Double-Balloon Enteroscopy-detected Lipid Islets in the Small Bowel are Strong Predictors of Cardiovascular Disease when associated with Angiectasia and Bleeding

Heinz Albrecht, Wolfgang H. Hagel, Alexander F. Hagel, Markus F. Neurath, Martin Raithel

ABSTRACT

Background & Aims: Double-balloon enteroscopy (DBE) is a sensitive and safe procedure for the detection and treatment of mid-gastrointestinal bleeding (MGIB). It combines the possibility of a panenteroscopy with the immediate chance for intervention. This study evaluates the yield of DBE for the detection and treatment of MGIB in an unselected patient cohort.

Methods: In a five-year period a total of 119 DBEs were carried out on 62 patients due to MGIB. Inclusion criteria were hematochezia, melena, anemia, positive hemoccult-test and iron deficiency. All pre-existing diseases or comorbidities were evaluated. Two main statistical methodologies were used in data analysis: descriptive statistics to describe the basic features of our data and Fisher's exact test for comparisons of proportions.

Results: The diagnostic yield was 69% (pathological findings in 43/62 patients) and the main diagnoses in all DBE-procedures were angiodysplasia (22%, 26/119 DBE), followed by lipid islets (18%, 21/119 DBE). In all patients with lipid islets this diagnosis was significantly connected with cardiovascular diseases. The combination of lipid islets and a relevant bleeding source appeared in 79% of the 19 patients with these findings. Of these, 53% had to be treated due to the bleeding event. The overall therapeutic intervention rate was 58%. Serious complications such as perforation or pancreatitis did not occur.

Conclusion: Double-balloon enteroscopy as the gold standard for small bowel investigation in MGIB confirmed its high diagnostic yield in an unselected cohort of patients. A new strong combination of lipid islets with cardiovascular disease was revealed, with a high incidence of angiectasia bleeding. This combination should be evaluated in more detail as a new risk factor for MGIB, and should be regarded in this population when therapeutic anticoagulation is needed.

Key words: double-balloon enteroscopy (DBE) – obscure gastrointestinal bleeding – lipid islets – cardiovascular disease.

INTRODUCTION

Small bowel endoscopy is difficult using conventional endoscopes. For a long period the push enteroscopy (PE), developed in 1990, was the only modality to endoscopically examine proximal parts of the small bowel [1-3]. Since 2001, the wireless capsule endoscopy (CE) developed by G. Iddan und P. Swain (Given Imaging Ltd., Yqneam, Israel) has been available. Capsule endoscopy is the first tool allowing a non-invasive evaluation of the entire small bowel [9, 10] and is mostly used in patients with suspected mid-gastrointestinal bleeding (MGIB) after normal esophagogastroduodenoscopy (EGD) and ileo-colonoscopy. On average, a diagnostic yield of 68% can be achieved by CE, but there is no possibility for therapeutic interventions. And aside from the limited capability to accurately localize potential gastrointestinal bleedings, also „blind spots“ due to the lack of motion control are unavoidable [11].

As an additional modality, in 2001 double-balloon enteroscopy (DBE) was introduced, enabling various therapeutic interventions such as hemostatic treatment in the entire small bowel. Obscure gastrointestinal bleeding (OGIB) is also the
most common indication for DBE, followed by less frequent indications, such as small bowel stricture dilation, postoperative endoscopic retrograde cholangio-pancreatography (ERCP) or adenoma resections (e.g. familial adenomatous polyposis-FAP, Peutz-Jeghers syndrome) [4, 12, 14].

In the first explorative, and then in the later confirmatory prospective DBE trials selected patients were analysed with pre-defined inclusion and exclusion criteria. Thus, very old patients and patients with severe comorbidities such as renal or cardiovascular disease, use of anticoagulants, mechanical ventricular assist device etc. were excluded [9, 10]. However, to examine the general value of DBE in the real world situation we included in this study consecutive patients with suspicion of MGIB from an unselected population over a five-year period.

METHODS

Patient recruitment and design of the study
A total of 119 DBEs were carried out in 62 patients (1.9 DBE/patient) in the endoscopy unit of the Department of Medicine 1 of the University Hospital of Erlangen over a period of 5 years. Indications for performing the procedure were the suspicion of a MGIB with known hematochezia or melena, or a positive Hemoccult test, anemia or iron deficiency. No specific exclusion criteria were applied: excluded were only the patients not able to undergo endoscopy because of vital emergency. All patients were evaluated on an intention-to-treat basis. The study was conducted according to the Declaration of Helsinki. Informed written consent was obtained from every patient or his legal guardian before any intervention. The study was approved by the Institutional Review Board of the Friedrich-Alexander-University Erlangen-Nuremberg, Germany.

The data regarding the patients were prospectively stored in an Access database and retrospectively evaluated using SPSS Version 19 (SPSS Inc., Chicago, IL, USA).

Double balloon enteroscopy
The DBE procedures were performed using enteroscopes of 200 cm working length (EN-450P5/20 and EN-450T5; Fujifilm Europe, Duesseldorf, Germany) with an outer diameter of 8.5 mm and a working channel diameter of 2.2 mm or 9.4 mm and 2.8 mm, respectively. All examinations were done with air insufflation.

The procedures were performed with the patients under monitored anesthesia care: pulse rate, oxygen saturation, blood pressure monitoring, electrocardiography (ECG) if appropriate.

Definition of comorbidities
The accompanying underlying diseases of the patients were classified qualitatively as comorbidity groups, as cardiovascular if one or more cardiovascular diseases were present, e.g. coronary heart disease, aortic valve disease, myocardial insufficiency, arterial hypertension etc. The number of cardiovascular diseases within the cardiovascular group was not further analyzed. In analogy, other comorbidities were documented as gynaecological, immunological, metabolic, neurological, oncological, renal or rheumatoid disease if one or more corresponding diagnoses were present.

Statistics
Descriptive statistics are used to describe the indications to perform DBE, the type of diagnostic imaging performed prior to DBE, the used sedatives, the macroscopic findings and the types of interventions performed. Fisher’s exact test was used for comparisons of proportions such as lipid islets and cardiovascular disease or lipid islets and angiodysplasia. A p value < 0.05 was considered to be significant.

RESULTS

Patients’ characteristics
In the examined period we performed 119 DBEs in 62 patients. The mean age of the patients was 70.36 (23-91) years; 17 (27%) were females and 45 (73%) males. Twenty-four patients underwent DBE one time, 29 patients two times, 3 patients three times, 2 patients four times, and 4 patients five times. Eighty-one procedures were done with an oral approach (68%) and 38 with anal approach (32%).

The indications to perform DBE in these patients were: obscure intestinal bleeding (e.g. iron deficiency anemia), suspicion of Crohn’s disease, suspicion of celiac disease, FAP or lymphoma, suspicion of tumor, positive findings on CE, polypectomy, stenosis, Zollinger-Ellison syndrome and others (removal of foreign body, suspicion of enteritis).

Table I presents the type of diagnostic imaging performed in these patients prior to DBE. The frequency of administration and mean dose of the used sedatives are shown in Table II.

Findings and therapy
Pathological findings were detected in 119 DBE-procedures (63%). In 44 out of all 119 DBEs no pathological findings could be detected (37%). The overall diagnostic yield of DBE in the study patients was 69% (pathological findings in 43/62 patients). Table III summarizes the macroscopic findings, both
in relation to the number of performed DBE examinations, and the number of patients investigated, as some patients had more than one procedure.

Table III. Macroscopic findings per DBE and patient.

<table>
<thead>
<tr>
<th>Macroscopic findings</th>
<th>Total number DBE</th>
<th>Percentage (of a total of 119 DBE)</th>
<th>Total number patients</th>
<th>Percentage (of a total of 62 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiodysplasia</td>
<td>26</td>
<td>22</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Lipid spots</td>
<td>21</td>
<td>18</td>
<td>19</td>
<td>31</td>
</tr>
<tr>
<td>Polyps</td>
<td>16</td>
<td>13</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Ectatic veins</td>
<td>9</td>
<td>8</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Diverticulum</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Ulcer</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Erosion</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Submucosal tumors</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Adenoma</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Petechial bleeding</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Status post bleeding</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Interestingly, all 19 patients with lipid islets (Fig. 1) had a pre-existing cardiovascular disease (see Table IV). Ten of these 19 patients were diagnosed with angiodysplasia (53%, Fig. 2), 6 patients (32%) with ectatic veins and 2 patients (11%) with further diseases associated with bleeding (e.g. bleeding from an ileal diverticulum and erosions). In 4 patients (21%) only lipid islets without further findings were detected. Furthermore, 10 of the above mentioned 19 patients (53%) required an endoscopic intervention to stop bleeding by argon plasma coagulation (APC), hemoclipping or epinephrine injection. The observed association between lipid islets and cardiovascular disease (p = 0.006), between lipid islets and angiodysplasia (p = 0.001) and between lipid islets and ectatic veins (p = 0.019) was highly significant (Table V).

In two further patients, the macroscopic findings detected by DBE substantiated an indication for surgery (removal of tumor).

Table IV. Patients with lipid spots and diagnostic yield.

<table>
<thead>
<tr>
<th>Lipid spots and cardiovascular disease</th>
<th>Total number</th>
<th>Percentage of all patients with lipid spots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid spots and endoscopic intervention</td>
<td>10</td>
<td>53</td>
</tr>
<tr>
<td>Lipid spots and angiodysplasia</td>
<td>10</td>
<td>53</td>
</tr>
<tr>
<td>Lipid spots and ectatic veins</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>Only lipid spots</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>Lipids spots and other source of bleeding</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

Endoscopic therapy

Eighty-one DBEs (68%) were performed without endoscopic therapy, whereas in the course of the remaining 38 DBEs (32%) a therapeutic intervention was required. Table VI summarizes the types of interventions performed. Multiple mentions were possible. In 25 patients out of 62 (40%) an endoscopic therapy was carried out; 33 patients (60%) did not require therapeutic intervention. The intervention rate in the 43 patients with positive results was 58% (25/43).

Table VI. Endoscopic interventions performed.

<table>
<thead>
<tr>
<th>Endoscopic therapy</th>
<th>Total number DBE</th>
<th>Percentage (of the total of 119 DBE)</th>
<th>Total number patients</th>
<th>Percentage (of a total of 62 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argon plasma coagulation (APC)</td>
<td>28</td>
<td>24</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Polypectomy</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Hemoclipping</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Epinephrine injection</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Fig. 1. Lipid islets in the small intestine.

Fig. 2. Angiodysplasia diagnosed by double balloon enteroscopy.

Table V. Correlation between lipid spots, cardiovascular disease, angiodysplasia and ectatic veins.

<table>
<thead>
<tr>
<th>Lipid spots yes</th>
<th>Lipid spots no</th>
<th>P (Fisher’s exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>yes</td>
<td>19</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Ectatic veins</td>
<td>6</td>
<td>13</td>
</tr>
</tbody>
</table>

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Complications

One hundred and eight DBEs (91%) could be performed without any complication in this unselected patient population investigating also elderly patients up to 91 years. No major complications, perforation or cardiocirculatory shock were detected and no fatality occurred. No patient required a surgical procedure resulting from any DBE complication.

In 11 examinations (9%), the following minor complications were observed: a seeping hemorrhage occurred on two occasions, caused in one case by a DBE instrument, and in the other case by a tattoo marking (1% each). On two occasions, an oozing hemorrhage (Forrest 1b) occurred after argon plasma coagulation (APC treatment) (2%). In three examinations, mucous membrane lesions without bleeding and in another three examinations pressure lesions without risk of perforation occurred, whereby in each of them mucous membranes with high vulnerability to physical contact were found (3%).

DISCUSSION

Mid-gastrointestinal bleeding has been evaluated in several studies as a favourable indication for DBE in terms of bleeding source identification and specific endoscopic treatment within the small intestine. In order to prove its true value in the real world situation, we analyzed our DBE examinations performed as clinical routine in a cohort of unselected patients referred to small bowel investigation because of suspected MGIB.

First, we were able to detect pathological findings within the small bowel in 43 patients (69%), reproducing similar results as published in previous studies [6, 15]. Twenty-five of these pathological findings (58%) were treated endoscopically. The remaining pathologies, such as diverticulae, ectatic veins, and erosions did not require immediate endoscopic interventions; however, they represented possible bleeding sources. Similar percentages (42-72%) of intervention-requiring pathologies are found in comparable studies [5, 15]. If endoscopic interventions are conducted, in consistency with other publications, the most common hemostatic measure undertaken in our study is APC of angiodysplasias.

In so far, this study does not significantly differ from previous controlled prospective DBE studies. But due to our unselected patient group without age and comorbidity restrictions, we were able to observe some new relevant findings which have not been described previously. The second most common pathological findings were the lipid islets in 19 patients (30.6%). Interestingly, all of these patients suffered from pre-existing cardiovascular diseases. Ten out of these 19 patients (52%) required endoscopic interventions. Up to now, there is no literature regarding a possible association between the intestinal lipid islets and cardiovascular risk factors or lipid islets and gastrointestinal bleedings from angiectasias. Hence, this might be an incidental finding. But the fact that in none of the comparable studies the diagnosis of lipid islets has been described yet, the conclusion may be drawn, that the present study is the first to describe a potential correlation between lipid islets and pre-existing cardiovascular diseases with a high incidence of angiectasia induction, growth and bleeding probability. And although the given sample size is rather small, lipid islets in patients with pre-existing cardiovascular disease could suggest an increased risk of gastrointestinal bleeding. Furthermore, these observed associations have been shown to be significant. This connection between lipid islets, cardiovascular disease and angiectasia emerged as we examined also elderly and very elderly patients in whom cardiac output, aortic valve stenosis, ventricular assist devices and often an altered pulse wave velocity were manifested. Pathophysiologically, it is of great interest that hypoxia in the small bowel mucosa resulting from reduced cardiac output or altered pulse wave velocity induced an angiogenetic response with an induction of angiectasia growth. Igawa et al. also demonstrated that cardiovascular disease is a significant independent major predictor of small-bowel angiectasia [20]. Thus, our unselected comorbid cohort apparently contained a high proportion of patients with a high angiogenetic potential in response to progredient cardiovascular disease. Lipid islets, which have not yet been described in many other studies with younger patients, may thus be only a marker of progressive cardiovascular disease or even atherosclerosis leading to a more or less relative mucosal hypoxia [13, 16, 19]. As we had to examine clinically a substantial number of consecutive patients with comorbidities, we were able to unravel this possible connection. Although the observed relation of lipid islets, advanced cardiovascular disease, and angiectasia bleeding should be confirmed in further prospective large-scale studies, these findings may be relevant in the future for patients in need of anticoagulation, in very elderly patients or those with advanced comorbidities. Despite a substantial number of comorbidities, the complication rate of DBE for MGIB was extremely low, indicating the high value of DBE even in this population [14, 15].

In summary, since 2001, double-balloon enteroscopy (DBE) has increasingly become the first line modality for the detection and therapy of MGIB. All comparable studies have come to the conclusion that DBE is a safe procedure. The high diagnostic yield and therapeutic intervention rate describe an efficient procedure for hemostasis, usually achieved with APC.

The correlation between lipid islets, pre-existing cardiovascular diseases, and its importance should be evaluated as a possible, new indication of cardiovascular diseases. Moreover, the increased occurrence of gastrointestinal bleedings with secondary diagnosis of lipid islets should be investigated more thoroughly in a larger patient cohort.

CONCLUSIONS

Although several reports of DBE in MGIB have been published, this study resumed this important issue in an unselected patient cohort. A high diagnostic and therapeutic result can be confirmed in patients undergoing standardized preliminary diagnostics. A strong association between lipid islets, pre-existing cardiovascular diseases, and its importance for angiectasia formation have been highlighted in this study. Future studies should continue to evaluate lipid islets in a larger patient cohort as a possible, new indication of cardiovascular diseases, gastrointestinal bleeding, or angiectasia bleeding in anticoagulated patients, respectively.
Conflicts of interest: All authors declare that they have no conflict of interest.

Authors' contribution: H.A., W.H.H. and M.R. contributed to the data-acquisition, concept and design of the research and drafted the manuscript. A.F.H. and M.F.N. contributed to the analysis and interpretation of the data. All authors critically revised the manuscript, agreed to be fully accountable for the integrity and accuracy of this article, and read and approved the final manuscript.

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