UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL
MEDICINE

ROLE OF CAPSULE ENDOSCOPY IN INFLAMMATORY BOWEL DISEASE

PHD THESIS SUMMARY

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2022

CONTENTS

Introduction

Since the incidence and prevalence of inflammatory bowel diseases (IBD) are increasing over time, affecting especially the young populatin, studies tried to improve both diagnostic and monitoring techniques as well as therapy.

The method of choice for diagnosing inflammatoy bowel disease remains ileocolonoscopy with biopsies, but in selected patients, capsule endoscopy (CE) represents a useful tool for diagnosis and follow up of this patients. The small bowel is difficult to investigate because it is inaccessible with conventional endoscopic methods. Capsule endoscopy represents a noninvasive method that can visualize the entire digestive tract, with the help of a miniature video camera, a light source, an energy source and a system of transmission of images, all assembled in a form of a pill administered orally to the patient. This inovation appeared in 2001 and revolutionized the exploration of the digetive tract, becoming the method of choice for the small bowel (1). In the late years, this method became an extremely useful tool for diagnosing and monitoring patients with inflammatory bowel disease. Recently, the paneteric capsule dedicated to Crohn's disease patients was approved.

The CE could be incorporated in a treat to target algorithm for patients with Crohn's disease, to regularly assess disease endoscopic activity (2). This method could be used for evaluation of the extension of the disease at the time of the diagnosis, with an impact on prognosis, especially in patients with lesions of the proximal portion of the small bowel and also, it may allow physicians to assess the achievement and monitoring endoscopic remission in treated patients. In Crohn's disease patients, after surgical resection, the disease recurrence is common and CE represents a valuable tool to monitor these patients and to detect early postoperative recurrence, especially if the recurrence is above the anastomosis.

Since it has been shown that jejunal extension of the disease is associated with an increased risk of complications, the capsule endoscopy has an important impact on prognosis because this method is the most sensitive in detecting jejunal lesions and an early aggresive therapeutic approach can modify the disease course.

The purpose of this paper, based on the Crohn's disease patients from Gastroenterology II Clinic (formerly Medical II) of the Bucharest University Emergency Hospital, is to obtain some conclusions regarding the optimal diagnostic and therapeutic

approach in the evaluation and management of patients with suspected or known Crohn's disease.

This study aims to confirm the role of capsule endoscopy in the diagnosis of Crohn's disease in the patients with a high suspicion index based on clinical and paraclinical data and also to evaluate the role of this investigation in the strict monitoring of patients with known Crohn's disease and the posibility of incorporating this method into a treat to target approch.

This project also emphasizes the complexity of treating patients with inflammatory bowel disease and the need for multidisciplinary teams in dedicated centers, such as our hospital. Also, patient involvement and adherence contribute to positive results, underlining the emerging role of individualized care for patients with inflammatory bowel disease.

I.   General Part

Inflammatory bowel diseases are inflammatory chronic disorders of the digestive tract, with cyclic evolution. They include two major entitis, Crohn's disease(CD) and ulcerative colitis (UC), which have relatively different clinical endoscopic and histological features, with an etiopathogenesis that remains incompletely elucidated (3). In 10-15% of cases the disease cannot be classified in one of those two and this form is called indeterminate colitis.

Regarding the small bowel investigation, over time, progress has been made in terms of imaging with CT and MR enterography, as well as in terms of endoscopy with the development of new endoscopic tehniques such as device assisted enteroscopy and capsule endoscopy. Intestinal ultrasonography is another useful technique, that has proven lately its importance in the evaluation of the small bowel.

Until recently, therapeutic strategies in IBD were based on a step up approach based on symptoms, but because a weak correlation was demonstrated between symptoms and endoscopic disease activity in Crohn's disease patients, the "treat to target" paradigm has emerged (4). This was developed in 2015 and is based on the assessment of the disease activity and the subsequent adjustement of treatment (5). It involves identifying an appropriate target, selecting initial therapy based on prognostic factors and risk of the disease progresssion, monitoring the evolution and optimizing therapy to achive the agreed goal. The goal of treatment has evolved to a new concept, which is to achieve and maintain deep remission, combining clinical and endoscopic remission (2).

In april 2021, the International Organization for the Study of Inflammatory Bowel Diseases STRIDE Working Group („Selecting therapeutic targets in inflammatory bowel disease") published un update of new therapeutic targets in IBD- STRIDE II. STRIDE II confirmed as long term targets the clinical and endoscopic remission established by STRIDE I in 2015(6). To these, were added as long term targets the absence of disabilites, the restoration of quality of life and, in pediatric patients, normal development (6). Short term goals are improvement of symptoms and normalization of serum and fecal inflammatory biomarkers (6). Although histological remission in UC and transmural healing in CD have not been established yet as formal targets, they sould be evaluated to monitor deep remission (6).

For suspected Crohn's disease patients, The European Society of Gastrointestinal Endoscopy (ESGE) recommends CE as main diagnostic tool for evaluating small intestine, if ileocolonoscopy is non-contributory and the patient has no known stenosis or obstructive symptoms (11). Those are absolute contraindications of this investigation. The diagnostic yield in CD for CE is superior to ileocolonoscopy, CT enterography (7) and some studies even show that it is superior to MR enterography in the evaluation of proximal portion of the small bowel and in the diagnosis of early disease. However, MR enterography is superior in detecting extraluminal disease and complications (8). CE that does not detect lesions of the small bowel also has a high negative predictive value, making the Crohn's disease diagnosis unlikely (9).

To increase the diagnostic yield of CE, careful selection of patients is mandatory, based on a high index of suspicion, with clinical (abdominal pain, chronic diarrhea, weight loss and perianal disease) and paraclinical (eleveted serum inflammtory biomarkers, eleveted fecal calprotectin) criteria (10).

In patients with known Crohn's disease, CE plays an important role in the evalution of mucosal lesions, being a good alternative for the strict monitoring of patients and influencing the subsequent therapeutic decision. At those patients, ESGE recomends CE investigation, especially if its results can influence subsequent management, after imaging methods (CT or MR enterography) are used to evaluate presence of stenoses and extraluminal complications, if they are non-contributory (11). Prior evaluation with CE, patency capsule is advised to reduce the retention risk, which is important at those patients (12).

Both, the small bowel capsule endoscopy and the panenteric capsule dedicated to Crohn's disease (Pillcam Crohn Capsule), represent sensitive methods of visualizing the mucosal surface of the entire small bowel, detecting early lesions and allowing a change in the therapeutic management and thus modifing the natural course of the disease, especially if used in a treat to target approach.

II. Original Part

1. Aim and objectives of the study

I performed an analytical, descriptive, retrospective study with the aim of evaluating the role of CE in diagnosis of patients with suspected Crohn's disease based on clinical and paraclinical data, and also to evaluate the role of CE in strict monitoring of patients with known Crohn's disease and the possibility of incorporating this investigation into the "treat to target" approach.

Study objectives:

- Appreciation of the role of CE in the diagnosis and the evaluation of patients with suspected or known Crohn's disease.
- Appreciation of the role of CE in thenevaluation of the localization, extension, activity and prognosis of the disease.
- Appreciation of the role of CE in the evaluation of mucosal healing in patients under treatment and the impact of this investigation on the optimization of the treatment, by a step up or step down approach.
- Identifing the feasible patients for the study: high suspicion of Crohn's disease or known Crohn's disease
- Description of the study population with Crohn's disease from our hospital: distribution according to sex, age at diagnosis, clinical manifestations and paraclinical results (serum and fecal inflammatory biomarkers), classifying them according the type of the disease (Montreal Classification) and disease activity detected using the CE (Lewis Score).
- Identification of possible complications and limitations of CE investigation.
- Evaluation of safety and tolerability profile of CE investigation.
- Evaluation of the impact of the CE investigation on the monitoring strategy and the therapeutic attitude.
- Comparative analysis according to the location of the disease and age in the study population.
- Establishing the relationship between thrombocytosis and the endoscopic activity detected with the aid of CE (Lewis Score) of the Crohn's disease patients.

2.   Materials and methods

Study population

In order to select the patients included in the study, we extracted from the database of the Bucharest University Emergency Hospital, patients admitted to the Gastroenterology II Department (formerly Medical II) between 2011 and 2021. From these patients, eligible patients were selected to participate in the study, according to the inclusion and exclusion criteria mentioned later. All patients have the informed consent and the acceptance consent signed, regarding the administration of CE, as well as for the use of anonymized results and anamnestic, biological and endoscopic data.

Study included 62 patients with suspected or known Crohn's disease, evaluated at the Bucharest Emergency University Hospital with CE, some of them undergoing several examinations with CE.

Study procedure
Inclusion criteria:
- Patients with suspected Crohn's disease based on clinical and biological data and patients with known Crohn's disease.
- Adult patients (over 18 years old), able to give their informed consent, without being coerced.
- Patient who agree to examination with the CE and the preparation before the procedure.

Exclusion criteria:
- Age < 18 years
- Suspicion/Confirmation of stenosis
- Known high flow fistulas
- Swallowing disorders
- Pregnancy
- Use of nonsteroidal anti-inflammatory drugs (NSAID) in the last month
- Other disorders that can explain the symptoms, such as vasculitis, lymphoma
- Intestinal bacterial infections (Clostridioides Difficile, Intestinal tuberculosis)
- Cognitive impaired patients who cannot give their informed consent.

We used the existing data in the patient files (hospital archive) and in the files regarding endoscopic investigations (department of advanced endoscopic techniques).

The anamnestic data (personal pathological history, heredocollateral history, NSAID/anticoagulant use history, smoker/nonsmoker status, disease history), demographic data, clinical and paraclinical (hemoleukogram, C-reactive protein, fecal calprotectin) data, imaging data and the results of endoscopic (ileocolonoscopy and capsule endoscopy) investigations of each patient were analized.

All patients included in the study are patients who underwent CE investigation. For all patients, in order to perform the complete examination of the small bowel, we used the Pillcam Colon2 capsule or the Pillcam SB3 small bowel capsule, depending on the availability in our hospital at the time of the investigation.

The preparation prior to the CE examination was similar with the preparation prior to colonoscopy. All patients were fasting for 12 hours prior the investigation and for colon capsule, 2 liters of macrogol solution were admistered 12-16 hours before the ingestion of CE. In order to improve the visualization of the small bowel, a bolus of macrogol solution was administered 2 h after the CE ingestion. At the end of the investigation, the recorder was connected to the workstation to download all the recorded images. Image interpretation was performed using RAPID 8 software. In order to detect potential lesions of the digestive tract, the entire set of frames were manually analized by an experienced endoscopist. The type, location, number of suggestive discovered lesions, like aphthoid ulcers, erosions, ulcers, strictures, fistulas were evaluated.

Each patient was classified according to the Montreal classification considering: age at diagnosis (A1: <17 years, A2: 17-40 years, A3: >40years), location of lesions (L1:ileal, L2: colonic, L3: ileo-colonic, L4: upper digestive tract, p: perianal) and the pattern (type) of the lesions: B1: non-stricturing, non-penetrating, B2: stricturing, B3: penetrating)

For every patient, the Harvey-Bradshaw index (HBI) was calculated for evaluating the severity of the clinical disease activity. Depending on the obtained score, each patient was assigned to: clinical remission (HBI<5), mild disease activity (HBI 5-7), moderate disease activity (HBI 8-16), severe disease activity (HBI>16).

The endoscopic activity was evaluated using Lewis score (LS), obtained after dividing the small bowel in three segments, using the capsule transit time from the first duodenal image to the first cecal image. Mucosal healing was defined by a LS less than 150, mild inflammation by a LS between 135 and 790, and moderate and severe inflammation was defined by a LS greater than 790.

In our study, aphthous erosions, ulcerations and stenoses were considered significant lesions and denudation, erythema and edema were considered possibly significant lesions.

Prior to the CE examination, all patients included in our study were evaluated with CTenterography (imagistic method available in Bucharest Emergency University Hospital) in order to reduce the risk of capsule retention. Due to the high costs, the patency capsule was not available.

Ethical considerations:

Patients signed the informed consent regarding the processing of their data, but also the informed consent for the use of the lab results and investigations in clinical trials, for research purposes in observational studies, which the patient express voluntarily, in full knowledge. Data confidentiality will be maintained during the study and after its completion. National laws and regulations regarding the protection of personal data will be strictly respected.

The study was approved by the Ethical Committee of the Bucharest University Emergency Hospital in accordance with the Declaration of Helsinki.

Statistical analisys

SPSS (Statistical Program for Social Sciences) was used to collect the data, create the database and also for statistical analysis. To determine the mode of distribution of continuous quantitative variables, the Shapiro-Wilk test was used. Depending on the results, the indicators of central tendency and dispersion were reported, as follows: mean and standard deviation (DS) for variables with parametric distribution and median and interquartile range (IQR) for variables with non-parametric distribution. Regarding the statistical analysis, for the first type of variables we used the T test for two independent groups, and for continuos quantitative variables with non-parametric distribution, we used the Wilcoxon-Signed Ranks test for paired samples and the Mann-Whitney test for two independent groups. For variables in the form of proportions, we used the Chi-Square test. For all the above tests, $P<0,05$ indicates statistical significance.

3.   Results and discussions

IBD represent a group of intestinal disorders with increased incidence and prevalence in Europe and also in Romania.

62 patients were included in our study, of which 40 were female and 22 were male. The average age of our patients was 33 years, with the patient's ages ranging from 20 to 67 years, but an increase in the number of patients with ages between 20 to 30 was noted. Of all the patients, 37 (59,67%) had suspected Crohn's disease based on symptoms and inflammatory biomarkers and 25 (40,32%) had known Crohn's disease.

Smoking and urban environment are known risk factors for Crohn's disease. In our group, 70,97% were smoking patients and 67,7% came from urban environment.

For every patient, the HBI was calculated for evaluating the disease severity. 21(33,9%) patients had mild disease, 8(12,9%) had moderate disease activity and 19 (30,6%) patients had severe disease activity. 14 (22,6%) patients were in clinical remission. Among the patients enrolled in the study, 47 (75,81%) presented an inflammatory syndrome (CRP>5mg/dl) and 41(66,13 %) presented an increase in faecal calprotectin>250microg/g. There were also statically significant more patients with anemia (80,65% vs 19,35%, p<0,001).

An extremly important result showed that in the analyzed group, among the asimptomatic patients, the majority presented mucosal lesions on CE examination. Of these patients in clinical remission, 11 (78,57%) had significant lesions detected with CE. The poor correlation between symptoms and endoscopic disease activity in Crohn's disease patients is also mentioned in universal literature (13,14).

The diagnostic yield of the CE is influenced by a complete and optimal vizualization of the bowel and this requires a proper preparation prior to investigation. Both preparation and tolerability were superior in the group of patients younger than 40 years, compared to the older ones, leading to a complete visualization to 67.74% of patients in this group and 24.19% of patients in the group aged >40 years.

After the first examination with CE, complications occurred in 6 (9.68%) of the patients, in 2 (3.2%) occurring the retention of the capsule, in 3 (4.8%) the incomplete visualization due to the depletion of the battery, and in one (1.6%) of the patients the capsule was not eliminated after >24h. Of the 62 patients, 4 also benefited from a second examination with CE and this time only one complication was noted, namely the non-elimination of the capsule in more than 72 hours. Two of the patients even benefited from the third examination with CE, with no complications. In the literature, the retention rates of the endoscopic capsule are 2-13% in the case of known Crohn's disease and 1.5% in the case of suspected Crohn's disease (15). A recent meta-analysis by *Pasha et al*. shows that the retention rate is even lower, only 4,63% in patients with known Crohn's disease and

2.35% in those with suspected Crohn's disease (16). In our study, the retention rate of CE was 3.22%, although in order to reduce this risk all patients, prior to the investigation with CE, were examined using CTenterography, where no significant stenosis was revealed and the patients did not show symptoms for suboclusive syndrome. Another peculiarity in the study conducted by us consisted in the fact that the 2 recorded cases of capsule retention were in the group of patients previously undiagnosed with Crohn's disease, without previous abdominal surgery, in the group of known patients with Crohn's disease, not registering this complication. A measure to prevent the retention of the capsule could have been the use of the patency capsule, prior to the CE examination, but due to the high costs, in our batch, we did not administer the patency capsule to any patient, suspected or diagnosed with Crohn's disease. In addition, according to the recommendations of the European Society of Gastrointestinal Endoscopy, the use of the patency capsule is not indicated in patients with suspicion of Crohn's disease, in the absence of known stenosis or suggestive symptomatology of obstructive syndrome (11). An explanation for the higher rate of complications in the group of undiagnosed patients with Crohn's disease at the time of examination with CE could be given by the fact that in our study, more patients with a high suspicion of Crohn's disease were selected, than those with known Crohn's disease.

Crohn's disease can affect any segment of the digestive tract, but it most commonly affects the ileum. Each patient was classified according to the Montreal classification. The full evaluation of the small intestine, both suspected and known patients with Crohn's disease, is necessary, since the full visualization of the mucosa of the small intestine can have prognostic impact with therapeutic implications. Depending on the location of the lesions, most patients, statistically significant (48.39% vs. 0 vs. 19.35% vs. 32.26%, $p<0.05$) were classified in category L1, with ileal impairment, followed as a percentage by those with jejunal impairment, L4. The investigation with CE is extremely useful, because the extension of the disease at the level of the proximal segment of the small intestine, which cannot be evaluated with the help of colonoscopy, has prognostic and therapeutic implications, as happened in our study, given that most patients had small intestine damage, jejunal damage, in particular, being associated with unfavorable prognosis, which allowed us to approach the early aggressive treatment, thus influencing the natural evolution of the disease. *Lazarev et al.* , who analyzed a group of more than 2000 patients, of whom 14% had damage to the proximal portion of the small intestine, showed that, in particular, jejunal damage is associated with an unfavorable prognosis, with more

hospitalizations and the risk of strictures with the need for surgery, making necessary a more aggressive therapeutic approach to prevent these complications (17).

In the studied group there was no patient with isolated colonic damage. This result can be explained by the selection of patients, most of them having lesions not accessible to colonoscopy. However, there were also patients who refused ileocolonoscopy or received incomplete examination.

In the studied group we can conclude that, statistically significant, most patients (79.00% vs. 17.70% vs. 3.20%, p<0.001) had non-stricturing non-penetrating pattern. The percentage of patients with complications such as stenosis or fistulas was significantly lower, since patients with these suspicions, clinically or imaging detected, were not selected for examination with CE. Given the natural evolution of Crohn's disease and its possibility to change its pattern, CE demonstrates its usefulness and impact on the monitoring strategy and therapeutic attitude and impact on the change in the evolution of the disease. *Greener et al.,* in a comparative study between CE and MRI, demonstrated that examination with CE can reclassify Crohn's disease in terms of localization by detecting new mucosal lesions in unapproachable areas by other techniques, while MRI has proven superior to reclassifying the disease in terms of pattern by evaluating transmural lesions. For this reason those investigations are considered to be complementary (18).

Regarding the optimization of the treatment secondary to CE examination, in a number of 6 (9.68%) patients the initial therapy was maintained, 7 (11.29%) needed a step down approach, and a statistically significant higher percentage of patients, 49 (79.03%) needed a step up approach (p<0.001) after the first examination with CE. Of the 62 patients included in our study, 4 also benefited from the second evaluation with CE, and 2 of them were investigated 3 times with CE. Therefore, we have 68 evaluations in total, which resulted in the adjustment of the treatment (step up/ step down) 62 times. Practically out of the total number of examinations with CE, the treatment was changed in 90.32% of the cases. Of these, 56 adjustments were made after the first examination with the CE, 4 after the second and 2 after the third. In conclusion, in our study, CE had a statistically significant impact in patient management, thus achieving one of the proposed objectives. This is also supported by other studies, such as the one conducted by *Kopylov et al.*, on a group of 187 patients who, after being evaluated with the help of CE, the change of therapywas made in 52% of them (19).

The goal of therapy, in Crohn's disease, is to obtain and maintain deep remission, which involves both clinical and endoscopic remission. In order to incorporate CE into a

treat to target strategy and be able to monitor the response to therapy, the target set was mucosal healing. The capsule transit time was used to divide the small intestine into three segments and intestinal inflammation was assessed using the Lewis score. 13 (21.00%) patients had a Lewis score <135, 22 (35.50%) patients had a Lewis score between 135-790, and 27 (43.50%) had a score of >790.

In order to assess if there is a correlation between the LS with elevated values and the therapeutic attitude, the Chi Patrat test was performed, with $p<0.001$, in the sense that at the values of the score >790 there were more patients in whom the adjustment of the step up type treatment was practiced. So, we can conclude that the step up therapeutic attitude was statistically significant more common in patients with an increased LS. Consistent results are also demonstrated in the literature, even at much lower Lewis score values, with a 2019 publication indicating that the Lewis score is an important predictor of activity and emergency hospitalization, and a cut-off of 264 justifies escalating treatment (20).

Given that jejunal lesions are associated with an unfavorable prognosis, we decided to conduct the comparative analysis of the studied group depending on the location of the lesions. To perform this analysis, we considered group 1 to be composed of patients who had lesions of type L1+L2+L3, and group 2 as being represented by patients with L4 lesions. Group 1, composed of patients with lesions of type L1+ L2+L3 sums up statistically significant more patients (42- 67,74% vs 20- 32,26%, $p < 0.05$) than the second group, consisting of patients with lesions of type L4. Thus, we can see that most patients with moderate or severe endoscopic activity (Lewis score > 790) were found in group 1 (30.65% vs. 12.90%), but relative to the number of patients in each group, the distribution was similar, namely 45.23% vs. 40% in the nonL4 group respectively L4. Relative to the number of patients in each group, inflammatory syndrome was present in 92.85% of group 1 and 40% of group 2, in 60% of patients with jejunal damage not being found the presence of inflammatory syndrome. Fecal calprotectin also showed values higher than 250microg/g in 40 of the 42 patients in the first group and only in one of the 20 patients in the second group. Studies are controversial regarding the correlation between fecal calprotectin values and Crohn's disease limited to the small intestine. *Koulaouzidis et al.* have demonstrated that elevated fecal calprotectin levels predict inflammation in the small intestine, demonstrated by means of the endoscopic capsule, when bidirectional endoscopy is negative and even suggest that CE investigation should not be performed in those with fecal calprotectin values below 100microg/g and non-contributory endoscopy

and colonoscopy (21). However, as in our case, there are also studies, such as the one conducted by *Sipponen et al.,* in which fecal calprotectin has not been shown to correlate optimally with endoscopic lesions of the small intestine (22).

The escalation of the therapy was carried out in the L4 group (group 2), in 19 patients out of the 20 with jejunal damage, representing a statistically significant percentage of patients (p=0,028). One of the patients refused biological therapy and for the remaining 19 patients, secondary to the CE investigation, the optimization of therapy was achieved, most of them initiating the anti-TNF therapy.

All patients evaluated in our study, were diagnosed with the help of CE. Basically, the diagnostic yield is 98.38% after the first examination with CE, a single patient not being diagnosed after the first examination with CE, but due to the high suspicion based on clinical and paraclinical data, it was reassessed with CE and aphthoid ulcers were detected in jejunum, thus being able to consider, that in our study, the diagnostic yield of CE was 100%. This was possible because the study was retrospective, and the patients selected to be evaluated in the study were already known to have Crohn's disease at that time. A recent study, conducted using panenterical capsule by *Yamada et al.* , shows that the sensitivity and specificity of CE in detecting small intestine ulcers are 90.0% and 87.5% respectively (23).

In the 25 patients diagnosed with Crohn's disease prior to CE examination, 10 of whom had lesions in the jejunum, CE has proven its role both in reclassifying the disease and escalating treatment, and in evaluating mucosal healing in patients under treatment. In patients with operated Crohn's disease, who numbered 5 in our study, the detection of postoperative lesions above the anastomosis, allowed for a step-up approach to therapy, thus allowing for close control of the disease and better evolution.

In the study group, damage to the small intestine was more common in the group under 40 years of age, but the difference was not significant. This correlation is also consistent with other international studies. Since 1996, *Polito et al.* have shown that an age under 20 years at diagnosis is more frequently associated with small intestine damage, stenosis pattern, the need for surgery and the prevalence of family history of Crohn's disease (24).

In order to be able to assess whether there is a correlation between the presence of thrombocytosis and the endoscopic activity of Crohn's disease, we divided the studied patients into two groups depending on the endoscopic activity, totalizing the patients with mild endoscopic activity (Lewis score between 135 and 790) and the patients in

endoscopic remission (Lewis <135 score) and the group 2 that included patients with endoscopic activity moderate and severe (Lewis score>790). In the group with moderate and severe endoscopic activity (Lewis score>790), thrombocytosis was present in a statistically significant number of patients (p<0,001), meening 24 of the 27 patients. The fact that the platelet count reflects the severity of Crohn's disease is also demonstrated by *Li et al.* in a study of 137 patients with Crohn's disease, in which they showed that the number of platelets correlates directly to the activity of the disease quantified with the help of CDAI (25). The association between platelet counts and endoscopic activity of IBD has been demonstrated since 1989, in the study conducted by *Holmquist et al.* on a pediatric population. They found that thrombocytosis is present in severe and extensive colitis in both Crohn's colitis and ulcerative colitis (26)..

From a personal review of the literature, there are no similar studies that assess the relationship between thrombocytosis and endoscopic activity of Crohn's disease established secondary to the investigation with CE. This proposed objective of determining whether thrombocytosis correlates with the LS represents the personal, original contribution in this study, with platelet counts being proposed for monitoring Crohn's disease, like the other inflammatory markers, such as C-reactive protein and fecal calprotectin. Also, in the case of IBD, thrombocytosis is a prognostic factor of the disease, being able to have an impact on the evolution and monitoring of the disease, as well as on therapeutic conduct.

In the analyzed group, elevated values above 450000 platelets/ml were found in statistically significant more patients who have fecal calprotectin higher than the value of 250micrograms/gram vs. those with lower values (48.39% vs. 11.29%, p =0.003). Thrombocytosis was also associated in a statistically significant higher percentage of patients with inflammatory syndrome (CRP>5mg/dl) and anemia. We can conclude that thrombocytosis, due to the fact that it reflects the severity of the disease in patients with Crohn's disease, can be a parameter that positively influences the diagnostic yield of CE, by corroborating with the other clinical and paraclinical parameters. Also, with a prognostic impact, platelet counting could be incorporated into a treat-to-target approach, in addition to measuring CRP, fecal calprotectin, endoscopic, clinical activity and quality of life monitoring.

4. Difficulties and limitations in the study:

• The absolute contraindication to the administration of the CE is represented by the existence of digestive stenosis, which could cause the capsule retention at a certain segment of the gastrointestinal tract. This can be prevented by using the patency capsule.

• Another difficulty could be the time allocated by the doctor for viewing and interpreting the images, a problem that can be diminished with the help of artificial intelligence by implementing the software that aims to help the examiner by automatically detecting and classifying the lesions.

• The main challenge of the future is the transformation of the endoscopic videocapsula from a diagnostic tool into a therapeutic tool, with biopsy sampling and drug release.

• The main limitation in our study is a low number of enrolled patients due to the high costs involved in investigation with CE.

• Another limitation was represented by the inhomogeneous group, comprising both suspected and diagnosed patients with Crohn's disease.

• The study is retrospective, which is why we could not evaluate all the useful parameters in carrying out the research, nor the real efficiency of the method by using it repetitively, at predetermined intervals of time. The impact of the research would have been far superior in the case of a prospective study, this project representing an objective for future personal research.

5. Conclusions and original contributions

• There is particular interest in international studies for improving diagnostic and therapeutic means on inflammatory bowel diseases.

• CE is an important tool in the diagnosis and monitoring of Crohn's disease patients, with prognostic and therapeutic impact, with excellent results only if it is integrated into a multidisciplinary approach, by corroborating clinical, biological, imaging, endoscopic and histopathological data, with the optimization of resources and experience.

• CE, as we have demonstrated in this study, is a useful diagnostic method, easily accepted and tolerated by the patient, with a low incidence of complications, which provides extremely important information in both known patients with Crohn's

disease and those suspected, with an effect on the reclassification of the disease, the monitoring of mucosal healing in response to therapy and the early establishment of postoperative recurrence, having both prognostic and therapeutic decision-making impact.

• CE had a high sensitivity (80.65%) in identifying mucosal lesions of the small bowel, which are established as the most common localization in our study. The same high diagnostic yield was established with regard to the detection of mucosal lesions for the purpose of diagnosing Crohn's disease, in patients with a high degree of suspicion.

• In our study, an important percentage of patients had lesions at the level of the jejunum, localization also known as being associated with an unfavorable evolution and with subsequent complications, thus the CE investigation proving its prognostic role.

• In current medicine, where the target in inflammatory bowel diseases is mucosal healing, the endoscopic capsule is a valuable method with high sensitivity in the detection and exclusion of mucosal lesions, and can be feasible for the strict monitoring of patients with Crohn's disease and the incorporation of this investigation into the "treat to target" algorithm.

• In our study, the investigation with CE had a significant impact on the optimization of therapy, with most patients undergoing the escalation of therapy. Although the iterative evaluation with the help of CE was performed in a low number of patients, after each of the examinations the treatment of the patients was reconsidered. Thus, this investigation was used to monitor patients, in a treat to target approach.

• The originality of this study lies in the innovative approach that we have achieved through the panenteric evaluation of patients with Crohn's disease with the help of CE, this study being started before the appearance of the new capsule dedicated exclusively to Crohn's disease (Pillcam Crohn's, Medtronic, USA) , which sets itself the same ideal. By evaluating both the small intestine and the colon, we have established the role of CE both in the diagnosis of Crohn's disease and in the monitoring of mucosal healing, the integration of CE into a routine treat to target strategy in the future can determine the increase in the percentage of patients with mucosal healing and deep remission, having a positive impact on the evolution of patients and the quality of life of patients.

• According to the personal review of the literature, this is the first study to show the correlation of thrombocytosis with the endoscopic activity of Crohn's disease established with the help of CE, by the Lewis score. Platelet count could be a simple parameter, in addition to those already used, to periodically assess the activity of Crohn's disease.

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