephrine alone with epinephrine plus fresh frozen plasma

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Background: Acute upper gastrointestinal bleeding is a common and potentially life-threatening emergency with substantial mortality. Fresh frozen plasma (FFP), a good source of coagulation factors, might be an ideal injection agent based on its physiologic properties. Therefore, we evaluated the role of FFP as a hemostatic agent in patients with high-risk bleeding peptic ulcers. **Materials and Methods:** From August 2015 to April 2016, 108 consecutive patients with high-risk bleeding ulcers were admitted to our university hospital. They were randomly assigned to undergo injection of epinephrine alone (A) or epinephrine plus FFP (B). The primary outcomes assessed were the initial hemostasis, recurrent bleeding, hospital stay, blood transfusion, surgery rate, and 14-day mortality. **Results:** Initial hemostasis was achieved in 47 of 50 patients (94%) in the Group A and 49 of 50 patients (98%) in the Group B ($P = 0.61$). There were no significant differences in the rate of recurrent bleeding between Group A (14%) and Group B (8%) ($P = 0.52$). We found no significant differences between Group A and Group B with respect to the surgery rate, bleeding death, procedure-related death, and duration of hospitalization ($P > 0.05$). **Conclusion:** It is concluded the injection of epinephrine alone was equally effective as injection of epinephrine plus FFP to endoscopic hemostasis. Epinephrine alone and epinephrine plus FFP were not different in recurrent bleeding, rate of surgery, blood transfusion, or mortality.

Key words: Bleeding peptic ulcer, endoscopic injection, epinephrine, fresh frozen plasma

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INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is a common and potentially life-threatening emergency facing clinicians with an overall annual incidence of approximately 100 hospital admissions per 100,000 population.[1] Peptic ulcer bleeding is a common medical emergency accounting for 50%–70% of cases of acute nonvariceal UGIB and is significantly associated with morbidity, mortality, and health costs.[2] Initial hemostatic rates of 80% to 95% can be achieved with effective endoscopic therapies such as local injection, contact thermal coagulation, and hemoclips.[3] Despite remarkable advances in diagnosis and treatment of peptic ulcer bleeding, bleeding recurs in 10%–30% of patients.[3] Therefore, recurrence of bleeding after initial endoscopic hemostasis has been described as the single most adverse independent prognostic factor for this group of patients. Endoscopic hemostasis including mechanical, thermal, and by injection of various agents, whether epinephrine, distilled water, cyanoacrylate, ethanol, or polidocanol, has been found to decrease the risk of rebleeding, need for surgery, and the mortality.[4] Although vigorous efforts have been made to delineate the ideal endoscopic method for achieving hemostasis, there is still a great deal of uncertainty about a highly effective and simple hemostatic technique to reduce the risk of rebleeding in patients with nonvariceal UGIB. Endoscopic injection of dilute epinephrine is considered a highly effective

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and popular endoscopic scheme for UGIB, owing to its low cost, wide availability, lack of severe local or systemic injury, and easy to administer. However, epinephrine injection may induce cardiovascular complications and mild histologic changes such as hematoma and perforation.[5] Because mechanical and chemical effects of epinephrine are short-lived, the addition of a second agent, such as polidocanol or ethanol, may be beneficial for preventing recurrent bleeding by prolonging hemostatic mechanisms of epinephrine.

Therefore, wide variation in the rate of rebleeding can be explained by difference in the mechanisms of the action of the injected agents and differences in injection volume. However, clinical trials in patients with bleeding ulcers disclosed that no single solution is superior to another for hemostasis.[6] Furthermore, results from several studies have revealed that injection of normal saline solution or distilled water has a primary role in hemostasis similar to those of epinephrine in the endoscopic therapy of patients with bleeding ulcers.[6,7] In this regard, there has been no clinical study that evaluates the effects of fresh frozen plasma (FFP) in the endoscopic therapy of patients with UGIB. FFP, the most commonly prescribed hemostatic agent, is prepared either from a single whole blood donation or obtained by apheresis, frozen within a specific period and stored at a proper temperature up to 1 year that will maintain all of the coagulation factors, electrolytes, and plasma proteins.[8] It has been shown that FFP is a good source of coagulation factors which can correct mild to moderate coagulopathy.[9] Therefore, if the injection of FFP has similar effects epinephrine, it might be an alternative solution for the treatment of patients with bleeding ulcers because of its low cost, wide availability, rapidity, ease of application, and lack of severe complication. This study was designed to shed light on the possible role of FFP as a hemostatic agent in patients with high-risk bleeding peptic ulcers.

MATERIALS AND METHODS

A prospective, randomized, single-blind, parallel group trial was conducted at Al-Zahra Hospital from August 23, 2015, to April 21, 2016. The Ethics Committee of Isfahan University of Medical Sciences investigates and approves this study. All cases were informed about the procedure of the survey and written informed consent was obtained from all them. All patients with hematemesis, melena, or hematochezia underwent for emergency endoscopy within 24 h of admission. Only men and women over 18 years of age with ulcers indicative of a high-risk for spontaneous recurrent bleeding including bleeding visible vessel (spurting or oozing), adherent clot, and nonbleeding visible vessel were selected.

Patients were excluded from the study if they had another possible bleeding site or an acute significant illness, were pregnant, had a severe bleeding tendency, and unable, or unwilling to give written consent. After an explanation of the nature of the study and patient consultation with their gastroenterologist, informed written consents were attained from all patients. The Ethical Institutional Committee of Isfahan University of Medical Sciences approved the protocol of study. Overall, a total of 100 patients with high-risk bleeding peptic ulcers were enrolled in the study, and completed interventions without interruption. The determination of sample size was done using the Krejcie and Morgan's table. Nonprobability consecutive sampling method was used. After the enrollment, all patients were randomly divided into one of the two groups using random allocation method.

Randomization was performed using a computer-generated randomization list and sealed envelopes. Patients were stratified according to their Forrest classification and then randomized 1:1 into two intervention groups: Group A who received injection of epinephrine diluted 1:20,000 in saline solution alone in volumes of 8 mL aliquots by multiple punctures into and around the bleeding point and Group B who received injection of epinephrine diluted 1:20,000 in saline solution plus thawed FFP in volumes of 8 mL around the ulcer base and beneath the bleeding source. During the period of endoscopic treatment, electrocardiographic monitoring was used to detect arrhythmias or ischemia. Before injection, endoscopic biopsy specimens from the gastric antrum and one from the gastric body were obtained for a rapid urease test for *Helicobacter pylori*.

In our study, initial hemostasis was defined as endoscopically verified cessation of hemorrhage for at least 5 min after the first endoscopic treatment and maximal water irrigation for 10 s. Recurrent bleeding was suspected clinically as one or more signs of ongoing or new bleeding, including vomiting of fresh blood, melena or bloody stool, instability of vital signs or hemodynamic, and a reduction of hemoglobin concentration by more than 20 g/L within 24 h after initial hemostasis.

Patients with rebleeding were confirmed by endoscopy immediately and retreated with endoscopic treatments such as epinephrine injection plus argon plasma coagulation (APC), transcatheter arterial embolization, and emergent surgery. After endoscopy treatment, all patients were closely monitored in an Intensive Care Unit until the first follow-up and blood transfusion was given to maintain the hemoglobin level at >10 g/L. The outcomes assessed in the study were the in-hospital recurrent bleeding, duration of hospitalization, surgery, and 30-day mortality.

Analysis of the current study was performed using the SPSS for hardware (version 20.0; SPSS, Chicago, IL, USA). Statistical analysis of endpoints was performed based on intention-to-treat principle. Therefore, all tests were appropriated with category and type of respective variables. *T*-test, Chi-square, and tests were applied to ensure homogeneity between the two groups in terms of age and gender. Results of endpoints parameter at baseline and 24 h after treatment were compared between the two groups using paired Student's *t*-tests. For quantitative data, results of the analysis were summarized by mean ± standard deviation or number (percent). All tests were two-tailed, and $P < 0.05$ was considered as a significant.

RESULTS

A total of 108 patients with UGIB were recruited during the study period. Of these, eight patients were excluded due to endoscopically uncontrollable bleeding, gastric malignancy, and multiple sites of bleeding at endoscopy. The two treatment groups well matched for demographic and clinical characteristics including age, gender, NSAID ingestion, comorbid disease, positive *H. pylori*, hemodynamic status at entrance, bleeding stigma, ulcer size, and transfusion requirements during the first 24 h [Table 1]. There were one hundred patients who were included in the study, fifty in each group. Other clinical and endoscopic data for the patients at study entry are summarized in Table 1. Initial hemostasis was achieved in 47 of 50 patients (94%) in the Group A and 49 of 50 patients (98%) in the Group B.

We found no statistically significant differences in the rate of initial hemostasis between Group A and Group B ($P = 0.61$). There were no significant differences in the rate of recurrent bleeding between Group A (14%) and Group B (8%) ($P = 0.52$). Seven patients in Group A had recurrent bleeding but were controlled in three patients with additional APC, and in three by surgical intervention. Recurrent bleeding was also controlled in three patients of Group B. Recurrent bleeding was controlled in one patient by APC, and in two patients by surgical intervention. The endoscopic findings indicated that duodenal ulcer was the source of bleeding in 54 patients. Gastric ulcer was the source of bleeding in 46 patients with UGIB. There were no significant differences between two groups in terms of ulcer type, ulcer size, volume of epinephrine used during endoscopic hemostasis, and Forrest class. Major complications from endoscopic treatment including severe abdominal pain following hemostasis, perforation, and endoscopic therapy induced bleeding were observed more frequently in the Group B than in the Group A and the differences were not statistically significant. We did not find procedure-related cardiovascular or respiratory complication such as cardiac arrhythmia, considerable change in oxygen saturation, significant changes in systolic pressure, and abrupt change in pulse rates after endoscopic hemostasis in Groups A and B. Furthermore, there were no significant differences between Group A and Group B with respect to the surgery rate, bleeding death, procedure related death, and duration of hospitalization [Table 2].

Table 1: Clinical and endoscopic characteristics of the patients at study entry

	Epinephrine	Epinephrine + fresh frozen plasma	*P*
Age, year (SD)	61.42±18.27	61.22±18.51	0.88
Gender, male/female	43/7	41/9	0.78
Location of ulcer (%)			
Stomach	24 (48)	22 (44)	0.84
Duodenum	26 (52)	28 (56)	
Bleeding stigma (%)			
Spurting vessel	3 (6)	3 (6)	0.26
Oozing vessel	2 (4)	4 (8)	
Nonbleeding visible vessel	13 (26)	23 (46)	
Adherent clot	8 (16)	6 (12)	
Flat pigmented spot	4 (8)	2 (4)	
Clean ulcer base	20 (40)	12 (24)	
Ulcer size, mm (SD)	10.95±5.61	12.70±8.56	0.45
Rockall score	4.75±1.88	4.97±1.74	0.43
Shock (%)	15 (30)	17 (34)	0.83
Comorbid diseases (%)	26 (52)	29 (58)	0.68
Helicobacter pylori infection (%)	32 (64)	27 (54)	0.80
NSAID ingestion (%)	23 (46)	31 (62)	0.16
Hemoglobin, g/dl (SD)	11.10±6.06	10.13±1.88	0.74
Platelet count (SD)	207,897.95±75,549.72	181,687.83±79,777.94	0.08

Data expressed as mean±SD and are number (%). *P* values calculated by independent sample *t*-test and Chi-square. SD=Standard deviation; NSAID=Nonsteroidal anti-inflammatory drug

Table 2: Clinical outcomes of the study groups

	Epinephrine	Epinephrine + fresh frozen plasma	*P*
Initial hemostasis (%)	47 (94)	49 (98)	0.61
Rebleeding (%)	7 (14)	4 (8)	
Spurting vessel	1 (2)	1 (2)	0.52
Oozing vessel	2 (4)	2 (4)	
Nonbleeding visible vessel	3 (6)	1 (2)	
Adherent clot	1 (2)	0	
Surgery (%)	3 (6)	2 (4)	1.00
Blood transfusion unit (SD)	3.32±1.65	3.22±1.98	0.78
Hospital stay, day (SD)	4.73±1.60	4.24±1.15	0.17
Mortality (%)	5 (10)	3 (6)	0.71

Data are *n* (%) or mean±SD. SD=Standard deviation

DISCUSSION

Bleeding peptic ulcer is a potentially life-threatening disease with a considerable mortality and morbidity. The effectiveness of endoscopic treatment for UGIB is well established; endoscopic therapy is commonly used as the first-line treatment in patients with nonvariceal upper GI, and epinephrine alone is among the most widely used injection solutions. In an effort for more effective hemostasis and to reduce the risk of rebleeding in patients with high-risk of UGIB, a number of endoscopic treatment modalities are firmly established including injection, thermal, and mechanical. Although the combination of epinephrine injection with a thermal method shows a consistent trend in favor of combined treatment, there is not yet strong evidence that any modality is superior to injection of epinephrine alone for treatment of patients with UGIB.[10]

One of the reasons might be that combined therapy is not available in all hospitals, and it is more technically demanding. It has been shown that unsatisfactory visualization of the bleeding site, unsuccessful application of epinephrine injection, and recurrent bleeding in actively bleeding ulcers may be associated with the age, gender, comorbid disease, positive *H. pylori*, hemodynamic status at entrance, ulcer size, ulcer location, and transfusion requirements during the first 24 h, which were similar between two groups in our study, indicating that the outcomes of the study are unlikely influenced by these factors. A number of agents with different mechanisms of action such as vessel compression, vasoconstriction, and platelet aggregation have been investigated. Therefore, the addition of FFP, the most commonly prescribed hemostatic agent, would be advantageous in theory. Despite the theoretical advantages of FFP, previous studies revealed no significant differences between injection of epinephrine alone or in combination with other solutions such as distilled water and normal saline solution.[6]

These conflicting results suggest that the main mechanism of hemostasis is local tamponed. Although it is difficult to sort out these inconsistent outcomes of previous studies, the difference may in part be clarified by a small number of patients, different subtype of peptic ulcer bleeding, combined with the fact that epinephrine injection is adequate in most cases with acute UGIB. These possible reasons are explained in previous meta-analyses that compared efficacy of injection of epinephrine alone with epinephrine and a second injected solution in the patients with peptic ulcer bleeding.[11,12] Meta-analysis of the recent controlled trials revealed that combined therapy seems to be more effective than epinephrine injection alone, but a particular form of treatment is not equal or superior to another. Although the absolute improvement in the outcomes of our study is relatively small, we failed to detect a significant reduction in the need for surgery, overall rate of mortality, duration of hospitalization, and rate of rebleeding. In a similar study, 140 patients with ulcers and endoscopic features indicative of a high-risk for spontaneous recurrent bleeding were assigned to endoscopic injection with epinephrine (Group A) and epinephrine plus human thrombin (Group B).[13] The results of their study are comparable to our results. They reported that endoscopic injection of epinephrine alone results in rebleeding rates of 20%, an overall mortality of 10%, and administration of 297 units of blood. The combination of endoscopic injection of epinephrine with an injection of human thrombin might be superior, resulting in rebleeding rates of 4.5%, an overall mortality of 0%, and administration of 219 units of blood. Our findings are inconsistent with the results of their study that highlighting advantages of the combination of epinephrine plus a second solution. A possible explanation for the discrepancy may lie in the fact that high-dose continuous intravenous PPIs greatly lowers the rate of rebleeding, resulting in the conflicting findings but cannot serve as a specific explanation for the failure of FFP because the dose of PPIs reported for both studies appears identical.

In another study, 415 patients with high-risk bleeding ulcers were randomized to injection of epinephrine alone or epinephrine plus ethanolamine.[14] They found no significant differences in the rate of mortality or in the proportions of the patients who required surgery. In addition, they showed a trend toward less recurrent bleeding after injection of the epinephrine plus ethanolamine. Therefore, the findings of their study suggested that adding ethanolamine to epinephrine can effectively prevent recurrent bleeding and might be some of the value in patients with peptic ulcer bleeding. However, Pescatore *et al*.[15] found that injection of epinephrine alone and epinephrine plus fibrin glue does not have comparable recurrent bleeding rates, indicating that adding fibrin glue to epinephrine is not superior to epinephrine injection alone in the treatment of high-risk bleeding peptic ulcers. Due to

increasing number of reports describing differential and conflicting results, more extensive studies in larger groups of patients should be undertaken to analyze the putative role of adding a second agent to epinephrine for injection treatment of patients with high-risk bleeding ulcers.

CONCLUSIONS

In summary, this single-center, prospective, randomized, controlled trial of patients with UGIB has shown that injection of epinephrine alone was equally effective as injection of epinephrine plus FFP to endoscopic hemostasis. Epinephrine alone and epinephrine plus FFP were not different in recurrent bleeding, surgery, blood transfusion, or mortality.

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Conflicts of interest

The authors have no conflicts of interest.

AUTHORS' CONTRIBUTION

MKH contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, agreed for all aspect of the work. MK contributed in the conception of the work, conducting the study, revising the draft, agreed for all aspects of work. ASH contributed in the conception of the work, conducting the study, agreed for all aspects of the work. VS contributed in the conception of the work, revising the draft, agreed all aspects of the work.

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