Risk Factors for Dieulafoy Lesion in Upper Gastrointestinal Tract

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Background/Aims: The purpose of this study is to verify the risk factors associated with Dieulafoy lesion formation in upper gastrointestinal tract.

Methods: A case-control study was performed by reviewing the electronic medical records of 42 patients who were admitted to a tertiary medical center in the Daejeon region for Dieulafoy lesion from September 2008 to October 2013 and the records of 132 patients who were admitted during the same period and who underwent endoscopic examinations for reasons other than bleeding. We analyzed the clinical and endoscopic findings retrospectively and looked for associated risk factors of Dieulafoy lesion formation.

Results: All 42 patients diagnosed with Dieulafoy lesion had accompanying bleeding, and the location of the bleeding was proximal in 25 patients (59.5%), middle portion in 7 patients (16.7%), and distal in 10 patients (23.8%). Antiplatelet agents (p=0.022) and alcohol (p=0.001) showed statistically significant differences between the two groups. The odds ratio (95% confidence interval) of the two factors were 2.802 [1.263-6.217] and 3.938 [1.629-9.521], respectively.

Conclusions: This study showed that antiplatelet agents and alcohol ingestion were risk factors associated with Dieulafoy lesion formation in upper gastrointestinal tract.

Keywords: Dieulafoy; Gastrointestinal bleeding; Endoscopic treatment; Antiplatelet agents; Alcohol

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INTRODUCTION

Upper gastrointestinal bleeding is a medical emergency, and a Dieulafoy lesion is an important cause of such bleeding that is potentially life threatening. It constitutes 6% of upper gastrointestinal nonvariceal bleeding and constitutes 1–2% of all gastrointestinal bleeding. While the death rate due to Dieulafoy lesions has a relatively low prevalence rate, it has a similar death rate to other causes of gastrointestinal bleeding.

A Dieulafoy lesion is typically composed of closely attached submucosal arteries of 1–3 mm radius within various distances from the gastric mucosa. Massive hemorrhage may result due to the erosion of the mucosa and arterial wall. Subintimal fibrosis and mucosal damage characteristically lack inflammatory reactions, and thus Dieulafoy lesions can be histologically differentiated from gastric ulcers.

The exact mechanism of bleeding in a Dieulafoy lesion has not yet been identified. Some authors have reported that it is due to the combined effect of atrophy of the gastric mucosa and ischemia. This means that pressure from vessels with a large diameter forms small erosions, which cause the rupture of the vessels into the lumen.

A Dieulafoy lesion clinically presents itself in the form of intermittent indolent gastrointestinal bleeding, most commonly in the stomach, especially in the lesser curvature. Eighty to ninety-five percent of Dieulafoy lesions are known to form within 6 cm of the gastroesophageal junction, due to arterial vessels directly branching from the left gastric artery. One third of Dieulafoy lesions form in places other than the stomach, mostly in the duodenum, followed by the colon. Elsewhere, Dieulafoy lesions have been reported in the esophagus, jejunum, ileum, rectum, and anal canal.

The endoscopic diagnostic rate of Dieulafoy lesions is known to be over 90%, but diagnosis may be difficult during the initial bleeding due to the small size of the lesion and intermittent bleeding patterns. Because of this, 6% of patients require more than three endoscopic examinations for an exact diagnosis.

The traditional method of treatment of Dieulafoy lesions has been surgery. But due to technological advancements in endoscopic treatment, the need for surgery has largely decreased, and the death rate has also decreased from 80% to 8.6%. Currently, the most important treatment method for a Dieulafoy lesion is endoscopic treatment, which is safe and highly effective for early hemostasis.

Many methods of endoscopic treatment are used, such as the injection of sclerosing agents, high temperature coagulation, and the use of apparatus such as band clipping or hemoclipping. The actual method of endoscopic treatment depends on the experience and decision of the endoscopists.

A Dieulafoy lesion is an important cause of bleeding without a clear cause. It is important to know the associated risk factors of Dieulafoy lesion formation, but presently, they are not well-known. The objective of this study is to verify the associated risk factors of
Dieulafoy lesion formation in the upper gastrointestinal tract and to assess the effect of endoscopic treatment of Dieulafoy lesions with bleeding of the upper gastrointestinal tract.

MATERIALS AND METHODS

Patients
A patient-control study was performed by reviewing the electronic medical records of 42 patients who were diagnosed with Dieulafoy lesions after receiving emergency endoscopic treatment due to hematemesis, melena, or hematochezia; these patients were admitted to a tertiary medical facility in the Daejon region from September 2008 to October 2013. A group of 132 patients who received endoscopic treatment for reasons other than bleeding, and who were admitted during the same period, served as the control group.

The 42 patients who were diagnosed with Dieulafoy lesions received basic treatment before receiving emergency endoscopic treatment. All procedures regarding the patients were performed within at least six hours of being admitted to the emergency room, by three endoscopic specialists. Consent forms were signed by all patients or their families. All patients received intravenous proton pump inhibitors before receiving emergency endoscopic treatment, and some received intravenous analgesics if necessary. However, not a single patient received intravenous sedatives. Follow-up endoscopy was performed within three days of the initial endoscopic treatment, and in patients with rebleeding, emergency endoscopic treatment was performed on the day of the bleeding, while follow-up was performed within three days. The 132 patients in the control group were selected from patients who were admitted during the same period who received endoscopic treatment for reasons other than bleeding. Information about patients was collected through reviewing the electronic medical records, which included information regarding basic biographical data, medication history (NSAIDs, anticoagulants, or antiplatelet agents), initial hemodynamic conditions, blood test results, and methods of endoscopic treatment and their results (rebleeding, survival and death, or need for surgery). For the precise selection of the Dieulafoy lesion patient group, electronic medical records were acquired for patients diagnosed with Dieulafoy lesions, and patients who received a definite diagnosis from endoscopic specialists who reexamined their endoscopic records were included in the study.

Definitions
Endoscopic diagnosis of a Dieulafoy lesion was made according to the following three criteria: 32 1) active arterial spurting or micropulsatile streaming from minute (< 3 mm) mucosal defects, 2) visualization of a protruding vessel with or without active bleeding within a minute mucosal defect with normal surrounding mucosa, or 3) a densely adherent clot with a narrow attachment point to a minute mucosal defect or normal-appearing mucosa.

Initial failure of endoscopic hemostasis was defined as continued active bleeding despite
endoscopic treatment or hematemesis, melena, hematochezia, and hemodynamically unstable conditions (systolic BP below 100 mm Hg, heart rate exceeding 100/min, decrease of standing systolic BP larger than 20 mm Hg, and heart rate 20/min) within 12 hours of initial endoscopic hemostasis. Rebleeding was suspected with hematemesis, melena and hematochezia, or hemodynamically unstable conditions, or with decreased hemoglobin exceeding 2 g/dL within 24 hours and was diagnosed if bleeding was endoscopically confirmed at the location of the previously treated lesion.

Affecting factors included the anticoagulants warfarin, rivaroxaban, and dabigatran, the antiplatelet agents aspirin, clopidogrel, and cilostazol, and the NSAIDs tramadol, acceleofenac, dexibuprofen, meloxicam, ketorolac, naproxen, celecoxib, nimesulide, sulindac, and zaltoprofen.

**Statistical analysis**

In order to verify the statistical meaning of baseline characteristics of Dieulafoy lesion formation between the two groups, cross analyses of Chi-square test, T-test, and logistic regression analysis were performed. In addition, frequency analysis was performed in order to verify the associated diseases between the two groups. All positive analysis of this study was verified at a significance level of p < 0.05, and all statistical treatment was performed using the SPSSWIN version 21.0 program.

**RESULTS**

Of all the patients who underwent endoscopic treatment during the study period, 51 patients were diagnosed with Dieulafoy lesions, but upon further review of their endoscopic records by endoscopic specialists, 9 were excluded, and 42 patients were definitively diagnosed with Dieulafoy lesions and were ultimately included in this study. (Table 1) All 42 patients had accompanying bleeding, and the location of the bleeding was proximal (cardia ~ upper body) in 25 patients (59.5%), in the middle (mid-body) portion in 7 patients (16.7%), and distal (lower body ~ pylorus) in 10 patients (23.8%). The initial endoscopic treatment method was hypertonic saline-epinephrine injection in 1 patient (2.4%), hemoclipping in 19 patients (45.2%), and a combination of hypertonic saline-epinephrine injection and hemoclipping in 22 patients (52.4%). All 42 patients who received initial endoscopic treatment achieved primary hemostasis, while no patient failed to achieve successful endoscopic hemostasis. Rebleeding occurred in 4 patients (9.5%) within 1–3 days of initial endoscopic treatment, but all achieved permanent hemostasis with additional endoscopic hemostatic treatment (hemoclipping in 1 patient and a combination of hypertonic saline-epinephrine injection and hemoclipping in 3 patients). (Figure 1)

The correlation of Dieulafoy lesion formation and sex, the administration of drugs (NSAIDs, anticoagulants, antiplatelet agents), associated diseases (diabetes, hypertension, etc.), and smoking and alcohol consumption between the patient and control groups were analyzed. (Table 2)

Upon analysis, antiplatelet agents (p=0.022)
and alcohol ($p=0.001$) showed statistically significant differences between the two groups. An analysis performed using the logistic regression model showing the contribution rate of these two factors showed that the odds ratios (95% confidence interval) were $2.802$ [$1.263$–$6.217$] for antiplatelet agents and $3.938$ [$1.629$–$9.521$] for alcohol. (Table 3)

In the analysis of the method of endoscopic treatment that resulted in rebleeding in 4 patients, none was due to hypertonic saline-epinephrine injection, 1 was due to hemoclipping, and 3 were due to a combination of hypertonic saline-epinephrine injection and hemoclipping. However, as the sample size was small, there was no statistically significant difference ($p=0.626$). (Table 4)

The methods and results of endoscopic treatment of the patients are summarized in detail in Figure 1.

The average outpatient follow-up period for the 42 patients diagnosed with Dieulafoy lesions was 12 months (5–24 months). No patient showed rebleeding during the follow-up period, and there were no complications associated with the treatment.

DISCUSSION

The Dieulafoy lesion was first described in 1884 by Gallarden, and in 1898, the French surgeon George Dieulafoy found common characteristics, which he named the Dieulafoy lesion, in three patients.

A Dieulafoy lesion is an important cause of life-threatening upper gastrointestinal bleeding. It comprises 6% of all upper gastrointestinal bleeding and comprises 1–2% of all gastrointestinal bleeding.

In this study, the clinical features of patients with Dieulafoy lesions were similar to the results of previous studies. During the study period, Dieulafoy lesions occurred in women two times as often as in men, while the patients’ average age was 64.8 years. Analysis of the study results showed that there were statistically significant differences between the studied group and the control group for antiplatelet agents ($p=0.022$) and drinking ($p=0.001$).

Some previous studies have suggested a correlation between Dieulafoy lesions and the administration of NSAIDs or aspirin, and there have been reports of NSAIDs and aspirin causing erosive gastritis through necrosis of vessel walls. In this study, the rates of administration of NSAIDs, anticoagulants, and antiplatelet agents were 16.7%, 7.1%, and 45.2%, respectively. However, only antiplatelet agents were statistically significant.

A previous study has shown the effects of chronic drinking on the gastric mucosa of animals, and the results are as follows. Chronic drinking firstly resulted in the damage of the mucosal epithelium, secondly resulted in the decrease of mucosal cells near the pylorus, and thirdly resulted in the decrease of gastric mucosal thickness. It is probable that chronic drinking damages gastric mucosa through such mechanisms, which, as a result, increases the risk of Dieulafoy lesion formation.

In this study, over 80% of patients with Dieulafoy lesions had associated diseases. Some authors of previous studies have
reported that associated diseases such as cardiac disorders, hypertension, and renal failure alter the normal process of angiogenesis, resulting in the formation of abnormal vessels of a certain diameter, which increases the prevalence rate of Dieulafoy lesions.\textsuperscript{35}

Endoscopic treatment is a key treatment method for Dieulafoy lesions. It is very safe and effective, leading to successful initial hemostasis.\textsuperscript{1,22} Many methods of endoscopic treatment leading to successful initial hemostasis have been reported, including injection of sclerosing agents\textsuperscript{22,23,36}, high temperature coagulation\textsuperscript{23,33}, and the use of apparatus such as band clipping\textsuperscript{37} or hemoclipping\textsuperscript{38} The success rate of hemostasis of the various endoscopic treatment methods ranges from 70% to 98%.\textsuperscript{23-26} Recent studies have shown that band clipping or hemoclipping increase the success rate of primary hemostasis while decreasing the need for additional endoscopic treatment.\textsuperscript{37} Theoretically, as the use of apparatus results in less damage to surrounding tissue compared to the injection of sclerosing agents or high temperature coagulation methods, it is being proposed as the primary treatment method of Dieulafoy lesions.\textsuperscript{31,39} In addition, another study has reported that the combination of hemoclipping and aethoxysklerol is the most effective treatment.\textsuperscript{40}

In this study, all 42 patients (100%) diagnosed with Dieulafoy lesions successfully achieved primary hemostasis, which is a higher success rate than those reported in previous studies.\textsuperscript{21,39,41} Four patients (9.5%) had rebleeding within 1–3 days of initial endoscopic treatment, but all achieved permanent hemostasis with additional endoscopic hemostatic treatment (hemoclipping in 1 patient and a combination of hypertonic saline-epinephrine injection and hemoclipping in 3 patients). Analysis of the association between rebleeding and the method of endoscopic treatment in the four patients showed that a combination of hypertonic saline-epinephrine injection and hemoclipping resulted in rebleeding in three patients. However, there was no statistically significant difference ($p=0.626$). Analysis of the initial hemoglobin values and hemodynamic conditions and the amount of total red blood cell transfusion during the admission period of the four patients with rebleeding showed that the selection of combination treatment rather than a single treatment method was probably due to the severity of the bleeding.

The long-term prognosis of the Dieulafoy lesion patients who received endoscopic treatment was very good\textsuperscript{27,37,42}. Immediate diagnosis and treatment generally results in a very low death rate. In this study, of the 42 patients diagnosed with Dieulafoy lesions, 16 patients (38%) showed hemodynamically unstable conditions, while all 42 patients (100%) showed accompanying active bleeding. All 42 patients survived the five-year study period, while two patients died during the follow-up period due to chronic renal failure and multiple myeloma, respectively, both of which were unrelated to the Dieulafoy lesion. The average outpatient follow-up period was 12 months (5–24 months); not a single patient showed rebleeding during that time, and there were no complications associated with the
treatment.

This study does have a few limitations. Firstly, due to the low prevalence rate of Dieulafoy lesions, the sample size is small. This is also a retrospective study, and as the electronic medical records were not created with research objectives in mind, there is a possibility that information regarding medication history and smoking and drinking may not be accurate. Additionally, there are limitations to giving statistical significance to the results, as the sample size is small. Secondly, there is a possibility that the composition of the control group may be different from that of the normal population. Although the control group was selected during the study period from among the admitted patients in order to reproduce the composition of the normal population, admittedly there are limitations in being able to do so. Thirdly, as all patients diagnosed with Dieulafoy lesions that were registered for this study were diagnosed and treated at only this hospital, there are limitations in overall representability.

Despite these limitations, this study has shown that the risk factors associated with Dieulafoy lesion formation in the upper gastrointestinal tract are antiplatelet agents and drinking.

**Conflicts of Interest**
The authors have no financial conflicts of interest.

**REFERENCES**

Gastrointest Endosc 2003;57:653-656.
Table 1. Location of the Dieulafoy Lesion and Hemostatic Methods

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>(n=42)</td>
</tr>
<tr>
<td>Proximal stomach</td>
<td>25 (59.5)</td>
</tr>
<tr>
<td>Mid-stomach</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>Distal stomach</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>Hemostatic methods</td>
<td></td>
</tr>
<tr>
<td>HSE injection</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Hemoclipping</td>
<td>19 (45.2)</td>
</tr>
<tr>
<td>HSE injection + Hemoclipping</td>
<td>22 (52.4)</td>
</tr>
</tbody>
</table>

Values are number (%).
HSE, hypertonic saline-epinephrine.
**Table 2.** Baseline Characteristics of the Dieulafoy Lesion and Control Group

| Parameters                  | Dieulafoy lesion group (n=42) | Control group (n=132) | p-value  
|-----------------------------|------------------------------|-----------------------|----------
| Age, year                   | 64.8±16.2                    | 61.9±16.5             | 0.326    
| Sex, male/female            | 14 (33.3) / 28 (66.7)        | 66 (50%) / 66 (50%)   | 0.059    
| NSAIDs intake               | 7 (16.7)                     | 26 (19.7)             | 0.663    
| Anticoagulant intake        | 3 (7.1)                      | 4 (3.0)               | 0.237    
| Antiplatelet intake         | 19 (45.2)                    | 35 (26.5)             | 0.022    
| Smoking                     | 13 (31.0)                    | 25 (18.9)             | 0.101    
| Alcohol                     | 16 (38.1)                    | 20 (15.2)             | 0.001    
| Diabetes                    | 15 (35.7)                    | 45 (34.1)             | 0.847    
| Hypertension                | 20 (47.6)                    | 60 (45.5)             | 0.806    
| Concomitant disease (excluding diabetes, hypertension) | 32 (76.2) | 117 (88.6) | 0.055 |

Values are number (%).

NSAIDs, non-steroidal anti-inflammatory drugs.
**Table 3.** Logistic Regression Model Analysis of the Two Factors

<table>
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<th>Parameters</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
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<tr>
<td>Antiplatelet intake</td>
<td>2.802</td>
<td>1.263-6.217</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3.938</td>
<td>1.629-9.521</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
Table 4. An Analysis of the Correlation Between the Hemostatic Methods and Rebleeding

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Rebleeding</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Hemostatic methods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSE injection</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(0)</td>
<td>(100)</td>
</tr>
<tr>
<td>Hemoclipping</td>
<td>18</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>(94.7)</td>
<td>(5.3)</td>
<td>(100)</td>
</tr>
<tr>
<td>HSE injection + Hemoclipping</td>
<td>19</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>(86.4)</td>
<td>(13.6)</td>
<td>(100)</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>(90.5)</td>
<td>(9.5)</td>
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</table>

Values are number (%).
HSE, hypertonic saline-epinephrine.
Figure 1. Summary of the Management Pathways and Treatment Outcomes

Dieulafoy bleeding (n=42)

Endoscopic treatment

HSE injection (n=1)

Hemoclipping (n=19)

HSE injection + Hemoclipping (n=22)

Primary hemostasis, success (n=42)

Non-rebleeding (n=38)  Rebleeding (n=4)

Hemoclipping (n=1)

HSE injection + Hemoclipping (n=3)

Permanent hemostasis (n=42)

HSE, hypertonic saline-epinephrine.