Diagnosis and treatment of obscure small bowel bleedings - analysis of double-balloon enteroscopy role in the diagnosis and treatment algorithm on basis of own material

ABSTRACT:
Introduction: Obscure gastrointestinal bleeding (OGIB) is defined as recurrent bleeding to gastrointestinal tract without evaluated origin, despite detailed endoscopic and image diagnostics. The most common reason of OGIB is small bowel bleeding (SBB).

Methodology: Retrospective analysis of patients hospitalized in the Gastroenterology Department of VII Navy Hospital in Gdańsk with suspicion of OGIB.

Results: Double balloon enteroscopy was performed in 31 cases. Origin of bleeding was founded in the small bowel in 87% of cases and in 64 % successful simultaneous therapeutic procedure was performed. No clinically relevant complications were noticed.

Conclusion: According to actual diagnostic algorithms of OGIB, double balloon enteroscopy is highly effective also in the Polish medical care system. This technique is a safe and effective tool in diagnostics and treatment of SBB, but its availability is still limited in Poland.

KEYWORDS: double-balloon enteroscopy, small bowel bleeding

INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is defined as bleeding into the gastrointestinal lumen, which does not cease or recur without a defined cause, despite detailed diagnostics including esophagogastroduodenoscopy, ileocolonoscopy, radiological examinations, arteriography and nuclear medicine [1]. This type of bleeding accounts for about 5% of all gastrointestinal bleeding. The incidence/recognition rate of OGIB is 2-8 cases per 100,000 inhabitants/year and mainly regards men over 60 years of age [2-3]. The main etiologic factor is vascular lesions like intestinal angiodysplasia [4-5]. The majority of lesions responsible for OGIB are located in the small intestine (SBB) and constitute 60-80% of all OGIB causes [6]. While SBB mortality is relatively low (1-2%), relatively high morbidity and problematic diagnostics pose a significant problem for the health care system [7].

AIM OF RESEARCH

The aim of the work is analysis of own material from the Gastroenterology Department of the VII Navy Hospital in Gdańsk-Oliwa. The analysis of collected material is aimed at assessment of the effectiveness of the currently recommended optimal diagnostic and therapeutic algorithm using double-balloon enteroscopy in the environment of the Polish health care system.

METHODS

Retrospective analysis was conducted on patients admitted to the Gastroenterology Department of the VII Navy Hospital from January 2015 to October 2017 due to unexplained gastrointestinal bleeding (OIBG) with suspected SBB to perform double-balloon enteroscopy. Patients who meet the OGIB definition criteria, i.e., lack of a defined cause of bleeding despite the performance of generally available and highly specialized diagnostic tests including endoscopic procedures (esophagogastroduodenoscopy, ileocolonoscopy) and imaging (CT, MRI, celiac angiography, scintigraphy with marked red blood cells) were included to further analysis.

Demographic data - age, sex, concomitant diseases and the fact of taking antiplatelet and anticoagulant drugs were analyzed. Assessment of effectiveness of the diagnostic procedure in determining the cause of SBB and the effectiveness of therapeutic measures taken during the procedure was performed. The percentage of complications of double-balloon enteroscopy was also analyzed.

LITERATURE ANALYSIS

Epidemiology and definitions

Obscure gastrointestinal bleeding (OGIB) is defined as bleeding into the gastrointestinal lumen, which does not cease or recur without a defined cause despite esophagogastroduodenoscopy, ileocolonoscopy and radiological examination of the small intestine [1,4]. This type of blood loss accounts for about 5% of all gastrointestinal bleeding and is a major clinical problem, as it mainly affects elderly patients with numerous comorbidities [1.4-5]. Most lesions responsible for OGIB are located in the small intestine (SBB small bowel bleeding), defined here as a section of the gastrointestinal tract between the ampulla of Vater and the final section...
of the ileum available in ileocolonoscopy. It is a section of the gastrointestinal tract that is difficult to be diagnosed and treated [1]

Etiology

The list of SBB causes is long. Etiological factors are dependent on the age of the patient, the co-existing pathologies or medications (an increasingly frequent variable, which should be taken into account). Common causes include: vascular lesions (50-70%), tumors (4-15%), ulcers or erosions (3-16%), especially drug-induced due to the use of non-steroidal anti-inflammatory drugs. The less common ones include: inflammatory bowel diseases, small intestinal tumors (sarcomas, lymphomas, neuroendocrine tumors), ulceration of the Meckel diverticulum, varicosis of small intestine. Frequent bleeding from the small intestine is a symptom of congenital diseases (Osler-Weber-Rendu disease, associated with Turner’s syndrome, Ehlers-Danlos or Peutz-Jeghers syndrome) or systemic diseases (scleroderma, hematological diseases) [4,6].

Diagnoses

Clinical symptoms of SBB depend on whether there is overt or occult bleeding. With occult bleeding, we can only observe a decrease in red blood cell parameters and the presence of occult blood in the feces without noticeable clinical symptoms of bleeding. Clinically evident cases include increased anemia with tarry stools and a negative result of esophagogastroduodenoscopy and ileocolonoscopy, which are first-line examinations in these cases. Cases in which the severity of bleeding is high may result in bleeding with fresh blood or blood clots, and the patient may develop symptoms of hemorrhagic shock. In these cases, SBB is usually confirmed by mesenteric angiography or CT angiography. In the situation where there is no availability of urgent embolization of the bleeding site by interventional radiology, these cases are qualified for laparotomy with intraoperative endoscopy.

OIGB diagnosis in the course of small bowel diseases is a challenge due to its length, contractility, overlapping loops and intra-peritoneal location. It is not possible to identify the bleeding site only on the basis of clinical history. In practice, patients with SBB, in comparison to patients with bleeding from the upper or lower gastrointestinal tract, are subjects of numerous specialized examinations, which accessibility is significantly reduced [8]. Patients require longer hospitalization, more blood transfusions [9], and in about 25% of cases, this does not lead to the definitive diagnosis [8].

Radiological tests

The small intestine passage and classical enteroclysis, due to low diagnostic efficacy, are currently only relevant in initial diagnosis of bleeding from the small intestine. There is no possibility of therapeutic treatment in their use. The indications currently only include suspicion of cancer, Crohn’s disease or bowel injury due to non-steroidal anti-inflammatory drugs [1].

MESENTERIC ANGIOGRAPHY

This highly effective method (90-100%) is based on the imaging of blood vessels supplying the small intestine and large intestine, i.e., the celiac trunk and both mesenteric arteries. It is often used as the first imaging examination in patients with severe bleeding or patients who are hemodynamically unstable due to massive hemorrhage [1,4]. During angiography, there is possibility of therapeutic intervention like embolization or precise selection of the bleeding site prior to planned surgical treatment. The limitation of the method is the fact that minimal active bleeding is required for effective imaging, (volume of approx. 0.5-1 ml/min) [1,4]. In addition, this examination involves the need to administer contrast agents. Contraindications include complications after previous administration of contrast agent, renal failure, severe asthma, paraproteinemia, severe cardiorespiratory failure, hepatic failure. The administration of contrast agents alone may result in anaphylactoid reactions, including development of shock (dose-independent reactions, including release or activation of histamine or serotonin, antigen-antibody responses and activation of complement) and nonanaphylactoid reactions (having a chemotoxic, osmotic or direct foundation associated with organ toxicity of the contrast agent). Among the complications of the procedure alone, one should mention damage to the vessel at the site of introduction of the venous catheter itself (hemorrhage, hematoma, pseudoaneurysm formation), arterial embolism, arrhythmias, or complications associated with the use of embolizing agent, including formation of ischemic necrosis of the embolized fragment of intestine.

Under the conditions of the Polish health care system, the restriction of the use of this method is limited availability to an interventional radiology laboratory and a high price of used instruments, especially in the case of superselective embolization.

Enteroclysis/entography CT/MRI

These studies combine the advantages of enteral contrast administration, cross-sectional imaging, multiplane imaging, especially in the arterial phase. The disadvantage of enteroclysis is use of a naso-intestinal tube, this inconvenience have no importance in enterography, in which contrast is administered orally. Both methods are characterized by approx. 50% efficacy and 64% diagnostic sensitivity [10]. A disadvantage is lack of simultaneous therapeutic measures. Intravenous administration of contrast significantly limits the possibility of examining patients with renal insufficiency and those with allergy to contrast agents, as described above. The sensitivity of examination decreases significantly if the cause of bleeding is slight inflammation, which results from the resolution of examination. Moreover, the presence of metallic bodies and any metallic implants limits the possibility of performing MRI [10]. Under the conditions of the Polish healthcare system, the availability of imaging in the MRI technique is significantly limited compared to CT.

Angiography CT/MRI

The examiation consists of multiple-row CT angiography before and after intraarterial administration of the contrast agent. The diagnostic efficiency of this method is estimated at around 86% and specificity at 95% [11]. Method limitations are identical to those described above.

What is important, when performing the above-mentioned examinations, we carry out the patient’s exposure to X-rays - highest exposure is required by angiographic CT scan, smallest - arteriography [12].
Scintigraphy (radioisotope test)

The examination is carried out with either red blood cells or technetium labeled sulphide colloid (99mTc). The main indication is active bleeding in hemodynamically stable patients. The sensitivity of this method is 78% in acute bleeding, and its effectiveness is about 60% [13]. The disadvantages of this method are: required minimal bleeding activity (0.1 ml/min), imprecise location of bleeding site, lack of identification of bleeding cause, large percentage of false negative results, long test time and need for proper patient preparation for examination and harmfulness of ionizing radiation [12]. Before implementation of surgical based treatment it is recommended that diagnosis should be confirmed using a different diagnostic technique (angiography, endoscopy, endoscopic capsule) [1]. Availability of radioisotope studies in Polish conditions is significantly limited by a small number of nuclear medicine laboratories.

Capsule endoscopy (CE)

Introduction of CE to clinical practice significantly improved the diagnosing process of the small intestine. This study has become the gold standard in the diagnosis of OGIB causes, especially in hemodynamically stable patients and without massive bleeding. The sensitivity of this method is estimated at 89%, its specificity at 95% [1,14-15]. Its disadvantages are lack of possibility of therapeutic intervention or biopsy, imprecise location of lesions, as well as the still high cost and low availability of this technique in our country. In addition, the use of CE is often associated with repeated examination in patients with both positive and negative results while still maintaining bleeding [1,6,14-15]. Entrapment of the capsule is rare but nevertheless in the case of Crohn’s (strictureting type) or when there is a significant suspicion of a tumor with an intestinal subileus, it is recommended to perform imaging examinations before, e.g., passage [1,4,6].

Endoscopic methods

Among varied endoscopic methods of examination of the small intestine: single-balloon enteroscopy, push and spiral enteroscopy, and double-balloon enteroscopy, the last one have the greatest significance and application. Double-balloon enteroscopy (DBE) allows for assessment of the entire small intestine. It base on a repetitive cycle, the elements of which are: introduction of the enteroscope, shifting of tube, withdrawal of enteroscope together with tube with proper filling and emptying of balloons. DBE may be performed both through the oral cavity and the rectum, and the choice of path depends on the expected pathology location. The diagnostic efficiency of this method is about 66% and it depends on several additional factors: indications for examination, previous capsule endoscopy, time elapsed from bleeding to performance of the examination and the performance of previous endoscopic examinations [16-19]. The advantages of this method are: full visualization of the small intestine, ability to perform tissue biopsies and therapeutic procedures.

Disadvantages are time-consuming nature (average procedure duration is about 2 hours) and technical difficulties of this method, especially performed through the anus. Unfortunately, this method is not widely available in Poland. In the pomorskie province, this type of procedure is performed in one center - in the Gastroenterology Department of the VII Navy Hospital in Gdańsk. For comparison, esophagogastroduodenoscopy and ileocolonoscopy is performed in almost every hospital and many independent endoscopic laboratories. Considering that the incidence of colorectal cancer ranges from 50/100,000/year and SBB 2-8/100,000/year, the accessibility to double-balloon enteroscopy is insufficient in relation to the scale of the clinical problem.

Intra-operative enteroscopy is a test performed as a last resort when no other diagnostic method can be performed or when DBE is unavailable or contraindicated (e.g., due to adhesions in the peritoneal cavity). Therapeutic effectiveness of this method is 58-88% [20]. Disadvantages include invasiveness and a high rate of complications (mortality up to 17%, ileus, bacteremia) [21]. An additional danger is that mucosal damage caused by introduction of the device and its maneuvering may be misinterpreted as angiectasias [1].

Small bowel bleeding - guidelines, algorithms.

Below are the ESGE guidelines from 2015 for the use of flexible enteroscopy in SBB, taking into account the category of evidence and strength of recommendations [1]

- In bleeding from the middle section of the gastrointestinal tract, the diagnostic efficacy of double-balloon enteroscopy is higher than push enteroscopy (category 1b, strength of recommendation A).
- In bleeding from the middle section of the gastrointestinal tract, diagnostic efficacy of double-balloon enteroscopy is comparable to efficacy of the endoscopic capsule (category 1b, strength of recommendation A).
- In patients who have been diagnosed with bleeding during endoscopic examination, enteroscopy should be performed for endoscopic treatment (category 2b, strength of recommendation B).
- Enteroscopy is the preferred method in patients with active bleeding from the middle gastrointestinal tract, if there is a high probability that endoscopic treatment will be required (evidence category 2b, strength of recommendation B).
The cause of bleeding was diagnosed in 27 patients (87%); in 4 patients, despite the exhaustion of available diagnostic methods, no definitive diagnosis was made (Tab. I). In 20 of the hospitalized patients (64%) a one-time treatment procedure was applied—argon plasma coagulation (Fig. 2) or endoscopic clipping (one patient). A total of 44 treatments were performed, which gives an average of 2.2 treatments per patient. The maximum number of treatments is 7, in 10 cases (50%) to achieve a lasting effect, 1 treatment was sufficient. In total, therapeutic and diagnostic procedures were performed during 44/56 (78.5%) hospitalizations (n = 43 with the help of APC, n = 1 with the use of endoscopic clips). Diagnostic and therapeutic efficacy is similar in literature [23]. No patient in the study population required a qualification for intraoperative enteroscopy.

In the study group, there were no clinically significant complications (on the DeOliveira scale, responsible for estimating the severity of complications, patients were assessed from 0 to 1 points which corresponds to lack of complications or events not requiring prolongation of hospitalization or significant changes to the planned treatment plan). No patient required repeated enteroscopy as a part of the same hospitalization. No patient required qualification for intraoperative enteroscopy. For comparison, in the meta-analysis of Xin et al. the number of minor complications was 9.1% and serious ones 0.72% [24]. The most frequently reported complication was acute pancreatitis (0.3 – 0.4%) which is explained by prolonged oppression and irritation of ampulla of Vater. Secondary gastrointestinal bleeding of varying severity was reported in 1.3%. Bowel perforation after diagnostic enteroscopy was observed in no more than 0.1% of cases, while in the case of

**ANALYSIS OF OWN MATERIAL**

In the period from January 2015 to October 2017, 31 patients were hospitalized in the Gastroenterology Department of the VII Naval Hospital for the performance of enteroscopy due to obscure bleeding with suspicion of SBB. 17 women and 14 men were hospitalized. In all hospitalized patients, available diagnostic methods to reveal the bleeding site were exhausted. The average age was 66.1 years (20-89 years). In total, 56 hospitalizations took place for the study group - on average 1.8 hospitalizations per patient (1 to 7 stays). In the case of rehospitalization due to the recurrence of bleeding, enteroscopy was repeated, omitting previously performed imaging diagnostics. The average duration of stay was 3.0 days (2 -12 days).

Due to the demographic characteristics of the examined patients, the percentage of comorbidities is significant. Cardiovascular diseases (atrial fibrillation n = 8, heart failure n = 7, arterial hypertension n = 7, coronary heart disease n = 6, condition after ischemic stroke n = 2) and diabetes (n = 7) dominated. There were 2 patients with renal failure. Drugs altering blood coagulation were taken by 12/31 patients, which constitutes 38.7% of the analyzed group (VKA n = 1, LMWH n = 4, antiplatelet drugs n = 7). All patients in this subgroup were over 60 years of age. During the course of diagnosis carried out before hospitalization in our unit, significant coagulation disorders that may result from liver failure, thrombocytopenia or overdose of anticoagulant or antiplatelet drugs were excluded. Despite the large percentage of patients taking blood coagulation drugs, only in one case we were unable to determine the organic cause of bleeding. In one patient diagnosed with Von Willebrand disease - during repeated enteroscopy, pathology that could explain SBB was not revealed.

- Intraoperative endoscopy should be reserved for patients with persistent, significant bleeding from the middle section of the gastrointestinal tract, when it was not possible to detect the source of bleeding during enteroscopy (category of evidence 5, strength of recommendation B).
- The choice of approach through the oral cavity or rectum depends on the suspected lesion location, for example when lesions in the endoscopic capsule or other imaging tests have been detected (evidence category 2b, strength of recommendation B).
- Polypectomy in the small intestine is associated with a similar risk of complications, as in the right part of the colon (category of evidence 4, strength of recommendation C).

**Fig. 2. Enteroscopy in bleeding jejunal ulcer.**

**Tab. I. Causes of bleeding (diagnosis).**

<table>
<thead>
<tr>
<th>CAUSE OF BLEEDING</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular malformation of the small intestine</td>
<td>13</td>
</tr>
<tr>
<td>Tumor of the small intestine</td>
<td>3</td>
</tr>
<tr>
<td>Small intestinal diverticulosis</td>
<td>1</td>
</tr>
<tr>
<td>Small intestinal ulcerations</td>
<td>3</td>
</tr>
<tr>
<td>Leśniowski-Crohn disease</td>
<td>1</td>
</tr>
<tr>
<td>Small bowel neoplasm</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disease outside the small intestine</td>
<td>4</td>
</tr>
<tr>
<td>Disorders of the coagulation system</td>
<td></td>
</tr>
<tr>
<td>(Von Willebrand disease)</td>
<td></td>
</tr>
<tr>
<td>Reason unknown</td>
<td>4</td>
</tr>
</tbody>
</table>
therapeutic procedures including polypectomy or submucosal resection, even up to 10% [24-28]. In 1% of patients, especially in the case of prolonged sedation, episodes of respiratory failure or aspiration have been reported [24]

The only factor that prolongs hospitalization above the average is the feeling of distension and abdominal pain in the period after procedure, which is associated with the need for intensive insufflation in the long term (compared with other endoscopic examinations) - in these patients, there was no need for above-standard medical interventions. Similar discomfort associated with bloating and abdominal pain is described in up to 20% of patients who have undergone double-balloon enteroscopy [29]

Vascular malformations - 60% (n = 22) were the most commonly described pathology during the study. A similar frequency of vascular malformations (65.9%) is found in the metanalysis of Xin et al. (n=12823), however, intestinal inflammatory changes were reported more often (37.6% vs. 18%) [24]. In the presented material, it should be noted that all cases of vascular malformations (n = 13) were observed only in the subgroup of patients above 60 years of age. However, in the group below the age of 60 (n = 6), the final diagnosis could not be made in 50%. Among these 3 patients, none of them took drugs that altered blood coagulation.

Based on the material presented in the paper, it can be concluded that the algorithms presented above are also fully applicable in Polish conditions. The performed procedures were the last stage of diagnostic process and gave the possibility of simultaneous treatment of 64% of detected changes. With limited availability of an endoscopic capsule, double-balloon enteroscopy offers a high probability of diagnosis and creates the possibility of effective, simultaneous treatment of causes of unexplained bleeding into gastrointestinal tract. It is an effective method, which is also confirmed by the collected clinical material. If the bleeding recurs, the procedure can be repeated and the complication rate is low.

CONCLUSION

Double-balloon enteroscopy on base of international guidelines is an important and last link in the diagnostic-therapeutic algorithm of obscure small bowel bleeding. This method is effective and safe, however, in Polish conditions, access to this examination is still limited.

REFERENCES:
16. Hsu C.M., Chiu C.T., Su M.Y. et al.: The outcome assessment of double-ballo-