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The Effect of Proton Pomp Inhibitor (PPI : Rabeprazole) on Reflux Esophagitis after Endoscopic Injection Sclerotherapy (EIS), a Randomized Control Study (24 hour-pH monitoring)

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Abstract

Background: Transient esophageal ulceration is a common finding after sclerotherapy of varices. These ulcers sometimes cause pain, ulcer bleeding, and stricture formation. Gastroesophageal reflux (GER) after Endoscopic injection sclerotherapy (EIS) is a known cause of worsening ulcer formation. Therefore, an efficient drug for GER is desirable to improve the quality of life of patients with esophageal varices.

Methods: We randomized 18 Japanese cirrhotic patients who had risky esophageal varices. The patients were randomly allocated into two groups, and during EIS sessions, one group was administered proton pump inhibitor (PPI) (Rabeprazole 20mg a person once a day), while the other received histamine H2 receptor antagonist (H2-blocker) (famotidine 20mg a person, twice a day). Gastroesophageal reflux was monitored by a 24-h pH-monitoring catheter introduced into the distal esophagus. Ulcer formation was evaluated using an endoscopic examination. The subjective and objective symptoms were also compared between the two groups.

Results: All patients in the H2-blocker group showed an increased percentage of time with pH < 4.0 after EIS sessions, but no patients in the PPI group showed an increased such symptoms. The H2-blocker group also experienced a significantly higher number of days of heartburn and dysphasia than did the PPI group (p = 0.017, p = 0.042). The rate of ulcer improvement was found to be faster in Rabeprazole group than in H2 blocker group (p = 0.008).

Conclusion: These results suggest that Rabeprazole treatment prevents EIS-associated gastroesophageal reflux and promotes ulcer healing. Rabeprazole also improve the subjective symptoms following EIS.

Key words: Esophageal varices ・ Portal hypertension ・ Proton pump inhibitor

Introduction

Endoscopic injection sclerotherapy (EIS) is one of standard therapy for esophageal varices1–3. The overall complication rate of the procedure is acceptably low, but the incidence of adverse effects following EIS increases with the duration and type of injection therapy4–6. Mucosal slough and/or ulceration or esophageal stricture are the most frequent adverse effects of EIS (13–78%)4–9.

Abbreviations

EIS : Endoscopic injection sclerotherapy, 24h-pH : 24-hour pH monitoring, PPI : Proton pump inhibitor, GER : Gastroesophageal reflux, GERD : Gastroesophageal reflux disease, H2-blocker : histamine H2 receptor antagonist

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It is suspected that the highly toxic nature of the sclerosant solutions used in EIS results in subacute mucosal or deep-tissue necrosis. Injection technique, frequency of injection, and amount and type of sclerosant injected are important in determining the frequency and severity of the complications seen\(^6\). Also, it has been shown that acid bathing the chemically-induced mucosal injury caused by EIS may have an effect on the healing or severity of the complications\(^7,8\).

Esophageal motility disorders and gastroesophageal acid reflux may result from repeated injections near the lower esophageal sphincter, leading to a delay in esophageal acid clearance or an increase in acid reflux.

There also have been several reports describing an increase in gastroesophageal reflux after EIS therapy\(^8\)\(^-\)\(^10\). Stricture of the esophagus after EIS is believed to be aggravated by gastroesophageal acid reflux\(^11\)\(^-\)\(^13\).

Therefore, we hypothesized that the use of more potent acid-suppressing agents should result in reductions in ulceration, symptoms (heartburn, chest pain, dysphagia) associated with EIS, and, ultimately, stricture formation.

**Patients and Methods**

From April to December 2001, 18 cirrhotic Japanese patients with esophageal varices were admitted to our hospital for treatment. All patients had esophageal varices of moderate or huge size (F2 or F3) that showed one of several marks (red wale marking (+ + , +++) , cherry red spot (+ + , +++) , and hematocystic spot (+)). These 18 patients were randomly allocated to two groups by the sealed envelope method before treatment. Nine of 18 patients were given H2-blocker (famotidine 20mg a person, twice a day) for 8 weeks (H2-blocker group), whereas the remaining 9 patients were given PPI (Rabeprazole 20mg a person once a day) for 8 weeks (PPI group) (Table 1). The protocol was approved before starting this study in the ethics committee of the department of surgery II in Kyushu university. The registry were strictly administrated in our research group.

These esophageal varices were given prophylactic injections, in accordance with our criteria\(^14\). All treatments were performed by two specialized endoscopists using a standardized technique. Briefly, the initial session of sclerotherapy was performed using a transparent over-tube, details of which have been described elsewhere\(^3\)\(^-\)\(^5\). The sclerosant used was 5% ethanolamine olate (Glehn CO., Ltd). Subsequent EIS sessions were performed using the free-hand technique weekly until all varices were eradicated.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics and clinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPI</td>
</tr>
<tr>
<td>Number of patients</td>
<td>9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.5 ± 9.1</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/2</td>
</tr>
<tr>
<td>Etiology of Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Alcoholic</td>
<td>1</td>
</tr>
<tr>
<td>C type hepatitis</td>
<td>7</td>
</tr>
<tr>
<td>B type hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Child’s classification</td>
<td></td>
</tr>
<tr>
<td>Child A</td>
<td>4</td>
</tr>
<tr>
<td>Child B</td>
<td>4</td>
</tr>
<tr>
<td>Child C</td>
<td>1</td>
</tr>
<tr>
<td>Child–Pugh score</td>
<td>6.8 ± 1.2</td>
</tr>
<tr>
<td>Number of sessions</td>
<td>4.1 ± 0.5</td>
</tr>
<tr>
<td>Used 5% ethanolamine olate (ml)</td>
<td>45.2 ± 5.5</td>
</tr>
</tbody>
</table>

PPI : Rabeprazole, H2-RA : Famotidine
**24-hour pH monitoring of esophagus, pre- and post-EIS**

This study employed 24-hour pH monitoring (24h-pH) using the pH 101-ZG system (Chemical INS co., Ltd. Tokyo Japan). A pH catheter was passed through the nose and the proximal sensor was positioned using X-ray guidance in the esophagus 5 cm above the esophagogastric junction. All patients remained without any antireflux or antiacid medication during the pH-monitoring study and the preceding 24-h period before EIS. Acid reflux was defined as whenever the pH in the esophagus dropped to 4.0 or less. Total time in minutes with esophageal pH less than 4.0 was calculated for each 24-hour period and mean esophageal pH was calculated as an average of all the pH values.

**Symptomatic assessment**

We assessed whether the symptoms were present. A bedside questionnaire revealed Heartburn, chest pain (retrosternal pain), and dysphagia (difficulty of swallow requiring soft meals). The total numbers of days for which symptoms were noted were compared for the H2-blocker group and the PPI group.

Evaluations of esophageal ulceration were assessed endoscopically a week after each session of EIS treatment. If present, the longitudinal diameter was measured. Then the number of weeks until the ulcer showed heal were calculated.

**Statistical analysis**

Data are expressed as the mean ± standard deviation. Intergroup comparisons were performed using Student’s t-test for continuous variables and a χ² test for categorical variables. Statistical significance was established at p < 0.05.

**Results**

**The patients characteristics**

Table 1 shows the characteristics of the patients. Because the two groups are comparable regarding age, sex, the severity of liver disease, and Child–Pugh score, there are no significant differences between the groups. Average number of sessions and usage of sclerosant did not significantly differ between the groups. In addition, during this investigation, there were no life-threatening complications, that prolonged hospital stays.

**24-hour pH monitoring during EIS sessions**

Before EIS, GERD (Gastroesophageal reflux disease: pH < 4.0) was seen in three patients (33.3%) of the H2-blocker group and four (44.4%) of the PPI group, but no patients had heartburn, dysphagia, or chest pain. Table 2 shows that although EIS session were followed by a significantly worsening of mean pH value in all patients of the H2-blocker group (p = 0.035), were not in all patients of PPI group (p = 0.023). In addition, H2-blocker patients showed a significant increase in the percentage of time with pH < 4.0 after the EIS session (p = 0.002), but no the PPI-group patients showed an increased percentage of time with pH...
< 4.0 after the EIS sessions (p < 0.001). Figure 1 shows the 24hr-pH monitoring of representative patients in H₂ blocker group and the PPI group.

**Symptoms and Endoscopic findings**

Table 3 shows the total days of chest pain, heartburn, and dysphagia occurrence. Heartburn and dysphagia lasted for significantly more days for the H₂-blocker group than for the PPI group (p = 0.017, p = 0.042). However, there was no significant difference in chest pain between the two groups (p = 0.269).

Table 4 shows that the longitudinal size of ulcer formation was not significantly different between the two groups, but the time required for ulcer healing was significantly shorter for the PPI group than for the H₂-blocker group (p = 0.008).

Stenosis of the esophagus after treatment of EIS was not found in either group during the follow-up periods.

**Discussion**

In our EIS technique, we performed intravariceal injection of sclerosant in the first and second sessions. Paraesophageal injection was performed in the third and fourth sessions. The average amount of sclerosant injected was about 40 ml. Accordingly, it seemed impossible to avoid some degree of GERD. A greater amount of injected sclerosant prevented the first bleeding and the rebleeding of the esophageal varices. However, an ulcer formation, a stricture of the esophagus, and post-EIS reflux esophagitis were correlated to the amount of sclerosant. Therefore,

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**Table 2** Effect of Rabeprazole or H₂blocker on gastroesophageal reflux monitored using a 24-hour pH monitor

<table>
<thead>
<tr>
<th></th>
<th>Mean Esophageal pH</th>
<th>Time pH &lt; 4.0 (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-EIS</td>
<td>Post-EIS</td>
</tr>
<tr>
<td>H₂blocker Group  (n=9)</td>
<td>5.32 ± 0.18</td>
<td>4.87 ± 0.48&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rabeprazole Group  (n=9)</td>
<td>5.21 ± 0.28</td>
<td>7.02 ± 0.52&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> p < 0.05 vs. Pre-EIS

<sup>b</sup> p < 0.05 vs. Post-EIS in H₂blocker Group

N.S.: Not significant

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**Table 3** Clinical symptoms

<table>
<thead>
<tr>
<th></th>
<th>Chest pain (days)</th>
<th>Heart burn (days)</th>
<th>Dysphagia (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂blocker Group  (n=9)</td>
<td>1.56 ± 1.00</td>
<td>1.68 ± 1.03</td>
<td>2.00 ± 1.50</td>
</tr>
<tr>
<td>Rabeprazole Group  (n=9)</td>
<td>0.83 ± 1.03</td>
<td>0.40 ± 0.69</td>
<td>0.71 ± 1.05</td>
</tr>
</tbody>
</table>

* < 0.05

N.S.: not significant

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**Table 4** Endoscopic findings

<table>
<thead>
<tr>
<th></th>
<th>Ulcer size (case)</th>
<th>Weeks until ulcer healing (week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 2 cm</td>
<td>2 cm ≤</td>
</tr>
<tr>
<td>H₂blocker Group  (n=9)</td>
<td>6 (66.7%)</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td>Rabeprazole Group  (n=9)</td>
<td>5 (55.6%)</td>
<td>1 (11.1%)</td>
</tr>
</tbody>
</table>

* p < 0.01

N.S.: Not significant
a method preventing these complications has been needed in order to improve the quality of life of patients receiving EIS.

Some previous reports suggested that acid–pepsin reflux might play a role in causing ulcers to worsen delaying the healing of post–EIS esophageal ulcerations, and following esophageal stricture. Previous investigators showed acid pepsin reflux worsened significantly with 24h–pH monitoring. The esophageal acidity correlated with the delayed healing of post–EIS and post-esophageal stricture. Accordingly, a more powerful inhibitor might be useful for the prevention of these complications.

Rabeprazole is a proton pump inhibitor, which is known that single 20mg daily dose significantly decreases 24–hour intragastric acidity. Williams et al. reported that Rabeprazole has a significantly faster onset of antisecretory activity than Omeprazole. Therefore, Rabeprazole is useful for reducing the complications following EIS treatment.

Some studies reported that, following EIS, sclerophate and H2–blocker failed to improve GERD, while PPI reduced the ulcer formation. However, the efficiency of PPI for GERD after EIS using pH monitoring had not been studied yet.

The aim of this study was to clarify the efficiency of PPI for GERD after EIS. Our study showed that PPI improved the mean value of esophageal pH and pH < 4.0 holding time of the esophagus, while H2–blocker did not improve them significantly. In addition, healing of post–EIS ulceration and symptoms in the PPI group improved significantly compared to the H2–blocker group.

Several randomized, controlled trials have shown that EIS can arrest acute bleeding, decrease the frequency of rebleeding, and increase survival in patients with bleeding esophageal varices. In some studies, especially in Japan, the effectiveness of prophylactic EIS treatment for esophageal varices has been demonstrated. However, endoscopic variceal ligation (EVL) is also an effective procedure to control bleeding of esophageal varices with less complications, but most studies have revealed that variceal recurrence was more frequent. Therefore, EIS is the first-choice therapy in most Japanese facilities, including our department.

Althogh esophageal ulceration is unavoidable with sufficient EIS treatment in some patients, the residue of the ulceration continues to cause discomfort for EIS patients. For ulcerations and following stricture and their concomitant symptoms, which can diminish a patient’s quality of life, PPI appears to be more cost effective than H2–blocker. Accordingly, the early healing of esophageal ulceration and the prevention of ulcer development is considered to be very important. The early healing of ulceration after EIS is considered to be important for relieving both mental and physical stress in patients during EIS treatment.

This study found that Rabeprazole treatment decreases the risk of development of EIS–associated gastroesophageal reflux and promotes ulcer healing and easing of chest discomfort in patients during EIS. Therefore, using Rabeprazole during EIS sessions might improve the quality of life of patients with esophageal varices.

Reference

1987.


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内視鏡的硬化療法後の胃酸逆流に対するプロトンポンプ阻害剤 ラベプラゾールの治療効果の検討：
(24時間 PHモニターを用いた無作為化比較研究)

【背景】食道静脈瘤に対する内視鏡的硬化療法（EIS）後の食道潰瘍は最も認められる合併症である。食道潰瘍は、疼痛の原因となり、悪化すれば潰瘍出血と狭窄形成が起きる。胃食道逆流（GER）は、潰瘍形成を悪化させる既知の原因である。従って、GERの薬剤であるプロトンポンプ阻害剤は、治療後の患者的QOLを改善する可能性がある。

【方法】我々は、易出血性食道静脈瘤が認められ、内視鏡的硬化療法を受けた18例の患者をヒスタミンH2レセプター拮抗剤（H2受容体遮断薬）（40mg 2x/day）を治療後1週間内服する群（H2-blocker群）、またはプロトンポンプ阻害剤（PPI）（20m 1x/day）を治療後1週間内服する群（PPI群）に分け、胃食道逆流（遠位食道にもたらされる24時間のPH監視カテーテル検査）、潰瘍形成所見（上部内視鏡検査）、治療後の自覚症状について2群間で比較した。

【結果】H2-blocker群では、EIS治療後、pH<4.0で示す胃酸逆流時間は有意に増加したが、PPI群では、胃酸逆流の時間は増加を認めなかった。胸やけと嚥下障害の日数はH2-blocker群に比べPPI群では有意に少なかった。（胸焼けp=0.017、嚥下障害p=0.042）。内視鏡的に評価した潰瘍改善率もPPI群で早期に認められた（p=0.008）。

【結論】プロトンポンプ阻害剤であるRabeprazoleは内視鏡的硬化療法後に合併する胃酸逆流による症状と潰瘍形成を改善する。