Could application of epinephrine improve hemostatic efficacy of hemoclips for bleeding peptic ulcers? A prospective randomized study

Da li se primenom epinefrina može poboljšati hemostatska efikasnost hemoklipseva kod krvarenja iz peptičkih ulkusa? Prospektivna randomizovana studija

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Abstract

Background/Aim. Bleeding from peptic ulcers can be effectively and safely treated with endoscopic hemoclips therapy. However, due to certain limiting factors of hemoclips, application of combination with another endoscopic method may give better results. The aim of this study was to examine the efficacy and safety of endoscopic hemoclips therapy and to evaluate potential benefits of this therapy combined with epinephrine in the treatment of bleeding peptic ulcers. Methods. This prospective randomized study included 70 patients with bleeding gastric or duodenal ulcer. In 34 of the patients endoscopic hemoclips therapy was applied (group I), and in 36 of them a combined therapy of hemoclips and epinephrine (group II). Results. Initial hemostasis was achieved in most patients treated with endoscopic hemoclips therapy (94.1%) as well as in the patients treated with combination therapy (97.2%). After initial hemostasis achieved rebleeding occurred in 3 (9.3%) patients treated with hemoclips and in 2 (5.7%) patients treated with combination therapy, but this difference was not statistically significant (p > 0.05). The difference in the achieved final hemostasis between the group I (91.1%) and the group II (94.4%) was not statistically significant. Also, the differences between the two groups of patients in the need for blood transfusions, length of hospital stay, need for surgery and mortality were not statistically significant (p > 0.05). Conclusion. Endoscopic hemoclips therapy is effective and safe in treatment of bleeding peptic ulcers. Combination therapy of hemoclips and epinephrine has no advantage over hemoclips monotherapy.

Key words: peptic ulcer hemorrhage; endoscopy, gastrointestinal; hemostasis, endoscopic; epinephrine; treatment outcome.

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Introduction

Endoscopic injection therapy is the most common method for treating bleeding peptic ulcer. Sanation of bleeding is achieved to a high degree using this technique, but the recurrence of bleeding is present in 6%–36% of cases. If rebleeding as an important factor of mortality as reduced, one might expect a potential reduction in mortality. It can be difficult to achieve permanent thrombosis of blood vessels in cases of bleeding in jet injections of epinephrine. The application of hemoclips would theoretically be the optimum method in case of visible blood vessels. Hemostasis can be definite if the vessel is adequately ligated by clips.

Recent data indicate that the application of endoscopic clips is efficient and safe, than sclerosing and thermal methods, with minor damage to the surrounding tissue, and with a smaller share of rebleeding. Therefore, their application is being increased. However, there are certain limitations in hemoclips applications. In fact, it is difficult to place clips in case of massive bleeding that covers the field of visualization of the lesion or bleeding in case of tangential approach to the lesion. Hemoclips, in combination with other methods such as epinephrine injection, would perhaps show better results. There are scarce literature records on the results of comparison of efficacy of endoscopic hemoclips therapy and a combined hemoclips therapy with epinephrine.

The aim of this study was to examine the efficacy and safety of endoscopic hemoclips therapy and evaluate potential benefits of hemoclips therapy combined with epinephrine in treatment of bleeding peptic ulcers.

Methods

This prospective randomized study included 70 patients (47 men and 23 women) hospitalized in the Department of Gastroenterology and Surgery because of acute bleeding from peptic ulcer (hematemesis and/or melena).

All the patients were asked to consent for upper gastrointestinal endoscopy, which was done mostly within 24 h of hospitalization. Endoscopy was performed under local oropharyngeal anesthesia with lidocaine. Bleeding from gastric or duodenal ulcer was diagnosed after endoscopy. The patients were divided into two groups depending on the applied type of endoscopic hemostasis: group I that included 34 patients (23 males and 11 females), average age 60.3 ± 11.19 years (from 29 to 83 years) with endoscopic therapy using hemoclips, and group II with 36 patients (24 males and 12 females), average age 62.3 ± 12.21 years (from 30 to 85 years) with combined therapy of hemoclips and epinephrine.

The examined groups of patients did not differ significantly according to sex, age, use of nonsteroidal anti-inflammatory drugs (NSAIDs), participation of comorbidity, hemoglobin initial values, the localization of the ulcer, ulcer size and affiliation to a certain Forrest group of bleeding ulcer (Table 1). Anamnestic data were obtained by using NSAIDs, in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hemoclips therapy (n = 34)</th>
<th>Combination therapy (n = 36)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>23/11</td>
<td>24/12</td>
<td>0.867</td>
</tr>
<tr>
<td>Age (years), X ± SD</td>
<td>60.3 ± 11.19</td>
<td>62.3 ± 12.21</td>
<td>0.704</td>
</tr>
<tr>
<td>NSAID use, n (%)</td>
<td>21 (61.7)</td>
<td>22 (61.1)</td>
<td>0.849</td>
</tr>
<tr>
<td>Comorbid diseases, n (%)</td>
<td>17 (50)</td>
<td>19 (52.7)</td>
<td>0.994</td>
</tr>
<tr>
<td>Hb level (g/dL), X ± SD</td>
<td>7.2 ± 1.4</td>
<td>6.9 ± 1.3</td>
<td>0.914</td>
</tr>
<tr>
<td>Stomach ulcer, n (%)</td>
<td>16 (47)</td>
<td>17 (47.2)</td>
<td>0.821</td>
</tr>
<tr>
<td>Duodenal ulcer, n (%)</td>
<td>18 (52.9)</td>
<td>19 (52.7)</td>
<td>0.821</td>
</tr>
<tr>
<td>Ulcer size (mm), X ± SD</td>
<td>12.6 ± 3.98</td>
<td>13.1 ± 4.12</td>
<td>0.508</td>
</tr>
<tr>
<td>Forrest group Ia, n (%)</td>
<td>2 (5.9)</td>
<td>5 (13.9)</td>
<td>0.429</td>
</tr>
<tr>
<td>Forrest group Ib, n (%)</td>
<td>30 (88.2)</td>
<td>28 (77.8)</td>
<td>0.399</td>
</tr>
<tr>
<td>Forrest group Ila, n (%)</td>
<td>2 (5.9)</td>
<td>3 (8.3)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

| Forrest group Ia – active bleeding in the jet; Forrest Ib – flowing venous bleeding; Forrest Ila – visible denuded blood vessels without active bleeding |

The criteria for excluding patients from the study were: pregnancy, multiple, other, non-ulcus causes of bleeding in the upper gastrointestinal tract, gastric malignancy, the coexistence of acute severe disease, such as septic shock, acute cerebrovascular incident, acute surgical abdomen, systemic condition of increased susceptibility to bleeding – low blood platelet counts below 50,000/mm³, prolonged prothrombin time with international normalized ratio (INR) over 2 and treatment with anticoagulant drugs.

Hemoclips endoscopic therapy was applied in the group I of the patients with bleeding from peptic ulcer. We used EZ clips of stainless steel material and standard ones curved at the top at the angle of 135° (HX-610-135) and a longer curved at the angle of 90° (HX-610-090L). Clips were placed with the applicator through the accessible channel of 2.8 mm in diameter of standard endoscopes.

The combined hemoclips and epinephrine therapy was applied in the group II of the patients with bleeding from peptic ulcer. The same clips were used as in the group I. Epinephrine diluted in physiological salt solution of 1:10,000 was applied. A standard injection needle was used for application, 23 gauge size, the length of the needles 4 mm. Basically, the first placed were clips (in 25 patients or 69.4%) in a visible bleeding place, immediately after diluted epinephrine was applied, fractionally from 0.5–2 mL in four quadrants around the ulcer at the distance of 2–3 mm and only the bleeding site. The injection was repeated in each quadrant until the mucosa turned to whitish color and until hemostasis was established. In case of more massive bleeding (in 11 patients or 30.5%), when it was not possible to see clearly the bleeding site, the diluted epinephrine was applied immediately after the clip to achieve the reduction of bleeding.

Initial hemostasis was considered successful in case of endoscopically verified cessation of bleeding for at least 5 min after the first endoscopic treatment. In case of continued bleeding, despite endoscopic treatment, urgent surgery is recommended.

Vital functions were monitored in all the patients, while control of bleeding was performed using nasogastric tube drainage. The treatment included partial parenteral nutrition and the use of proton pump inhibitors (PPIs) in the form of intravenous bolus of 80 mg and then infusion of 8 mg/h during 72 h, followed by oral application of PPIs. In case of hemoglobin (Hb) fall below 7 g/dL, a continuation of hematemesis and/or melena, increased heart rate to more than 100 beats per minute or systolic blood pressure fall to less than 100 mmHg, red blood cell transfusions were prescribed.

By recurrent bleeding, we meant the appearance of new hematemesis and/or melena after initial hemostasis, the emergency of fresh blood nasogastric tube aspiration and increasing heart rate over 100 beats per minute with systolic pressure drop over 30 mmHg, as well as a new decline in Hb of at least 2g/dL. Reapplied upper gastrointestinal endoscopy and secondary endoscopic clips hemostasis or clips with epinephrine was used in case of suspicion of recurrent bleeding. Urgent surgery was recommended in case of secondary endoscopic hemostasis failure.

By final hemostasis, we meant the absence of recurrent bleeding 7 days after initial or secondary endoscopic hemostasis. All the patients were clinically followed for 8 weeks after initial endoscopy.

Statistical analysis was performed using descriptive statistics such as measures of central tendency [average value, (X)] and measures of dispersion [standard deviation (SD)]. Statistical analysis methods that were used in assessing the significance of difference were Student's t-test, Mantel-Haenszel's $\chi^2$ test with Yates's correction and Fisher’s exact probability test of the null hypothesis. A statistically significant differences between individual characteristics were considered for $p < 0.05$.

Results

Initial hemostasis was achieved in most of the patients treated with endoscopic hemoclips therapy (32/34 or 94.1%) and the patients treated with combination hemoclips and epinephrine therapy (35/36 or 97.2%). The difference in the success of initial hemostasis was not statistically significant ($p > 0.05$).

Rebleeding occurred in 3 (9.3%) patients treated with endoscopic clips therapy and 2 (5.7%) patients treated with combination therapy of clips and epinephrine, after achieving initial hemostasis. However, the difference in the participation of rebleeding was not statistically significant ($p > 0.05$). Also, the difference in the achieved final hemostasis between the patients treated with clips (91.1%) and the patients treated with combination therapy (94.4%) was not statistically significant ($p > 0.05$).

The amount of epinephrine administered in the patients treated with combination therapy of clips and epinephrine, was $11.2 \pm 4.56$ mL (4–20 mL). The average number of placed clips was slightly higher in the patients treated with clips monotherapy ($1.7 \pm 0.49$, the minimum of 1 and the maximum of 4 clips on bleeding ulcer) than in the patients treated with combination therapy ($1.5 \pm 0.68$, at least 1 clip at the maximum of 3 clips on bleeding ulcer), but the difference was not statistically significant ($p > 0.05$). We had difficulties with placement the clips in 3 patients of the group I and 5 patients of the group II, with ulcer on the posterior wall of the stomach, as well as with ulcer in the duodenal bulb of fibrotic characteristics. Five clips fell off in 3 patients of the group I and 8 clips in 5 patients of the group II. However, replacement of clips was successful. Unsuccessfully placed clips were not counted in the number of clips used to control bleeding.

There were no complications after clips treatment and after combined therapy of clips and epinephrine in the examined groups of patients.

An average of $4.3 \pm 1.58$ units of blood (from 0 to 9 units) was prescribed to the patients treated with hemoclips. An average of $3.9 \pm 1.82$ units of blood (from 0 to 8 units) was prescribed to patients whose ulcers were treated with combination therapy. The difference in the number of units of given red blood cell concentrate between the two groups of patients was not statistically significant ($p > 0.05$).

The average length of hospitalization of the group I patients was $9.2 \pm 4.54$ days (from 4 to 16 days), and of the group II patients $8.9 \pm 4.32$ days (from 3 to 14 days). The difference in the length of hospitalization was not statistically significant ($p > 0.05$).

One (2.9%) patient, in the group I patients was operated on for recurrent ulcer bleeding on the posterior wall of subcardial area of gastric corpus and secondary failure of endoscopic hemostasis. In the remaining 2 of 3 patients, treated with hemoclips and who had recurrent bleeding ulcers, a
successful secondary endoscopic hemostasis was achieved. In the group treated with combination therapy of epinephrine and hemoclips, 1 (2.7%) patient underwent surgery with recurrent bleeding from duodenal ulcer after the failure of secondary endoscopic hemostasis. A successful secondary endoscopic hemostasis was achieved in another patient with rebleeding from ulcer. The difference in the number of operated patients between the groups was not statistically significant ($p > 0.05$).

Death occurred in 2 (5.8%) patients, in the group treated with hemoclips, with bleeding from ulcer of the stomach corpus and duodenal ulcer after failure of initial hemostasis, continuing bleeding and development of irreversible hemorrhagic shock. Death occurred in 1 (2.7%) patient, in the group treated with combination therapy, with severe bleeding from the stomach ulcer and the inability of establishing initial hemostasis. The presence of significant comorbidity such as angina pectoris, chronic obstructive pulmonary disease or renal insufficiency was established in cases of death in both groups of patients. The difference in mortality was not statistically significant between the two groups of patients (Table 2).

There was no significant difference in the two examined groups of patients, regarding the success of initial hemostasis achieved to a high percentage in both groups. The difference in the participation of rebleeding was not statistically significant. Also, there was no statistically significant difference in achieving final hemostasis in bleeding ulcers, need for blood transfusions, length of hospitalization, needs for surgery and mortality.

According to the results of most studies, combined hemoclips therapy with other agents, such as epinephrine or absolute alcohol has an advantage over epinephrine monotherapy or absolute alcohol in terms of rebleeding, need for surgery and in some cases in terms of mortality. However, there have been a few studies dealing with comparative analysis of hemoclips efficiency and hemoclips combined with other hemostatic agent. One study investigated the clips effectiveness with clips combined with absolute alcohol, while the other study investigated the clips effectiveness with clips combined with epinephrine. The results of both studies, similar to our results, showed no statistically significant difference in the participation of rebleeding, need for surgery and mortality. Therefore, the combined treatment is not favored in comparison with clips monotherapy.

In the group of patients treated with combination therapy, clips were first placed in a visible bleeding place and immediately after it diluted epinephrine was applied. In case of more massive bleeding, when it was not possible to see clearly the bleeding site, diluted epinephrine was first applied to achieve the reduction of bleeding and immediately after that clips were used. Theoretically, local injection therapy applied before placing clips can lead to tissue edema, and there can appear difficulties in placing a blood vessel clip. Gevers et al. first applied epinephrine in all patients and then clips. They showed that the combined therapy of epinephrine and clips was even less efficient in comparison with the epinephrine monotherapy. The study of Lo et al. had an identical approach to epinephrine and hemoclips, as in this study injection. They compared combined hemoclips and epinephrine therapy with epinephrine monotherapy, showing the superiority of combination therapy.

### Discussion

Epinephrine monotherapy is considered to be suboptimal due to the high participation of rebleeding. Thermal methods such as electrocoagulation, photocoagulation and argon plasma coagulation were effective but the potential damage to tissues is possible. Hemoclips are new therapeutic alternatives with the effect identical to surgical ligature. The advantages of hemoclips application are direct application on the blood vessel, no damage to bleeding lesion, no limit to the number of applied clips, interventions can be repeated and in case of failure of hemostasis they are a useful marker for radiologists in the application of transcatheter embolization. Due to the existence of some limiting factors of hemoclips applications such as chronic ulcer with a fibrous base, precise identification of bleeding lesion and lesion location, we wanted to examine whether application of combined methods of hemoclips and epinephrine could give better results.
According to some authors, a higher volume of epinephrine, such as 13–20 mL or even 35–45 mL, can be significantly more effective in achieving hemostasis, reducing the need for urgent surgery, reducing hospitalization time and mortality. The higher amount of applied epinephrine proved to be safe, not leading to the occurrence of cardiac arrhythmias.\textsuperscript{20,21}

The size of ulcers and the presence of active bleeding from ulcers, as well as Forrest I bleeding lesions, could have an impact on the success of endoscopic hemostasis. It is difficult to achieve hemostasis with larger ulcers over 20 mm\textsuperscript{22}. There was no statistically significant difference in the size of ulcer, and all ulcers were less than 20 mm in both groups of patients. Also, there was no statistically significant difference between the two groups of patients regarding the Forrest group of bleeding ulcers. Therefore, it can be concluded that for the success of endoscopic hemostasis, the kind of therapy (hemoclips or hemoclips with epinephrine) was responsible first, while the size of ulcer bleeding and the Forrest group had no effect in our examines.

Addition of epinephrine to clips had no significant effect on reducing the average number of clips placed on bleeding ulcers in our patients. Specifically, the average number of placed clips was ranked slightly higher in the patients treated with monotherapy clips than in the patients treated with combination therapy, but the difference was not statistically significant. We had difficulties in placing clips in ulcers of fibrous characteristics and the ulcers localized subcardially on the back wall of the stomach. Five clips fell off in 3 patients of the group I and 8 clips in 5 patients of the group II. However, replacement of clips was successful. Similar data were presented by Lo et al.\textsuperscript{4} who had failed at placing 6 clips in 4 patients. According to some authors\textsuperscript{14,19}, implementation of a transparent cylinder on top of an endoscope could help or the use of endoscopes with optics side in cases of difficult access to a lesion such as subcardial region.

We prescribed PPIs to all the patients parenterally within 72 h and then orally, before endoscopic intervention and/or immediately after the initial endoscopic hemostasis was achieved. It was proven that a significant suppression of acid secretion with PPIs improves the success of endoscopic hemostasis while the benefit is missing when applying H2 receptor antagonists. Achieving pH values above 6 in the stomach, under the influence of IPPs makes stabilization of blood clot possible.\textsuperscript{23,24}

Complications after endoscopic clips therapy and epinephrine injection therapy are rare. We have to be cautious with deeper ulcerations due to the possibility of perforation in applying clips. Also, it is possible to cause formation of active bleeding in the lesions that are not actively bleeding, such as a visible vessel or clot in the ulcer\textsuperscript{14}. Epinephrine is considered to be the safest of injectable agents that are used in repair of bleeding from peptic ulcers. The possibility of cardiac arrhythmia is described, but as a very rare complication\textsuperscript{2}. There were no complications following endoscopic application of clips and application of clips with epinephrine in the studied patients.

**Conclusion**

This study showed that endoscopic hemoclips therapy is efficient and safe in treatment of bleeding peptic ulcers. Combination therapy of hemoclips and epinephrine has no advantage over hemoclips monotherapy. Therefore, the combination therapy is not currently recommended until obtaining the eventual more relevant data from larger studies.

**References**


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