

*Original research-Orijinal araştırma*

# Comparison of endoscopic dual versus monotherapy in patients with high-risk bleeding ulcers: a retrospective trial

*Yüksek riskli veya kanayan ülserlerde ikili endoskopik tedaviler ile tekli tedavilerin karşılaştırılması: retrospektif bir çalışma*

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## Abstract

**Aim.** Peptic ulcer bleeding is a common medical emergency and a potentially life-threatening event. Endoscopic treatment reduces the morbidity and mortality associated with peptic ulcer bleeding. The aim of this study is to compare the efficacy of dual endoscopic therapies versus endoscopic monotherapy in reducing rate of recurrent bleeding, need for surgery, and death in patients with active peptic ulcer bleeding. **Method.** Data of 125 patients who applied to Akdeniz University Hospital with active bleeding, or high-risk ulcers detected by endoscopy were retrospectively investigated. Epinephrine alone injection was applied to 43 patients and epinephrine plus heater probe treatment were applied to 33 patients. Gold probe and epinephrine injection combination were applied to 29 patients and only heater probe treatment was applied to 20 patients. **Results.** Initial endoscopic haemostasis was achieved in 39/43 patients (81.7%) who received epinephrine injection alone, 33/33 patients (100%) who received additional heater probe treatment, 28/29 patients (86.4%) who received additional gold probe treatment, and 19/20 patients (95%) who received heater probe treatment alone. Treatment outcome was determined in four treatment groups by clinical rebleeding ratios during the hospital stay. Clinical rebleeding was observed in 6 patients (15.4%) in the epinephrine alone group, in 2 patients (6.1%) in additional heater probe treatment group, in 3 patients (10.7%) in additional gold probe group, and in 2 patients (10.5%) in heater probe treatment alone group. We did not find a significant difference between these four groups by means of clinical rebleeding ratios. There was no statistically significant difference in four groups. Requirement for emergent operation was observed in 6 patients, and mean blood transfusion was  $3.2 \pm 2.88$  units, and mean hospital stay was  $5.18 \pm 2.88$  days. **Conclusion.** Addition of heater probe and gold probe treatment after endoscopic adrenaline injection could have an advantage in bleeding and high-risk ulcers. Lack of statistical difference between the groups could be due to low number of patients.

**Keywords:** Endoscopic therapy, ulcer bleeding

## Özet

**Giriş.** Peptik ülser kanamaları potansiyel olarak hayatı tehdit eden ve sık karşılaşılan bir tıbbi acil durumdur. Endoskopik tedaviler peptik ülser kanamasına bağlı morbidite ve mortaliteyi azaltır. Bu çalışmada çiftli ve tekli endoskopik tedavilerin, aktif kanayan ülserli hastalarda, kanama tekrarı, cerrahi gereklilik ve kanamaya bağlı ölüm üzerine tedavi etkinliğinin karşılaştırılması amaçlanmıştır. **Yöntem.** Akdeniz Üniversitesi Hastanesi Endoskopi Ünitesine başvuran, endoskopilerinde aktif kanama veya yüksek riskli ülsere sahip 125 hastanın verileri retrospektif olarak değerlendirildi. 43 hastaya yalnızca epinefrin enjeksiyon tedavisi ve 33 hastaya epinefrin ve heater probe tedavisi uygulandı. 29 hastaya gold probe ve epinefrin enjeksiyon tedavisi ve 20 hastaya sadece heater probe tedavisi uygulandı. **Bulgular.** Tedavi gruplarında başlangıç hemostaz oranları, sadece epinephrine enjeksiyonunda 39/43 (%81,7), epinefrin heater probe kombinasyonunda 33/33 hasta da (%100), epinefrin enjeksiyonu ve gold probe kombinasyonunda 28/29 hastada (%86,4), ve sadece heater probe tedavisinde 19/20 hastada (%95) gerçekleşti. Tedavi sonucu olarak, hastanede yatılan süre içerisinde tekrar kanama, sadece epinefrin enjeksiyonunda 6 hastada (%15,4), epinefrin ve heater probe kombinasyonunda 2 hastada (%6,1), epinefrin enjeksiyonu ve gold probe kombinasyonunda 3 hastada (%10,7), ve sadece heater probe

tedavisinde 2 hastada (% 10,5) gözlenmiş olup; dört grubun arasında istatistiksel olarak anlamlı bir farklılık yoktu. 6 hastada kanama durdurulamadı ve cerrahi operasyona verildi. Hastaların ortalama yatış süreleri  $5,18 \pm 2,88$  gün ve ortalama transfüzyon sayıları  $3,2 \pm 2,88$  ünite olarak bulundu. **Sonuç.** Yüksek riskli veya kanamakta olan ülserlerde, endoskopik adrenalin enjeksiyonunu takiben heater veya gold probe tedavisinin eklenmesinin yalnızca epinefrin enjeksiyon tedavisine göre daha avantajlı olabileceği gözlemlendi. Çalışmadaki hasta sayısının düşük olması nedeniyle gruplar arasında istatistiksel olarak anlamlı bir fark saptanamadı.

**Anahtar sözcükler:** Endoskopik tedavi, ülser kanaması

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## Introduction

Peptic ulcer bleeding is a common medical emergency and a potentially life-threatening event [1]. Endoscopic treatment reduces the morbidity and mortality associated with peptic ulcer bleeding and is superior to conservative treatment. Methods are based on the injection of vasoconstrictor substances (epinephrine), sclerosing substances (poliodocanol, absolute alcohol), clotting factors (thrombin, fibrin glue), or adhesives (cyanoacrylate). The thermal therapies include laser, monopolar electrocoagulation, argon plasma coagulation, bipolar probes, and heater probe. More recently, mechanical devices to clip the bleeding vessels have been used. These methods have been proved to be clinically useful [2-11]. Which one of these methods is superior remains controversial. We can expect to achieve primary hemostasis in over 95% of patient with actively bleeding peptic ulcers, but recurrent bleeding still occurs in 4-30% of cases [12]. A recent meta-analysis reported that additional endoscopic treatment after epinephrine injection significantly reduces the risk of further bleeding [13]. Epinephrine injection alone or in combination with another technique have become the most popular endoscopic method for emergency endoscopic haemostasis and prevention of recurrent hemorrhage. The primary aim of the present study was to assess the efficacy of dual endoscopic therapies (epinephrine injection plus gold probe coagulation and epinephrine injection plus heater probe coagulation) versus endoscopic monotherapies (epinephrine injection or heater probe coagulation) in reducing the rate of recurrent bleeding, need for surgery, and death in patients with active peptic ulcer bleeding who applied to the endoscopic unit of Akdeniz University Hospital between the years of 2004 and 2010. The second aim was to evaluate clinical outcomes, such as the requirement for blood transfusion, recurrent bleeding, surgery, length of hospital stay, and mortality between different endoscopic haemostatic methods.

## Materials and methods

We retrospectively evaluated 125 patients with active bleeding or high-risk ulcer who applied to the endoscopic unit of Akdeniz University Hospital between 2004 and 2010 years. Medical history and demographic data were collected from patient file system which included age, sex, location, size of ulcers, drug history, units of transfusion given, duration of hospitalization, and mortality rate. Patients were included if an emergency endoscopy disclosed a peptic ulcer with an actively bleeding visible vessel, a non-bleeding visible vessel (NBVV), or adherent clots. All patients were hospitalized for upper GI (Gastrointestinal) bleeding. Medical history and demographic data were taken from patient file system which included age, sex, drug history, units of transfusion given, duration of hospital, and mortality rate. Written informed consent was taken from all of the patients or, a close relative before endoscopic procedures. The groups did not differ

with respect to age, sex, site and severity of bleeding.

*Exclusion criteria were the following:* (1) known chronic liver disease, (2) age  $\leq$  18 years, (3) anticoagulant drug usage, (4) severe coagulopathy (INR $>$ 1.5), (5) history of malignancy and (6) pregnancy.

*Four different treatment methods were applied to patients;* (1) gold probe plus epinephrine injection, (2) heater probe treatment and epinephrine injection, (3) epinephrine injection alone, (4) heater probe treatment alone.

#### ***Endoscopic techniques:***

We used the Forrest classification for endoscopic grading of bleeding peptic ulcers (14). We applied endoscopic therapy to patients with Forrest Ia, Ib, IIa, and IIb ulcer. The first group of patients received combination of epinephrine solution injection around the ulcer and then gold probe bipolar electrocoagulation (n=29). The second group of patients received combination of heater probe coagulation and epinephrine solution injection (n=33). Epinephrine injection were performed with 1 to 2 ml boluses to a maximum of 18 mL. Solutions were injected around the bleeding point in all four quadrants until hemostasis was achieved, and after applying the second endoscopic method. If a large clot covered the ulcer, the clot was washed away or removed with snare before any haemostatic method. If there was a massive bleeding, first epinephrine solution was injected, then heater or gold probe coagulation methods were applied. The third group of patients received only epinephrine solution (n=43). The fourth group of patients received heater probe treatment alone (n=20).

#### ***Posthaemostasis therapy***

Oral intake of patients with bleeding was stopped for three days. Both groups of patients received parenteral nutrition and intravenous administration of pantoprazole (40 mgr) or esomeprazole (40 mgr) for 2 days. After the 48-hour observation period, the patients were given a soft diet for 2 days and then a regular diet. Patients were closely monitored, and only received a second endoscopy when there was clinical or biochemical evidence of recurrent bleeding. Hemoglobin levels were checked daily for 4 days. The criteria of recurrent bleeding during hospital stay included a drop of haemoglobin levels  $\geq$ 4 gr/dl, heart pulse rate  $\geq$ 100 beats/min, systolic blood pressure  $\leq$  100 mm Hg, fresh hematemesis or passage of fresh melena, and requirement of blood transfusions  $\geq$  4 units within 24 hours to maintain hemoglobin level. If hemostasis could not be achieved by the second hemostatic treatment, surgery was performed. Primary outcome measure was initial hemostasis, recurrence of bleeding, number of patients requiring surgery, mortality within the hospital stay. Patients were treated with proton pump inhibitors for 8 weeks after discharge.

#### ***Statistics:***

Data were analyzed by using a statistical SPSS 15.0 and Medcalc 11.04 program. Summary statistics for quantitative data are given as mean (standard deviation [SD]), and interquartile range. Categorical variables were given as percentage. Numeric variables of the treatment groups were compared with Kruskal Wallis analysis. Categorical variables were compared with the chi-square test. Mann Whitney U test was used for comparison of numeric variables of two groups and the chisquare test was used for comparison of categorical variables of two groups. Kolmogorov Smirnov test was used for normalizing analysis.  $p < 0.05$  was regarded as significant.

#### **Results**

Active bleeding or persistent high-risk stigmata (Forrest Ia-Ib-IIa-IIb) were observed in 125 patients between 2004 and 2010. All of the patients received primary therapeutic endoscopy within 12 hours after admission. Clinical characteristics and endoscopic pictures of patients at study were presented at Table 1. There was no significant

difference in age, sex distribution, severity of bleeding, and the proportion of duodenal and gastric ulcers between four groups. A total of 125 high-risk patients with an active bleeding forrest Ia ulcer (n=11), oozing bleeding forrest Ib ulcer (n=42), non bleeding visible vessel forrest IIa ulcer (n=52), and non bleeding adherent clot forrest IIb ulcer (n=20) ulcer were included in our trial.

**Table 1. Demographic data of patients at study entry**

Number of patients	125
Mean age(SD)	56.85±16.27
Male	101(80.8%)
<b>Ulcer site</b>	
Stomach	46
Duodenum	79
Number of units transfused unit (Range)	3.2(0-10)
<b>Forrest</b>	
Ia	11(8.8%)
Ib	42(33.6%)
IIa	52(41.6%)
IIb	20(16%)
Mean size of ulcer in mm (Range)	8.6(3-25)
NSAID history	57(37.6%)

The average of ulcer diameter was 8.6±3.9 mm (mean±SD). All patients were hospitalized for upper gastrointestinal bleeding. A mean of 8.41±2.63 mL (mean±SD) epinephrine solution was required to obtain complete hemostasis per patient. Median duration of hospital stay for patients was 5.18(0-19) days. Assessment of outcome according to endoscopic treatments were presented at Table 2 and 3. Initial endoscopic hemostasis was achieved in 39/43 patients (81.7%) who received epinephrine injection alone, 33/33 patients (100%) who received additional heater probe treatment, 28/29 patients (86.4%) who received additional gold probe treatment, and 19/20 patients (95%) who received heater probe treatment alone. Treatment outcome was determined in the four treatment groups by clinical rebleeding ratios during the hospital stay. Clinical rebleeding was observed in 6 patients (15.4%) in the epinephrine alone group, in 2 patients (6.1%) in additional heater probe treatment group, in 3 patients (10.7%) in additional gold probe group, and in 2 patients (10.5%) in heater probe treatment alone group. We did not find a significant difference between these four groups by means of clinical rebleeding ratios. Requirement for emergency operation was observed in 6 patients, and mean blood transfusion was 3.2±2.88 units, and mean hospital stay was 5.18±2.88 days. Only one patient died from sepsis. Primary therapeutic endoscopy failed to achieve hemostasis in 6 patients and they were subjected to immediate surgery. There was no statistically significant difference between the four groups with respect to the number of blood units transfused, need for surgical intervention, hospital stay or number of deaths.

**Table 2. Assessment of outcome according to dual endoscopic treatment**

	Epinephrine injection and heater treatment	Epinephrine injection plus Gold probe treatment
Number of patients	33	29
Initial hemostasis	33(100%)	28(96.5%)
Recurrent bleeding	3(9%)	3(10.3%)
Surgery	0	1(3.4%)
Mean units of blood transfused (units)	3.21(0-9)	2.54(0-9)
Mean day of hospital stay (day)	4.86(2-12)	5.27(3-19)
Mortality	0	0

**Table 3. Assessment of outcome according to endoscopic monotherapies**

	Epinephrine injection	Heater probe treatment
Number of patients	43	20
Initial hemostasis	39(90.6%)	19(95%)
Recurrent bleeding	5(11.6%)	2(10%)
Surgery	4(9.3%)	1(5%)
Mean units of blood transfused (unit)	3.55(0-10)	3.74(0-8)
Mean day of hospital stay(day)	5.72(1-18)	4.68(1-12)
Mortality	1	0

## Discussion

In recent years many randomized clinical trials on the endoscopic treatment of bleeding ulcers have been reported [3-9]. Most reports that compared endoscopic treatment against standard medical treatment reported improvement in the outcome of patients as measured by reduced blood transfusion, decreased requirement for surgical intervention, and reduced length of hospital stay. In up to 80% of patients with bleeding ulcers, bleeding stop spontaneously. Endoscopic treatment should be targeted to those who are at high risk of developing further bleeding. Active bleeding or visible vessels should be treated endoscopically [15]. Patients having an ulcer with an adherent clot may also constitute a high risk group [16]. After the introduction of primary endoscopic therapy, mortality from bleeding peptic ulcers was reduced to approximately 5-14% [1, 17, 18]. Although these techniques stop the majority of ulcer bleeding, acute recurrent bleeding still occurs in 5% to 30% of cases [19]. Active bleeding during the endoscopy is a primary factor predisposing to failure of injection therapy [20]. Recurrent bleeding is one of the most important risk factors for mortality. If recurrence of bleeding can be prevented, then the rate of mortality from ulcer bleeding can be reduced. In our report initial hemostasis was achieved in 95.2% of patients. We have successfully used diluted epinephrine injection in patients with actively bleeding peptic ulcers. The mean volume of epinephrine injected in treatment groups was  $8.41 \pm 2.63$  ml (mean  $\pm$  SD). There was no significant difference between our treatment groups. In epinephrine alone group, rebleeding was higher than dual groups. But there was no significant difference. Both the heater probe and the Gold probe therapies were effective in controlling active bleeding by applying firm tamponade and captive coagulation. Combination of epinephrine with both heater and gold probes are superior to epinephrine injection alone and heater probe alone [21, 22]. The best hemostatic result after dual therapies were obtained in our study. But we found no significant difference because the number of patients was low. Endoscopic hemoclip placement is also a safe and effective hemostatic method superior to injection therapy for management of bleeding ulcers [23]. The length of stay in hospital was not different between groups. As an entire group, clinical outcomes in treatment groups were not significantly different. Four patients in the epinephrine injection group required surgical intervention for further bleeding. Only one patient in the gold probe combination group required surgical intervention. In our report, we demonstrated that combination therapy was superior to epinephrine injection alone in reducing recurrent bleeding and further bleeding. We defined recurrent bleeding using clinical parameters, and confirmed this with endoscopy. The mean of injected epinephrine was not different between groups. In a meta-analysis, suggesting that adding a second endoscopic procedure after epinephrine injection reduced recurrent bleeding rates, the need for surgery, and mortality rates in patients with bleeding peptic ulcers [13]. Additionally, a previous study also showed that combination treatment with both injection and thermal coagulation was associated with statistically significant reduction in absolute rates of recurrent bleeding compared with injection alone [24]. Accurate placement of the probe in ulcers with active bleeding is the main problem of coagulation therapies. No complications occurred in any group in our study. In literature, iatrogenic perforation of patients with heater probe treatment was reported [8, 25, 26].

This study demonstrated that the endoscopic combination therapies are superior to conventional epinephrine injection therapy in reduction of recurrent bleeding and emergency operation rates in treatment of high-risk bleeding ulcers.

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