Comparison of the efficacy of two combined therapies for peptic ulcer bleeding: adrenaline injection plus haemoclipping versus adrenaline injection followed by bipolar electrocoagulation

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Abstract

Introduction: Peptic ulcer remains the most frequent cause of upper gastrointestinal bleeding. Treatment of bleeding with simultaneous combination of two endoscopic techniques has proved to be more efficient than monotherapy. None of the published comparative studies of various contact coagulation modalities have confirmed the superiority of one of these techniques over the others.

Aim: To compare the therapeutic outcomes of the use of a device enabling both injection of adrenaline solution and bipolar electrocoagulation (A + BE) to those of combined adrenaline injection with mechanical therapy (haemostatic clips) (A + HC) in the treatment of peptic ulcer bleeding.

Material and methods: Fifty-two subjects with bleeding ulcers were assigned to the A + BE group, and 55 patients were treated with A + HC.

Results: Overall, treatment failed in 20 patients (20/107, 18.7%): in 10 individuals from the A + BE group (10/52; 18.2%) and in 10 individuals from the A + HC group (10/55; 19.2%) ($p > 0.05$). Primary haemostasis was not obtained in 7 patients (6.5%): in 4 patients in the A + BE group and in 3 patients in the A + HC group ($p > 0.05$). Ten individuals (9.3%) experienced recurrent bleeding during hospitalisation: 4 patients from the A + BE group and 6 patients from the A + HC group ($p > 0.05$). Finally, in 96.3% of the patients ($n = 103$) the endoscopic treatment proved efficient with regards to obtaining haemostasis during hospitalisation. Surgical intervention was required in 4 individuals (3.7%): 2 patients in the A + BE group and 2 patients treated with A + HC ($p > 0.05$). Three patients (2.8%) – all from the A + HC group – died during hospitalisation. No significant intergroup differences were documented with regards to the mean number of transfused blood units and the mean length of hospital stay.

Conclusions: The efficacy of combined endoscopic treatment of ulcer bleeding with a probe enabling simultaneous bipolar electrocoagulation and adrenaline injection seems comparable to the widely used dual technique of adrenaline injection and haemostatic clipping.

Introduction

Gastrointestinal bleeding is one of the most frequent emergency states in gastroenterology, and it is characterised by considerable incidence and mortality. The incidence of gastrointestinal bleeding amounts to 50–150 cases per 100,000, and peptic ulcer bleeding remains the most frequent cause of upper gastrointestinal bleeding. Despite significant progress observed in recent years, related to the implementation of endoscopy and the availability of newer and more sophisticated methods of endoscopic treatment and therapy inhibiting the secretion of hydrochloric acid, the mortality still ranges between 3% and 14%. The mortality is documented mostly in individuals above 60 years of age, especially in those with other advanced comorbidities [1–8].

Several endoscopic findings have a higher risk for recurrent bleeding – the probability of bleeding recurrence in patients with actively bleeding ulcer and ulcer with visible vessel is 100% and 50%, respectively [3]. Clini-

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cal research suggests that in those patients endoscopic therapy can markedly reduce morbidity and mortality [3]. The efficacy of many methods, including injection techniques, mechanical techniques, contact coagulation (e.g. heat probe), and non-contact coagulation (e.g. argon plasma coagulation – APC), is comparable. None of the published comparative studies of various contact coagulation modalities have confirmed the superiority of any one of these techniques over the others. Recently, combining two different endoscopic techniques has been recommended. The combination of injection and mechanical or thermal technique has proved to be more efficient than injection monotherapy [3, 9–11].

Gold Probe™ is one of the methods of bipolar contact coagulation. The round distal tip of the probe and specific orientation of the electrode pair enables good contact with the tissue surface, which is reflected by effective coagulation irrespective of probe position. Additionally, by using the Injection Gold Probe™, which enables the simultaneous use of injection (adrenaline) and thermal method (bipolar electrocoagulation), replacing the probe is not required during examination, which shortens the duration of endoscopy and reduces the patient's discomfort. Therefore, adrenaline injection with bipolar electrocoagulation combined in one device seems to be a promising endoscopic method in the treatment of bleeding ulcers. The results of only a few studies involving bipolar electrocoagulation with injection of adrenaline have been published thus far; most of these studies were conducted in an experimental setting [12–15]. Moreover, no comparative studies of this modality and the most frequently applied technique, i.e. injection with the insertion of haemostatic clips, have been performed in the case of actively bleeding ulcers.

Aim

The aim of our study was to compare the therapeutic outcomes of bipolar electrocoagulation with injection of adrenaline (Injection Gold Probe) to those of combined injection of adrenaline solution and mechanical therapy with haemostatic clips in the treatment of peptic ulcer bleeding.

Material and methods

Patients

We prospectively included in the study only patients with peptic ulcer bleeding treated with adrenaline injection and bipolar electrocoagulation (Injection Gold Probe), admitted between 2008 and 2011 to the Department of Gastroenterology and Internal Medicine, Medical University of Bialystok. For comparative analysis of endoscopic treatment outcome, from all patients

hospitalised in the same period time due to upper gastrointestinal bleeding, we retrospectively matched the control group consisting of patients with peptic ulcer bleeding treated with adrenaline injection combined with haemostatic clipping. All patients (aged over 18 years) had peptic ulcer bleeding requiring endoscopic intervention (according to the Forrest scale: grade I – active bleeding – spurting or oozing; grade IIa – ulcer with visible non-bleeding vessel) [16, 17]. Exclusion criteria included the following: (1) inactive bleeding not requiring endoscopic intervention, (2) non-ulcer bleeding, and (3) use of other endoscopic techniques, e.g. monotherapy (adrenaline injection, clipping, heater probe). All patients expressed their written informed consent for the endoscopic therapy.

The following information was obtained from all the patients: (1) demographic data: age, gender; (2) number of patients in whom bleeding occurred during hospitalisation or in an outpatient setting; (3) bleeding episodes; (4) comorbidities – diseases of liver (cirrhosis, chronic hepatitis, fatty liver disease), heart (ischaemic disease, history of myocardial infarction), lungs (chronic obstructive pulmonary disease, asthma), kidneys (chronic renal failure), central nervous system (CNS) (history of stroke, transient ischaemic attack), diabetes; (5) arterial blood pressure and pulse on admission; and (6) laboratory parameters on admission, including the serum level of haemoglobin (Hb), haematocrit, platelet count, urea, creatinine, bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The risk of recurrent bleeding and mortality was assessed with the Rockall score [4, 8, 18].

Treatment

All patients were treated according to the current guidelines [9, 10, 18]: omeprazole (intravenously, 80 mg in bolus, followed by 72-hour infusion at 8 mg/h), and optimisation of vascular bed (1000–2000 ml of physiological saline or polyelectrolyte solution). The lack of haemodynamic compensation after fluid administration constituted indication to the transfusion of blood preparations.

Endoscopy was performed within 24 h after admission by one of three experienced specialists. All endoscopic techniques were used on a routine basis, following the manufacturer's instructions and recommendations. Olympus (GIF-Q165) therapeutic endoscopes were used for all procedures. In general, diluted (1 : 10,000 in saline) adrenaline was injected in 0.5–2 ml aliquots in and around the stigmata of haemorrhage in the ulcer base until active bleeding slowed or stopped. Clips (Olympus, HX-610-135) were placed (1–3 clips) over the bleeding site and on either side of the stigmata in

an attempt to seal the underlying artery. Bipolar electro-coagulation was performed with *Injection Gold Probe™* Bipolar Haemostasis catheter (Boston Scientific), which was applied as close as possible to the bleeding point or visible vessels (setting 15–20 W); energy was delivered in 8–10-second pulses. Prior to coagulation, injection of adrenaline solution (in 1 to 2 ml boluses) to the surrounding area of the bleeding site was performed by using the gauge inside the probe.

Treatment outcomes

The therapeutic outcomes were compared between the two groups of patients identified on the basis of the employed endoscopic technique: adrenaline injection + haemostatic clips (A + HC group) vs. adrenaline injection + bipolar electrocoagulation (A + BC group). The following parameters were determined in both groups: (1) frequency of recurrent bleeding, (2) necessity of surgical intervention, (3) hospital mortality, (4) length of hospital stay, and (5) number or transfused blood units or blood preparations. Treatment failure was defined as the lack of primary haemostasis, recurrent bleeding, necessity of surgical intervention, or patient death. The primary haemostasis was defined as haemostasis obtained during the initial endoscopic treatment, and the lack of bleeding 5 min thereafter. Recurrent bleeding was defined as an episode of further bleeding oc-

curring after primary haemostasis, and manifesting as haematemesis and/or melena co-existing with signs of haemodynamic instability (systolic blood pressure below 100 mm Hg, heart rate over 100 beats per minute, or a decrease in Hb by about 2 g/dl during 24 h). Patients with recurrent bleeding were subjected to a second endoscopy. The inability to obtain haemostasis with endoscopic techniques constituted indication to surgical intervention [18].

Statistical analysis

Relative (%) frequency measurements in the qualitative variables were used for the descriptive analysis of the characteristics of the patients. Continuous variables were expressed as means and standard deviations. The differences between qualitative variables were determined by using χ^2 tests. Comparison of quantitative variables between the two treatment groups was performed using the Mann-Whitney U test. A p-value < 0.05 was required for significance. Calculations were performed with the use of the Statistica 10 statistical package.

Results

Characteristics of the patients

During the analysed period, 353 patients were admitted due to signs of upper gastrointestinal bleed-

Table I. Risk stratification

Parameter	A + BC group (*n* = 52)	A + HC group (*n* = 55)	Value of *p*
Gender, M/F, *n* (%)	29 (55.8%)/23 (44.2%)	36 (65.5%)/19 (34.5%)	0.305
Age, mean (SD, min-max) [years]	66.8 (16.1, 30–92)	62.7 (18.9, 21–95)	0.277
Episode of bleeding, *n* (%):			
First	44 (84.6)	47 (85.5)	0.903
Second and subsequent	8 (15.4)	8 (14.5)	
Onset of primary bleeding, *n* (%):			
At hospital	14 (26.9)	13 (23.6)	0.696
Outside hospital	38 (73.1)	42 (73.4)	
Comorbidities, *n* (%):			
Heart	34 (65.4)	32 (58.2)	0.261
Lungs	7 (13.5)	12 (21.8)	0.261
Kidneys	11 (21.2)	11 (20.0)	0.883
CNS	4 (7.7)	6 (10.9)	0.811
Liver	10 (19.3)	10 (18.2)	0.889
Malignancy	5 (9.6)	3 (5.5)	0.653
Mean Rockall score, mean (SD)	4.8 (2.3)	4.5 (2.1)	0.493
Forrest grade, *n* (%):			
I	25 (48.1)	22 (40.0)	0.400
IIa	27 (51.9)	33 (60.0)	

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Table II. Physical examination and laboratory data

Parameter, mean (SD)	A + BC group (n = 52)	A + HC group (n = 55)	Value of p
Pulse [beats/min]	91.6 (21.2)	93.9 (16.3)	0.306
Systolic blood pressure [mm Hg]	122.3 (22.6)	120.6 (19.6)	0.492
Haemoglobin [g/dl]	8.4 (2.0)	8.6 (1.8)	0.389
Haematocrit (%)	25.3 (6.5)	25.7 (5.5)	0.717
Platelet count [10^3/µl]	211.6 (108.1)	210.2 (96.1)	0.801
INR	1.9 (2.7)	1.7 (2.1)	0.830
Fibrinogen [mg/dl]	269.8 (126.6)	321.6 (129.6)	0.051
Blood urea [mg/dl]	85.7 (80.0)	91.6 (47.3)	0.087
Creatinine [mg/dl]	1.45 (1.6)	1.2 (0.8)	0.359
Bilirubin [mg/dl]	1.6 (3.3)	1.1 (0.5)	0.446
Alanine aminotransferase [IU/l]	25.07 (30.1)	30.3 (60.9)	0.177
Aspartate aminotransferase [IU/l]	44.7 (91.7)	21.1 (10.1)	0.723

ing. The inclusion criteria of the study were fulfilled by 107 patients. Fifty-two subjects (52/107; 49%) with bleeding ulcers were assigned to the A + BE group. Another 55 patients (55/107; 51%) were treated with A + HC. The characteristics of the studied group are presented in Tables I and II.

On admission, the analysed groups did not differ significantly in terms of age, gender, presence of comorbidities, and Rockall scores. In 91 patients (91/107; 85%) the present episode was the first episode of bleeding. Forty-seven individuals (47/107; 43.9%) presented with active bleeding corresponding to Forrest grade I, and 60 patients (60/107; 56.1%) had a visible vessel (Forrest grade IIa). The analysed groups did not differ significantly with regards to the frequency of the above-mentioned parameters (Table I).

Additionally, the studied groups did not differ significantly in terms of basic laboratory parameters determined on admission (Table II).

Failures of treatment

The therapeutic outcomes are summarised in Table III. Treatment failed in 20 patients (20/107; 18.7%): in 10 individuals from the A + BC group (10/52; 18.2%) and in 10 individuals from the A + HC group (10/55; 19.2%) (p = 0.889). Primary haemostasis was not obtained in 7 patients (7/107; 6.5%): in 4 patients (4/52; 7.7%) from the A + BC group and in 3 patients (3/55; 5.5%) from the A + HC group (p = 0.939). Ten individuals (10/107; 9.3%) experienced recurrent bleeding during hospitalisation: 4 patients from the A + BC group (4/52; 7.7%) and 6 patients from the A + HC group (6/55; 10.9%) (p = 0.811). Finally, in 96.3% of the patients (103/107) the endoscopic treatment proved efficient with regards to obtaining haemostasis; among them were 50 out of

52 individuals from the A + BC group, and 53 out of 55 individuals from the A + HC group. Surgical intervention was required in 4 individuals (4/107; 3.7%): in 2 patients in the A + BC group and in 2 patients treated with A + HC (p = 0.651). Three patients (3/107; 2.8%) died during hospitalisation. All those patients were from the A + HC group patients, and they died during hospitalisation mainly due to complications of other serious comorbidities (1 patient with acute coronary syndrome, 1 patient with pneumonia along with cardiovascular and pulmonary insufficiency, and 1 patient with liver insufficiency).

Transfusion of erythrocyte concentrates

Eighty-five individuals (85/107; 79.4%) required transfusion of erythrocyte concentrate, among them 44 patients from the A + BC group (44/52; 84.6%) and 41 patients from the A + HC group (41/55; 74.5%; p = 0.199). The mean number of transfused erythrocyte concentrate units was similar in both subgroups (Table III).

Duration of hospitalisation

The mean length of hospital stay of patients from the A + BC group and the A + HC group was 9.1 and 9.0 days, respectively. This difference did not prove significant on statistical analysis (Table III).

Discussion

Our study compared the efficacy of two methods of combined endoscopic treatments of actively bleeding ulcers: adrenaline with bipolar electrocoagulation and adrenaline injection with clipping. Both techniques represent examples of a combined approach, which is considered the best amongst all currently recommended

Table III. Clinical data

Parameter	A + BC group (*n* = 52)	A + HC group (*n* = 55)	Value of *p*
Treatment failure, *n* (%):	10 (18.2)	10 (19.2)	0.889
Lack of primary haemostasis	4 (7.7)	3 (5.5)	0.939
Recurrent bleeding	4 (7.7)	6 (10.9)	0.811
Necessity of surgical intervention	2 (3.8)	2 (3.6)	0.651
Death	0 (0.0)	3 (5.5)	0.262
Successful endoscopic treatment, *n* (%)	50 (96.2)	53 (96.4)	0.651
Transfusion of erythrocyte concentrate:			
Patients requiring transfusion, *n* (%)	44 (84.6)	41 (74.5)	0.199
Number of transfused units, mean (SD)	2.9 (2.4)	2.7 (2.6)	0.349
Number of transfused FFP units, mean (SD)	0.75 (1.6)	0.87 (1.9)	0.739
Length of hospital stay, mean (SD) [days]	9.1 (4.7)	9.0 (4.3)	0.816

treatment modalities for non-variceal upper gastrointestinal bleeding [3, 9, 10, 18]. The efficacy of these two techniques had not been compared previously.

Although adrenaline injection in monotherapy is characterised by nearly 100% efficacy (i.e. primary haemostasis) in the case of active bleeding, it does not reduce the incidence of recurrent bleeding or the necessity of surgical intervention [11, 19, 20]. The administration of adrenaline in monotherapy is inferior to other monotherapeutic modalities (bipolar electrocoagulation, clips, fibrin glue) with regards to the prevention of recurrent bleeding and surgical treatment [11]. In contrast, combining adrenaline injection with another technique (e.g. bipolar electrocoagulation, sclerotising agents, and clips) is significantly more effective in preventing recurrent bleeding, and surgical treatment as compared to the administration of adrenaline alone [11, 21, 22].

A meta-analysis of 15 randomised trials revealed that thermal methods are more efficient in terms of obtaining primary haemostasis and are associated with lower frequency of surgical intervention and lower mortality as compared to the absolute lack of endoscopic treatment [11]. However, the previously mentioned meta-analyses did not distinguish between the methods involving multipolar or bipolar electrocoagulation probes. In randomised trials comparing these two thermal methods no significant differences were seen [11]. A comparison of combined approach, including adrenaline injection and thermal method, with the lack of endoscopic therapy was the subject of three trials [23–25]; the combined therapy proved significantly better with regards to the prevention of further bleeding, but not in the case of surgical treatment and mortality.

Jutabha *et al.* [13] and Sugawa *et al.* [15] were the first to describe the use of bipolar electrocoagulation prototypes in combination with injection therapy (a prototype of *Injection Gold Probe*). The advantages of their prototype included the ability to irrigate, inject, and coagulate without probe removal [13, 15]. In another study the use of bipolar electrocoagulation with 10-Fr catheter after adrenaline injection was associated with a reduced number of electrocoagulation procedures and shorter duration of the procedure as compared to 7-Fr catheter alone [26]. Laine *et al.* [27, 28] determined the optimal technique for bipolar electrocoagulation treatment.

Two small studies compared the efficacy of bipolar electrocoagulation combined with adrenaline injection (*Injection Gold Probe*, 7F) and the efficacy of bipolar electrocoagulation alone [12, 14]. According to Bianco *et al.* [12], the frequency of obtaining haemostasis was higher in the case of the combined approach (absolute risk reduction 31.6%). No differences were documented in the prevalence of other endpoints: the need for surgical intervention, length of hospital stay, and mortality. The only exception pertained to significantly fewer blood units transfused in the combined therapy group [12]. Lin *et al.* [14] compared the outcomes in patients with actively bleeding ulcers (I and IIa, according to the Forrest scale) treated with three various methods: adrenaline alone, bipolar electrocoagulation alone (Gold Probe), and the combination of both (*Injection Gold Probe*). Recurrent bleeding was less frequent in the *Injection Gold Probe* group (2/30, 6.7%) than in the Gold Probe group (9/30, 30%; *p* = 0.04) and in the adrenaline group (11/31, 35.5%; *p* = 0.01). Additionally, individuals who received the combined therapy required fewer transfused blood preparations. In contrast, the analysed groups did not differ significantly with regards to the frequency of surgical intervention, the length of hospital stay, and mortality [14]. Although the number of high-quality studies is insufficient to confirm this hy-

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pothesis, it was postulated that adrenaline followed by thermal contact therapy may be more efficacious than thermal therapy alone [10].

We compared the efficacy of the most frequently applied endoscopic technique for the treatment of actively bleeding ulcers, i.e. adrenaline injection combined with clipping, with the efficacy of the combination of injection (with adrenaline) and thermal method (bipolar electrocoagulation). Both combined methods of endoscopic treatment were characterised by comparable efficacy. Recurrent bleeding was documented in 9.3% of the patients, among them 4 individuals were primarily subjected to the adrenaline with bipolar electrocoagulation group, and 6 patients were subjected to adrenaline injection with haemostatic clips. The epidemiological data reported that rebleeding in the upper gastrointestinal bleeding occurs in 7–16% of cases despite endoscopic therapy and is especially high in variceal bleeding and peptic ulcer bleeding [1, 6]. However, the observed discrepancy of rebleeding rates might be caused by the use of different definitions of rebleeding and different endoscopic therapies, as well as heterogeneous sources of bleeding [1]. In our study surgical intervention was required in only 4 individuals (2 patients in each group), in whom haemostasis could not be obtained endoscopically. Moreover, there was a low mortality. Three patients, who were assigned to the adrenaline with haemostatic clips group, died during hospitalisation mainly due to complications of other serious comorbidities. There are large differences observed in the literature in the mortality, ranging from 3% to 14%; mostly due to differences in case mix in the population-based surveys [1]. However, higher age, co-morbidity, the onset of bleeding in hospital patients, and rebleeding are significantly associated with mortality [1, 4]. The mortality is very low in patients younger than 60 years of age without organ failure [1, 4, 29].

Our study suffers from several limitations. The main flaw is that our study in not a randomised prospective study and therefore the conclusions should be regarded with caution. The lack of significant differences between the efficacies of various endoscopic techniques could result from a small number of patients included in our analysis. It is possible that a randomised controlled study with a higher number of patients enrolled would provide sufficient statistical power to show differences between both studied protocols. Moreover, we were unable to evaluate the long-term therapeutic outcomes, due to the retrospective character of our analysis. Follow-up of our patients was limited to the duration of their hospitalisation. Finally, we were unable to determine the duration of specific procedures, which precluded the comparison of this parameter between the subgroups.

Conclusions

Combined therapy is characterised by high efficacy in obtaining haemostasis of actively bleeding ulcer. In such cases, the efficacy of endoscopic treatment with a probe enabling simultaneous bipolar electrocoagulation and adrenaline injection seems comparable to the widely used dual technique of adrenaline injection and haemostatic clipping. However, due to the fact that the probe does not need to be removed and the consequent shorter duration of the procedure, this technique could become the therapy of choice in future in the case of active upper gastrointestinal bleeding. This has to be preceded by further prospective randomised trials of larger patient groups.

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