Polidocanol injection therapy for small-bowel hemangioma by using double-balloon endoscopy

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Background and Aims: Small-bowel hemangioma is a rare disease that often causes active bleeding. The standard therapeutic method for small-bowel hemangioma is surgical resection. The aim of this study was to evaluate the usefulness of polidocanol injection (PDI) for small-bowel hemangiomas.

Methods: This study included 12 patients with obscure GI bleeding (6 male; mean age 62 years) with 39 small-bowel hemangiomas; patients were treated with PDI by using double-balloon endoscopy (DBE). EUS with DBE was performed before PDI. The lesions were divided into 2 groups according to tumor size: Group A (size <10 mm; 20 lesions) and group B (size ≥10 mm; 19 lesions). The outcomes of PDI treatment for small-bowel hemangiomas were evaluated between the 2 groups. Additionally, in order to standardize the amount of PDI injected, the total amount of polidocanol according to lesion size was calculated.

Results: There was no difference in the location of lesions and treatment times between the 2 groups. Group B had a significantly higher injection time per lesion (P < .05) and amount of polidocanol per lesion than group A (P < .01). Rebleeding occurred in only 1 case (8%). There were no adverse events related to PDI. The contribution ratio between the lesion size and amount of polidocanol showed a correlation (r = 0.77). The optimal amount of polidocanol for small-bowel hemangioma was determined to be 0.2 mL/mm.

Conclusions: PDI is an easy, safe, and effective method to treat small-bowel hemangiomas.

Small-bowel bleeding accounts for 5% of all GI bleeding.1 In a systematic review, Xin et al² reported that small-bowel vascular lesions account for 40.4% of small-bowel bleeding. Small-bowel hemangiomas, a rare disease that is characterized by small-bowel vascular lesions, can be a major cause of small-bowel bleeding. In the Yano-Yamamoto classification, which is a well-known endoscopic classification for small-bowel vascular lesions, small-bowel hemangiomas are categorized as type 4. However, there is no consensus about therapeutic indications, and surgical resection remains the most common treatment method for patients diagnosed with small-bowel hemangioma.

Polidocanol is widely accepted for endoscopic therapy of esophageal varices as a safe and effective hemostatic treatment for GI bleeding.8-10 Previously, we reported the usefulness of polidocanol injection (PDI) for small-bowel angiectasia by using double-balloon endoscopy (DBE).11 The aim of this study was to evaluate the usefulness of PDI for small-bowel hemangiomas.

Polidocanol is widely accepted for endoscopic therapy of esophageal varices as a safe and effective hemostatic treatment for GI bleeding.8-10 Previously, we reported the usefulness of polidocanol injection (PDI) for small-bowel angiectasia by using double-balloon endoscopy (DBE).11 The aim of this study was to evaluate the usefulness of PDI for small-bowel hemangiomas.

METHODS

Patients
A total of 652 patients with obscure GI bleeding (OGIB) underwent capsule endoscopy (CE) at Hiroshima University Hospital consecutively between August 2007 and March 2014. Twelve patients (1.8%) who were suspected to have small-bowel hemangiomas by CE and who were diagnosed with 39 small-bowel hemangiomas by DBE were enrolled in the study. All patients were treated with PDI by using DBE. We performed DBE within 2 weeks after CE.

Abbreviations: BRBNS, blue rubber bleb nevus syndrome; CE, capsule endoscopy; DBE, double-balloon endoscopy; OGIB, obscure GI bleeding; PDI, polidocanol injection.

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The patients were divided into 2 groups according to lesion size: group A (size <10 mm; 20 lesions) and group B (size ≥10 mm; 19 lesions). Follow-up CE or DBE was performed 3 to 6 months after endoscopic hemostasis, and all patients were followed up for a minimum of 1 year.

We had informed consent from all patients who enrolled in the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Hiroshima University Hospital.

**CE procedure**

CE was performed by using PillCam SB1, PillCam SB2, or PillCam SB3 capsules (Given Imaging Ltd, Yokneam, Israel). The capsule was swallowed with a dimethicone solution after an overnight fast, without any other preparation. Patients were allowed to drink clear liquids and eat a light meal 2 and 4 hours after swallowing the capsule, respectively. The sensor array and recording device were removed 8 hours after each patient swallowed the capsule.

**DBE procedure**

DBE procedures were performed by using the DBE system (FUJIFILM; Saitama, Japan) using a FUJIFILM EN-450 P5, EN-450 T5, or EN-580T endoscope. Patients were required to fast for 8 to 12 hours before oral insertion of the endoscope, similar to the preparation for upper GI endoscopy. All rectal insertions required a preparation similar to that used for colonoscopy. Patients were lightly sedated with pentazocine (15 mg) and midazolam (0.05 mg/kg). All patients underwent CE, and the oral or rectal route was selected based on results of the examination. If the source of bleeding was not identified during the examination, the small-bowel mucosa was marked with pure carbon at the most distal point. When the targeted lesion was encountered, we performed EUS and measured tumor size after endoscopic observation. EUS was attempted by using a miniature EUS probe. As preparation for EUS, both the endoscopic and the overtube balloons were inflated to fix the endoscope to the small-bowel...
wall and to fill balloons with water in the small bowel. We usually used 15-mHz miniature EUS probes (Sonoprobe P series; FUJIFILM). In the cases of strong deep echo attenuation, we used 12-mHz EUS probes (Sonoprobe P series; FUJIFILM) instead of 15-mHz EUS probes.

**PDI procedure for small-bowel hemangiomas**

A 25-gauge local injection needle for the small bowel (TOP Corporation, Tokyo, Japan) was used for PDI. The polidocanol preparation (1%) was created at Hiroshima University Hospital. We punctured the lesions under direct vision, checked to ensure no backflow of blood, and injected 0.5 mL polidocanol (Fig. 1). The color change and degree of swelling at the time of injection were monitored.

**Evaluation**

We evaluated the clinical characteristics of the patients and PDI outcomes (location of lesion, injection time per lesion, amount of polidocanol injected) between the 2 groups. We also analyzed the rebleeding rate and PDI-related adverse events. Rebleeding was defined as evidence of recurrent visible GI bleeding (melena or hematochezia) on recent negative upper and lower GI endoscopies and/or a subsequent decrease in hemoglobin level >2 g/dL from baseline. Furthermore, in order to standardize the amount of PDI, we calculated the total amount of polidocanol used according to lesion size.

**Statistical analysis**

Comparisons were performed by using the unpaired t test for quantitative data and the chi-square test for categorical data. Yates correction or the Fisher exact test were used when necessary. All tests were 2-sided, and P < .05 was considered statistically significant. In addition, we analyzed the correlation between tumor size and amount of polidocanol injected. The JMP10 statistical software package (SAS Institute Inc, Cary, NC) was used for all calculations.

**RESULTS**

Twelve patients were included in the study (6 male, 6 female; average age = 62 years). The clinical characteristics of the study patients are shown in Table 1. Of the 12 patients, 6 patients (50%) required blood transfusion. The mean lowest hemoglobin level was 6.7 ± 1.8 g/dL (normal hemoglobin level is 11.4 g/dL), and the median follow-up period was 65 months (range 12-91 months).

In EUS, small-bowel hemangiomas were visualized as multiple small-round anechoic lesions in mucosal, submucosal, and muscularis layers in all cases. The outcomes of PDI for small-bowel hemangiomas according to lesion size are shown in Table 2. In group A, there were 18 lesions in the jejunum and 2 lesions in the ileum. In group B, there were 14 lesions in the jejunum and 5 lesions in the ileum. The lesion location and treatment duration were not significantly different between the 2 groups. The number of injections and the amount of polidocanol used per lesion were significantly higher in group B than in group A (P < .05 and P < .01, respectively). The 12 cases treated with PDI for small-bowel hemangiomas are shown in Table 3. Two cases in this study (cases 3 and 6) were blue rubber bleb nevus syndrome (BRBNS). The average total amount of polidocanol used was 6.4 mL case, and 11 patients required only 1 round of endoscopic therapy. Case 6 needed 2 rounds of therapy because of the existence of 11 lesions. We performed the second DBE 2 days after the first PDI. Rebleeding occurred in 1 lesion (9%, diameter = 10 mm) 7 days after the first PDI and was managed endoscopically with additional PDI. The final hemostasis rate was 100% (12/12), and the adverse event rate related to PDI was 0% (0/12). The relationship between the lesion size and amount of polidocanol used is shown in Figure 2. The contribution ratio between the lesion size and the amount of polidocanol had a correlation of r = 0.77.

**DISCUSSION**

Small-bowel hemangiomas involve nonepithelial benign tumors composed of proliferating blood vessels. Small-bowel vascular tumors account for 7% to 10% of all benign small-bowel tumors. Small-bowel hemangiomas may cause OGIB and be accompanied by abnormal pain, and they usually manifest as single and small lesions of ≤20 mm in diameter. BRBNS associated with multiple

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**TABLE 1. Clinical characteristics of the study patients (n = 12)**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>6 (50)</th>
<th>Female</th>
<th>6 (50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (± SD), median (range), y</td>
<td>62.1 (± 19.8), 68 (17-86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding type, no. (%)</td>
<td>Occult</td>
<td>3 (25)</td>
<td>Overt</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Lesions, no. (%)</td>
<td>Single</td>
<td>7 (59)</td>
<td>Multiple</td>
<td>5 (41)</td>
</tr>
<tr>
<td>Blood transfusion, no. (%)</td>
<td>6 (50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug use, no. (%)</td>
<td>Antithrombotic</td>
<td>1 (8)</td>
<td>NSAID</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Laboratory data, mean (± SD)</td>
<td>Hemoglobin (g/dL)</td>
<td>6.7 (± 1.8)</td>
<td>Iron (μg/dL)</td>
<td>67.9 (± 72.0)</td>
</tr>
<tr>
<td>Follow-up period, median (range), mo</td>
<td>65 (12-91)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD, Standard deviation; NSAID, nonsteroidal anti-inflammatory drug.
rubbery cavernous hemangiomas on the skin and GI tract mucosa has been reported frequently with small-bowel hemangiomas.\textsuperscript{13}

Small-bowel hemangiomas are relatively soft submucosal tumors that appear as blue or dark red in color on endoscopic findings. Histopathologically, GI hemangiomas are classified as capillary hemangiomas, cavernous hemangiomas, or mixed capillary and cavernous hemangiomas, according to the diameter of the injured vessel.\textsuperscript{14} Capillary hemangioma is the most frequently encountered form of small-bowel hemangioma.\textsuperscript{15} In general, diagnosis of small-bowel hemangioma is confirmed by color and/or EUS. Diagnosis of endoscopic biopsy carries a risk of bleeding and is contraindicated. We have reported the usefulness of EUS with DBE for diagnosis of small-bowel diseases.\textsuperscript{16} In particular, EUS with DBE makes it possible to confirm small-bowel hemangioma.\textsuperscript{17} The balloon of DBE stabilizes the small bowel at the targeted site of the lesion, and the endoscopic balloon obstructs the intestinal lumen to facilitate filling the small-bowel lumen with water at the site of the lesion. Therefore, EUS of DBE is easy and safe.

As a clinical trial, we performed EUS to confirm small-bowel hemangioma precisely in all cases to avoid PDI into the artery directly. Small-bowel submucosal tumors in BRBNS patients are mainly recognized as cavernous hemangiomas;\textsuperscript{13} therefore, these lesions may allow the omission of EUS.

Surgery is the standard therapeutic method for small-bowel hemangiomas.\textsuperscript{4-7} Recently, there have been reports of successful endoscopic therapies for small-bowel hemangiomas, which use argon plasma coagulation, polypectomy, and EMR by using balloon endoscopy.\textsuperscript{18-20} The small-bowel wall is thinner than that of the stomach

### Table 2. Outcomes of PD injection therapy for small-bowel hemangiomas (n = 39)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (n = 39)</th>
<th>&lt;10 (n = 20)</th>
<th>≥10 (n = 19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection times per lesion (range)</td>
<td>1.5 (1-9)</td>
<td>1.1 (1-2)</td>
<td>1.8 (1-9)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Amount of PD per lesion, mL</td>
<td>1.7 (0.5-6.5)</td>
<td>0.9 (0.5-2.5)</td>
<td>2.5 (1.0-6.5)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Rebleeding lesions, no. (%)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Adverse events, no. (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

PD, Polidocanol; NS, not significant.

### Table 3. Summary of patients receiving PD injection therapy for small-bowel hemangiomas*  

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Bleeding type</th>
<th>Lesion no.</th>
<th>Location</th>
<th>Amount of PD, mL</th>
<th>Treatment times</th>
<th>Rebleeding</th>
<th>Follow-up period, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>54</td>
<td>Occult</td>
<td>1</td>
<td>Ileum</td>
<td>2.5</td>
<td>1</td>
<td>No</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>73</td>
<td>Overt</td>
<td>8</td>
<td>Jejunum</td>
<td>5.5</td>
<td>1</td>
<td>No</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>42</td>
<td>Occult</td>
<td>6</td>
<td>Jejunum</td>
<td>6.0</td>
<td>1</td>
<td>No</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>57</td>
<td>Overt</td>
<td>1</td>
<td>Jejunum</td>
<td>4.7</td>
<td>1</td>
<td>No</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>76</td>
<td>Overt</td>
<td>1</td>
<td>Ileum</td>
<td>4.5</td>
<td>1</td>
<td>No</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>32</td>
<td>Overt</td>
<td>11</td>
<td>Jejunum</td>
<td>32.0</td>
<td>2</td>
<td>No</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>73</td>
<td>Occult</td>
<td>1</td>
<td>Jejunum</td>
<td>3.0</td>
<td>1</td>
<td>No</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>17</td>
<td>Overt</td>
<td>3</td>
<td>Ileum</td>
<td>11.5</td>
<td>1</td>
<td>Yes</td>
<td>66</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>86</td>
<td>Overt</td>
<td>4</td>
<td>Jejunum</td>
<td>3.0</td>
<td>1</td>
<td>No</td>
<td>63</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>66</td>
<td>Overt</td>
<td>1</td>
<td>Jejunum</td>
<td>1.0</td>
<td>1</td>
<td>No</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>69</td>
<td>Overt</td>
<td>1</td>
<td>Ileum</td>
<td>1.5</td>
<td>1</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>84</td>
<td>Overt</td>
<td>1</td>
<td>Jejunum</td>
<td>1.5</td>
<td>1</td>
<td>No</td>
<td>12</td>
</tr>
</tbody>
</table>

PD, Polidocanol; F, female; M, male.
*There were no adverse events reported.

![Figure 2. Amount of polidocanol for small-bowel hemangioma per lesion size.](image)
and colon, and small-bowel hemangiomas form lesions in the submucosal layer. Thus, we think that polypectomy or EMR for small-bowel hemangiomas is dangerous because of the risk of perforation.

The usefulness of PDI for GI bleeding has been reported in several studies. Moreover, we have reported that PDI is useful for the endoscopic hemostasis method of small-bowel angiectasias. Okano et al have described the early and late hemostatic properties of polidocanol from research conducted with dogs. The early hemostatic effects were the result of pressure on the blood vessels with associated interstitial edema and thrombosis formation in small blood vessels, and the late hemostatic effects were caused by thrombus formation from vascular inflammation. Takeuchi et al also reported how PDI affected the gastric wall, especially the submucosal layer in dogs. Microangiography was performed in order to evaluate the status of the gastric submucosal vessels after injection of polidocanol. Soon after injection, marked edema appeared in the submucosal layer, and an avascular area formed. After 3 days, inflammatory cell infiltration was noted in the submucosal layer, and after 7 days, vasculitis and thrombus appeared extensively in the submucosal layer. The extent of the avascular area in microangiography after 7 days was slightly less than that of the avascular area that was formed first. After 14 days, fibrosis and arterial organization occurred in the submucosal layer, and the avascular area was reduced slightly in size. Effects of PDI were limited to the submucosal layer; deeper penetration and perforation after PDI did not occur. The main advantage of PDI is that it is easily performed and requires only an injection needle for use in the small bowel. In this study, the final hemostasis rate was 100%, and there were no adverse events. One point to highlight in carrying out PDI is that it is necessary to precisely inject the polidocanol into the small-bowel hemangioma in order for it not to leak into the abdominal cavity outside the small-bowel wall. In addition, the average amount of polidocanol used to treat the small-bowel hemangiomas in this study was 0.2 mL/mm (Fig. 2).

Our study had some limitations. It was a retrospective study and it included only patients from a single center; therefore, a large-scale, prospective study is needed to confirm the utility of PDI for small-bowel hemangioma.

In conclusion, PDI under DBE is an easy, safe, and effective treatment for small-bowel hemangiomas. We think PDI should become the standard treatment alternative to surgery for small-bowel hemangioma. The optimal amount of polidocanol for small-bowel hemangioma is 0.2 mL/mm.

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