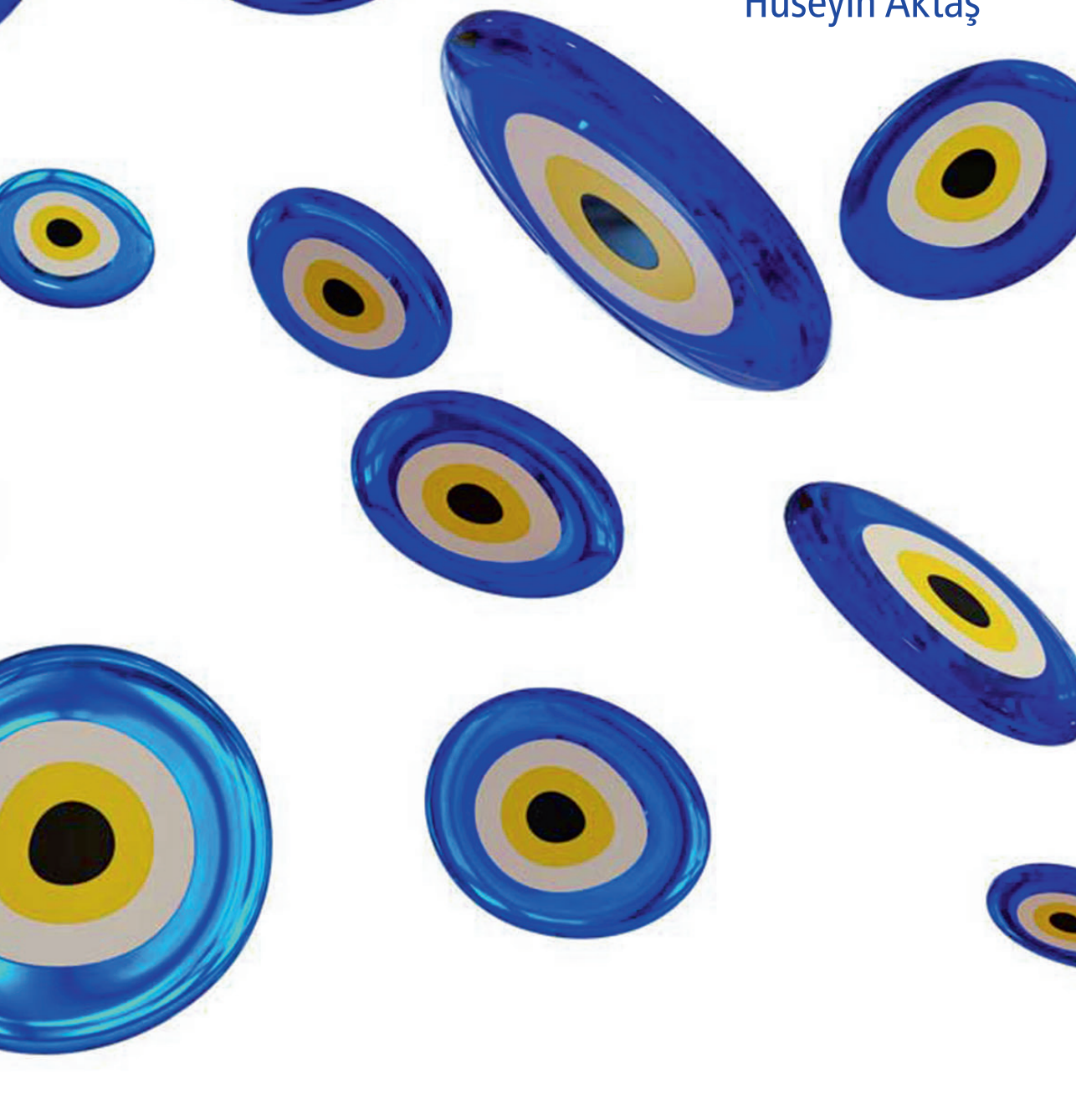
Going to Where No One Went Before:
Endoscopic Procedures of the Small Bowel

Hüseyin Aktaş



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Contents

List of abbreviations

BAE = balloon-assisted enteroscopy
CD = Crohn's disease
CDAI = Crohn's disease activity index
CE = capsule endoscopy
CRP = C-reactive protein
CTE = computed tomography-enteroclysis or -enterography
DAE = device-assisted enteroscopy
DBE = double-balloon enteroscopy
DPEJ = direct percutaneous endoscopic jejunostomy
GIST = gastro-intestinal stromal tumours
IBD = inflammatory bowel disease
LCL = lower 95% confidence limit
MRE = magnetic resonance-enteroclysis or -enterography
OGIB = obscure gastrointestinal bleeding
PE = push enteroscopy
PEG-J = percutaneous endoscopic gastrostomy with jejunal extension
PJS = Peutz-Jeghers syndrome
SB = small bowel
SBE = single-balloon enteroscopy
SBFT = small bowel follow through
SE = spiral enteroscopy

Part One

Introduction

Chapter 1

Aims and outline of the thesis

Aims and outline

Since the introduction of the first balloon-based enteroscopic technique in 2001, balloon-assisted enteroscopy (BAE) using either the single or double balloon enteroscopy technique (respectively SBE and DBE) has evolved rapidly. Before the introduction of these new small bowel endoscopy techniques, the small bowel was considered the 'black box' of the gastrointestinal tract, and only in selected cases enteroscopy procedures were performed. Methods used to evaluate the small bowel were push enteroscopy and intraoperative enteroscopy. This all changed after the introduction of two revolutionary technological innovations that occurred at the start of the last decade. More recently, spiral enteroscopy was introduced as an alternative method for BAE. The term device-assisted enteroscopy (DAE) covers all modern methods of endoscopic procedures of the small bowel.

This thesis focuses on the diagnostic, therapeutic impact and safety of DAE in small bowel pathology in adult patients.

Part 1: introduction

The small bowel has historically been a difficult area to examine due to its anatomy, location and relative tortuosity. Until recently small-bowel follow-through (SBFT) was the only method of diagnosing diseases of the small bowel, characterized by a known low diagnostic yield in this field. The latter particularly in the context of the major indication for small bowel imaging, being obscure gastrointestinal bleeding [1–3]. Currently, various radiological, endoscopic and surgical options are available for assessment of the small bowel, each of which with their own advantages and shortfalls. **Chapter 2** is a review on small bowel diagnostics. The aim of this review is to discuss the different options and indications for modern diagnostic methods for visualization of the small bowel. We also try to provide a clinical rationale for the use of these different diagnostic options in less established, newly emerging, indications for small bowel evaluation.

Part 2: Diagnostic and therapeutic feasibility of device-assisted enteroscopy

The single-balloon enteroscopy system is introduced as a simplification of the double balloon method [4]. In theory, use of this system might lead to decreased preparation and examination time. However, SBE may be less efficient for deep intubation of the small bowel compared with the DBE system, and may cause adverse effects due to the hooking technique during straightening of the single-balloon endoscope. In **Chapter 3**, a prospective, randomized, controlled trial is presented comparing the DBE and SBE technique in endoscopic performance and diagnostic yield.

Identification of patients with small bowel (SB) localization of Crohn's disease (CD) represents an important tool to optimize therapy and modify the disease course. In **Chapter 4**, we present a prospective study that investigates the feasibility and safety of DBE for detecting SB lesions in CD patients suspected of SB activity.

Device assisted enteroscopy (DAE) has the potential advantage over capsule endoscopy (CE) that it permits tissue sampling for histological investigation. However, until now no study has evaluated the additional value of biopsy sampling in reaching a diagnosis in patients suspected for small bowel disease. In **Chapter 5** we describe the additional yield of biopsy sampling and histological evaluation during balloon assisted enteroscopy.

Push enteroscopy (PE) was until the introduction of the DBE the established endoscopic method of examining the proximal part of the small bowel, and with its facilities for treatment it has continued to hold its place. However, the insertion depth is generally limited to the proximal jejunum [5,6]. This restriction led to significant failures in placement of direct percutaneous

endoscopic jejunostomy (DPEJ). In **Chapter 6**, we assessed the efficacy and safety of single-balloon enteroscopy (SBE)-assisted DPEJ.

Part 3: complications of device assisted-enteroscopy

The SBE technique, using only the overtube balloon for fixation, demands angulation of the tip of the endoscope while the endoscope is pulled back or the overtube advanced. In theory, this "hooking" might lead to mucosal damage or extended stretching of the mesenterium, especially in patients with adhesions or otherwise fixated small-bowel segments [7,8]. An advantage of the SBE technique might be the prevention of increased intraduodenal pressure, because use of the single balloon avoids occlusion of a duodenal segment. In **Chapter 7** we assessed the safety of diagnostic and therapeutic SBE procedures, focusing on the occurrence of hyperamylasemia and pancreatitis, and to identify risk factors for hyperamylasemia.

In general, DBE has been shown to be safe endoscopic procedure, but a few severe complications have been reported. The most frequently reported, but still rare, complication after diagnostic DBE is acute pancreatitis [9,10]. There are several hypotheses concerning the cause of this severe complication, one suggests that the inflation of the DBE balloons in the duodenum causes reflux of duodenal fluids into the pancreatic duct, being the trigger for the pancreatitis [11]. In **Chapter 8** we presented the risk factors for hyperamylasemia and we determined the incidence of hyperamylasemia and pancreatitis when a modified cautious DBE insertion protocol was used.

One of the unexpected complications of DBE, as discussed previously, was the development of acute pancreatitis [11]. However, it is unclear whether spiral enteroscopy (SE), which involves rotation of a spiral overtube rather than inflation of balloons, may also be complicated by (post-) procedural acute pancreatitis or hyperamylasemia. This question was addressed by the final study included in this thesis presented in **Chapter 9**.

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Chapter 2

Small bowel diagnostics:

current place of small bowel endoscopy

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Abstract

The small intestine has been difficult to examine by traditional endoscopic and radiologic techniques. Until the end of the last century, the small bowel follow through was the primary diagnostic tool for suspected small bowel disease. In recent years capsule endoscopy, deep enteroscopy using balloon-assisted or spiral techniques, computerized tomography and magnetic resonance enteroclysis or enterography have facilitated the diagnosis, monitoring, and management of patients with small bowel diseases. These technologies are complementary, each with its advantages and limitations. In the present article, we will discuss the different options and indications for modern diagnostic methods for visualization of the small bowel. We also try to provide a clinical rationale for the use of these different diagnostic options in less established, newly emerging, indications for small bowel evaluation.

Introduction

The first part of the small bowel, up into the third part of the duodenum, is in a standard fashion intubated and assessed by regular upper endoscopy. The same applies for the last part of the small bowel, i.e. the terminal ileum, which is in general easily intubated and assessed with a regular ileo-colonoscopy procedure. While intubating the terminal ileum with the colonoscope the distal segment of the ileum can be examined, varying from a minimal segment of five centimetres, up to a maximum of 50 cm in to the distal ileum. The remaining 'in between' part of the small bowel may vary in length from four to up to eight m, and is more difficult to access with endoscopy procedures. Due to its total length and tortuous anatomy, the mid-gut part of the small bowel has historically been a difficult area to examine. Until the end of the last century, the small bowel follow through (SBFT) was the primary diagnostic tool for suspected small bowel disease. However, the SBFT has shown to have a relatively low diagnostic yield for small bowel disease [1] and [2]. In recent years, there have been significant innovations in radiological small bowel imaging using a variety of techniques, such as computed tomography (CT) or magnetic resonance imaging (MR or MRI) enteroclysis and/or enterography. Moreover, in the past decade new small bowel endoscopy techniques have been introduced, which have revolutionized daily gastroenterological practice worldwide. The introduction of capsule endoscopy (CE), followed by double balloon enteroscopy (DBE), single-balloon enteroscopy (SBE) and more recently spiral enteroscopy (SE) have opened the 'black box' of the small bowel. The aim of this review is to discuss the different options and indications for modern diagnostic methods for visualization of the small bowel. We also try to provide a clinical rationale for the use of these different diagnostic options in less established, newly emerging, indications for small bowel evaluation.

Radiological imaging of the small bowel

Radiological imaging tools of the small bowel are defined as any investigations using radiological techniques to visualize the intraluminal space of the small bowel and small bowel wall, with the use of intravenously and/or intraluminal contrast agents. Currently, the radiological options for visualization of the small bowel are the small bowel follow through, computerized tomography and magnetic resonance imaging, whether using enterography or enteroclysis technique. Enterography is being defined as using only oral contrast, and enteroclysis as a 'double contrast' technique involving oral contrast as well as intraluminal air insufflation. The latter is often combined with spasmolytic agents to improve visualization of the small bowel lining.

Small bowel follow through (SBFT) and enteroclysis

The development of newer forms of small bowel imaging and endoscopy has dramatically reduced the employment of conventional barium studies for the evaluation of the small bowel. One of the main reasons being the low diagnostic yield of small bowel follow through (SBFT) series and enteroclysis, ranging between an in general disappointing diagnostic yield of estimated 0–21% [3-7]. Especially, the diagnostic yield of mucosal lesions such as angiodysplasias, as well as mild to moderate active inflammatory lesions, is reported to be disappointingly low. Unfortunately, vascular malformations and minor inflammatory changes are both reported as the most common causes of small bowel pathology in daily clinical gastroenterology practice [8,9]. Currently, emerging diagnostic tools in assessment of small bowel disease are computerized tomography (CT)- and magnetic resonance (MR)-based enterography or enteroclysis studies. These modern diagnostics offer an alternative means of detecting mass lesions as well as improved visualization of small bowel mucosa, including vascular lesions such as angiodysplasias, previously poorly or non-visualized using conventional radiography studies.

CT-enteroclysis or -enterography (CTE)

The development of multidetector-row technology has introduced new opportunities for the CT guided evaluation of the gastrointestinal tract, owing to the use of thinner collimation and faster acquisition times. CTE combines the advantages of barium enterography or enteroclysis and conventional abdominal CT examinations using intravenous administration of iodine contrast agents, allowing simultaneous evaluation of intraluminal bowel content, bowel wall, bowel mesentery, and extra-intestinal abdominal organs and vessels. In CT enteroclysis insertion of nasojejunal tube is required for administration a total volume of 1500–2000 mL of enteral contrast medium at a rate of 60–120 mL/min with a pressured-controlled electric pump directly into the proximal jejunum. CT enterography is more patient-friendly not requiring a nasojejunal tube insertion for enteral contrast infusion. During CT enterography the contrast agent is orally administered, and often divided into multiple doses given every 20 min, beginning 60 min before the actual scanning. Due to the fact that oral contrast intake is often slower, a larger total volume of enteral contrast medium intake might be required, which can be again challenging for patients. CT enteroclysis provides better bowel distension than CT enterography, and for this reason enteroclysis is in general regarded the preferred method. Therefore, CT enterography is therefore mainly used in patients not tolerating a nasojejunal tube. Nevertheless, studies have shown no significant differences in diagnostic accuracy between CT enteroclysis and CT enterography in patients with suspected bowel disease [10,11]. The main drawback of CTE is the increased exposure to radiation, being reported consisting of up to 63 mSv in different studies, which is a major concern in younger and pregnant patients [12,13]. Furthermore, CTE is a

purely diagnostic tool, not allowing biopsies of suspect gastrointestinal lesions and not allowing direct therapeutic intervention [14].

MR-enteroclysis and -enterography (MRE)

Recent improvements in MRI soft- and hardware have extended the role of MR imaging in the evaluation of the small bowel, allowing demonstration of intraluminal, mural, and extra-intestinal diseases simultaneously, with improved image quality and resolution. As with CTE, an adequate contrast enhancement with or without bowel distension is required for optimal visualization; intraluminal contrast agents may be administered orally, defined as MR-enterography, or through a nasojejunal tube, defined as MR-enteroclysis using the 'double contrast' technique, in a more or less similar fashion as with the CTE procedure. At this stage, MRE is often used in patients with known or suspected Crohn's disease, but they have an emerging role in the detection of other small bowel diseases, including small bowel tumours. In the aforementioned settings, the major advantages of the MR examinations include information revealing intra- and extramural small bowel disease at the same time, and the lack of radiation exposure. Current limitations of MRE include costs, accessibility, variability in examination quality, and, as with CTE, the impossibility to perform biopsies from suspected lesions and not allowing therapeutic interventions [15].

Small bowel endoscopy

Small bowel endoscopy is defined as any endoluminal visual examination of the small bowel, including laparotomy assisted enteroscopy, push enteroscopy, capsule endoscopy, and balloon- or device-assisted endoscopy.

Laparotomy assisted or intraoperative enteroscopy

Laparotomy assisted or intraoperative enteroscopy is defined as an endoscopic examination of the small bowel during abdominal surgery with manual external assistance of the surgeon for endoscope progression. The endoscope can be introduced either orally or via an enterotomy during a laparotomy performed by a surgeon. The advantage of intraoperative enteroscopy is the fact that with this technique the complete small bowel can be evaluated, and during the same procedure, if indicated, surgical therapy can be performed. The main disadvantages of intraoperative enteroscopy are its invasiveness, the need for surgical assistance and the high complication rate. Morbidity associated with intraoperative enteroscopy has been reported in 3 – 42% of cases, including serosal tears, avulsion of the superior mesenteric vein, anastomotic leakage, intra-abdominal abscess, and prolonged ileus [16]. After the introduction of balloon- or

device assisted enteroscopy, intraoperative enteroscopy has become rarely needed. Currently, the role of intraoperative enteroscopy seems to be limited to selected patients in which balloon- or device assisted enteroscopy fails to achieve the diagnostic and / or therapeutic goal. For example due to limited insertion depths by balloon- or device-assisted enteroscopy as a result of adhesions often as result of earlier abdominal surgery.

Push enteroscopy

Push enteroscopy (PE) is a trans oral endoscopic examination technique using a 200- to 250-cm long flexible endoscope, often combined with an overture system to avoid intragastric looping. PE allows tissue sampling, polypectomy, and treatment of bleeding lesions of the proximal jejunum [17]. The main advantages of PE are that it is easy and quick to perform technique, and that it is readily available as there is no need to acquire a specific endoscopic and /or pump control system. All these facts avoid extra costs and, therefore, PE seems a cost-effective technique for diagnostic and therapeutic endoscopy of the proximal small bowel [18]. The main disadvantage is its limited insertion depth, reported maximally up to 130 – 150 cm in the proximal jejunum. In recent years, balloon-assisted endoscopic techniques have largely replaced PE in diagnostic and therapeutic procedures of the small bowel [19].

Capsule endoscopy

Capsule endoscopy (CE), introduced in 2000, is a method of endoluminal examination of the small bowel using a wireless capsule shaped tool. In most patients the capsule is swallowed and then propelled through the gastrointestinal tract by gut motility. If the patient is unable to swallow the capsule or the anatomy of the proximal gastrointestinal tract is altered due to earlier surgery, the capsule can be introduced via a gastroduodenoscopy. Special endoscopic delivery devices have been introduced to provide easy direct placement of the capsule in the proximal small bowel. Capsule endoscopy can be performed using the Given M2A video capsule system (Given Imaging Ltd, Yoqneam, Israel), the Olympus Endocapsule (Olympus America Inc., Center Valley) or MiroCam (IntroMedic Co., Seoul, Republic of Korea). The most commonly used Given capsule consists of a 26 by 11 mm device, containing a battery-powered complementary metal oxide silicon imager (CMOS), a transmitter, antenna and four light emitting diodes [20]. During the battery life of the capsule, images are recorded, and these images are reformatted into a continuous video file that can be reviewed on a normal computer using specially adapted software. After eight–ten hours, the antenna and storage unit are removed and the images transferred to a computer for analysis and reviewed by an experienced capsule endoscopist.

The main advantages of CE are the ability to visualize, in theory, the complete small bowel with minimal discomfort for the patient. The procedure also requires less physician training than advanced endoscopic techniques. The main disadvantages of this technique are the inability

to manoeuvre the capsule, the lack of therapeutic options, and the relative contraindication of possible strictures, because of the risk of capsule impaction [21,22]. Furthermore, although most images are excellent, they are still not comparable to the view achieved at conventional endoscopy with gas insufflation. Moreover, incomplete small bowel visualization has been reported in approximately 30% of CE investigations, leaving especially the distal part of the ileum uninspected. The combination of suboptimal and incomplete visualization of the small bowel lining, have been put forward as the main cause of false-negative outcomes of CE procedures [23].

Balloon- and device-assisted enteroscopy techniques

Balloon assisted enteroscopy (BAE) is a generic term for endoluminal examination of the small bowel by any endoscopic technique using balloons to promote deeper insertion into the small bowel, including single balloon enteroscopy (SBE) and double balloon enteroscopy (DBE). Device assisted enteroscopy (DAE) is a generic term for endoluminal examination of the small bowel by any endoscopic technique that includes assisted progression, i.e. by a balloon, overtube, or other stiffening device. Currently, DAE is considered the 'gold standard' diagnostic tool for small bowel pathology. The main advantage of DAE is the fact that it combines the possibility to perform additional biopsies for histopathological evaluation, together with the ability to perform therapeutic interventions during the same procedure. These DAE therapeutic options cover the whole range of widely used upper endoscopy and colonoscopy interventions, including electrocoagulation, argon plasma coagulation, polypectomy, balloon dilation of strictures, and retrieval of foreign bodies, including removal of retained wireless capsules. In majority of DAE therapeutic interventions, specially manufactured devices are used, which in general are longer and limited in external diameter, as compared to regular endoscopy devices. Another exciting and innovative diagnostic tool is the use endoscopic ultrasound for evaluation of small bowel tumours. The latter is performed using a specialized longer, and smaller in diameter, ultrasound catheter probe, which allows differentiation between gastrointestinal stromal tumours (GIST) and adenocarcinoma of the small bowel wall.

Double balloon enteroscopy (DBE)

The DBE system, first introduced by Yamamoto and colleagues in 2001, allows deep intubation of the small bowel by pleating the bowel onto a long, flexible endoscope fitted with an overtube. The DBE system consists of a diagnostic and therapeutic endoscope, the EN-450P5 and EN-450T5 (Fujinon, Saitama, Japan) respectively, in combination with a special balloon sufflation device and remote control of the latter device [24]. The endoscope and the accompanying overtube have both an in- and deflatable balloons at their distal end. By intermittent inflation and deflation of these two balloons, combined with instrument insertion and retraction, large

portions of the small bowel can be pleated on the overtube using the so-called ''push and pull technique'' [24,25]. During withdrawal of the endoscope, small parts of the small bowel are 'released' from the overtube, enabling the endoscopist to assess the small bowel lining and, if indicated, perform biopsies and / or therapeutic interventions. In theory, this enables the endoscopist to achieve complete visualization of the small bowel. However, in general practice a combination of the anterograde, i.e. proximal or oral, route and the retrograde, i.e. distal or anal, route is used to achieve complete small bowel examination. The procedure is performed using conscious sedation or general anaesthesia. A range of accessories has been developed to allow tissue sampling and to perform 'thought the endoscope' therapeutic procedures. DBE is a complex examination and should only be carried out by trained and experienced endoscopists. The standard method requires two individuals: an operator who handles the enterosocope and an assistant who handles the overtube. Complete evaluation of the small bowel, or total enteroscopy, performed by single approach or combined antero- and retrograde approaches, have a reported success rate ranging from 16 up to 86% [24,26]. However, DBE is not without limitations. The prolonged duration of the procedure, increased amounts of sedation used, and the frequent requirement of additional assistance are all potential problems that impact widespread use of this challenging technique. Furthermore, the overall complication rate of diagnostic DBE procedures is reported to be up to 1%, and is therefore higher as compared to other diagnostic endoscopic procedures. The most reported significant complication during or after diagnostic DBE procedures is acute pancreatitis. Two large multi-centre, one national and one internationally, conducted studies both showed a comparable incidence of this serious complication. The range of incidence of acute pancreatitis was respectively reported to be 0.2 and 0.3% after anterograde DBE procedures [27,28]. Quite some studies have addressed the issue of the relation of acute pancreatitis and anterograde DBE, by investigating the pancreatic enzyme levels (serum amylase and/or lipase levels) before and after anterograde DBE procedures. All these published studies seem to agree on the fact that there is an evident relation between a prolonged total procedural duration time and hyperamylasemia. Moreover, there seems to be a role for early insufflation of the DBE balloons, i.e. in the proximal part of the duodenum and/or jejunum. The clinical significance of this reported post-procedural hyperamylasemia is still open for debate: elevation of enzymes is reported in 13-51% of procedures, while the incidence of clinical acute pancreatitis is much lower, ranging from 1-13% of cases [29-33]. Whilst interpreting the data of these studies, one should take in mind that three studies, out of in total five, consisted of a relatively small number of patients, ranging from 13 to 48 procedures in total [29,30,32]. In the two larger studies, including a total of 135 and 92 patients, both the incidence of hyperamylasemia and acute pancreatitis were reported to be the lowest, 17-39% and 0.7 and 3%, respectively [31,33]. The current advice to minimize the risk of acute

pancreatitis during or after anterograde DBE procedures is to prevent longer duration of the anterograde DBE procedure, and to insufflate both DBE balloons only after introduction beyond ligament of Treitz. The overall risk of acute pancreatitis during or after retrograde DBE seems to be very low, or even non-existent. In a prospective study no post-procedural rise of serum amylase or lipase was found in 8 patients during or after a retrograde DBE procedure [32]. Until now, no cases of acute pancreatitis after retrograde DBE have been published. In line with the reported complication rates with conventional diagnostic and therapeutic endoscopy, the risk of significant complications is higher in therapeutic DBE procedures, as compared to diagnostic DBE procedures. The rate of complications after therapeutic DBE procedures is estimated to be around 3-4%, comparable or slightly higher than the reported complication rates of conventional therapeutic colonoscopy procedures [27,28].

Single balloon enteroscopy

The SBE system was introduced in 2007 as a simplification of the DBE system. The enteroscope (X SIF-Q160Y or -Q180, Olympus Optical Co, Tokyo, Japan]) is also a high-resolution video endoscope. The system uses only one balloon, which is attached to distal end of the overtube. In contrast to the DBE, the SBE system uses angulation of the tip of the enteroscope instead of the inflated balloon as 'fixation' of this point. In theory, the same 'push and pull technique' as advocated by the DBE system is used to pleat the small bowel on to the overtube, and to inspect on withdrawal [34]. At present, fewer data are available with regards to the complication rates in diagnostic and therapeutic SBE. The largest prospective study to date, suggests that the risk of post procedural hyperamylasemia and acute pancreatitis following anterograde SBE procedures is comparable to that after anterograde DBE procedures, being reported after 16 and 0% of procedures, respectively [35]. The risk of deep mucosal tears or perforation is estimated between 0 and 3% in diagnostic procedures [34,35]. It is suggested that the 'hooked tip' technique used during SBE procedures increases the risk of small bowel perforation during this procedure. Therefore, an alternative fixation technique of the tip of the SBE endoscope was suggested, named the 'power suction technique', which in theory should reduce the risk of this complication [36]. Until now, no data have been published to compare these different fixation techniques used during SBE procedures, in regards to performance, outcome and/or complication rates. The complication rate of therapeutic SBE procedures seems comparable to the rate of therapeutic DBE procedures, varying between 0 and 5%. However, in interpreting these therapeutic SBE complication data, one should realize that so far all presented studies consisted of a limited number of therapeutic SBE procedures [34,35,37].

To date, one case of acute pancreatitis after a retrograde, i.e. anal, SBE has been published. The authors of the latter case suggest that insufflation of the overtube balloon in the colon,

resulting in local compression and irritation of the pancreas, as being the cause of to the pancreatitis. The authors suggest to postpone insufflation of the overtube balloon until the terminal ileum is reached, to prevent this rare and unlikely complication of retrograde SBE [38].

Spiral enteroscopy

Spiral enteroscopy (Spirus Medical Inc., Stoughton, MA, USA) is the most recently introduced device assisted enteroscopy technique. An enteroscope is passed through a disposable overtube, which has raised helical spirals of 5 mm in height at its distal 21 centimeters end, facing the tip of the endoscope. The enteroscope can be locked in the overtube allowing the option of spiralling the overtube and enteroscope, in to the small bowell using clockwise rotation. Alternatively, the overtube can be unlocked, allowing the endoscope to be advanced into the small bowel through the overtube [39,40]. One of the advantages of the spiral enteroscopy system is that it requires no further specific equipment. The spiral overtubes can be used both with 'older types' enteroscopes and paediatric colonoscopes. Another advantage seems the 'speed' of introduction during the anterograde spiral enteroscopy procedure: experienced endoscopists are able to perform deep enteroscopy procedures within a time frame of 30-45 minutes. The latter being fairly quick, as compared to DBE and SBE procedures which require at least 60 minutes for completion. Until now, no cases of acute pancreatitis after spiral enteroscopy have been published. The main complication with diagnostic spiral enteroscopy seems to be perforation of the small bowel, occurring in 0.3% in a retrospective analysis of 1750 anterograde spiral enteroscopy cases [41]. A prospective study performed in the USA showed that spiral enteroscopy was feasible and safe in an elderly population, only four mild complications and no perforations were reported [42]. A recently published study showed that retrograde spiral enteroscopy was feasible and successful in 22 patients, one minor complication and no perforation was reported [43].

Indications and choice of small bowel imaging and/or endoscopy

Obscure gastrointestinal bleeding (OGIB)

The most common indication for small bowel imaging and / or endoscopy is obscure gastrointestinal bleeding (OGIB). OGIB is defined as occult or overt bleeding of unknown origin that persists or reoccurs after an initial negative endoscopic evaluation including upper endoscopy and colonoscopy, the latter both often repeatedly performed. OGIB has been shown to be defined to occur in approximately 5% of all patients who present with gastrointestinal haemorrhage [44]. In the evaluation and treatment of OGIB, capsule endoscopy and DAE are considered complementary procedures [45,46]. DBE and CE have shown comparable diagnostic yields in patients evaluated for OGIB. A recent updated and revised meta-analysis of ten studies,

of in total 642 patients, demonstrated that the pooled overall diagnostic yield for CE and DBE was 62 and 56%, respectively [47]. Unless contraindicated, CE is usually the initial diagnostic test in patients with suspected OGIB, because of its minimally invasive nature and therefore excellent tolerability, and theoretical the ability to visualize the entire small bowel. A secondary DAE is indicated if CE detects a lesion requiring biopsy or endoscopic intervention, or in patients whom have a high suspicion of small bowel bleeding despite a negative initial CE. This approach leads to a significant clinical improvement in over 75% of treated patients, including reduced transfusion and iron requirement needs [48]. However, from a cost minimization perspective, an initial DAE approach is the least expensive strategy when the need for therapeutic intervention or definitive diagnosis is highly probable [49]. As the fast majority of lesions responsible for OGIB are located in the proximal small bowel, it is reasonable to start with an anterogradel DBE in these cases [48,50]. An initial capsule endoscopy study remains the preferred initial strategy because of its relative non-invasive nature and acceptable diagnostic yield in OGIB patients. Current guidelines, including the ASGE guideline, advocate the use of CE as primary diagnostic tool for evaluation of the small bowel in OGIB patients [51].

Currently, the use of modern non-invasive diagnostic radiological investigations, as CTE or MRE in context of OGIB seems to be limited. The diagnostic yield of multidetector CT enterography or enteroclysis in OGIB patients is overall disappointing, ranging from 22 to 42%. A higher sensitivity, up to 55%, was reported in patients with massive bleeding or recurrent overt OGIB [52,53]. There are limited data concerning the use of MR enterography or enteroclysis in OGIB patients. A recently published prospective study comparing CE, DBE and MRE in a total of 38 consecutive OGIB patients, showed a disappointing sensitivity of only 21% for MRE as compared to the findings with DBE, the latter diagnostic tool which was considered the 'gold standard' in this study [54]. The relatively low sensitivity of CTE and MRE in OGIB patients may not come as a surprise, as the most coming finding in these particular patients group is reported to be small bowel angiodysplasia or vascular malformations. The latter vascular lesions are, in general, small in size and do not show as 'masses' and therefore are easily missed by these radiological investigations, which mainly focus on identification on small bowel masses and / or differences in contrast enhancement. In future, further refinements of the CT and MR techniques might improve resolution and therefore the detection rate of these lesions.

Suspected or known Crohn's disease (CD)

Most cases of CD affect the distal small bowel, i.e. terminal ileum, and right colon, whereas 20 – 30% of patients may have disease limited to upper gastrointestinal tract, including the small bowel. Especially the paediatric CD population is well known to present with a higher incidence of proximal small bowel involvement as compared to the adult CD population [55]. Small bowel involvement of CD is known as an independent risk factor for complicated disease. CD patients

with small bowel activity more often need step-up medical treatment and surgical interventions [56]. Therefore, it seems critical to evaluate the small bowel in all patients with suspected inflammatory bowel disease to assess small bowel disease activity, and to 'stage' the extent and severity of disease. Until recently, the diagnosis of small-bowel CD was made on the basis of ileocolonoscopy and/or small bowel radiological diagnostics. The newer endoscopic techniques have improved the clinician's ability to identify, often subtle, lesions that may be associated with small bowel CD [51,52]. A recently published large meta-analysis of 12 studies, of in total 552 included patients, compared the diagnostic yield of CE with other diagnostic modalities, including ileocolonoscopy, push enteroscopy, SBFT, CT enterography and MR enterography in both suspected and established CD patients. CE demonstrated to be superior to SBFT, CTE, and ileocolonoscopy in suspected CD patients. Moreover, CE also proved to be more effective in established CD patients, as compared to SBFT, CTE and push enteroscopy [57]. A recently published prospective study in 38 patients compared the use of CE, MR enteroclysis and DBE in patients with suspected or known CD. The results of the latter study demonstrate a better performance for MRE as compared to CE, especially due to the fact that a high incidence of significant small bowel stenosis prohibited the use of CE as a diagnostic modality in this patient group. MRE was recommended as the first-choice, and non-invasive, diagnostic procedure in patients with suspected small bowel CD. Guided by the outcome of the MRE, a CE can be conducted to assess mild to moderate ulcerative small bowel disease, or a BAE can be scheduled to arrange histopathological confirmation or to perform therapeutic intervention, i.e. dilation therapy [58]. The risk for CE retention in CD patients is estimated to be 5 to13%, which is a notable limitation for this procedure in this patient group [59]. European guidelines, published by the ECCO and ESGE, both state that CE is the first choice diagnostic procedure for evaluation of small bowel mucosal lesions in suspected and known CD, and that small bowel imaging or a patency capsule should precede CE to minimize the risk of capsule retention [60-61]. The ECCO guideline specifically states that it is important to realize that the clinical significance of these small bowel mucosal lesions identified with CE in patients with known CD remains unclear. Furthermore, it mentions that there might be a role for CE in inflammatory bowel disease unclassified patients, to identify patients with lesions compatible with CD. The ECCO guideline also states that the potential role for CE in paediatric patients with suspected or known CD, is comparable to that of the adult population. CE seems to have a comparable diagnostic yield in paediatric patients, and can be used safely in this specific patient population [61]. DAE is indicated in patients with suspected small bowel CD disease, in order to confirm the diagnosis of CD and to exclude alternative diagnosis, i.e. abdominal tuberculosis, small bowel lymphoma, or carcinoma. Adequate endoscopic evaluation of small bowel strictures with additional biopsies for histopathology or dilation of medical therapy refractory strictures can be successfully performed

using DAE [62]. Also DAE is indicated for endoscopic removal of foreign bodies such as a capsule or bezoar, and can in this way prevent the necessity for surgical intervention [63].

Table 1. Comparison of diagnostic yield for different techniques in OGIB or CD patients.

Diagnostic yield	*OGIB*	*CD*
SBFT	0-21%	0-32%
MRE/CTE	22-48%	21-39%
CE	38-83%	60-71%
DAE	43-80%	50-57%

OGIB, obscure gastrointestinal bleeding; CD, Crohn's disease; SBFT small bowel follow through; MRE/CTE, MR/CT-enteroclysis or enterography; DAE, device assisted enteroscopy

(Inherited) Polypoid syndromes

Peutz-Jeghers syndrome (PJS) is an inherited, autosomal dominant disorder distinguished by pigmented mucocutaneous lesions and hamartomatous polyps in the gastrointestinal tract. Prevalence of PJS is estimated to range from one in 8300-280000 individuals. The two main challenges in the management of gastrointestinal tract related complications in PJS patients are firstly to prevent polyp related complications, such as intussusception and bleeding, and secondly to reduce the long term cancer risk. Therefore, regular assessment of the gastrointestinal tract, including the small bowel, is part of the screening program in these patients. Currently, there is discussion about at what age small bowel screening should be initiated, taking into account that over two-thirds of PJS patients already had at least one intussusception at a median age of 16 (range 3–50) years [64]. Two studies have confirmed that CE has a significant improved diagnostic yield for small bowel polyp detection in PJS patients, as compared to SBFT [65,66]. Comparative studies using CE and MRE in PJS patients has already shown that CE is superior for detection of smaller polyps, both modalities seem to have comparable diagnostic yields for polyps 15 mm, or larger in size. MRE demonstrated improved determination of localization and actual size of the small bowel polyps [67]. However, a recent study showed that MRE may be superior for detection of larger small bowel polyps, which are clinically more relevant, and may be more reliable in size assessment of small bowel polyps, as compared to CE [65]. DBE has already shown to be of use in detection and removal of small bowel polyps in PJS patients [68]. However, long-term prospective studies on the outcomes of PJS patients screened with CE and/or DAE are currently lacking. In theory, DAE combines the 'gold standard' diagnostic and therapeutic tool, to prevent small bowel polyp related complications, but it invasiveness inhibits it use as a primary diagnostic in PJS patients. Centers of excellence with larger PJS patient cohorts, currently promote the use of CE and/or MRE as the first diagnostic procedure for screening of small bowel polyps, this followed by a guided DAE procedure for endoscopic removal of small

bowel PJS polyps. According to a group of European PJS experts it is recommended to a perform small bowel surveillance every three years if polyps are found at the initial examination, starting from the age of 8 years, or earlier if the patient is symptomatic [69]. SBFT is currently regarded obsolete in surveillance of PJS, since it has shown a lowered diagnostic yield for small bowel polyps and due to its significant radiation exposure.

Until now, the use of CE and/or DAE for small bowel screening in patients with familial adenomatous polyposis (FAP) has only been reported in smaller patient cohorts. Using CE in up to 87% of patients small bowel polyps were detected, as with DBE in up to 75% of patients adenomatous polyps were found and resected [70,71]. There seems to be a potential role for new endoscopic imaging techniques, i.e. chromoendoscopy and/or narrow band imaging, for improved detection and staging of small bowel polyps in these particular patients [72].

Summary

Currently, various radiological, endoscopic and surgical options are available for assessment of the small bowel, each with their own advantages and shortfalls. To date the classical SBFT has completely been replaced by newer radiological and endoscopic techniques for evaluation of the small bowel. Currently, the first line radiological diagnostics for small bowel evaluation are CTE and MRE. Both seem to have comparable diagnostic yields, and clinical applicability mainly depends on the availability of techniques. The introduction of CE and DAE procedures has transformed the approach to the evaluation and management of small bowel diseases over the past decade, especially for the indication obscure gastrointestinal bleeding. CE is generally accepted as the first choice investigation in the latter patient group. CE combines a minimal invasive approach with an acceptable diagnostic yield. DAE is in this patient group reserved for patients with abnormal findings on previous CE, i.e. a 'guided DAE'. DAE has already shown to be the 'gold standard' endoscopic investigation of the small bowel, with the superior capacity to perform additional diagnostics, i.e. biopsies for histopathology, and to ability to perform endoscopic therapeutic interventions. These properties make DAE the first choice in patients with known small bowel pathology, needing histopathological confirmation and/or endoscopic therapeutic intervention. The potential clinical benefit of DAE therapeutic intervention has already been shown in patients with Crohn's disease related small bowel strictures and Peutz-Jeghers syndrome related small bowel polyps.

Practice points:

1. Small bowel follow through is obsolete in modern small bowel imaging due to its low sensitivity.
2. Capsule endoscopy is the first line diagnostic choice in OGIB patients.
3. Capsule endoscopy and MR enteroclysis or enterography can both be used as first line small bowel diagnostic in patients suspected for or with known Crohn's disease.
4. Device assisted enteroscopy is best performed complementary to capsule endoscopy, or MR of CT enteroclysis or enterography, to provide additional histopathology or to perform endoscopic therapeutic interventions.
5. To date device assisted enteroscopy remains the 'gold standard' for small bowel pathology.

Research points:

1. Larger prospective studies comparing CE, BAE and newer CT and MR techniques for diagnostic yield and long-term outcomes in the different patient groups.
2. Cost-effectiveness studies for patient selection and strategies in OGIB patients.
3. Prospective, preferably placebo-controlled, studies to clarify the clinical significance of small bowel mucosal lesions in patients with known Crohn's disease.
4. Long-term prospective studies to provide evidence-based guidelines for small bowel screening for familiar polypoid syndrome; including the evaluation of newer endoscopic imaging techniques as chromoendoscopy, narrow band imaging and FICE in these patients.

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Part Two

Diagnostic and therapeutic impact of device-assisted enteroscopy

Chapter 3

Single- versus double-balloon enteroscopy in small bowel diagnostics: a randomized multicenter trial

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Abstract

Background and study aim: Double-balloon enteroscopy (DBE) is the first choice endoscopic technique for small-bowel visualization. However, preparation and handling of the double-balloon enteroscope is complex. Recently, a single balloon-enteroscopy (SBE) system has been introduced as being a simplified, less-complex balloon-assisted enteroscopy system.

Patients and methods: This study was a randomized international multicenter trial comparing two balloon-assisted enteroscopy systems: DBE vs. SBE. Consecutive patients referred for balloon-assisted enteroscopy were randomized to either DBE or SBE. Patients were blinded with regard to the type of instrument used. The primary study outcome was oral insertion depth. Secondary outcomes included complete small-bowel visualization, anal insertion depth, patient discomfort, and adverse events. Patient discomfort during and after the procedure was scored using a visual analog scale.

Results: A total of 130 patients were included over 12 months: 65 with DBE and 65 with the SBE technique. Patient and procedure characteristics were comparable between the two groups. Mean oral intubation depth was 253 cm with DBE and 258 cm with SBE, showing noninferiority of SBE vs. DBE. Complete visualization of the small bowel was achieved in 18% and 11% of procedures in the DBE and SBE groups, respectively. Mean anal intubation depth was 107 cm in the DBE group and 118 cm in the SBE group. Diagnostic yield and mean pain scores during and after the procedures were similar in the two groups. No adverse events were observed during or after the examinations.

Conclusions: This head-to-head comparison study shows that DBE and SBE have a comparable performance and diagnostic yield for evaluation of the small bowel.

Introduction

Until recently, the small bowel was considered a "black box" for gastrointestinal endoscopy, as most of the small bowel was not accessible with conventional endoscopy techniques. The Fujinon double-balloon enteroscopy (DBE) system, introduced by Yamamoto and colleagues in 2001, was the first endoscopic procedure for visualizing, in theory, the entire small bowel [1]. At present,

DBE is considered the standard technique for endoscopic visualization of the small bowel, combining diagnostic and therapeutic functions during the same procedure [2–4]. Although DBE has widely been introduced into gastroenterological practice, some issues hamper its daily clinical use. Preparation and handling of the double-balloon enteroscope are complex and cumbersome, involving attachment of a balloon to the tip of the endoscope as well as inflation and deflation of a two-balloon system. Therefore, the development of a simpler, easier-to-handle, small-bowel endoscopy systems would be of interest to endoscopists.

In 2008, a novel, simplified balloon enteroscopy system was introduced by Olympus employing one instead of two balloons to facilitate enteroscopic access to the small bowel [5,6]. In theory, use of this single-balloon enteroscopy (SBE) system might lead to decreased preparation and examination time. However, SBE may be less efficient for deep intubation of the small bowel compared with the DBE system, and may cause adverse effects due to the hooking technique during straightening of the single-balloon endoscope.

Recently, a German study group showed that using the Fujinon DBE system with double- or single-balloon technique, the single-balloon technique was inferior in both complete small-bowel visualization and insertion depth compared with the double-balloon technique [7]. However, the latter study has some limitations: first, it did not compare the DBE and the SBE systems, and secondly the participating centers did not have experience in applying the SBE technique.

To our knowledge, this paper presents the first randomized controlled trial comparing the Fujinon DBE system with the SBE system by Olympus for small-bowel enteroscopy. The primary aim of this study was to compare the technical performance of the two balloon-assisted enteroscopy systems [8].

Patients and methods

An international multicenter single-blinded randomized controlled trial was performed. Participating centers were: the Rikshospitalet University Hospital (Oslo, Norway), University Hospital of Münster (Germany), and Erasmus MC – University Medical Center (Rotterdam, The Netherlands). The study protocol was approved by the institutional review boards of all participating centers. Before the start of recruitment, the study was registered in a clinical trial

database (ClinicalTrials.gov Identifier: NCT00708253). Randomization to either SBE or DBE was performed in blocks of six patients (at each of the participating centers) using computerized randomization software. This yielded approximately equal groups assigned to each method at each of the participating centers. The patients, but not the endoscopists, were blinded with regard to the type of instrument used.

Patients

Consecutive patients who were scheduled for a balloon-assisted enteroscopy with the intention of total enteroscopy were asked to participate in the present study. Exclusion criteria were: age under 18 years, inability to understand patient information, and inability to give informed consent. All included individuals provided written informed consent before entering the trial.

Endoscopic procedures

All patients underwent bowel preparation with 4 L polyethylene glycol solution. DBE procedures were performed employing the Fujinon endoscope system (EN-450P5/EN-450T5, Fujinon Inc., Saitama, Japan) [1–4,9]. SBE procedures were performed using the SBE endoscope system (SIF-Q180, Olympus Optical, Tokyo, Japan). Insertion of the SBE system followed the method used for DBE, but instead of inflation of the balloon at the proximal part of the endoscope (as for DBE) the tip of the endoscope was angulated during straightening ("hooked-tip" procedure) [5,6].

All endoscopic procedures were performed by endoscopists who were experienced in DBE and SBE techniques. Each of the trial centers has extensive experience using the DBE system, and at least 50 SBE procedures had been performed before the start of the trial. Sedation was given according to current standards at the participating centers. Oral approach enteroscopy was performed first, followed by the anal route on the same day, or scheduled for the following day. In all patients, complete small-bowel visualization was attempted. The oral or anal procedure was stopped when no further endoscopic advancement was achieved. During oral enteroscopy, submucosal ink marking (SPOT™, GI Supply Inc., Camp Hill, Pennsylvania, USA) or hemoclip placement was carried out at the most distal point reached in order to ascertain whether or not total enteroscopy had been achieved when the oral approach was complemented by the anal route. Fluoroscopy was not used in a standard fashion, and therefore radiation exposure times were not documented. During all procedures, oral and anal small-bowel insertion depth was estimated using the method described by May et al. [3,10].

Procedure time was defined as beginning with the insertion of the endoscope and ending with removal of the endoscope from the patient. Set-up time for the equipment and therapeutic

interventions were not included. CO2 was used as insufflation gas during enteroscopy, which had proved to enable significantly extended intubation depth and to reduce patient discomfort [9].

Postprocedural pain and discomfort were rated by the patients using a 100-mm visual analog scale (VAS) from 0–100, with the left boundary indicating "no pain", and the right boundary indicating "very heavy pain" [9,11,12].

Study outcomes

The primary outcome measure of the present study was direct comparison of DBE and SBE procedures with regard to small-bowel insertion depth during the oral. Secondary outcomes included completeness of small-bowel visualization, diagnostic yield, procedure time, and patient discomfort.

Statistics

The present study was a noninferiority study, aiming at equality between the two endoscope systems with regard to the study outcomes [13]. The maximal acceptable reduction of mean insertion depth was defined to be 25 cm (i.e. SBE insertion depth >DBE insertion depth –25 cm). For complete small-bowel visualization we defined 10% to be the maximum acceptable difference.

The objective "complete small-bowel visualization", which was initially considered to be another primary endpoint, could not be accomplished, as complete visualization was not achieved in the patient group of the pilot study (n = 20). The power analysis showed that approximately 11500 patients in each group would have been necessary to confirm noninferiority. Furthermore, for technical reasons, the anal route access proved to be an unreliable parameter. We therefore decided to define oral access as the only primary endpoint of this study. We focused the analysis of the secondary endpoints - anal access and complete visualization - on a descriptive assessment.

The study endpoints were analyzed in all patients who successfully completed the study and were thus eligible for data analysis.

Noninferiority test was performed by calculation of the one-sided 95% confidence intervals (CIs) of the study endpoint. According to the literature, the reference value of oral insertion depth was set to be 250 cm (with a standard deviation of 60 cm) for both enteroscopic procedures [2, 9]. By determining a margin of 25 cm we achieved a power of 75% for the noninferiority test. Differences in mean VAS scores were analyzed by ANOVA for repeated measurements. All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA) and SAS (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient characteristics

During the study period from June 2008 until May 2009, a total of 130 patients were included and randomized. DBE or SBE procedures were performed in 65 patients in both arms of the study.

All patients were available for follow-up, and all completed the patient questionnaire. In four patients, two in each group, the anal route enteroscopy could not be performed/completed due to stenosis (n = 2) or inability to introduce the distal ileum without obvious cause (n = 2). Patient characteristics were comparable, including the proportion of patients with previous abdominal surgery, which was almost identical in both groups (Table 1).

Table 1. Patient characteristics.

	DBE (n=65)	SBE (n=65)	p-value
Mean age in years (range)	52 (18 – 84)	53 (21 – 80)	0.74
Males / females	32 / 33	35 / 30	0.73
Previous abdominal surgery (%)	16 (25%)	16 (25%)	1.00
Indication for enteroscopy (%)			
– occult / overt GI bleeding	29 (45%)	26 (40%)	0.72
– Crohn's disease	11 (17%)	12 (18%)	0.81
– abdominal pain	9 (14%)	9 (14%)	1.00
– diarrhea	7 (11%)	6 (9%)	0.77
– polyposis syndromes	2 (3%)	3 (5%)	0.65
– other	7 (11%)	9 (14%)	0.79

Small-bowel visualization

With respect to the primary study outcome, oral insertion depth, SBE showed noninferiority compared with DBE (Table 2).

The lower limits of the 95% one-sided CIs for the differences (SBE minus DBE) were –19.6 cm for oral intubation depth and –9.8 cm for anal intubation depth, showing both parameters to be within the defined margins of 25 cm.

Due to inadequate sample size concerning small-bowel visualization, 18% (n = 12) for the DBE group vs. 11% (n = 7) for the SBE group were not sufficient to prove noninferiority within the 10% margins (Table 2).

The diagnostic yield of both techniques was comparable. Also, no differences were found comparing number and type of therapeutic interventions and duration of procedures in both groups (Table 2).

Table 2. Procedure characteristics.

	DBE (n = 65)	SBE (n = 65)	p-value	LCL*
Approach, n (%)				
– only oral	11 (17)	15 (23)	0.51	
– combined oral and anal	54 (83)	50 (77)		
Insertion depth (cm, range)				
– oral approach	253 (120 – 450)	258 (100 – 560)		-19.6
– anal approach	107 (10 – 250)	118 (5 – 300)		-9.8
– combined approach (n = 53)	360 (180 – 550)	373 (100 – 620)		-16.6
Complete small-bowel visualization, n (%)	12 (18)	7 (11)		-20%
– only oral approach	1	1		
– combined oral and anal approach	11	6		
Procedure duration, mean (range), minutes	105 (40 – 140)	96 (35 – 135)	0.13	
Primary diagnosis achieved, n (%)	28 (43)	24 (37)	0.59	
– angiodysplasias	7 (11)	3 (5)		
– Crohn's disease activity	7 (9)	4 (5)		
– polyposis	3 (5)	3 (5)		
– other	11 (17)	14 (22)		
Therapeutic procedures, n (%)	6 (9)	3 (5)	0.49	

DBE, double-balloon enteroscopy; LCL, lower 95% confidence limit of difference (SBE–DBE); SBE, single-balloon enteroscopy.

Patients' discomfort

The mean pain score during and after the examination showed no significant difference between the groups at any of the times evaluated (Table 3). The mean pain scores of 33 compared with 36 on the 100-mmVAS indicate moderate abdominal pain during the respective procedures. Patients reported light pain 1 hour after examination, which resolved in the majority of patients during the following hours.

Table 3. Abdominal pain during and after double- and single-balloon enteroscopy.

	Mean (SD) VAS,mm		
	DBE (n = 65)	SBE (n = 65)	p-value
Pain during examination	33.0 (26)	36.2 (33.6)	0.55
Pain after 1 hour	12.2 (21.9)	12.5 (24.2)	0.87
Pain after 3 hours	3.9 (11.1)	3.6 (12.0)	0.57
Pain after 6 hours	2.3 (5.2)	3.1 (8.6)	0.82
Pain after 24 hours	2.4 (5.5)	3.8 (9.0)	0.41

DBE, double-balloon enteroscopy; SBE, single-balloon enteroscopy; VAS, visual analog scale.

Adverse events following balloon-assisted enteroscopy

No adverse events or procedure-related mortality was observed after the DBE or SBE procedures.

Discussion

The present study is the first head-to-head comparison trial of DBE vs. SBE, comparing the Fujinon DBE system with the Olympus SBE system. Noninferiority was shown with respect to the insertion depths. With regard to complete visualization, we could not show noninferiority; whether SBE is inferior, equivalent or even superior compared with DBE remains an open question. Diagnostic yield, rate of complications between the two systems, and patient discomfort scores during and after the procedures were comparable.

In theory, one might expect that DBE, because of the improved grip on the small bowel, would have produced superior results with regard to small-bowel visualization, rate and insertion depth, compared with the SBE technique. The results of this study show that only a trend for more complete small-bowel visualization was seen with DBE, but this difference was not statistically different. Moreover, no statistical difference was found with respect to oral and anal insertion depths in both groups. May and colleagues showed, in a recently published study, a superior performance of the DBE technique compared with the SBE technique using the Fujinon system. These contradictory findings might be explained by the fact that the endoscopists participating in the May study were rather inexperienced in using the SBE technique.

The endoscopists participating in our study were experienced in the SBE technique, and had performed over 50 SBE procedures before commencement of the current study. As being quite a different technique compared with DBE, the SBE "hooked-tip" technique during the pull phase of the enteroscopy, is most likely to have a learning curve, which might be comparable to the earlier reported learning curve of the DBE technique [14]. Furthermore, it is possible that the Olympus SBE system might not be comparable to the Fujinon system used in a SBE fashion due to differences in technical and material composition.

The diagnostic yield rates presented here, support those of earlier balloon-assisted enteroscopy reports [2,15–18]. The overall percentage of therapeutic interventions might be lower compared with earlier published series; this can be explained by the relatively high percentage of enteroscopies in (suspected) Crohn's disease patients. In the latter patients, with clinical suspicion of small-bowel activity, mainly diagnostic procedures are performed.

In the SBE group the total procedural duration appeared to be somewhat shorter compared with the DBE group, but this difference was not statistically significant. Although of great interest, we did not record the preparation time of either enteroscopy systems in the present study. As the DBE and SBE systems were comparable in this study in terms of performance and diagnostic

yield, preparation time and handling might be of great interest. Future studies comparing DBE and SBE techniques should include preparation time and handling to provide further insight to this matter.

Surprisingly, the patient discomfort reports during and after procedures were comparable between groups. In theory, one might expect that the hooked-tip pull technique used during SBE procedures induces more abdominal complaints peri-procedurally. On the other hand, the proximal DBE procedure is known to cause post-procedural hyperamylasemia, which might be related to the development of acute pancreatitis. Earlier reports have shown that the majority of patients with post-DBE acute pancreatitis present with abdominal complaints directly after the procedure.

The discomfort scores of our study show that peri-procedural pain scores were comparable between the groups, showing that these factors seem not to play a major role, or were equally divided, in both groups.

No complications were reported during or after the procedures. No acute pancreatitis was encountered after the proximal DBE or SBE procedures. This absence of cases of pancreatitis, especially in the DBE group, might reflect the adjustment of insertion technique of both enteroscopy systems that is practiced by the endoscopists of all participating centers. This adjustment consisted of inflating the balloon(s) only after insertion of the overtube beyond the Ligament of Treitz [19,20].

This study has some limitations. First, with respect to statistical power calculation the percentage of complete small-bowel visualization achieved by both DBE and SBE was low. The number of patients to be recruited to reach adequate statistical power with regard to equivalence of the two methods was far from what we could achieve with the clinical resources available. The question remains whether the technically appreciated end-point "complete small-bowel visualization" is preferred above the more clinically relevant end-point of "diagnostic yield". The second limitation concerns the relatively low percentage of complete small-bowel visualization in the DBE group. However, this percentage seems comparable to the majority of other Western studies performed in larger patients groups (> 40 patients included), which have shown percentages of complete bowel visualization varying between none and 16% [2,21–24]. Only two other larger Western studies have shown higher small-bowel visualization rates of 42% and 66%, respectively [7,25]. This relatively low rate of complete small-bowel visualization might be partly explained by the fact that a rather large portion of patients (17%) had Crohn's disease. In these patients, complete small-bowel visualization is difficult to achieve due to postoperative and postinflammatory adhesions. Thirdly, a prolonged learning curve for SBE procedures cannot be ruled out. The somewhat lower, although statistically insignificant, number of complete small-bowel visualizations in the SBE patients group might be caused by the fact that at initiation of the study all participating endoscopists were very experienced in DBE procedures, but less so in SBE

despite carrying out at least 50 pre-trial SBE examinations. A study focusing on learning curves in DBE procedures showed that, particularly in distal procedures, no improved performance was seen even after 40 procedures [14], suggesting that more procedures (> 40) are needed to achieve a certain level of competence. Whether this learning curve also represents the learning process with respect to the SBE technique has not been addressed in previous studies.

The presented comparative study of DBE and SBE techniques for small-bowel evaluation fails to show a significant difference between the two systems with respect to insertion depth and diagnostic yield. Accordingly, both techniques seem to be interchangeable in daily clinical gastroenterology practice.

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Chapter 4

Impact of double-balloon enteroscopy findings on the management of Crohn's disease

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Abstract

Objective. It is estimated that 10%–30% of Crohn's disease (CD) patients have small-bowel lesions, but the exact frequency and clinical relevance of these findings are unknown. Double-balloon enteroscopy (DBE) enables endoscopic visualization of the small bowel. The aim of this study was to evaluate the use of DBE for detecting small-bowel lesions in CD patients suspected of having small-bowel involvement. Furthermore, the clinical impact of adjusting treatment in these patients was assessed.

Material and methods. A prospective study was performed in a tertiary referral center. CD patients suspected of small-bowel involvement and in whom distal activity had previously been excluded were included. All patients underwent DBE, followed by step-up therapy in patients with small-bowel lesions. The presence of small-bowel lesions during DBE was noted and clinical outcome was assessed after adjusting therapy.

Results. Thirty-five patients (70%) showed small-bowel lesions; these lesions could not be assessed by conventional endoscopy in 23 (46%). At 1-year follow-up, step-up therapy in 26 patients (74%) led to clinical remission in 23 (88%). This was confirmed by a significant decrease in Crohn's disease activity index and mucosal repair on second DBE.

Conclusions. DBE showed a high frequency of small-bowel lesions in known CD patients with clinically suspected small-bowel activity. Most of these lesions were not accessible for conventional endoscopy. Adjusting treatment in patients with small-bowel CD involvement led to clinical remission and mucosal repair in the majority of cases.

Introduction

It is estimated that 30%–40% of Crohn's disease (CD) patients have small-bowel (SB) lesions [1]. Although upper gastrointestinal CD predicts a more disabling course of the disease, current diagnostics mainly focus on ileocolonic disease [2,3]. Identification of patients with SB localization represents an important tool to optimize therapy and modify the disease course. SB follow-through (SBFT) has limited sensitivity for the detection of CD activity, especially mild to moderate activity [4,5]. Recently, several new modalities for detecting small-bowel CD activity have been introduced. These comprise capsule endoscopy (CE) and CT- or MRenterography, which are able to identify SB lesions in 20%–60% of CD patients [6–8]. However, CE is contraindicated in approximately 40% of CD patients due to the risk of capsule retention in a stenotic region [9,10]. Compared to CE, CTand MR-enterography have been demonstrated to have a lower sensitivity for detecting mild to moderate SB activity in CD patients [11–16]. Thus, these imaging techniques have limited value in the evaluation of SB involvement in a large number of CD patients. Double-balloon enteroscopy (DBE) has been introduced for the diagnosis and treatment of various SB diseases [17,18]. Currently, the data concerning DBE in CD patients are scarce and preliminary data have indicated a relatively high frequency of SB lesions in CD patients detected using this technique [19–21].

This prospective study investigated the feasibility and safety of DBE for detecting SB lesions in CD patients suspected of SB activity. Secondly, the clinical impact of therapy adjusted for abnormalities found during DBE was evaluated.

Material and methods

Study design

In a prospective study, consecutive CD patients with suspected SB involvement and no distal disease activity were evaluated using DBE. The inclusion criterion was suspected SB involvement in known CD. The diagnosis of CD had to be confirmed by histopathology, and made > 6 months before inclusion. Suspected SB involvement was defined as: (1) persistent abdominal complaints, consisting of symptoms compatible with obstruction and/or abdominal distension, and/or (2) iron-deficiency anemia, and/or (3) hypomagnesemia. Exclusion criteria were: distal CD activity on recent ileocolonoscopy; patients aged < 18 years; patients using non-steroidal anti-inflammatory drugs within 4 weeks prior to the DBE; and pregnancy. All patients gave their informed consent for the procedure. Results from earlier performed SB diagnostics, i.e. SBFT, CE, CT- and/or MR-enterography, were not considered relevant and were not evaluated in this study. If SB diagnostics had been performed earlier, the endoscopists were not aware of the outcome. All patients were

classified using the Montreal Classification [22]. Laboratory measurements included full blood count, C-reactive protein (CRP), albumin and electrolytes prior to the DBE. The Crohn's disease activity index (CDAI) was assessed 1 week before and 1 year after the DBE procedure. Clinical remission was defined as a CDAI score < 150 and a decline in CDAI score of ≥ 75 points from baseline.

DBE procedure

All patients underwent bowel preparation using a polyethylene glycol solution. Patients underwent DBE using conscious sedation, consisting of intravenous administration of midazolam and fentanyl, or general anesthesia, using propofol sedation. The enteroscopes used were the Fujinon EN-450P5 or -450T5 (Fujinon Inc., Saitama, Japan). In all patients, visualization of the entire SB was attempted: starting with a trans-oral approach, combined with a transanal procedure if the distal ileum was not reached by the trans-oral route.

Definition of SB CD lesions

The SB segments proximal to the Treitz ligament and the distal 50 cm of the (neo-) terminal ileum were defined as within reach of conventional endoscopy. The SB 'in between' was divided into four segments: (1) proximal jejunum, from Treitz ligament to 150 cm distally; (2) distal jejunum, 150–300 cm from Treitz ligament; (3) proximal ileum, 300–450 cm from Treitz ligament; and (4) distal ileum, up to 150 cm proximal from the (neo-) terminal ileum. Currently, there is no validated enteroscopic SB CD severity scale. SB lesions were defined as (0) absent, (1) minor: erythematous and/or edematous mucosa and/or small ulcerative lesions < 0.5 mm within normal mucosa, (2) moderate: larger ulcerative lesions ≥ 0.5 and < 20 mm, or (3) severe: ulcerative lesions ≥ 20 mm and/or non-significant stenotic lesions and (4) stenotic: significant stenotic lesions, with or without inflammation.

Clinical impact of SB findings

Step-up medical therapy was offered if SB lesions were found during DBE, consisting of azathioprine or methotrexate in immunosuppressive-naïve patients and anti-tumor necrosis factor (TNF) therapy in patients already on immunosuppressive therapy. Patients using infliximab with no clinical response after 6 months were considered for switching to adalimumab therapy. Surgery was considered in patients with no clinical response who had been on optimal medical therapy, i.e. anti-TNF therapy, for > 6 months and with localized and resectable active CD. In the patients without SB lesions, no step-up medical therapy was offered.

Statistical analysis

Continuous variables were reported by using means (and SDs) or medians (and ranges) and were compared by using the unpaired *t*-test or the Wilcoxon rank-sum test, where appropriate. Qualitative variables were compared using chi-square testing. A *P*-value of < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL).

Results

Patient characteristics

Between September 2006 and July 2007, 50 CD patients were included: 25 males, mean age 45 (23–75) years. Mean duration of CD was 17.2 (1–44) years. The majority, 88%, of patients had previous CD-related surgery. Only six patients (12%) had known involvement of the upper gastrointestinal tract. The median CDAI prior to the DBE procedure was 194 (44–343). Indications for DBE were abdominal complaints in 37 patients (74%), iron-deficiency anemia in 11 (22%) and hypomagnesemia in two (4%) (Table 1). No patients were excluded from evaluation and all patients were available for follow-up.

Table 1. Patient characteristics.

	Total (n = 50)	SB lesions + (n = 35)	SB lesions - (n = 15)
Age (yrs)	45 (23 – 75)	45 (23 – 75)	46 (24 – 64)
Male	25 (50 %)	20 (57 %)	5 (33 %)
Duration of CD (yrs)	17.2 (0.9 – 44.0)	16.7 (0.9 – 44.0)	17.0 (2.0 – 37.0)
Age of onset CD (yrs)	28.2 (2 – 61)	28.3 (2 – 61)	28.1 (12 – 45)
CD characteristics #			
A1	7 (14 %)	6 (17 %)	1 (7 %)
A2	34 (68 %)	22 (63 %)	12 (80 %)
A3	9 (18 %)	7 (20 %)	2 (13 %)
L1	20 (40 %)	15 (43 %)	5 (33 %)
L2	12 (24 %)	3 (9 %)	9 (60 %)*
L3	17 (34 %)	16 (46 %)	1 (7 %)**
L4	1 (2 %)	1 (2 %)	0
B1	7 (14 %)	3 (9 %)	4 (27 %)
B2	25 (50 %)	19 (54 %)	6 (40 %)
B3	18 (36 %)	13 (37 %)	5 (33 %)
P	16 (32 %)	12 (34 %)	4 (27 %)
CDAI	194 (44 – 343)	196 (58 – 343)	178 (44 – 310)
CDAI < 150	16 (32 %)	12 (34 %)	4 (27 %)
Previous anti-TNF treatment	11 (22 %)	7 (20 %)	4 (27 %)

Yrs = years; CD = Crohn's disease; DBE = double balloon enteroscopy; CDAI = Crohn's Disease Activity Index; # Montreal Classification, * p = 0.009, ** p = 0.0003

DBE procedures

Of the 50 DBE procedures, 35 (70%) were performed using both the trans-oral and -anal routes. In 11 patients (22%), only a trans-oral procedure was performed, of whom eight patients refused a combined procedure. In four patients (8%) a trans-anal procedure was performed only, because the patients refused a trans-oral approach. Complete SB visualization was achieved in three patients (6%), all using the trans-oral route. The median oral and anal insertion depths were 236 (80–440) cm and 73 (5–200) cm, respectively. The median duration of DBE procedures was 73 (35–150) min. No complications occurred during or after the DBE procedures.

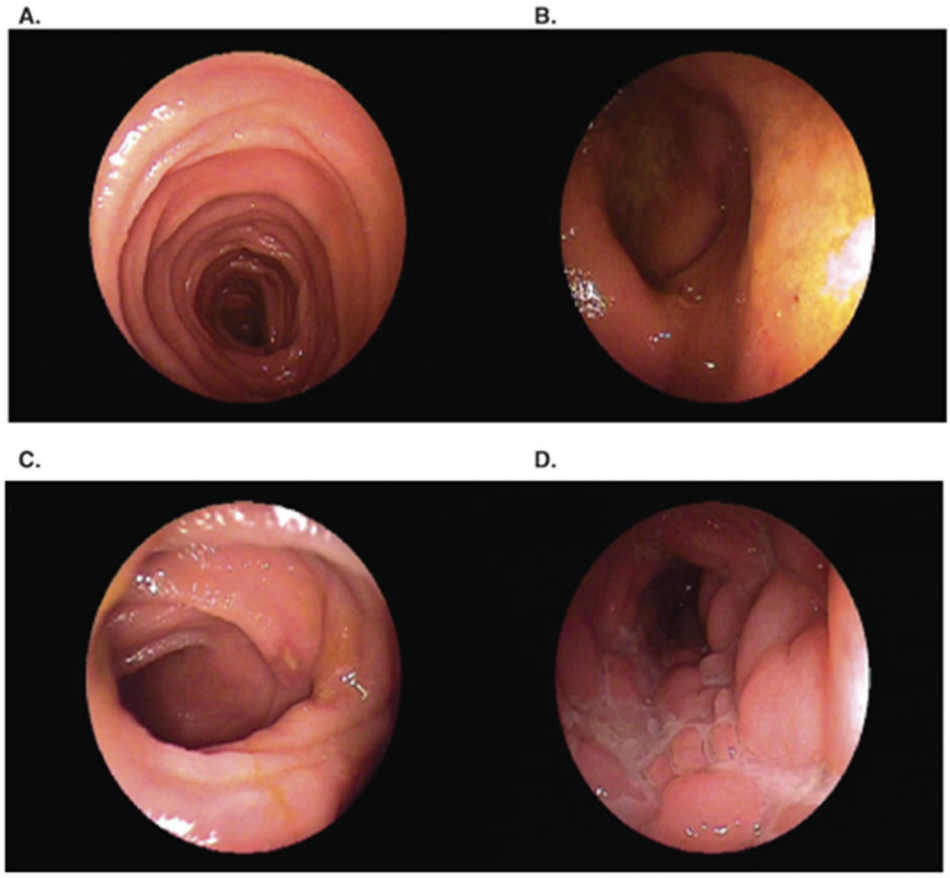

Figure 1. Enteroscopic findings in CD patients.
A: normal jejunal mucosal appearance proximal jejunum, grade 0, B: mild patchy edemateus mucosa proximal ileum, grade 1, C: mild edematous mucosa with small ulcerations distal jejunum, grade 1, D: edematous, ulcerative stenotic lesion in distal jejunum, grade 3.

DBE findings

In 35 patients (70%) CD SB lesions were found. These lesions were located at the proximal jejunum in 12 patients (34%), distal jejunum in five (14%), proximal ileum in two (6%), distal ileum in 13 (37%) and three patients (9%) had lesions in both the jejunum and ileum. The severity of the SB lesions was graded as mild in 14 patients (40%), moderate in seven (20%) and severe in 14 (40%). In 23 patients (46% of the total), the SB lesions could not be assessed by means of conventional endoscopy (Figure 1).

Patients with and without SB lesions

The primary presenting localization of CD differed significantly between the patients with and without SB lesions. Patients with SB lesions had significantly more primary ileocolonic localization of CD and less colonic localization (P = 0.009 and P = 0.0003, respectively). In the group of patients with SB lesions, there were more male patients and more patients with upper GI involvement; however, these differences were not significant (Table 1). In addition, there was no significant difference in laboratory findings for patients with or without SB lesions (Table 2). The CDAI in patients with SB lesions was higher compared to that in patients without SB lesions, but this difference was not statistically different.

Table 2. Laboratory findings.

	Total (n = 50)	SB lesions + (n = 35)	SB lesions – (n = 15)
– CRP (< 3 mg/L)	8 (1 – 126)	6 (1 – 30)	12 (1 – 126)
– Hemoglobin (12 – 16.8 g/dL)	12.7 (8.2 – 16.3)	12.7 (8.2 – 16.3)	12.7 (9.6 – 15.2)
– Thrombocytes (150 – 370 *10E9/L)	288 (112 – 549)	297 (112 – 549)	269 (133 – 508)
– Leucocyte count (3.5 – 10 *10E9/L)	7.1 (3.1 – 17.1)	7.3 (3.1 – 17.1)	6.9 (4.2 – 13.1)
– Magnesium (0.7 – 1.05 mmol/l)	0.76 (0.40 – 0.98)	0.75 (0.40 – 0.98)	0.79 (0.61 – 0.96)
– Phosphate (0.8 – 1.4 mmol/l)	1.05 (0.58 – 1.63)	1.04 (0.58 – 1.63)	1.05 (0.68 – 1.29)
– Calcium (2.2 – 2.65 mmol/l)	2.26 (1.91 – 2.64)	2.24 (1.91 – 2.49)	2.33 (2.14 – 2.64)
– Albumin (35 – 50 g/l)	43 (28 – 56)	42 (28 – 51)	44 (36 – 56)

Clinical impact of findings and follow-up

Treatment was adjusted in 26 patients (74%) after DBE. Eight patients (29%) started with azathioprine or methotrexate. Anti-TNF therapy was introduced in seven patients (26%) and four (15%) changed from infliximab to adalimumab. Surgical therapy was performed in seven patients (26%), five underwent a re-resection of the neoterminal ileum and two a strictureplasty. Step-up therapy, either medical or surgical, was refused by the remaining nine patients with SB lesions. After a follow-up period of 12 months, 23 patients (88%) were in clinical remission. A significant decrease in CDAI was seen in these patients from 196 (58–343) to 52 (0–227); P < 0.0001.

No major complications or mortality were reported after adjustment of therapy. One patient naïve to immunosuppressive therapy with stenotic, but not active, lesions in the distal ileum died 22 months after DBE due to complicated chronic myelogenous leukemia.

A significantly higher remission rate was found in patients with SB lesions in whom treatment had been adjusted (67%) compared to patients without SB lesions and without adjustment treatment (20%); $P = 0.009$.

Findings during second DBE

Of 22 patients with SB involvement not accessible for conventional endoscopy, 10 (45%) had a second DBE after a mean time of 9 (4–14) months. The second DBE showed improvement or normalization of the mucosal lesions in nine patients (90%) and no change was seen in one. The mean activity grading score improved significantly, from 1.5 (1–4) initially to 0.6 (0–1); $P = 0.03$. In seven out of nine patients with endoscopic improvement, anti-TNF therapy had been introduced (4/7) or infliximab therapy had been changed to adalimumab (3/7). In the one patient with unchanged findings at the second DBE, adalimumab was started afterwards. This gave a good clinical result, and the CDAI decreased from 183 to 66. DBE was not repeated after adjustment of treatment in this patient.

Discussion

This prospective study, performed in patients with known CD and persistent symptoms despite a normal colonoscopy, showed a high frequency of SB lesions using DBE. In almost half of patients these SB lesions were not accessible for conventional endoscopy. Adjustment of therapy in patients with SB lesions led to clinical improvement in most patients. This clinical improvement correlated with improved enteroscopic findings during a second DBE. To our knowledge, this is the first large prospective study using DBE as a diagnostic tool for SB lesions in CD patients and the first to show the clinical impact of treatment for these findings.

SB involvement of CD is known as an independent risk factor for complicated disease. CD patients with SB activity more often need step-up medical treatment and surgical interventions [1–3]. This study demonstrated a relatively large number of SB lesions compared to previous reports [1]. This high incidence has also been reported previously in studies using CE in patients with known CD, which showed an incidence of SB lesions in 50%–95% of patients [6,7,24–26]. An interesting and new finding is the fact that CD patients with SB lesions significantly benefited from step-up therapy. Adjusting treatment resulted in a clinical improvement in most patients and correlated with a significant improvement in enteroscopic findings. In the majority

of patients with SB lesions anti-TNF therapy was initiated, intensified or altered, demonstrating an additional benefit of anti-TNF therapy in this particular patient group.

CD manifestation in the upper gastrointestinal (GI) tract is one of the predictors of a more disabling course of the disease. Current diagnostics in CD patients are mainly focused on distal luminal disease activity. A minority of our patients were known to have upper GI tract involvement prior to DBE. However, endoscopic lesions were found in the upper GI tract, i.e. the proximal jejunum, in a large proportion of patients with negative upper endoscopies in the past. Although histological confirmation of CD was not available in these patients, the upper GI lesions might have been related to CD. Analysis of predisposing factors for SB involvement showed that only a primary localization of CD in the ileocolonic region was a predictive factor. Sex, duration of CD, fistulizing CD, CDAI and CRP level were comparable in both groups. Therefore, differentiation of patients with and without SB lesions cannot be performed on clinical presentation only, and additional imaging is required. The CDAI does not seem to be predictive of SB activity of CD in these patients, as the CDAI in patients with and without SB lesions was not statistically significantly different. Currently, no validated enteroscopic classification for SB lesions associated with CD exists. We therefore aimed to introduce a simple and clinically easy-to-use classification for SB CD lesions found during enteroscopy, which also has its limitations.

Earlier studies have shown that both CE and MR-enterography are valuable diagnostic tools for assessing SB involvement in CD patients, especially compared to SBFT and ileocolonoscopy [6–14]. Although CE is patient-friendly, in CD patients with suspected SB disease activity its use might be hampered due to capsule retention in up to 7% of the patients. In addition, 30% of patients were excluded from these studies because of suspected stenotic SB lesions during screening [9,10,27]. Incomplete SB visualization has been reported in approximately 30% of CE investigations, leaving especially the distal part of the ileum un-inspected [28–30]. Furthermore, DBE has the advantage that biopsies can be taken for histological evaluation and that dilation of strictures can be performed in one procedure [30]. Although this study was not designed to compare different SB diagnostics, i.e. CE and DBE, we are convinced of the potential role and additional value of DBE in this particular patient group.

A limitation of the current study is that only patients in whom SB activity was suspected were included. The incidence of SB lesions may also be high in CD patients without complaints and therefore clinically not suspected for SB activity. Furthermore, a repeat DBE was not performed routinely after a change in therapy, possibly leading to selection bias. In addition, no randomized, placebo-controlled study was performed concerning initiation of step-up treatment in patients with SB lesions. Only patients with SB lesions during enteroscopy were offered medical step-up therapy, and not those with normal findings during enteroscopy. This may have led to an evident bias and overestimation of the results found.

In conclusion, this study clearly demonstrates that DBE is of additional value in CD patients with suspected SB activity and no distal disease activity. Furthermore, a clinical and enteroscopic improvement was seen in patients with solitary SB lesions which were treated with step-up therapy. DBE seems feasible and safe for assessing SB disease activity in these patients.

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Chapter 5

Low additional yield of histopathology in patients with suspected small bowel pathology and normal endoscopic findings during balloon assisted enteroscopy

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Submitted

Abstract

Background: Balloon assisted enteroscopy (BAE) has the potential advantage over capsule endoscopy (CE) that it permits tissue sampling for histological investigation. The aim of this study was to critically analyse the additional diagnostic yield of biopsy sampling during BAE.

Methods: All patients undergoing BAE for evaluation of small bowel pathologies at two large university referral hospitals were retrospectively analysed. Endoscopic and histological findings were evaluated, and were compared with the definitive diagnosis. Histological findings were categorized as contributing or non-contributing to diagnosis.

Results: Over a 5 year period, a total of 1380 BAE procedures were performed in 1023 patients: 522 (51%) males, mean age 53 (4-93) years. Small bowel histological samples were taken in 454 (44%) patients. In 147 (32%) patients, endoscopic findings and histological findings were normal. In 165 (36%) patients, histological findings were compatible with abnormal endoscopy findings. In 130 (29%) patients the endoscopy showed abnormalities, but histopathology was normal. In 12 (3%) patients with normal endoscopic findings, histology showed abnormal findings, in particular celiac disease in 5 (1%) patients. In 47 (73%) patients with small bowel tumours the diagnosis was confirmed with histopathology.

Conclusions: The overall additional value of random biopsies during BAE with normal endoscopic findings is low and should only be performed in selected cases. The diagnostic yield of histopathology in small bowel tumours is high.

Introduction

Currently, both capsule endoscopy (CE) and balloon assisted enteroscopy (BAE) using double balloon (DBE), single balloon (SBE) or spiral enteroscopy, are used for visualization of the small bowel [1-9]. The main advantage of CE is its non-invasive nature, compared to the invasiveness of BAE with the additional need for sedation. However, BAE also has some advantages over CE such as the opportunity to perform therapeutic interventions, the excellent visualization of the small bowel mucosa, and the ability to perform biopsy sampling for histological evaluation [10,11]. Histological confirmation of pathological small bowel abnormalities has already been proven to be of pivotal importance in small bowel polyps, ulcerative lesions and stenotic lesions [12-14]. Thus, in clinical practice, histological analysis is mainly used for polyposis syndromes, i.e. familial adenomatous polyposis, Peutz-Jeghers syndrome, malignant tumours, and refractory celiac disease [15,16]. Nonetheless, the additional value of histological confirmation or exclusion of pathology during BAE, in patients with normal, minor, or non-specific endoscopic findings, might be significant. This additional value of histopathological evaluation could, in theory, guide the choice of small bowel diagnostic, e.g. CE or BAE. However, until now no study has evaluated the additional value of biopsy sampling in reaching a diagnosis in patients suspected for small bowel disease. The aim of this study was to critically analyse the additional yield of biopsy sampling and histological evaluation during balloon assisted enteroscopy (BAE, either DBE or SBE).

Methods

A retrospective study was performed in all consecutive patients referred for BAE at two large tertiary referral centers: the Otto von Guericke University, Magdeburg, Germany and the Erasmus MC University Medical Center, Rotterdam, The Netherlands. Biopsy sampling was performed in all patients with suspicion of small bowel pathology. Patients undergoing BAE for other reasons, like incomplete colonoscopy or ERCP with altered anatomy, were excluded. The study was approved by the institutional review boards of both institutions.

BAE procedure

BAE procedures were performed using the Fujinon DBE, FN 450P 5/20, EN-450T5, or the Olympus SBE, the Olympus SIF-Q160Y enteroscope. All patients were prepared with a standard polyethylene glycol solution (Kleanprep®, or Colofort®) and underwent the procedure after an overnight fast. A small bowel relaxant (butyl scopolamine, Buscopan®) was administered if the bowel motility was increased or if a therapeutic intervention was performed. In the Magdeburg center all procedures were performed using conscious sedation with propofol (Disoprivan®).

In the Rotterdam center the majority of procedures were performed under conscious sedation, i.e. a combination of midazolam and fentanyl, while selected cases were performed using anesthesia-administered propofol. BAE procedures were defined as 'BAE including biopsies for histopathological evaluation' when ≥ two biopsies were taken during the procedure.

Definition and classification of mucosal lesions

Mucosal lesions that were found during BAE were defined as follows. Polyps were defined as any mucosal protuberance, either sessile or pedunculated. Sessile lesions larger than 3 cm were considered masses. The polyp or mass was considered submucosal if the overlying mucosa was intact. The size of the polyps and masses was estimated with the use of an open biopsy forceps. Inflammation was defined as reddening and localized swelling with or without ulcerative lesions of the small bowel mucosa. Ulcerative lesions were defined as any lesion of any size in which the mucosa appeared destroyed. During endoscopy the size and extension of the lesion was described. Angiodysplasias and mucosal atrophy were defined based on accepted criteria [7,8]

Comparing endoscopic and histopathological findings

Endoscopic and histological findings of all BAE procedures were evaluated, and compared with the definitive diagnosis. All BAE procedures were categorized as follows:

1- Normal endoscopic findings, no biopsies obtained,
2- Normal endoscopic findings, biopsies obtained,
3- Abnormal endoscopic findings, no biopsies were obtained,
4- Abnormal endoscopic findings, biopsies obtained.

All positive histopathological findings of biopsies taken during BAE were defined as follows:

A- Contributing to diagnosis with negative endoscopic findings,
B- Non-contributing to diagnosis with negative endoscopic findings,
C- Contributing to diagnosis with positive endoscopic findings,
D- Non-contributing to diagnosis with positive endoscopic findings.

'Contributing' was defined as clinically relevant findings, i.e. leading to a change in therapy in that particular patient. Positive histopathological outcome in small bowel tumours was considered 'contributing'. 'Non-contributing' was defined as clinically irrelevant or non-significant findings, i.e. non-adding to a diagnosis and / or not leading to a change in therapy. In patients with known Crohn's disease, findings of chronic inflammation on histopathological evaluation and reported as abnormal during enteroscopy, were defined as 'non-contributing'.

Statistics

Data were collected in a Microsoft Excel database (Microsoft, Seattle, WA, USA). After completion the database was imported into SPSS for Windows (16.0, SPSS, Chicago, IL, USA). Descriptive statistics were employed to describe the patient's demographics and clinical characteristics, presenting means and ranges. Continuous baseline descriptive variables were expressed as means with standard deviation and were compared using Student's t -test. Categorical variables were expressed as absolute numbers and proportions. The Chi-square statistic was used to compare most categorical variables, whereas the Fisher's exact test was used for small numbers. A two-sided P value < 0.05 was considered statistically significant.

Results

Patient characteristics

In the period between June 2004 and September 2009 a total of 1373 BAE procedures were performed in 1023 patients: 522 (51%) males, mean age 53 (range 4 – 93) years. The most common indications for BAE were anemia (n = 430), evaluation of known Crohn's disease (n = 226), polyposis syndromes (n = 56), and evaluation of chronic abdominal pain (n = 55); see Table 1 and Figure 1.

Table 1 Patient characteristics and indications for balloon assisted enteroscopy

Patients characteristics	All patients (n=1023)	With histology (n=454)	No histology (n=569)	P-value
Age (years; range)	53 (4 – 93)	49 (4 – 93)	56 (5 – 88)	<0.0001
Males	51%	49%	52%	0.42
Indication for BAE				
– Anemia (OGIB)	430 (42%)	124 (27%)	306 (54%)	<0.0001
– Known CD	226 (22%)	100 (22%)	126 (22%)	0.96
– Polyposis syndromes	56 (5%)	25 (6%)	31 (5%)	0.97
– Abdominal pain	55 (5%)	44 (10%)	11 (2%)	<0.001
– Suspected CD	34 (3%)	22 (5%)	12 (2%)	0.02
– Other	222 (22%)	139 (31%)	83 (15%)	<0.001

OGIB = obscure gastrointestinal bleeding; CD = Crohn's disease

Enteroscopy procedural data

DBE and SBE procedures were performed in 886 (87%) and 137 (13%) patients, respectively. A total of 350 patients (34%) underwent a combined antero- and retrograde BAE procedure; a single antero- or retrograde BAE procedure were performed in 560 (55%) and 113 patients

(11%), respectively. The mean total procedure time was 66 (20 – 150) minutes. The mean insertion depth was 248 (10 – 580) cm and 87 (4 – 300) cm for the antero- and retrograde BAE procedures, respectively.

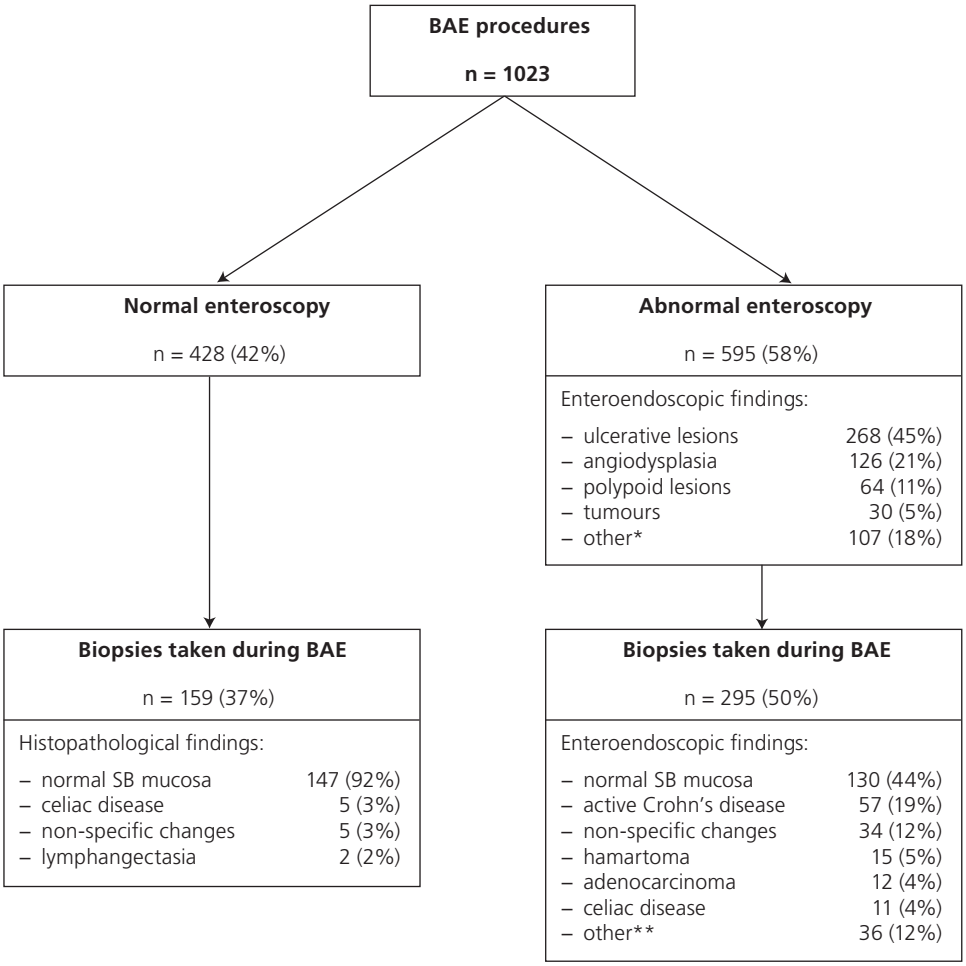

Figure 1. Flowchart of all study subjects (n = 1023). Endoscopic and histopathological findings.
BAE = Balloon Assisted Enteroscopy; SB = small bowel.
* Consisting of: lymphangectasia (n =69), small bowel diverticulae (n=28), and submucosal lesions (n=10).
** Consisting of: lymphangectasia (n=11), adenomatous lesions (n=9), ischemia (n=5), gastrointestinal stromal tumour (n=5), lymphoma (n=3), Giardia infection (n=1), ganglioneuroma (n=1), and metastasized melanoma (n=1).

Endoscopy and histopathology findings

Normal and abnormal findings during BAE were reported in 428 (42%) and 595 (58%) patients, respectively. The most common endoscopic abnormal findings were ulcerative lesions (45%) and

angiodysplasias (21%). In 454 (44%) patients, biopsy sampling for histopathological evaluation was performed: in 159 (35%) and 295 (65%) patients with normal and abnormal endoscopic findings, respectively (p=0.0001).

Histopathology was defined normal in 277 (61%) and abnormal in the remaining 177 (39%) patients. In 147 (32%) patients both endoscopy and histopathology were normal, and in 165 (36%) patients both endoscopy and histopathology were considered abnormal. In 130 (29%) patients the endoscopy showed abnormalities, but histopathology was defined as normal. Overall, only in 12 (3%) patients with normal findings during BAE, histopathology showed abnormalities; see Figure 1.

Contributing or non-contributing histopathology

Of 159 patients with negative endoscopic findings, 12 (7%) patients had positive findings on histopathology. In 7 (4%) of these patients the histopathology was defined as actually contributing to the definitive diagnosis, i.e. diagnosis code A: five patients diagnosed with celiac disease and two patients with chronic inflammatory changes, which in one patient was compatible with Crohns' disease. In the other five (3%) patients the histopathological findings were considered non-contributing, i.e. diagnosis code B: three patients with non-specific inflammation and two patients with lymphangiectasia. Of 295 patients with positive endoscopic findings, 165 (56%) patients had positive findings on histopathology. In 63 (21%) of these patients the histopathology contributed to the endoscopic diagnosis, i.e. diagnosis code C. In the remaining 102 (35%) patients the additional histopathology did not add to the endoscopic diagnosis or was inconclusive, i.e. diagnosis code D; see Table 2.

Additional diagnostic yield of histopathology in obscure gastrointestinal bleeding (OGIB) patients

Of the in total 430 patients evaluated for OGIB, in 124 (29%) were biopsied. In 52 (42%) patients both enteroscopy and histopathology showed normal findings. In 42 (34%) patients histopathology confirmed the endoscopic diagnosis: inflammatory changes in 17, adenocarcinoma in 10, lymphangiectasia in 6, gastro-intestinal stromal tumours (GIST) in 5, ischemia in 2 patients, lymphoma and (metastasized) melanoma. In 27 (22%) patients enteroscopy showed abnormalities, but histopathology was negative: ulcerative lesions in 10, angiodysplasia in 5, lymphangectasia in 5, polypoid lesions in 3 patients, and one case of Meckel's diverticulum and tumorous lesion each. In only three (2%) patients with reported normal findings during BAE, histopathology showed abnormal findings, defined as non-specific inflammation in all three patients; see Table 2.

Table 2. Contributing and non-contributing histopathology diagnosis.

Indications BAE (n=454)	**Enteroscopy negative Histopathology positive (n=12)**		**Enteroscopy positive Histopathology positive (n=165)**	
	Code A (n=7)	***Code B (n=5)***	***Code C (n=63)***	***Code D (n=102)***
Anemia (n=124)	-	A-specific inflammation 3	Adenocarcinoma 9 Chronic inflammation 6 GIST 5 GI ischemia 2 Adenoma 1 Lymfoma 1 Melanoma 1	A-specific inflammation 11 Lymphangiectasia 6
Known CD (n=100)	Celiac disease 1 Chronic inflammation 1		Celiac disease 1	Chronic inflammation 34 A-specific inflammation 3
Polyposis syndromes (n=25)	-	-	-	Hamartoma (PJS) 14 Adenoma 7
Abdominal pain (n=44)	Celiac disease 1 Chronic inflammation 1		Chronic inflammation 2 GI ischemia 1 Lymfoma 1 Hamartoma 1	A-specific inflammation 4
Suspected IBD (n=22)	-	-	Chronic inflammation 6	A-specific inflammation 2
Other (n=139)	Celiac disease 3	Lymphangiectasia 2	Celiac disease 10 Chronic inflammation 9 Adenocarcinoma 3 GI ischemia 2 Adenoma 1 Lymfoma 1	A-specific inflammation 15 Lymphangiectasia 5 Ganglioneuroma 1

BAE = Balloon Assisted Enteroscopy, CD = Crohn's disease, IBD = Inflammatory Bowel Disease, Code A = contributing to diagnosis with negative endoscopic findings, Code B = non-contributing to diagnosis with negative endoscopic findings, Code C = contributing to diagnosis with positive endoscopic findings, Code D = non-contributing to diagnosis with positive endoscopic findings, GI ischemia = gastrointestinal ischemia.

Additional diagnostic yield of histopathology in patients with suspected or known Crohn's disease, or abdominal pain

Biopsies during BAE in patients evaluated for small bowel activity of known or suspected Crohn's disease, or abdominal pain, were taken in 100 (44%), 22 (65%), and 44 (80%) patients, respectively. In the patients with known Crohn's disease, endoscopic findings were normal in

two (2%) patients, but histopathological evaluation showed abnormalities: one patient with celiac disease and one patient with chronic inflammation, compatible with active Crohn's disease. In 38 (38%) patients histopathology confirmed the endoscopic diagnosis of active ulcerative disease. In 39 (39%) patients endoscopic abnormalities were seen, ulcerative lesions in 37 and mucosal oedema in two patients, but histopathology was reported normal. Overall, histopathology was positive in 40 (40%) of these patients. In the patients evaluated for suspected Crohn's disease, histopathology confirmed the endoscopic diagnosis of inflammatory change in 8 (37%) patients. In the patients evaluated for abdominal pain, histopathological findings showed positive findings in 11 (25%) patients: two with normal endoscopic findings (one celiac and one chronic inflammatory disease), and 9 patients with abnormal endoscopic findings; see Table 3.

Table 3. Endoscopic and histopathological findings in patients evaluated with BAE for known or suspected Crohn's disease or abdominal pain.

Indication BAE	**Endoscopy negative**			**Endoscopy positive**		
	Histo neg	***Histo pos***		***Histo neg***	***Histo pos***	
Known CD (n = 100)	21 (21%)	2 (2%)	1 Celiac disease 1 A-specific inflammation	39 (39%)	38 (38%)	-
Suspected CD (n = 22)	4 (18%)	0	-	10 (45%)	8 (37%)	6 Chronic inflammation 2 A-specific inflammation
Abdominal pain (n = 44)	21 (48%)	2 (5%)	1 Celiac disease 1 Chronic inflammation	12 (27%)	9 (20%)	4 A-specific inflammation 2 Chronic inflammation 1 Ischemia 1 Hamartoma 1 Lymphoma

BAE = Balloon Assisted Enteroscopy, CD = Crohn's disease, Histo = histopathological findings, neg = negative, pos = positive.

Additional diagnostic yield of histopathology in small bowel polyps and tumors

Of the 94 patients endoscopically diagnosed with small bowel bowel tumors, 64 (68%) patients were biopsied. Histopathology confirmed the macroscopic diagnosis in 47 (73%) patients. In the remaining 17 (27%) patients the outcome of histopathological evaluation was negative or inconclusive.

Discussion

To our knowledge, this is the first study evaluating the additional diagnostic yield of biopsy sampling in patients evaluated with balloon assisted enteroscopy for small bowel pathology. The results of this study show that the overall contribution of histopathological evaluation in endoscopically negative enteroscopies is low. Especially in the main indication for enteroscopy, obscure GI bleeding, histopathology seems non-contributing when endoscopic findings are normal.

The major advantages of BAE over CE are its excellent visualization of the small bowel, the opportunity to perform therapeutic interventions, and to perform biopsies for histopathological evaluation [9,10]. Currently, OGIB is the main indication for small bowel diagnostics, and CE is considered to be the first diagnostic approach. This CE is than followed by a 'CE-guided' BAE for endoscopic therapy or additional histopathological confirmation of CE findings, if required [17]. However, we know that in certain patient groups histopathological examination of otherwise endoscopically normal appearing mucosa can be of crucial diagnostic value, i.e. celiac disease, pediatric Crohn's disease, microscopic colitis, eosinophilic gastroenteritis and chronic infectious diseases. The results of the presented study show a low additional yield of histopathological evaluation of endoscopically normal appearing mucosa. The overall additional yield of biopsies in normal endoscopic findings was only 4%. Especially in OGIB patients, the additional value showed to be low: in only 2% of these patients with normal endoscopic findings abnormal histopathology was found, which in all patients was considered non-contributing to the diagnosis (being non-specific inflammation in all patients). These results are in line with the findings of Castro et al that showed that performing routine duodenal biopsies during gastroduodenoscopy in patients with normal endoscopic findings were not useful and that clinicians should limit biopsies to patients with high-risk symptoms or endoscopic stigmata [18].

Therefore, we conclude also that standard biopsy sampling for histopathological evaluation in OGIB patients with macroscopically normal appearing small bowel is not useful during DAE.

In patients with known Crohn's disease, the additional value of histopathological evaluation seems logical, especially to confirm the endoscopic diagnosis of active small bowel disease. However, biopsies with histological analysis could confirm the endoscopic suspected activity of Crohn's disease in only about one third of patients. One can debate about the relevance of this additional information, but in clinical practice it might be the adding up of endoscopic and histopathological information leading to step-up medical therapy in these patients [13]. In patients evaluated for suspected Crohn's disease or abdominal pain, adding of histopathological

evaluation seems useful: in one out of four patients histopathology contributed to the definitive diagnosis. Again, this additional diagnostic yield was mainly in the patients with macroscopic endoscopic abnormalities.

In patients presenting with small bowel polyps or tumors, histopathological sampling added to the diagnosis in ¾ of cases. These findings seem in line with earlier reports of small bowel tumours evaluated with BAE, reporting positive histopathological findings in biopsies from small bowel tumours ranging from 79 to 86% [19-21]. As presented in earlier reports, the patients endoscopically suspected for GIST had the lowest proportion of positive histopathology [22]. The latter finding is in line with the submucosal growth patterns of this specific tumor. We conclude that adding of histopathological evaluation in patients with macroscopic suspected small bowel tumors or polyps is essential for the diagnosis, staging and treatment of these patients, but caution should be exerted in submucosal lesions such as GIST.

The presented study has several limitations. Firstly, the study was retrospective in design, and therefore biopsy was not performed in all patients. Moreover, the biopsy strategy in patients who had histopathological evaluation was in a large portion of patients 'at random': biopsies were not taken following a strict prospective study protocol. These latter two facts might lead to selection bias. However, the databases from which our data were extracted were both of prospective design: epidemiological, BAE-related, histopathological data and definitive diagnosis, were all prospectively registered. In addition, our biopsy protocol does not limit the validity of our results as it reflects 'real-life practice', which might even be considered as an advantage of this study. Secondly, the data was collected in two large tertiairy referral centres for BAE, so these outcomes might not reflect daily general gastroenterology practice.

In summary, the results of the presented study show that the additional value of histopathological evaluation in patients with normal enteroscopic findings is very low. The presented data confirm the additional value of histopathology in patients with small bowel lesions in suspected or known Crohn's disease, as well as in those with small bowel tumors or polyps. Prospective studies with standard small bowel biopsy protocols during BAE procedures are needed to confirm these findings.

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Chapter 6

Single-balloon enteroscopy-assisted direct percutaneous endoscopic jejunostomy

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Abstract

Direct percutaneous endoscopic jejunostomy (DPEJ) has emerged as a viable alternative for percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) in patients who cannot tolerate gastric feeding. Reportedly, DPEJ placement with regular endoscopes fails in up to one-third of cases. The aim of the current study was to assess the efficacy and safety of single-balloon enteroscopy (SBE)-assisted DPEJ. The DPEJ placement technique was comparable to conventional PEG placement. A total of 12 DPEJ procedures were performed in 11 patients (mean age 55 years [range 24–83 years]; seven males). SBE-assisted DPEJ was successful in 11 of the 12 procedures (92 %). Post-procedural complications included gastroparesis and aspiration pneumonia in one case each. We conclude that SBE-assisted DPEJ placement seems a safe and successful approach for patients requiring jejunal enteral feeding.

Introduction

Percutaneous endoscopic gastrostomy (PEG) is a well-known, safe, and effective procedure for individuals requiring long term tube feeding [1]. However, in some cases a jejunal route is necessary for functional reasons (such as gastroparesis) or due to morphology (such as stomach or duodenal cancer and previous gastric surgery). Jejunal access using a jejunal tube through a PEG (PEG-J) was first described in 1984 [2]. However, these smaller-diameter tubes are more prone to clogging and in addition frequently become displaced into the stomach. Both events require renewed endoscopy with repositioning or replacement [3].

Direct percutaneous endoscopic jejunostomy (DPEJ) is a push enteroscopy technique that was first described by Shike et al., and offers another approach to provide direct postpyloric enteral nutritional support [4]. DPEJ tubes have a wide caliber, which are unlikely to clog. Furthermore, they cannot migrate due to their intrinsic jejunal fixation. In patients with aspiration pneumonia, DPEJ has been reported to decrease the risk of recurrences [5]. The limitation of DPEJ is the difficulty of the technique. In contrast to the stomach, the jejunum is relatively narrow, making it more difficult to advance a needle directly into the lumen [6]. In addition, identifying a superficial jejunal loop with adequate transillumination may be particularly problematic with conventional push techniques considering the often limited extent of jejunal intubation [7]. Balloon-assisted enteroscopy (BAE) may allow controlled deep intubation of the small intestine [8-10], which may result in easy identification of a superficial jejunal loop.Recently Despott et al. showed that the placement of DPEJ using the double-balloon enteroscopy (DBE) technique is an effective method [11]. Until now there are no published reports on SBE-assisted DPEJ placement. We report here our early experience with this technique at a single, tertiary referral university hospital center in patients requiring direct proximal small-bowel access.

Case series

Consecutive patients referred for DPEJ placement between December 2009 and December 2010 were eligible for participation in the study. All patients were given prophylactic antibiotics. Conscious sedation was used in the majority of procedures. SBE was performed using the Olympus SIF-Q160Y enteroscope (Olympus, Tokyo, Japan), ST-SB-1 overtube with balloon, and balloon control unit. The insertion process followed the method used for DBE, except that straightening of the endoscope required angulation of the tip instead of inflation of an endoscope balloon. The enteroscope was inserted into the proximal jejunum where, using transillumination and fingertip indentation, a superficial jejunal loop was identified. After a suitable insertion site had been located, the access area was sterilized. The abdominal wall and peritoneum were anesthetized

by insertion of a percutaneous needle and simultaneous injection of 1% lidocaine until the needle emerged into the jejunum. In order to reduce gut motility, hyoscine-N-butylbromide was administered intravenously in doses of 20mg after identification of an appropriate insertion site. The DPEJ placement technique was largely comparable to a conventional PEG placement ([Fig.1], [Fig.2] and [Fig.3]). In all cases a 15-Fr Freka (3.6mm internal diameter, 35cm length) PEG feeding tube (Fresenius Kabi AG, Germany) was used. Fluoroscopy was not used in any case.

The primary endpoint of the study was the rate of successful placement of DPEJ. Secondary outcomes were the rate of complications, including recurrent aspiration after DPEJ placement.

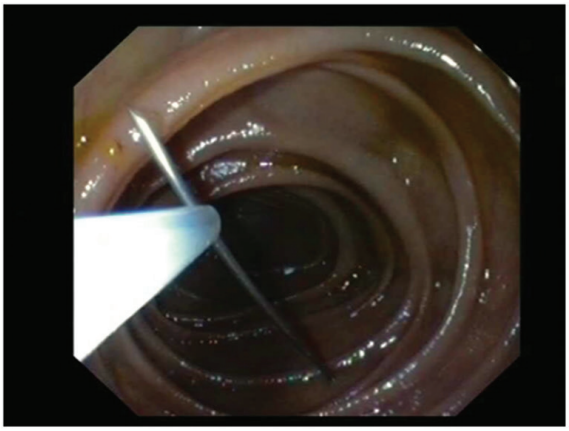

Fig. 1. A finder needle was passed into the jejunum and grasped and held in place using a snare.

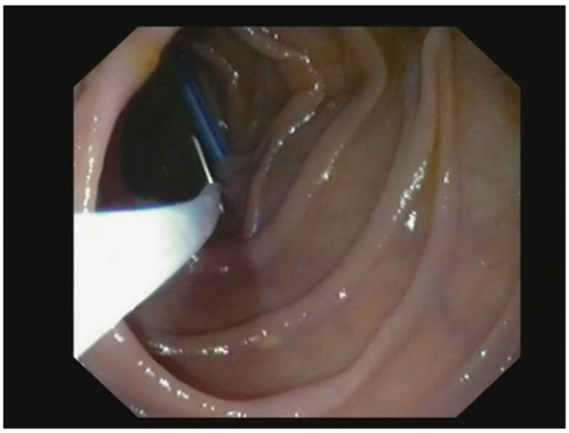

Fig. 2. Insertion of a trocar and sheath alongside the snared seeker needle.

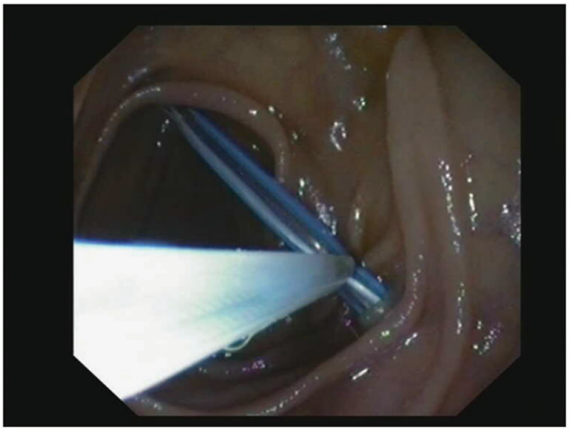

Fig. 3. The sheath was snared and a thread was passed through the sheath after removal of the trocar.

Results

Between December 2009 and December 2010, 12 SBE-assisted DPEJ procedures were performed in 11 patients (mean age 55 years [range 24–83 years]; seven males). The indications for DPEJ procedures were recurrent aspiration pneumonia (n=5; 42%), gastric dysmotility (n=4; 33%), duodenal cancer (n=2; 17%), and gastric cancer (n=1; 8%). Four patients had previously been treated with a PEG or PEG-J. A total of 11 procedures (92%) were performed under conscious sedation using midazolam (mean dose 6mg) and fentanyl (mean dose 0.06mg). Propofol sedation was used in one patient. The mean total procedure time was 47 minutes (range 20–120 minutes). The DPEJ placement was successful in 11 of the 12 procedures (92%; [Table 1]). In one patient with duodenal cancer, who had persistent inability to tolerate oral intake despite previous palliative gastrojejunostomy surgery, a DPEJ was first placed, unintentionally, in the afferent loop.When this did not lead to improved oral intake, a second procedure was required for DPEJ placement in the efferent loop, which was also not successful due to inadequate insertion of the enteroscope into the jejunum. This patient went on to have a percutaneuous radiologic jejunostomy.

One procedure-related complication was noted (8%): a patient with multiple sclerosis was admitted to the hospital with sudden onset of nausea and vomiting 1 day after DPEJ placement. Based on computed tomography and small-bowel contrast study, gastroparesis was diagnosed. The patient was treated conservatively with intravenous fluid resuscitation and a nasogastric tube to decompress the distended stomach. The jejunal feeding could be restarted quickly without recurrence of symptoms.

One patient (8%) had a recurrence of aspiration pneumonia 4 weeks after the DPEJ placement. A contrast study showed adequate positioning of the tube and the feeding was restarted within a few days. No further recurrences were observed.

Table 1. Individual data of patients, indications, success of the direct percutaneous endoscopic jejunostomy placement, and complications.

Patient	Sex	Age, years	Indication	Management with PEG or PEG-J before DPEJ	Total procedure time, minutes	Successful DPEJ placement	Complications
1	M	70	Gastric dysmotility	No	30	Yes	No
2	M	53	High-aspiration risk	PEG-J	40	Yes	No
3	M	58	High-aspiration risk	PEG-J	50	Yes	No
4	F	77	High-aspiration risk	No	60	Yes	No
5*	M	45	Duodenal cancer	No	20	Yes	No
6	M	59	High-aspiration risk	PEG	25	Yes	No
7*	M	45	Duodenal cancer	No	120	No**	No
8	M	83	High-aspiration risk	No	53	Yes	No
9	F	57	Gastric dysmotility	PEG-J	20	Yes	Gastroparesis
10	F	24	Gastric dysmotility	No	72	Yes	No
11	M	24	Gastric dysmotility	No	50	Yes	No
12	F	65	Gastric cancer	No	29	Yes	No

* Procedures 5 and 7 were performed in the same patient.
**Failure due to inadequate transillumination.
DPEJ, direct percutaneous endoscopic jejunostomy; PEG, percutaneous endoscopic gastrostomy; PEG-J, percutaneous endoscopic gastrostomy with jejunal extension.

Discussion

In this prospective case study, SBE, with its ability to provide deeper small-bowel intubation, was shown to facilitate the identification of an ideal DPEJ insertion site for the placement of a direct percutaneous jejunal feeding tube. Recently, small case series have reported successful placement of DPEJ using DBE [11,12]. The current study is the first to focus on the placement of DPEJ using the SBE technique. The results were similar to those achieved in the small DBE case series, in which successful placement was achieved in 90% of patients [11].

Technical success rates for placement of DPEJ with conventional push enteroscopy vary from 68% to 98% [4,6,7,13]. Adequate transillumination is essential for successful DPEJ placement [7]. SBE enables deep intubation of the small bowel. This facilitates successful intubation of a suitable superficial jejunal segment resulting in adequate transillumination. The advantage of the SBE system for this indication compared with DBE is its simplified design. However, SBE may be less efficient for deep intubation of the small bowel compared with the DBE system [14]. We

believe that this disadvantage is not an important factor in cases of SBE used for DPEJ placement in the proximal jejunum. In one of our patients, DPEJ placement was not successful because this was done in the afferent jejunal loop after previous gastrojejunostomy. Identification of the end of this loop or of the papilla can potentially be helpful in avoiding this problem. In addition, fluoroscopy and contrast administration might aid the differentiation of the afferent and efferent loops.

DPEJ placement has become more common since it was shown to be an effective technique with acceptable safety. Most studies have reported that the complications related to DPEJ are similar in incidence and character to those of PEG tubes. In the largest study to date, DPEJ placement was associated with perforation, volvulus, major bleeding, and fistula formation in up to 10% of cases [7]. In the current study, one case of postprocedural gastroparesis was observed. Aspiration pneumonia is a particular concern regarding postprocedure complications; however, reported data for DPEJ showed a 3% incidence of aspiration compared with 3%–17% with PEG/-J [4, 15-17]. This lower incidence of aspiration pneumonia with DPEJ is likely to be due to the fixed position of the tube in the jejunum compared with PEG-J. We observed aspiration in one patient (8%) following DPEJ.

One of the limitations of the present study is that it is a single-center study that observed the success rate of SBE-assisted DPEJ procedures in only a limited number of patients. Secondly, this study is not a randomized study comparing SBE-assisted DPEJ placement with other endoscopic methods such as conventional push enteroscopy or other overtube-assisted modalities. Nevertheless, the findings described are the first prospective data addressing the success rate of SBE-assisted DPEJ placement. Based on these findings, we conclude that SBE-assisted DPEJ placement appears effective and safe in patients requiring long term jejunal access for feeding.

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Part Three

Complications of device assisted enteroscopy

Chapter 7

Complications of single balloon enteroscopy:

a prospective evaluation of 166 procedures

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Abstract

Background and study aim: Double-balloon enteroscopy (DBE) has proven to be a relatively safe method for small-bowel evaluation, with a complication rate of 1%. The main concern after diagnostic DBE is acute pancreatitis. Single-balloon enteroscopy (SBE) has emerged as a viable alternative to DBE. Until now, no incidence of pancreatitis has been reported for SBE. The aims were to evaluate complication rate and occurrence of hyperamylasemia and to identify the risk factors for hyperamylasemia after SBE.

Patients and methods: Prospectively, consecutive patients undergoing peroral ("proximal") or combined approach SBE were included. Complications were assessed at 1 and 30 days afterwards. Serum amylase and C-reactive protein (CRP) were assessed immediately before and 2–3 hours after SBE.

Results: 166 SBE procedures were performed in 105 patients (53-male; mean age 51 years, range 9–87). The indications for SBE were: anemia (n = 55), Crohn's disease (n = 31) and abdominal complaints suspicious for inflammatory bowel disease (n = 5), Peutz-Jeghers syndrome (n = 1) and other (n = 13). Therapeutic interventions were performed during 21 procedures (13%). One perforation (1/21 therapeutic interventions, 4.8%) occurred after dilation of a benign stricture. While 13 patients (16%) had post-SBE hyperamylasemia, none had complaints suggesting acute pancreatitis. Factors such as sex, indication, procedure duration, number of passes, route of SBE, findings, and/or treatment showed no significant correlation with presence of hyperamylasemia.

Conclusions: SBE appears to be a safe diagnostic endoscopic procedure. The incidence of hyperamylasemia and pancreatitis after peroral SBE seems comparable to that after DBE.

Introduction

Until recently, most of the small bowel was not accessible with conventional endoscopes. In 2001 Yamamoto et al. introduced the double balloon enteroscopy (DBE) system that enabled endoscopic inspection of the entire small bowel [1]. More recently, single balloon enteroscopy (SBE) was introduced as a viable alternative endoscopic technique for visualization of the small bowel [2-4]. The main advantages of both DBE and SBE over wireless capsule endoscopy are the ability to perform biopsy sampling and therapeutic interventions during the same procedure [2-6]. DBE has already proven to be a relatively safe endoscopic procedure with an overall complication rate of approximately 1% [7,8]. The major complication reported after diagnostic DBE is acute pancreatitis, occurring in 0.3% of cases [7,8]. Several hypotheses concerning the cause of this complication co-exists. In particular the one that the inflation of the DBE balloons in the duodenum causes reflux of duodenal fluids into the pancreatic duct [9]. To date, little is known about the complication rate of both diagnostic and therapeutic SBE procedures. In the two of the three published SBE series 2 perforations were reported as an only major complication, in 1.3% to 2.7% of the cases [2-4]. No clinical acute pancreatitis was reported in these studies, but serum amylase levels after the procedures were not determined [2-4]. The SBE technique, using only the overtube balloon for fixation, demands to hook the tip of the endoscope while pulling back the endoscope or advancing the overtube. In theory, this 'hooking' might lead to mucosal damage or extended stretch to the mesenterium, especially in patients with adhesions or otherwise fixated small bowel segments [3,5]. An advantage of the SBE technique might be the prevention of increased intraduodenal pressure, because the single balloon prevents occlusion of a duodenum segment.

The aim of this study was to assess the safety of diagnostic and therapeutic SBE procedures focusing on the occurrence of hyperamylasemia and pancreatitis and to identify risk factors for hyperamylasemia.

Materials and methods

Study design

Consecutive patients undergoing a peroral ("proximal") or a combined peroral and peranal SBE procedure were prospectively studied. During the inclusion period of the study, both SBE and DBE procedures were performed at our endoscopy department. There was no preference for either of the enteroscopy systems and patients had alternately an SBE or a DBE procedure. No age restriction was applied. Patients over 18 years of age gave written informed consent. For patients younger than 12 years, written informed consent from both parents was required, and

for patients of 12–17 years written informed consent from both the patient and parents was required.

A complication was defined as any event that changed the health status of a patient negatively, occurring within 30 days after SBE. Complications were categorized according the literature as minor (requiring up to 3 days of hospitalization), moderate (requiring 3–10 days of hospitalization) and major (requiring > 10 days of hospitalization, and/or an endoscopic, radiological, or surgical intervention, and/or contributing to the death of the patient) [10]. Procedure-related mortality was defined as mortality within 30 days after SBE. A therapeutic SBE was defined as a SBE with the use of argon plasma coagulation (APC), a polypectomy snare, injection of fluids (other than ink for marking), or balloon dilation.

Acute pancreatitis was defined as typical pancreatic abdominal pain (midepigastric with radiation to the back) persisting for several hours, in association with hyperamylasemia (serum amylase above the normal upper limit of > 99 U/L). If abdominal complaints suggestive for acute pancreatitis were reported, patients had a follow-up interview daily up to 1 week after the procedure until symptoms had completely resolved. Blood samples were drawn before and 2–3 hours after the peroral SBE procedure for measurement of serum amylase and C-reactive protein (CRP) levels. The normal values for serum amylase and CRP levels that were applied were 0–99 U/L and < 9 mg/L, respectively.

SBE procedure

All adult patients had bowel preparation using 4 L of polyethylene glycol. The dose of polyethylene glycol was 50 mL/kg for patients younger than 18 years weighing less than 60 kg. SBE was performed with the Olympus SBE endoscope system (XSIF-Q160Y; Olympus Optical Co., Tokyo, Japan). The SBE endoscope consists of a 200 cm long video endoscope with an outer diameter of 9.2 mm and a flexible overtube with a length of 140 cm and an outer diameter of 13.2 mm. A single balloon is attached to the tip of the overtube. The insertion process follows the method used for DBE, except that straightening of the endoscope requires angulation of the tip instead of inflation of an endoscope balloon. The balloon on the tip of the overtube was inflated after the ligament of Treitz had been passed. A peroral SBE was done in all patients, followed in selected cases by a distal approach during the same procedure. One doctor and one assistant who handled the overtube performed the SBE.

For each procedure, SBE insertion depth, numbers of passes (i.e. "push-and-pulls"), and procedure time were noted. The insertion depth of the enteroscope into the small bowel was measured using the DBE method described by May et al. [11]. Most procedures were performed using conscious sedation with midazolam and fentanyl. In patients younger than 18 years and in selected adult cases, procedures were performed under deep sedation with propofol or general anesthesia.

In the majority of cases complete small-bowel intubation was intended; in selected cases only a limited procedure was performed.

Statistical analysis

Numerical data were reported by using means or medians with range. Continuous variables were compared with the (un-) paired t-test or the Wilcoxon rank-sum test. Qualitative variables were compared using chi square testing. A two-sided p-value <005 was considered significant.

Results

Patient characteristics

During a period of 20 months, January 2008 to September 2009, 166 SBE procedures were performed in 105 patients: 53 males, mean age 51 (range 9 – 87) years. Nine patients (9%) were younger than 18 years at the time of SBE. The major indication for SBE was iron deficiency anemia (n=55), followed by small bowel Crohn's disease (n=31), unexplained abdominal pain or suspicion of Crohn's disease, and Peutz-Jeghers syndrome; see Table 1.

Table 1. Patient characteristics and indications for single balloon enteroscopy (SBE).

Patients characteristics (n=105)	
Age, mean (range) years	51 (9-87)
Male / female	53 / 52
Indication for SBE	
– Anemia	55 (52%)
– Crohn's disease	31 (30%)
– Abdominal pain	5 (5%)
– Peutz-Jeghers syndrome	1 (1%)
– Other	13 (12%)

SBE procedure

No technical difficulties were encountered with the introduction of the SBE system. Conscious sedation, deep sedation with propofol and general anesthesia were used in 86%, 8%, and 6% of the patients, respectively. The mean total procedure time was 70 minutes (range 30–120). In four patients (4%) visualization of all of the small bowel was achieved, in three patients with a combined procedure and in one patient with the peroral approach only. In six patients (6%) only a limited visualization of the small bowel was performed, because the purpose of the enteroscopy had been accomplished and/or a stenotic lesion could not be passed. The mean insertion depths were 243 cm (range 60–400) and 95 cm (0–200) for the proximal and distal

SBE procedures, respectively. The mean number of passes during the oral SBE procedure was 12 (range 4–24); see Table 2.

Findings and therapy during SBE procedures

Pathologic findings were reported in 65 patients: ulcerations in 30 (29%), angiodysplasia in 16 (15%); strictures in 8 (8%); polyps in 3 (3%); tumors in 1 (1%); and other findings in 7 (7%) patients; see Table 2.

The strictures were benign in 7 patients (caused by Crohn's disease in 6, and radiation enteritis in 1), and malignant in 1 (caused by an adenocarcinoma). These strictures could not be passed in 6 patients (5 benign strictures and 1-malignant).

Therapeutic interventions were done during 21 procedures (13% of procedures): argon plasma coagulation in 15 (71% of interventions), polypectomy in 3 (14%), balloon dilation in 2 (10%), and injection therapy in 1 (5%); see Table 3.

Table 2. Procedure data and findings during SBE.

SBE procedures in 105 patients	
Route of approach	
– proximal	44
– both proximal and distal	61
Procedure time, mean (range), minutes	70 (30-120)
Number of passes, mean (range)	12 (4-24)
Sedation, n (%)	
– conscious	90 (86%)
– propofol or general anaesthesia	15 (14%)
Findings, n (%)	
– no abnormalities	40 (38%)
– ulcerations	30 (29%)
– angiodysplasias	16 (15%)
– benign strictures	7 (7%)
– polyps	3 (3%)
– tumors	1 (1%)
– other findings	7 (7%)

SBE= Single balloon enteroscopy

Table 3. Therapeutic interventions (n=21) during single balloon enteroscopy (SBE).

Endoscopic treatment, n (%)	
– argon plasma coagulation	15 (71%)
– polypectomy	3 (14%)
– dilation	2 (10%)
– injection therapy	1 (5%)

Complications

In the 145 diagnostic SBE procedures, no complications occurred.

After 21 therapeutic SBE procedures, one complication (4.8%) was noted: a perforation occurred during dilation, through the scope, of a radiation stricture in the distal ileum. A laparotomy was performed and the tear was closed by surgical suturing. The patient was discharged after 1 week. No other complications or mortality were noted.

Serum amylase and CRP measurements

Nine patients had an elevated serum amylase (mean 128 U/L, range 105–190) at baseline, without clinical signs or symptoms of pancreatitis. The mean serum amylase level did not differ significantly before and after the procedure in this patient group ($P=0.2$). These patients (9%) were defined as having possible macroamylasemia and were excluded from further analysis. In 15 patients serum amylase and CRP measurements were incomplete, so serum measurements were analyzed in 81 patients.

In these 81 patients, the mean post SBE serum amylase level was significantly higher than the baseline level (78 vs. 55 U/L, $P=0.000$). Among these patients 13/81 (16%) developed hyperamylasemia after the peroral SBE, with a mean serum amylase of 169 U/L (range 102–355). In the patients with hyperamylasemia the mean CRP levels before and after peroral SBE were 8.7 mg/L and 11.2 mg/L, respectively ($P=0.13$). The mean CRP levels after the SBE procedure did not differ significantly between patients with or without hyperamylasemia, at 8.0 mg/L and 11.0 mg/L, respectively ($P=0.76$). None of the patients with hyperamylasemia reported post-procedural complaints that suggested acute pancreatitis. Risk factors such as sex, indication, duration, number of passes, route of SBE (including only peroral or combined peroral and peranal during the procedure), sedation, findings, and/or treatment were not associated with the occurrence of hyperamylasemia.

Also when the patients in whom complete small-bowel intubation had been intended were compared with those where there was limited small-bowel visualization, the mean post-procedure serum amylase levels were similar, at 78 U/L (27–355) and 79 U/L (38–123), respectively ($P=0.95$).

Serum measurements were evaluable in six of the nine pediatric patients, and no significant difference in the incidence of hyperamylasemia was found when the pediatric (< 18 years) and adult patients were compared.

Discussion

SBE has been recently introduced as a new technique for endoscopic visualization of the small bowel [2-4,12]. The first published small series suggest that SBE is a safe endoscopic technique with a complication rate similar to that of DBE. The most serious reported complications associated with SBE are perforations [2,3,5]. So far no cases of acute pancreatitis have been reported after SBE, in contrast to the earlier reports of pancreatitis after DBE procedures [9,13-18]. In the present prospective study, a relatively low incidence of complications during and after SBE has been found. Also, SBE seems to be a safe procedure for pediatric patients. The frequency of post-procedural hyperamylasemia was comparable to that found in our earlier DBE study [18].

In the three published SBE series so far, the overall risk of perforation has been zero, 1.3% and up to 2.3% of procedures, respectively [2-4]. This is a rather high complication rate compared with the perforation rate of diagnostic DBE (0.3%), but is based on only two individual patients [7]. Perforations were caused by advancing the overtube, either with the tip of the scope being angulated or over an anastomotic stricture [2,3,5]. These preliminary data might suggest that the hook-shaped tip of the SBE enteroscope is more dangerous than the ballooned tip of the DBE enteroscope. A careful approach is therefore recommended on account of the hooked shape of the tip of the enteroscope during the pushes and pulls, especially in patients with known adhesions or strictures. The perforation in our study was clearly related to the dilation of a radiation stricture and not to the SBE technique. The incidence of complication after therapeutic SBE was 4.8%, comparable to the reported incidence after therapeutic DBE [7,8].

Strikingly, in contrast to peroral ("proximal") DBE, no acute pancreatitis has been reported as a complication of SBE [2-4]. Acute pancreatitis is the major complication of concern for diagnostic peroral DBE, reported in 0.3% of cases [7]. The mechanism of acute pancreatitis after DBE is unknown and there are currently several theories. We hypothesized, regarding the first reported cases of acute pancreatitis after peroral DBE, that inflation of two balloons in the duodenum results in an increase of intraluminal pressure, leading to reflux of duodenal fluids into the pancreatic duct [9]. Others hypothesized that the repeated 'push-and-pull' with stretching of the small intestine, or direct obstruction of the pancreatic duct by the insufflated balloon(s) are causes of acute pancreatitis [13,14,19,20].

In our recently published series, we found incidences of post DBE hyperamylasemia and acute pancreatitis of 17% and 1%, respectively [18]. These incidences are relatively low compared with those in studies published earlier, reporting an incidence of hyperamylasemia of up to 51%, and of acute pancreatitis up to 8% [16,17]. We think that this lowered incidence is due to the modification of our DBE insertion technique, with inflation of the DBE balloons after the overtube has been passed distal to the ligament of Treitz [18]. The repeated stretching of the small-bowel and/or mesenteric ligaments is the possible cause of the remaining cases of

hyperamylasemia post DBE. Nevertheless there was no significant difference in occurrence of hyperamylasemia between the patients who underwent proximal and those who had combined procedures. We had expected, with this "repeated stretching" hypothesis, a significantly greater incidence of hyperamylasemia in those patients who underwent combined procedures (with a greater number of passes). The incidence of post-SBE hyperamylasemia, as presented in the current study, was similar to the incidence of post-DBE hyperamylasemia in our previous study, these being 16% and 17% respectively. The actual incidence of clinically relevant pancreatic injury, that is, acute pancreatitis, seems to be different, when post-SBE and post-DBE studies are compared, at 0% versus 1%–8%, respectively [16-18]. These findings must be interpreted with care, as in our study and other published series the numbers of procedures are small. In theory, this possibly lower incidence of acute pancreatitis after SBE might be explained by a lower intraduodenal pressure with the technique that uses only one balloon. The similar incidence of hyperamylasemia with SBE and DBE suggests that the different 'push-and-pull' techniques, hook-tipped versus balloon-tipped, do not induce additional stretching or damage to the small bowel and/or pancreas. The relation between the occurrence of hyperamylasemia and acute pancreatitis remains unclear.

One of the drawbacks of the present study is that this is a single-center study that observed the safety of SBE procedures in only a limited number of cases. Secondly, this study is not randomized with a head-to-head comparison of SBE and DBE techniques. Nevertheless the findings shown are the first prospective data addressing the safety of SBE. Thirdly, we did not visualize all of the small bowel in all patients. However, our proximal insertion depths and procedure durations were comparable to those in other published SBE series, with reported ranges of 255 to 270 cm and 63 to 173 minutes, respectively [2-4]. Furthermore, this study presents a relatively low number of therapeutic interventions (13%).

We conclude that SBE appears safe for diagnostic evaluation and endoscopic therapy of the small bowel. The observed incidence of hyperamylasemia and acute pancreatitis reflects that, using SBE, injury to the pancreas and small bowel seems to be similar to or even lower than that associated with the DBE technique.

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Chapter 8

Low incidence of hyperamylasemia after proximal double-balloon enteroscopy: has the insertion technique improved?

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Abstract

Background and study aim: Reported complications of double-balloon enteroscopy (DBE) include post-enteroscopy pancreatitis. Hyperamylasemia after proximal DBE is reported frequently, but the relationship to development of pancreatitis remains unclear. Hyperamylasemia may be related to balloon inflation in the pancreatic head region. The aims of the study were to identify risk factors for hyperamylasemia and to determine the incidence of hyperamylasemia and pancreatitis when a modified cautious DBE insertion protocol was used.

Patients and methods: In a prospective study, involving consecutive patients undergoing a proximal DBE, serum amylase activity was assessed immediately before and after the procedure.

Results: 135 patients were included (men 78, women 57; mean age 49 years [range 17–88]). The mean total procedure time was 73 minutes (range 30–150 minutes), and mean number of passes during the proximal DBE was 14 (6–24). While patients (17%) developed hyperamylasemia after the DBE procedure, only one patient with hyperamylasemia had clinical symptoms indicating a mild acute pancreatitis (0.7%). Total procedure time and number of passes correlated significantly with the occurrence of hyperamylasemia.

Conclusions: We found a low incidence of hyperamylasemia and pancreatitis post-DBE. Theoretically, this could result from the modified insertion technique, with local strain and friction of the small bowel as remaining causes of hyperamylasemia, a notion supported by the significant relation between hyperamylasemia and duration of DBE and total number of passes. We therefore advise use of the cautious insertion technique and, if possible, reduction of duration and of number of passes in every proximal DBE.

Introduction

Double balloon enteroscopy (DBE) is currently the standard endoscopic technique for visualization of the small bowel [1–3]. The main advantages of DBE are its sensitivity for the detection of mucosal abnormalities, and the abilities to take biopsies for histological confirmation and to perform therapeutic endoscopic interventions [4]. In general DBE has been shown to be safe, but a few severe complications have been reported. The most frequently reported complication after diagnostic DBE is acute pancreatitis [5,6].

The pathophysiologic mechanism leading to post-DBE pancreatitis is debated. One hypothesis is that the inflation of the DBE balloons in the duodenum leads to an increase in the intraduodenal pressure that subsequently promotes reflux of duodenal contents into the pancreatic duct [7]. Another hypothesis is that local straining of small intestine during proximal DBE activates pancreatic enzymes [8]. In our department, the occurrence of severe post-DBE pancreatitis led to modification of the insertion protocol for proximal procedures so that during insertion balloons were only inflated after the overtube was distal to the ligament of Treitz [7].

The aim of this study was to determine the risk factors for hyperamylasemia, and to measure the incidence of hyperamylasemia and pancreatitis after proximal DBE procedures that were done using this amended insertion technique.

Patients and methods

Study design

Consecutive patients referred for proximal DBE were included in the study. All patients gave written informed consent.

At DBE, the insertion depth and the duration were noted for each procedure. Blood samples were collected before and 2–5 hours after the proximal DBE procedure, for measurement of serum amylase and C-reactive protein (CRP). The normal values for serum amylase and CRP levels were taken to be 0–99 U/L and <9 mg/L, respectively.

After the inclusion of the first 50 patients, the study design was extended, with additional recording of number of passes and of post-procedural abdominal complaints. A pass was defined as every combined insertion and drawback of the endoscope and overtube ("push-and-pull"). Abdominal complaints were scored 2–5 hours after the procedure, using a 4-point scale, with pain scored as: absent (grade 0), mild (grade 1), moderate (grade 2) or severe (grade 3). If grade 2 or 3 abdominal complaints were reported, patients had a follow-up interview after 1 day, up to 1 week after the procedure until symptoms had completely resolved.

Definition of hyperamylasemia and pancreatitis

Hyperamylasemia was defined as an increase of serum amylase to above the normal upper limit (>99 U/L), or to three times the baseline level before the procedure. Clinical (acute) pancreatitis was defined as typical pancreatic abdominal pain (mid-epigastric with radiation to the back), persisting for several hours, in association with hyperamylasemia.

DBE procedure

All patients had bowel preparation with 4 L polyethylene glycol solution. The enteroscopes used were the Fujinon EN-450P5 or the Fujinon EN-450T5 (Fujinon Inc., Saitama, Japan). Most procedures were performed using conscious sedation (midazolam and fentanyl). In selected cases, deep sedation with propofol was employed.

Statistical analysis

Numerical data were reported by using means and range. Continuous variables were compared using the unpaired or paired *t* test or the Wilcoxon rank-sum test. Qualitative variables were compared using chi-squared testing. A two-sided *P* value of <0.05 was considered statistically significant.

Results

Patient characteristics

Over a period of 16 months 135 patients were included (78 males; mean age 49 years, [range 17–88]). The main indications for DBE were iron-deficiency anemia and (suspected) small-bowel Crohn's disease; for patient characteristics see **Table 1**.

DBE procedure

Conscious sedation was used in 87% of the patients. The P- and T-type enteroscopes were used in 94 (70%) and 41 patients (30%), respectively. The mean total procedure time was 73 minutes (range 30–150). A total of 80 patients (59%) underwent a combined proximal and distal DBE procedure; in 55 patients (41%) only a proximal DBE procedure was performed. Complete visualization of the small intestine was achieved in 13 (10%) patients; in four patients this was completely achieved via the proximal approach. The mean insertion depth for the proximal DBE procedure was 264 cm (range 100–420). The mean number of passes during the proximal DBE procedure was 14 (range 6–24). Grade 1 abdominal complaints were reported after the procedure by 11 patients (13%), grade 2 by one patient (1%), and no grade 3 complaint was reported. In only one patient, with grade 2 abdominal complaints, did these persist >1 day after the procedure.

Table 1. Patient characteristics and indications for double-balloon enteroscopy (DBE).

Patient characteristics (n = 135)	
Age, mean (range),years	49 (17–88)
Male, female	78, 57
Indication for DBE	
Anemia	49 (36%)
Crohn's disease	39 (29%)
Peutz–Jeghers' syndrome	7 (5%)
Abdominal pain	8 (2%)
Other	32 (24%)

Findings and therapy during DBE procedures

Pathologic findings were reported in 73 patients (54%), comprising ulcerations in 30 (22%), angiodysplasia in 15 (11%), polyps in 11 (8%), tumors in 3 (2%), and other findings in 14 (10%) patients. Therapeutic procedures were carried out in 21 patients (16%), being argon plasma coagulation in 11 (52% of therapeutic procedures), dilation in 5 (24%), and polypectomy in 5 (24%).

Laboratory results

Serum samples were taken at a mean of 150 minutes after the DBE procedure (range 90–300 minutes). Ten patients had an elevated serum amylase at baseline (mean 122 U/L, range 100–231), without clinical signs or symptoms of pancreatitis. One of these patients developed post-procedural hyperamylasemia defined as three times the baseline level before procedure. The other nine patients (7 %) were defined as having possible macroamylasemia and showed no elevation of serum amylase post procedure (mean 136 U/L, range 112–215). These nine patients were excluded from further analysis.

In 22 patients (17 %) hyperamylasemia was found after the procedure (mean 191 U/L, range 101–468). The mean CRP levels after proximal DBE did not differ significantly between patients with or without hyperamylasemia, at 6 mg/L (range 1–24) and 7 mg/L (range 1–126), respectively.

Hyperamylasemia and clinical outcome

Out of 22 patients with hyperamylasemia, 18 (82 %) reported no complaints after the procedure. Of the four patients with complaints, three reported grade 1 abdominal complaints that resolved spontaneously within 24 hours after the procedure. Only one patient reported grade 2 abdominal complaints directly after the procedure. This patient had persistent complaints, which resolved after 3 days with conservative treatment. Because of the mild course of the pancreatitis, no additional radiological imaging or repeat measurement of serum amylase or lipase was done.

When total procedure time and number of passes were compared between the patient groups with hyperamylasemia and those with normal amylase levels, statistically significant differences were found. (Regarding procedure duration, mean [range] for the hyperamylasemia group was 82 minutes [50–150] and for the normal amylase group it was 71 minutes [30–120], $P=0.048$. Regarding number of passes, the mean [range] for the hyperamylasemia group was 16 [12–23], and for the normal amylase group it was 13 [6–24], $P=0.006$). No other associations with the occurrence of hyperamylasemia were found (see **Table 2**).

Table 2. Patient characteristics, double-balloon endoscopy (DBE) procedure-related data and laboratory results in patients with and without hyperamylasemia. (Total n = 126; 9/135 patients were deemed to possibly have macroamylasemia and were removed from analysis.)

	Normal amylase (n = 104)	**Hyperamylasemia (n = 22)**	***P* value**
Age, mean (range) years	49 (17–88)	50 (20–76)	0.67
Male, female	57, 47	13, 9	0.71
Indication for DBE, n (%)			0.45
Anemia	40 (39%)	6 (27%)	
Crohn's disease	29 (28%)	5 (23%)	
Peutz–Jeghers' syndrome, n (%)	5 (5%)	2 (9%)	
Abdominal pain	5 (5%)	3 (14%)	
Other	25 (24%)	6 (27%)	
Enteroscope model, n (%)			0.546
Fujinon EN-450P5	73 (70%)	14 (64%)	
Fujinon EN-450T5	31(30%)	8 (36%)	
Sedation			0.576
Conscious	90 (87%)	20 (91%)	
Propofol	14 (13%)	2 (9%)	
Route of approach, n (%)			0.90
Oral	44 (42%)	9 (41%)	
Both	60 (58%)	13 (59%)	
Procedure time, mean (range), minutes	71 (30–120)	82 (50–150)	0.048
Number of passes*, mean (range)	13 (6–24)	16 (12–23)	0.006
Insertion depth, mean (range), cm	263 (100–400)	262 (130–350)	0.91
Findings during DBE, n (%)			0.68
No abnormalities	48 (46%)	12 (55%)	
Ulcerations	23 (22%)	3 (14%)	
Angiodysplasia	11 (11%)	3 (14%)	
Polyps	8 (8%)	3 (14%)	
Tumors	3 (3%)	0	
Treatment during DBE (%)	18 (86%)	3 (14%)	0.15
Amylase after DBE, mean (range), U/L	61 (17–99)	191 (101–468)	<0.001
CRP levels after DBE, mean (range), mg/L	7 (1–126)	6 (1–24)	0.58

CRP, C-reactive protein

* Scored for 76 patients (after the inclusion of the first 50 patients).

Discussion

Recently, two large retrospective cohort studies on complications after DBE reported an incidence of 0.3% of acute pancreatitis following diagnostic proximal DBE procedures [5,6], while two prospective studies reported a surprisingly high frequency of hyperamylasemia post DBE, with no clear association with the development of acute pancreatitis [9,10]. In the present prospective study, involving a large number of consecutive DBE procedures, relatively low incidences of hyperamylasemia and pancreatitis were found following DBE. The total procedure time and number of passes were significantly correlated with development of hyperamylasemia post-DBE.

The actual mechanism causing post-DBE hyperamylasemia and acute pancreatitis is unknown, and there is an ongoing discussion concerning this issue [7,8]. Our center was the first to report two cases of pancreatitis after proximal DBE [7]. We hypothesized that inflation of two balloons in the duodenum (distal before the ligament of Treitz and proximal in the duodenal bulb) can cause an increase in duodenal intraluminal pressure, leading to reflux of duodenal fluids into the pancreatic duct. Others hypothesized that prolonged mechanical stress on the upper abdominal organs due to the repeated "push-and-pull," or the direct trauma by compression of the papillary area, or direct obstruction of the pancreatic duct by the insufflated balloon(s) could cause acute pancreatitis [8,11,12,13].

Earlier studies showed a large discrepancy between the incidence of procedure-related hyperamylasemia and the actual development of clinical acute pancreatitis. In our study, both the incidence of hyperamylasemia and of post-DBE pancreatitis were lower compared with those reported by these other prospective studies. The incidences of post-DBE hyperamylasemia were 46%, 51% and 17%, and those of pancreatitis were 8%, 3% and 1%, as reported by Honda et al. [9], Kopacova et al. [10], and in the present study. From these data, one might conclude that there seems to be a trend for an association between the incidences of hyperamylasemia and pancreatitis, but nevertheless there still remains a discrepancy between the incidences of post-procedural hyperamylasemia and acute pancreatitis.

In theory, the lower incidence found in our study might be due to the modification of the insertion technique at the start of the DBE procedure, and the remaining cases of hyperamylasemia might be caused by local friction and strain of the small bowel by the repeated push-and-pulls during the DBE procedure. The latter theory is supported by our findings of a positive relation between presence of hyperamylasemia and duration of the procedure, also shown by Honda et al., and between hyperamylasemia and number of passes during the DBE procedure. These findings may indicate that post-DBE pancreatitis can be prevented by shortening the duration of the procedure, and minimizing the number of passes. This is in line with the advice of the guidelines from the 2nd International Conference on DBE that total enteroscopy should be attemped in only selected cases [14].

A drawback of the present study is that patients' serum amylase levels were only measured after the change in the insertion technique had been implemented. A randomized controlled trial would have given more insight, but this was considered to be unethical because of the theoretical relation to the development of acute pancreatitis. Considering this, we have to be careful with our conclusions about the impact of the modification of the insertion technique.

Secondly, serum lipase levels were not measured in combination with serum amylase. In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis [15]. At our institution serum amylase is generally used as the first choice serum marker for pancreatitis. Also, recent series concerning DBE and hyperamylasemia have shown an excellent correlation between serum amylase and lipase measurements [9,10]. Therefore we decided only to measure serum amylase in the present study.

We found relatively low incidences of hyperamylasemia and acute pancreatitis compared with other prospective studies. This different finding might be related to the modification in the insertion technique, but nevertheless this change does not seem to prevent the development of post-DBE hyperamylasemia and pancreatitis. These might also be caused by local friction and small-bowel strain, especially in DBEs with a high number of total passes and of longer duration. Considering these findings, we suggest that duration and number of passes for each DBE procedure should be minimized. Furthermore, we do not recommend routine serum amylase determination following DBE, but that it should be done only in patients with prolonged abdominal pain after the procedure.

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Chapter 9

Hyperamylasemia and pancreatitis after spiral enteroscopy

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Abstract

Background: Acute pancreatitis is a significant potential complication with double balloon enteroscopy (DBE). Hyperamylasemia is frequently observed after both DBE and single balloon enteroscopy (SBE) but often without associated pancreatitis. Whether the same phenomenon occurs with spiral enteroscopy is currently unknown.

Aims: To determine the incidence of pancreatitis and hyperamylasemia with spiral enteroscopy.

Study methods: A prospective cohort study of consecutive patients undergoing proximal spiral enteroscopy was conducted. Serum amylase levels were measured immediately before and following the procedure, combined with observation for clinical signs of pancreatitis.

Results: 32 patients underwent proximal spiral enteroscopy with a mean total procedure time of 51 minutes (range 30 – 100) and depth of insertion of 240 cm (range 50 – 350). The diagnostic yield was 50%, with 31% of all procedures being therapeutic. While no patients exhibited signs that raised suspicion of pancreatitis, hyperamylasemia was common (20%). Hyperamylasemia was not significantly associated with procedure duration or depth of insertion but was linked to patients with Peutz-Jeghers syndrome and with the use of propofol sedation, suggesting that it may be more common in difficult cases.

Conclusions: Postprocedural hyperamylasemia occurs frequently with proximal spiral enteroscopy, while no associated pancreatitis was observed. This finding suggests that hyperamylasemia may not necessarily reflect pancreatic injury nor portend a risk of pancreatitis.

Introduction

Spiral enteroscopy[1, 2] is the latest form of small bowel endoscopy to join the techniques of single balloon enteroscopy (SBE)[3] and double balloon enteroscopy (DBE)[4, 5] for the investigation of small intestinal diseases. Large series have been performed with DBE demonstrating that the most common, significant adverse events with the procedure are bleeding (0.2-0.8%), perforation (0.3-0.4%) and pancreatitis (0.2-0.3%).[6, 7] While considerable attention has focused on the occurrence of post-DBE pancreatitis, asymptomatic hyperamylasemia remains quite common.[8] In the first study reporting complications with SBE, there were no cases of pancreatitis but again hyperamylasemia was frequently encountered.[9] Currently, there are no published studies on complications with spiral enteroscopy, and the risks of pancreatitis and hyperamylasemia remain unknown. Thus, the aim of this study was to determine the incidence of pancreatitis and hyperamylasemia after proximal spiral enteroscopy.

Materials and methods

Study design

Consecutive patients undergoing proximal spiral enteroscopy at Erasmus MC University Medical Center, a tertiary referral university hospital in Rotterdam, The Netherlands, were prospectively included in the study after providing written informed consent. Demographic and clinical data were noted and the insertion depth, duration, sedation requirements, diagnostic and therapeutic outcomes, and adverse events were recorded. Blood samples were collected immediately prior and 2 – 4 hours following the proximal spiral enteroscopy procedure for measurement of serum amylase and C-reactive protein (CRP). All patients were clinically evaluated 2 – 5 hours after the procedure to assess for abdominal complaints that could be suggestive of pancreatitis. Any need for overnight hospital stay or readmission was noted. All patients were contacted the following day for evaluation of complaints. Referring physicians and/or general physician were asked to report adverse outcomes within 30 days of the procedure. The study was approved by the institutional review board of Erasmus MC University Medical Center.

Spiral enteroscopy procedure

Spiral enteroscopy was performed using the Discovery SB spiral overtube (Spirus Medical Inc.; Stoughton, Mass) in combination with either the Olympus SIF-Q160Y SBE endoscope (Olympus Optical Co., Tokyo, Japan) or the Fujinon EN-450P5 or EN-450T5 DBE endoscopes (Fujinon Inc., Saitama, Japan) without attached balloons. The spiral overtube has raised helices at its distal end, a locking device to fix the overtube to the endoscope, and two foam handles at its

proximal end to facilitate overtube rotation. Clockwise rotation of the spiral overtube acts in a similar manner to that of a screw, advancing the endoscope while pleating the bowel onto its surface.[1] The procedure was performed by two physicians: an endoscopist with considerable small bowel enteroscopy experience (P.M.) together with an advanced endoscopy fellow (C.T. or H.A). The endoscope was inserted into the proximal esophagus in the usual fashion, after which further advancement was achieved by rotation of the overtube by twisting of the foam handles. While the first operator rotated the overtube, the second operator steered the endoscope tip. Withdraw of the endoscope was achieved by counter-clockwise overtube rotation. The depth of insertion was estimated during endoscope withdrawal according to the previously described and accepted spiral enteroscopy method.[1, 2]

All patients had bowel preparation with 4 L of a polyethylene glycol solution and an overnight fast, which is the standard practice for small bowel enteroscopy at our institution due to our belief that improved mucosal views are obtained once deep insertion reaches the ileum. Most procedures were performed under conscious sedation (midazolam and fentanyl) while selected cases were done using anesthesia-administered propofol. Propofol was selected for cases expected to be prolonged or more difficult (e.g. multiple polypectomies in Peutz-Jeghers patients), as well as for cases performed during live endoscopy courses. With few exceptions, spiral enteroscopy was performed without prior capsule endoscopy, which is not performed at our center, and was chosen in favor of DBE or SBE according to the endoscopist's discretion. All procedures were performed on an outpatient basis.

Definition of hyperamylasemia and pancreatitis

Hyperamylasemia was defined as a twofold or greater increase in serum amylase (ratio of post-procedure to pre-procedure amylase ≥ 2) to a level exceeding the upper limit of normal (> 99 U/L). Clinical pancreatitis was defined according to the revised 2008 version of the Atlanta Classification of acute pancreatitis, which consists of typical abdominal pain strongly suggestive of acute pancreatitis, serum amylase at least three times greater than the upper limit of normal and/or characteristic findings of acute pancreatitis on contrast-enhanced CT scan.[10] Radiological imaging was not routinely performed in all patients but instead was reserved for cases when pancreatitis was suspected based on clinical grounds (abdominal pain with abnormal amylase between 100-299 U/L that was less than 3 times the upper limit of normal). An abnormal pre-procedure serum amylase of $\geq$ 100 U/L in combination with the absence of postprocedural abdominal pain was considered sufficient to exclude pancreatitis and suggest macroamylasemia. The normal values for serum amylase and CRP were 0 – 99 U/L and < 9 mg/L, respectively.

Statistical analysis

The statistical software Stata 10.1 (Stata Corp, College Station, Texas) was used to analyze the data. Means and ranges were used to summarize data for continuous variables and percentages were used to summarize data for categorical variables. Continuous data were compared using Student's t-test (with Welch's approximation to correct for unequal variances) while categorical data were assessed with the Chi-squared test. A two-sided p-value of < 0.05 was considered statistically significant. Univariate and multivariable logistic regression were planned but not performed because the number of positive outcomes was too low to draw reliable conclusions from that analysis.

Results

Patient characteristics

Between November 2008 and March 2010, 32 patients underwent proximal spiral enteroscopy, with a mean age of 64 (range 32 – 86) years; 19 (59%) were females. The most common indications for small bowel enteroscopy were anemia (81%) and Peutz-Jeghers syndrome (13%); see Table 1. Two patients with anemia had undergone prior video capsule endoscopy, whereas two of the Peutz-Jeghers patients previously had DBE. None of the included patients had a medical history of acute or chronic pancreatitis. While 6 (19%) patients consumed $\geq$ 2 units of alcohol per week, no patient consumed more than 5 units.

Spiral enteroscopy procedure

The mean depth of insertion beyond the ligament of Treitz was 240 cm (range 50 - 350) with an average total procedure time of 51 (range 30 - 100) minutes. Conscious sedation was used for 20 (62%) while anesthesia-administered propofol was used in 12 (38%) patients. All Peutz-Jeghers syndrome patients received propofol, compared to 29% of the remaining cohort. The majority of patients (91%) underwent just the proximal procedure, with only 3 (9%) having both a proximal and a distal spiral enteroscopy. Among those 3 patients, total enteroscopy with complete visualization of the small bowel was not achieved. The proximal spiral enteroscopy was diagnostic in 50% of cases, identifying angiodysplasia in 7 (22%), polyps in 4 (13%), a tumor in 3 (9%), and ulcerations in 2 (6%) procedures. Spiral enteroscopy was therapeutic in 10 (31%) patients, with argon plasma coagulation used to treat angiodysplasia in 6 (19%) (performed when angiodysplasias were considered clinically significant, defined as "large" lesions or ones that bled when probed by a catheter) and polypectomy performed in 4 (13%) cases, removing a total of 24 polyps.

Table 1. Clinical and endoscopic data.

	Entire cohort (n=32)
Patient characteristics	
Age, years (range)	64 (32 – 86)
Female sex	19 (59%)
Indication for enteroscopy	
– *anemia*	26 (81%)
– *Peutz-Jeghers*	4 (13%)
– *other*[a]	2 (6%)
Enteroscopy data	
Conscious sedation	20 (63%)
Propofol sedation	12 (37%)
Insertion depth, cm (range)	240 (50-350)
Procedure time, min (range)	51 (30 – 100)
Diagnostic yield	16 (50%)
– *angiodysplasia*	7 (22%)
– *polyp(s)*	4 (13%)
– *tumor*	3 (9%)
– *ulcer(s)*	2 (6%)
Therapeutics[b]	10 (31%)

[a] Abdominal pain with abnormal imaging (n=2)
[b] Polypectomy (n=4; removed 24 polyps), argon plasma coagulation (n=6)

Hyperamylasemia and pancreatitis

Serum samples were taken at a mean of 175 (range 130 – 270) minutes after the spiral enteroscopy procedure. Two patients had an elevated amylase prior to the procedure, 101 and 112 U/L respectively, without any signs or symptoms suggestive of pancreatitis. Neither of these patients developed an elevation in serum amylase after the procedure greater than two times the baseline value, rising to 112 and 167 U/L respectively. Both were considered to have macroamylasemia and were excluded from subsequent analysis. Six (19%) patients developed hyperamylasemia with a mean ratio of post- to pre-procedure amylase of 2.9 and a mean post-procedure amylase level of 210 (range 104 – 510) U/L, reflecting an average increase in amylase of 139 (range 56 – 403) U/L. These changes significantly exceeded those among the 24 (80%) patients without hyperamylasemia, who had a mean post-procedure amylase of 73 U/L ($p < 0.01$) and an average increase of only 21 U/L ($p < 0.01$). The mean CRP levels did not increase after the spiral procedures and did not differ significantly between patients with normal amylase and those with hyperamylasemia. Comparing the patient group with post-procedural hyperamylasemia with the

normal amylase group, the only significant differences were the indication for the procedure (p=0.01) and the type of sedation used (p=0.01) (hyperamylasemia was more likely with Peutz Jeghers patients and propofol sedation; normal amylase levels were more likely with anemia as the indication and conscious sedation). There were no significant differences in terms of demographic features or endoscopic outcomes, including both depth of insertion and procedure time (see Table 2). In addition, there was no significant linear relationship between the duration of the enteroscopy procedure and the subsequent change in serum amylase level (p=0.34).

Table 2. Comparison of normal amylase and hyperamylasemia groups.

	Normal amylase (n=24)	Hyperamylasemia (n=6)	p-value
Patient characteristics			
Age, years (range)	65 (32 – 86)	60 (34 – 83)	0.59
Female sex	15 (63%)	3 (50%)	0.58
Indication (anemia)	22 (92%)	3 (50%)	**0.01**
Enteroscopy data			
Conscious sedation	18 (75%)	1 (17%)	**0.01**
Propofol sedation	6 (25%)	5 (83%)	**0.01**
Insertion depth, cm (range)	233 (50 – 350)	250 (200 – 300)	0.43
Procedure time, min (range)	50 (30 – 100)	62 (30 – 80)	0.26
Diagnostic yield	11 (46%)	4 (67%)	0.36
Therapeutic yield	7 (29%)	3 (50%)	0.17
Serum measurements			
Amylase (U/L) (all range)			
Pre-procedure amylase	52 (28 – 98)	71 (27 – 113)	0.08
Post-procedure amylase	73 (28 – 130)	210 (104 – 510)	**<0.01**
Absolute Δ (Post – Pre)	21 (-3 – 44)	139 (56 – 403)	**<0.01**
Ratio Post-amylase/pre-amylase	1.4 (0.9 – 2.3)	2.9 (2.0 – 4.8)	**<0.01**
CRP (mg/L) (all range)			
– pre-procedure	17 (1 – 190)	5 (1 – 16)	0.17
– post-procedure	17 (1 – 206)	6 (1 – 20)	0.23
Clinical pancreatitis[a]	0	0	-

Data presented with percentages unless otherwise stated.
[a] Defined according to the revised (2008) Atlanta Classification for acute pancreatitis

There were no cases of acute pancreatitis. In fact, none of the patients experienced post-procedural abdominal pain that raised suspicion for possible pancreatitis and so no imaging studies were performed. Furthermore, no adverse events were recorded at follow-up.

Discussion

Acute pancreatitis is a concerning potential complication with DBE. Large, multicenter, retrospective studies suggested the risk of pancreatitis after diagnostic DBE procedures was 0.2-0.3%.[6, 7, 11] Two prospective studies demonstrated a much higher frequency of hyperamylasemia (up to 50%) after DBE than the observed rate of pancreatitis (nearly 5%).[12, 13] This has been interpreted as evidence of a causative link between oral DBE, hyperamylasemia and pancreatic injury. However, multiple theories have been put forth speculating about the mechanism by which DBE leads to pancreatitis with no clear consensus.[14] Recently, we performed two prospective studies with DBE[8] and SBE[9] demonstrating that after modifying the insertion technique to delay balloon inflation until beyond the ligament of Treitz, the incidence of pancreatitis was very low; 0.7% and 0% for DBE and SBE respectively. However, hyperamylasemia remained relatively common, 17% and 16% for DBE and SBE respectively, although much less so compared to earlier reports.[12, 13] It is unclear if this persistent hyperamylasemia results from injury to the pancreas or if it is caused by other factors, such as local strain or mucosal injury to the small bowel itself.

In this current study, 20% of patients developed hyperamylasemia after proximal spiral enteroscopy, with no patients developing suggestive abdominal pain symptoms and no cases of pancreatitis. Interestingly, the development of hyperamylasemia was not associated with the duration of the procedure as has been suggested by previous DBE studies.[8, 13]. However, the development of hyperamylasemia was significantly associated with Peutz-Jeghers syndrome and with propofol sedation. Since propofol was specifically selected for cases anticipated to be more technically challenging and since Peutz-Jeghers patients each underwent multiple polypectomies (mean 6 polyps per patient), it is interesting to speculate that the development of hyperamylasemia may be more closely linked to *difficult* procedures, which may not necessarily be longer than other cases but may involve more strain on the pancreas or on the small bowel itself.

The present study has several limitations, chief among them its small sample size. We observed a high frequency of hyperamylasemia without associated pancreatitis, but the sample was insufficient to capture these events. Indeed, only multicenter registry data are likely capable of identifying complications as infrequent as pancreatitis. In fact, a large, multicenter registry exists that has reported in abstract form the early experience with spiral enteroscopy, and found no cases of pancreatitis after 1750 spiral procedures.[15] While amylase levels were not reported, the absence of pancreatitis after such a considerable number of procedures implies that the risk is low with spiral enteroscopy, and suggests that the hyperamylasemia observed in our study is not necessarily a harbinger of pancreatitis. A second notable limitation is our lack of measurement

of serum lipase or fractionation of pancreatic and salivary amylase isoenzymes, which may have been useful for differentiating the origin of the elevated amylase. Even though other series examining DBE and hyperamylasemia have shown a strong correlation between serum amylase and lipase measurements,[12, 13] it is regrettable that these were not measured in our study to provide more definitive evidence regarding the source of hyperamylasemia.

Nevertheless, the findings of this study begin to shed more light on the etiology of hyperamylasemia observed after deep enteroscopy. Since the spiral method does not involve the inflation of balloons nor the same degree of stretching of the small bowel with repetitive insertion and shortening of the endoscope and overtube, a number of previously considered causative theories seem less likely given the persistent observation of hyperamylasemia after spiral enteroscopy. In particular, duodenal hypertension from balloon inflation,[16] mechanical strain on the pancreas from repetitive stretching of the endoscope and overtube,[17-19] irritation of the pancreatic sphincter from the inflation of the overtube balloon or compression of the sphincter from the back-and-forth movements of the overtube[20] seem much less likely. However, the suggestion of mechanical strain on the pancreas from the profound straightening of the duodenum at the ligament of Treitz,[11] as well as the ischemic vascular injury theory due to compression or stretching of the peri-pancreatic vessels[18, 20] remain. In addition, it is still possible that overtube-induced strain on the small bowel itself is responsible for the hyperamylasemia.[21]

In summary, this study is the first to report the incidence of hyperamylasemia after proximal spiral enteroscopy, being a frequent finding occurring after one-in-five procedures despite no cases of pancreatitis. Thus, we hypothesize that while DBE can clearly cause pancreatitis, patients who develop elevated amylase levels after deep enteroscopy do not necessarily have injury to the pancreas or elevated risk for pancreatitis. In fact, patients with significant abdominal pain after enteroscopy, even in the context of an elevated amylase, should first be evaluated for other, possibly more serious complications such as intestinal perforation before considering pancreatitis, particularly in light of reports of perforations resulting from spiral enteroscopy,[15, 22] and the growing realization that pancreatitis is an unlikely event for which hyperamylasemia may be a non-specific finding.

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Part Four

Summary, general discussion and closing remarks

Chapter 10

Summary and conclusions

Samenvatting en conclusies

General discussion and future perspectives

Summary and conclusions

Diagnostic and therapeutic endoscopic procedures of the small-bowel have for a long time been a great challenge to gastroenterologists. Especially the anatomy of the small intestine in combination with the lack of adequate, non-invasive, diagnostic tools, made it an almost 'no-go' zone. Only in selected cases push enteroscopy and intraoperative enteroscopy were performed. Push enteroscopy has both diagnostic and therapeutic capabilities, but typically only examines a limited part of the proximal small bowel. Intraoperative enteroscopy permits examination of the entire small bowel and therapeutic interventions, but is much more invasive. The need for endoscopic access to improve diagnosis and treatment of small bowel disease has led to the development of novel endoscopic technologies.

In 2000 the diagnostic and non-invasive video capsule endoscopy was introduced, followed by the more invasive double-balloon enteroscopy system in 2001, the latter combining diagnostic and therapeutic capabilities. The following years, single balloon enteroscopy and spiral enteroscopy were introduced as alternatives for double balloon enteroscopy, with in theory, comparable diagnostic and therapeutic capabilities. Complete enteroscopy of the small bowel is now in reach: 'easy' and much less invasive, and can be performed world wide in any endoscopy unit.

This thesis focuses on two issues:

1) the diagnostic and therapeutic feasibility of the different types of device-assisted enteroscopy (DAE) in daily endoscopy practice, and
2) the clinical safety of the different types of device assisted enteroscopes (DBE, SBE and SE), especially focusing on one of the major complications, being acute pancreatitis.

In **Chapter 1** via a short introduction, the aims and the outline of this thesis are presented. In **Chapter 2** small bowel diagnostics are reviewed. We showed the different options and indications for modern radiological and endoscopic diagnostic methods for visualization of the small bowel. We concluded that capsule endoscopy is generally accepted as the first choice investigation of obscure gastrointestinal bleeding, the latter being the most common indication for small bowel imaging and / or endoscopy. We also try to provide in a clinical rationale for the use of these different diagnostic options in less established, newly emerging, indications for small bowel evaluation. The therapeutic benefit of DAE has evidently been shown in patients with Crohn's disease related small bowel strictures and Peutz-Jeghers syndrome related small bowel polyps.

The first part of this thesis consists of 4 studies, which focus on the diagnostic and therapeutic options of different device-assisted enteroscopy modalities. In **Chapter 3** we presented the

results of randomized international multicenter trial comparing two balloon-assisted enteroscopy systems: the DBE vs. SBE system. In theory, one might expect that DBE, due to a more pronounced grip on the small bowel by the second balloon, would have performed superior with regard to small bowel visualization rate and insertion depth, as compared to the SBE technique. Up to the present, there are only three randomized controlled trials comparing both balloon-assisted enteroscopy techniques. May et al. and Takano et al. saw advantages of DBE referring complete small bowel visualization rates but not with regard to the diagnostic yield [1,2]. The results of our study are in line with the recently published study by Efthymiou et al [3]. There was no statistical difference with respect to oral and anal insertion depths comparing both techniques. The diagnostic yield rates presented were equal to earlier balloon-assisted enteroscopy reports. First limitation of this study is that it was initially designed as a non-inferiority study, however, after an interim analysis, the number of patients needed to demonstrate equivalence between SBE and DBE was too large and thus, the design was modified to do a comparative study. As expected, with regard to complete visualization, we could not show non-inferiority; whether SBE is inferior, equivalent or even superior compared with DBE remains an open question. Second limitation was the relatively low percentage of complete small bowel visualization in our study with the two techniques, however this seems to be comparable to the majority of other Western studies performed in larger patients groups (> 40 patients included), which have shown percentages of complete bowel visualization varying between 0 and 16% [4-8]. Only two other larger Western studies showed higher small bowel visualization rates of 42 and 66% [1, 9]. Despite these limitations, our study suggests that SBE and DBE can achieve comparable diagnostic yields, therapeutic yields and insertion depths. Therefore we conclude that both enteroscopy techniques – DBE ànd SBE – seem to be equally suitable in daily clinical practice. The method of choice should be based on availability and physicians' experience with the technique(s). Future randomized controlled trials with larger numbers of patients can be considered to characterize the relative efficacy of SBE in comparison with DBE, to determine if they can be considered equivalent tests, and to identify the clinical scenarios in which each method may be optimally used.

Crohn's disease (CD) is characterised by potential involvement of any part of the gastrointestinal tract. Especially the small bowel is often part of the intraluminal activity of this disease: in 40% of CD patients the small bowel is involved. Detection of small bowel involvement of CD is important, considering the fact that this is one of the predictors of a more disabling course of the disease [10]. There are several reasons stressing the importance of prognostic factors: (1) recent available drugs, namely anti-tumour necrosis factor (TNF), having the potential of inducting mucosal healing and prolonged clinical remission; (2) mucosal healing has been considered a therapeutic goal; and (3) early therapeutic interventions are considered to be of benefit of the patient, by delivering an overall better clinical outcome. CE is useful in detecting small bowel

lesions, particularly superficial mucosal lesions [11,12]. Although CE is patient-friendly, in CD patients with suspected SB disease activity its use might be hampered due to capsule retention in up to 7% of the patients. In addition, 30% of patients were excluded from these studies because of suspected stenotic SB lesions during screening [13-15]. DBE is an invasive procedure, however it offers the possibility to take biopsies for pathological examinations and to carry out therapeutic interventions (i.e. in cases of strictures) [7,16]. In **Chapter 4** we showed the results of a prospective study evaluating the feasibility and safety of DBE in patients with known in Crohn's disease (CD) and persistent symptoms despite a normal colonoscopy for detecting small bowel (SB) lesions. Secondly, the clinical impact of therapy adjusted for abnormalities found during DBE was evaluated. To our knowledge, this is the first larger prospective study using DBE as a diagnostic tool for SB lesions in CD patients and the first to show the clinical impact of treatment for these findings. Active small bowel CD was found in 70% of the cases. The therapy was adjusted in 74% of these cases, which led to a clinical remission in most of the patients (88%). A limitation of the current study is that only patients in whom SB activity was suspected were included. The incidence of SB lesions may also be high in CD patients without complaints and therefore clinically not suspected for SB activity. This might be interesting to know, considering that SB involvement is a prognostic factor of disabling course of disease. Early therapeutic interventions in these patients might be followed by a better outcome. Future prospective studies are required to answer the question if early step-up treatment in patients with SB involvement and without complaints has a better outcome. Despite this limitation, this study clearly demonstrates that DBE is of additional value in CD patients with suspected SB activity and no distal disease activity. DBE seems feasible and safe for assessing SB disease activity in these patients. Furthermore, a clinical and enteroscopic improvement was seen in patients with solitary SB lesions, which were treated with step-up medical therapy.

The major advantages of DAE over CE are its excellent visualization of the small bowel, the opportunity to perform therapeutic interventions, and to perform biopsies for histopathological evaluation [17]. In **Chapter 5** we showed in a large retrospective study, the results concerning the diagnostic yield of biopsy sampling and histological evaluation during balloon assisted enteroscopy (BAE, either DBE or SBE). In 36% of the patients, histological findings were compatible with abnormal endoscopy findings. In 29% of the patients the endoscopy showed discrepancy with histopathology. In 73% of the patients with small bowel tumours the diagnosis was confirmed with histopathology. In only 3% of the patients with normal endoscopic findings, histology showed abnormal findings. This latter result is not surprising knowing that routine duodenal biopsies during gastroduodenoscopy in patients with normal endoscopic findings are also very low [18]. One of the limitations of our study was that it was retrospective in desgin, and therefore biopsies were not performed in all patients. Secondly the biopsy strategy in patients who had histopathological evaluation was in a large portion of patients 'at random': biopsies

were not taken following a strict prospective study protocol. These latter two facts might lead to selection bias. Nevertheless we can conclude in our study with large number of patients, that the additional value of histopathological evaluation in patients with normal enteroscopic findings is very low and in patients with small bowel tumours is high. Therefore we suggest that biopsies should be obtained in patients with abnormal findings during DAE, and not in a routine fashion in patients with normal endoscopic findings during DAE. Future prospective, multicenter studies or larger studies with standard small bowel biopsy protocols during BAE procedures are needed to confirm these findings.

The major advantages of SBE over traditional push enteroscopy (PE) include deeper and more controlled small-bowel intubation. Direct percutaneous endoscopic jejunostomy (DPEJ) tube placement is an intervention with conventional push enteroscopy in patients who require prolonged enteral feeding but are not suitable candidates for percutaneous endoscopic gastrostomy (PEG) or when attempted PEG placement fails [19]. The reported overall success rate of DPEJ placement with conventional push enteroscopy was relatively low [20]. The inability to intubate a suitable jejunal loop accounted for 95% of the failed procedures [20]. Single-balloon enteroscopy (SBE) may increase the likelihood of finding a suitable site for percutaneous endoscopic jejunostomy (PEJ) placement by allowing deeper access into the proximal small intestine. In **Chapter 6** we presented the efficacy and safety of SBE-assisted placement of DPEJ. In our study the DPEJ placement was successful in 92% of the procedures. In the current study, one case with a minor complication was observed. The results of our study were similar to those achieved in the small DBE case series, in which successful placement was achieved in 90% of patients [21]. We appreciate the limitations of this rather small series, single institution, patient cohort. We concluded that SBE-assisted DPEJ placement appears effective and safe in patients requiring long-term jejunal access for feeding. Nonetheless, we advise centers which have access to both systems (SBE and DBE-system) to use the SBE as it is much easier to prepare. Further comparative studies are now required to confirm the potential advantages of SBE over and above the original PE- or DBE-assisted PEJ technique.

The second part of this thesis consists of 3 studies focussing on the safety of device assisted enteroscopy systems (SBE, DBE and SE) and in particular focusing on the occurrence of hyperamylasemia and pancreatitis.

In **Chapter 7** we showed the results of a prospective study that assessed the safety of SBE procedures with particular focus on the occurrence of hyperamylasemia and pancreatitis. The incidence of post-SBE hyperamylasemia was 16%, but none of the cases had clinical symptoms suggestive for acute pancreatitis. This finding is in line with the reported literature that to date only one case of SBE-related acute pancreatitis has been reported, suggesting that this this risk is quite low [22]. In theory, this possibly lower incidence of acute pancreatitis after SBE might be explained by a lower intraduodenal pressure with the technique that uses only one

balloon instead of two balloons with DBE that might result in higher intraduodenol pressure. This finding supports also our hypothesis of development of acute pancreatitis after proximal DBE, that inflation of two balloons in duodenum results in an increase of intraluminal pressure, leading to reflux of duodenal fluids into the pancreatic duct [23]. On the other hand, it is equally possible that hyperamylasemia reflects subclinical pancreatitis, and so ongoing alertness remains necessary regarding the possibility of this serious complication during or after SBE procedures. The major limitation of this study is its lack of an active comparison with other device-assisted modalities. Nevertheless we conclude that SBE appears safe for diagnostic evaluation and endoscopic therapy of the small bowel. The observed incidence of acute pancreatitis seems to be lower than that associated with the DBE technique. Prospective large randomized trials comparing DAE-systems are required that supports our conclusion.

In **Chapter 8** we determined the risk factors for hyperamylasemia and we measured the incidence of hyperamylasemia, and pancreatitis, after proximal DBE procedures performed with an adjusted insertion technique. We hypothesized in the first reported cases of acute pancreatitis after proximal DBE, that inflation of two balloons in duodenum results in an increase of intraluminal pressure, leading to reflux of duodenal fluids into the pancreatic duct [23]. Therefore we have adjusted our insertion technique by inflating the overtube balloon only after passing the ligament of Treitz.The incidences of post-DBE hyperamylasemia and pancreatitis, with this adjusted insertion technique, were low 17% and 1%, respectively, comparing with other prospective studies [24,25]. We concluded that this different finding might be related to the modification in the insertion technique, but nevertheless we have to be careful with our conclusion about the impact of the modification of the insertion technique, since the serum amylase levels were only measured after the change in the insertion technique had been implemented. A randomized controlled trial would have given more insight, but this was considered to be unethical because of the theoretical relation to the development of acute pancreatitis. Two recent studies performed in animal models, one in pigs and one with dogs, have evaluated the effect of DBE procedure on pancreatic injury [26,27]. In the study conducted with the pigs, the balloons were only inflated after passing the descending part of the duodenum to avoid 'compression' of the minor duodenal papilla. Unfortunately, only the adjusted insertion technique was used, and no comparison could be made with 'old'insertion technique in regard to pancreatic injury [26]. Prospective randomized controlled trial using an animal model, comparing these adjusted insertion technique with inflating balloons in descending part of duodenum, might help us in verifying our hypotheses of development of pancreatitis after DBE.

The final study included in **Chapter 9** examined the risk of acute pancreatitis and hyperamylasemia following anterograde spiral enteroscopy. While no cases of acute pancreatitis were observed, the incidence of hyperamylasemia remained also rather high (20%) being comparable with hyperamylasemia incidence following SBE procedures. This mirrors the

increasingly common observation that significant elevations of serum amylase occur with many forms of overtube-assisted small bowel endoscopy without associated pancreatitis, raising the possibility that hyperamylasemia in the context of small bowel endoscopy may not necessarily represent pancreatic injury. Therefore reducing the overall risk for acute pancreatitis after small bowel endoscopy, might be due to using the right technique of DAE. The relation between the occurrence of hyperamylasemia and acute pancreatitis still remains unclear and needs further investigation.

Samenvatting

Tot aan het begin van de 21e eeuw waren diagnostische en therapeutische endoscopische procedures van de dunne darm een grote uitdaging voor MDL-artsen. De anatomie van de dunne darm, in combinatie met het ontbreken van adequate, niet-invasieve, diagnostische hulpmiddelen, maakte het bijna een 'no-go' zone. Alleen in uitzonderlijke gevallen werden push enteroscopie en intra-operatieve enteroscopie uitgevoerd. Push enteroscopie heeft zowel diagnostische en therapeutische mogelijkheden, echter slechts een beperkt deel van de proximale dunne darm kan hiermee onderzocht worden. Intra-operatieve enteroscopie maakt onderzoek van de gehele dunne darm mogelijk, maar heeft als belangrijke nadeel dat het een zeer invasieve methode is. De behoefte aan eenvoudige endoscopische toegang van de dunne darm, ter verbetering van de diagnose en behandeling van dit deel van het maag-darm kanaal, heeft geleid tot de ontwikkeling van nieuwe technologieën.

In 2000 werd de diagnostische en niet-invasieve video capsule endoscopie geïntroduceerd, gevolgd door de invasieve dubbel-ballon enteroscopie in 2001, waarvan de laatste combinatie bezit van diagnostische- en therapeutische mogelijkheden. Daaropvolgende jaren werden single-ballon enteroscopie en spiraal-enteroscopie geïntroduceerd als mogelijk alternatief voor de dubbel-ballon enteroscopie, met in theorie vergelijkbare diagnostische en therapeutische eigenschappen. Complete enteroscopie van de dunne darm was nu binnen handbereik: 'makkelijk' en veel minder invasief en zou in elke endoscopie afdeling wereldwijd uitgevoerd kunnen worden.

Dit proefschrift heeft de focus op twee thema's:

1) de diagnostische en therapeutische mogelijkheden van de verschillende types van moderne enteroscopie in de dagelijkse endoscopie praktijk en,
2) de veiligheid van de verschillende types moderne enteroscopen (DBE, SBE en SE), met aandacht vooral gericht op een van de belangrijkste complicaties, zijnde acute pancreatitis.

In de introductie van dit proefschrift worden de doelstellingen en de hoofdlijnen van dit proefschrif beschreven. In **hoofdstuk 2** wordt een review gepresenteerd betreffend de dunne darm diagnostiek. We toonden hierbij de mogelijkheden en indicaties van verschillende moderne radiologische en endoscopische methods voor de visualisatie van de dunne darm. We concludeerden onder andere dat de capsule endoscopie algemeen aanvaard is als eerste keuze onderzoek bij patiënten met obscure gastro-intestinale bloedingen, welke een meest voorkomende indicatie is voor de dunne darm diagnostiek. We proberen ook bij deze review informatie te verstrekken over het gebruik van deze verschillende diagnostische middelen bij minder bekende indicaties. Het therapeutische voordeel van moderne enteroscopie is duidelijk

aangetoond bij patiënten met de ziekte van Crohn met dunne darm stricturen en Peutz-Jeghers syndroom gerelateerde dunne darm poliepen.

Het eerste deel van dit proefschrift bestaat uit 4 studies die zich richten op de diagnostische en therapeutische mogelijkheden van de verschillende modern enteroscopie systemen. In **hoofdstuk 3** worden de resultaten van gerandomiseerde internationale multicenter studie gepresenteerd waarin twee-ballon geassisteerde enteroscopie systemen vergeleken worden: DBE versus SBE. In theorie zou men verwachten dat DBE, door een meer uitgesproken grip van de tweede ballon op de dunne darm, superieur zou zijn met betrekking tot volledige darm visualisatie en insertie-diepte, vergeleken met de SBE techniek. Tot op heden zijn er drie gerandomiseerde gecontroleerde studies die ballon geassisteerde enteroscopie technieken vergeleken. May et al. en Takano et al. toonden de voordelen van DBE betreft complete dunne darm visualisatie echter niet wat betreft de diagnostische opbrengst [1,2]. De resultaten van onze studie zijn in lijn met het onlangs gepubliceerde studie van Efthymiou et al. [3]. Er was geen statistisch verschil met betrekking tot orale en anale insertie dieptes bij vergelijking van beide technieken. De diagnostische opbrengst die we zagen was vergelijkbaar met eerder verschenen ballon geassisteerde enteroscopie studies. Belangrijke beperking van deze studie is dat het oorspronkelijk ontworpen was als een niet-inferioriteitsstudie echter, na een tussentijdse analyse, bleek het dat aantal patiënten om equivalentie tussen SBE en DBE aan te tonen, te groot was en derhalve werd het ontwerp van onze studie aangepast tot een vergelijkende studie. Wat betreft de volledige visualisatie van de dunne darm konden we geen non-inferioriteit aantonen; of SBE minderwaardig, gelijkwaardig of zelfs superieur is in vergelijking met DBE blijft een open vraag. Tweede beperking is de relatief lage percentage volledige dunne darm visualisatie in onze studie met beide technieken, echter dit lijkt vergelijkbaar met de meeste andere Westerse studies met grotere patiëntengroepen (> 40 patiënten), waarbij volledige dunne darm visualisatie varieerde tussen 0 en 16% [4-8]. Slechts bij twee grote westerse studies waren er hogere percentages van volledige dunne darm visualisatie (42 en 66%) [1, 9]. Ondanks deze beperkingen suggereert onze studie dat SBE en DBE vergelijkbare insertie-dieptes, diagnostische- en therapeutische opbrengst hebben. Beide enteroscopie technieken – DBE èn SBE - lijken even geschikt te zijn in de dagelijks praktijk. De keuze van het techniek moet worden gemaakt op basis van de beschikbaarheid en de ervaring van de arts met een bepaalde enteroscopie techniek. Grote gerandomiseerde en gecontroleerde studies die SBE vergelijken met DBE zijn vereist, voor het beantwoorden van de vraag of ze als equivalente tests beschouwd kunnen worden en voor het bepalen van de klinische setting waarin elke werkwijze optimaal gebruikt kan worden.

De ziekte van Crohn (CD) wordt gekenmerkt door de potentiële betrokkenheid van elk deel van het maagdarmkanaal. Vooral de dunne darm is vaak onderdeel van de intraluminale activiteit van deze ziekte: in 40% van de CD is de dunne darm betrokken. Detectie van dunne darm betrokkenheid van CD is belangrijk aangezien deze een van de voorspellers is van een invaliderende

beloop van de ziekte [10]. Er zijn verschillende redenen die de belang van de prognostische factoren benadrukken: (1) recente beschikbare geneesmiddelen, met name anti-tumor necrosis factor (TNF), hebben het potentieel van mucosale genezing en langdurige klinische remissie; (2) mucosale genezing wordt beschouwd als een therapeutisch doel; en (3) vroege therapeutische interventies worden in voordeel van de patiënt beschouwd, aangezien deze in het algemeen tot een betere klinische resultaat leidt. CE is nuttig bij de detectie van de dunne darm laesies, met name van de oppervlakkige mucosa laesies [11,12]. Hoewel CE patiëntvriendelijk is, kan gebruik hiervan bij patiënten met CD beperkt worden wegens risico op capsule retentie (tot 7% van de patiënten). Daarnaast werden bij deze studies belangrijke deel (30%) van de patiënten uitgesloten wegens verdachte stenotische laesies [13-15]. Hoewel DBE een invasieve procedure is, biedt deze toch de mogelijkheid van therapeutische interventies (bijvoorbeeld dilatatie van stenose) en afname van biopten voor de pathologie [7,16]. In **hoofdstuk 4** presenteren we de resultaten van een prospectieve studie waarbij de bruikbaarheid en de veiligheid van DBE geëvalueerd werd voor detectie van dunne darm laesies bij patiënten met de ziekte van Crohn en klachten hebben, ondanks een colonoscopie zonder afwijkingen. Ten tweede werd de klinische consequentie van de behandeling geëvalueerd die aangepast werd naar aanleiding van de afwijkingen welke gevonden werden tijdens de DBE. Volgens ons is dit de eerste grote prospectieve studie die DBE als diagnostisch onderzoek toepast voor het aantonen van dunne darm laesies bij patiënten met CD en de eerste die de klinische consequentie van aanpassing van de behandeling naar aanleiding van de laesies evalueert. Actieve dunne darm laesies werden gevonden in 70% van de patiënten. De therapie werd aangepast bij 74% van deze patiënten die leidde tot een klinische remissie in meeste van deze gevallen (88%). Een belangrijke beperking van deze studie is dat alleen patiënten bij wie dunne darm activiteit vermoed werd, geïncludeerd zijn. De incidentie van dunne darm laesies kunnen ook hoog zijn bij patiënten zonder klachten en dus klinisch niet verdacht zijn voor dunne darm activiteit. Deze bevinding zou interessant geweest zijn om te weten, aangezien het feit dat dunne darm betrokkenheid een belangrijke prognostische factor is voor het invaliderende beloop van de ziekte. Vroege therapeutische interventies zal juist ook bij deze patiënten wellicht op termijn ook van belang zijn voor het onderhoud van klinische remissie. Prospectieve studies zijn nodig om de vraag, of een vroege step-up behandeling bij patiënten zonder klachten met dunne darm betrokkenheid tot een beter resultaat leidt op termijn, te kunnen beantwoorden. Ondanks deze beperking, toont deze studie duidelijk aan dat DBE van toegevoegde waarde is bij patiënten met CD en verdenking op dunne darm-activiteit. DBE lijkt bruikbaar en veilig voor de beoordeling van dunne darm ziekte-activiteit bij patiënten met CD. Bovendien werd er klinische en endoscopische verbetering getoond bij patiënten met solitaire dunne darm leasies, die behandeld werden met een step-up therapie.

De belangrijkste voordelen van modern enteroscopie ten opzichte van CE zijn onder andere de uitstekende beeldkwaliteit, de mogelijkheid tot uitvoeren van een therapeutische behandeling

en afname van biopten voor histopathologische beoordeling [17]. In **hoofdstuk 5** hebben we in een grote retrospectieve studie, de resultaten met betrekking tot de diagnostische opbrengst van biopties voor pathologie geëvalueerd, die tijdens ballon geassisteerde enteroscopie (BAE, ofwel DBE of SBE) verricht zijn. Bij 36% van de patiënten kwamen de histologische bevindingen overeen met afwijkende endoscopische bevindingen. Bij 29% van de patiënten vertoonden de endoscopie beelden discrepantie met de histopathologie. Bij 73% van de patiënten met dunne darm tumoren werd de diagnose bevestigd met behulp van histopathologie. Biopten die afgenomen werden bij normale endoscopische bevindingen toonden slechts in 3%van deze patiënten afwijkende histopathologie. Dit laatste resultaat is niet verwonderlijk wetende dat random duodenum biopten tijdens gastroduodenoscopie bij patiënten met normale endoscopische bevindingen ook weinig bijdragend zijn [18]. Een van de beperkingen van onze studie was dat deze retrospectief was opgezet en dat we hierdoor niet bij elke patiënt biopties verricht hebben. Tweede bepereking is dat de biopties niet afgenomen zijn volgens een strict prospectief studie protocol en dat deze 'ad random' afgenomen zijn op basis van de kliniek of endoscopische bevindingen. Deze laatste twee feiten zou tot tot een selectie bias geleid kunnen hebben. Desalniettemin kunnen we concluderen we dat de toegevoegde waarde van histopathologie bij patiënten met normale endoscopische bevindingen zeer laag is en dat bij patiënten met dunne darm tumoren hoog is. Daarom stellen we voor dat biopten best afgenomen worden bij patiënten met abnormale bevindingen tijdens moderne enteroscopie, en dat deze niet routinematig afgenomen worden bij patiënten met normale endoscopische bevindingen. Prospectieve multicenter of uitgebreidere studies met standaard dunne darm bioptie protocollen zijn nodig om deze bevindingen te bevestigen.

De belangrijkste voordelen van SBE ten opzichte van traditionele push enteroscopie (PE) is de mogelijkheid van diepe en meer gecontroleerde introductie in de dunne darm. Plaatsing van een directe percutane endoscopische jejunostomie (DPEJ) sonde wordt verricht met een conventionele push enteroscopie bij patiënten die langdurig sondevoeding nodig hebben en niet geschikt zijn voor percutane endoscopische gastrostomie (PEG) [19]. De success percentage van DPEJ plaatsing met conventionele push enteroscopie is relatief laag [20]. De beperking van een diepe introductie in een geschikte jejunale lis was verantwoordelijk voor het falen van 95% van deze procedures [20]. Single-ballon enteroscopie heeft de mogelijkheid tot een diepe introductie in de dunne darm waardoor de kans groter is op het vinden van een geschikte jejunale lis voor percutane endoscopische jejunostomie (PEJ) plaatsing. In **hoofdstuk 6** presenteren we de effectiviteit en veiligheid van SBE-geassisteerde plaatsing van een DPEJ gepresenteerd. In deze studie was de DPEJ plaatsing succesvol in 92% van de procedures. Er was een geval met een milde complicatie. Deze resultaten waren vergelijkbaar met de eerder gepubliceerde kleine DBE case series, waarbij succesvolle plaatsing bij 90% van de patiënten werd bewerkstelligd [21]. Ondanks de beperking dat we hier te maken hebben met een kleine studie, kunnen we toch

concluderen dat SBE-geassisteerde DPEJ plaatsing effectief en veilig lijkt te zijn bij patiënten die langdurig enterale voeding nodig hebben. We adviseren centra die beschikken over beide systemen om de SBE te gebruiken i.p.v. DBE aangezien deze veel eenvoudiger te voorbereiden is. Vergelijkende DPEJ-studies zijn nu vereist om de potentiële voordelen van SBE ten opzichte van de conventionele PE of DBE te bevestigen.

Het tweede deel van dit proefschrift bestaat uit 3 studies die zich richten op de veiligheid van het moderne enteroscopie systemen (SBE, DBE en SE) en in het bijzonder aandacht voor de incidentie van hyperamylasemia en pancreatitis.

In **hoofdstuk 7** worden de resultaten van een prospectieve studie gepresenteerd die de veiligheid van SBE procedures evalueert en in het bijzonder aandacht voor de incidentie van hyperamylasemie en pancreatitis. De incidentie van post-SBE hyperamylasemie was 16%, echter geen van de patiënten had klachten suggestief voor acute pancreatitis. Deze bevinding stemt overeen met de tot op heden verschenen literatuur waarbij slechts een geval met SBE-gerelateerde acute pancreatitis gerapporteerd is, hetgeen suggereert dat dit risico behoorlijk laag is [22]. In theorie zou deze lagere incidentie van acute pancreatitis na SBE verklaard kunnen worden door een lagere intraduodenale druk met een techniek die slechts een ballon bevat in plaats van twee ballonnen met de DBE techniek. Deze bevinding ondersteunt onze hypothese over de ontwikkeling van acute pancreatitis na proximale DBE, die ontstaat door het opblazen van beide ballonnen in het duodenum welke resulteert in een toename van intraluminale druk en leidt tot reflux van duodenale vloeistoffen naar de ductus pancreaticus [23]. Anderzijds is het ook mogelijk dat de hyperamylasemie een subklinische pancreatitis weerspiegelt, waardoor een voortdurende alertheid noodzakelijk blijft over de mogelijkheid van deze ernstige complicatie tijdens of na SBE procedures. De belangrijkste beperking van dit onderzoek is het gebrek aan een actieve vergelijking met andere moderne enteroscopie modaliteiten. Ondanks deze beperking kunnen we concluderen dat SBE veilig lijkt voor diagnostische evaluatie en endoscopische behandeling van de dunne darm. De incidentie van acute pancreatitis lijkt lager te zijn dan die van de DBE techniek. Prospectieve grote gerandomiseerde studies, met verschillende moderne enteroscopie systemen, zijn vereist die onze conclusie kunnen ondersteunen.

In **hoofdstuk 8** bepaalden we de risicofactoren voor hyperamylasemia en de incidentie van hyperamylasemie en pancreatitis, na proximale DBE procedures die uitgevoerd zijn met een aangepaste insertietechniek. De hypothese over de ontwikkeling van acute pancreatitis na proximale DBE bij eerste gevallen was dat het opblazen van twee ballonnen resulteert in een toename van intraluminale druk resulteert welke uiteindelijk leidt tot reflux van duodenale vloeistoffen naar de ductus pancreaticus [23]. Hierdoor hebben we onze insertie-techniek aangepast en blazen we de ballon van de overtube na passage van het ligament van Treitz. De incidentie van post-DBE hyperamylasemie en pancreatitis, met dit aangepaste insertie-techniek was laag 17% en 1%, respectievelijk, vergeleken met andere prospectieve studies [24,25].

Wij concludeerden dat deze lagere incidenties mogelijk gerelateerd zijn aan de wijziging van de insertie-techniek. Deze conclusie moet met voorzichtigheid worden getrokken aangezien de serum-amylase waardes gemeten zijn nadat de de insertie-techniek gewijzigd was. Een gerandomiseerd studie met opblazen van ballonnen in het tweede deel van duodenum zou deze hypothese kunnen bevestigen of verwerpen. Deze studie zal ethisch niet uit te voeren zijn aangezien er een theoretische mogelijkheid bestaat van ontwikkeling van acute pancreatitis. Wij zouden het interessant gevonden hebben als er bij de recent gepubliceerde DBE studies met varkens en honden, ook het effect van het opblazen van ballonnen in tweede deel van duodenum geëvalueerd was [26,27]. In deze studie met de varkens werd de effect van DBE op de pancreas geëvalueerd en werden de ballonnen voorbij tweede deel van het duodenum opgeblazen [26]. Prospectieve gerandomiseerde gecontroleerde studie met behulp van een diermodel, waarbij het aangepast insertie techniek vergeleken wordt met het opblazen van ballonnen in tweede deel van het duodenum zou ons kunnen helpen bij het verifiëren van onze hypotheses over de ontwikkeling van pancreatitis na DBE.

De laatste studie die gepresenteerd wordt in **hoofdstuk 9** onderzocht het risico op acute pancreatitis en hyperamylasemia na anterograde spiraal enteroscopie. Hoewel er geen gevallen met acute pancreatitis was, was de incidentie van hyperamylasemie eveneens vrij hoog (20%) en vergelijkbaar met hyperamylasemie incidentie na een SBE procedures. Deze bevindingen weerspiegelen wederom de waarneming van een verhoogde serum-amylase waarde met een overtube geassisteerde dunne darm endoscopie techniek zonder dat er aanwijzingen zijn voor een pancreatitis, welke suggereert dat hyperamylasemie in het kader van de dunne darm endoscopie niet noodzakelijkerwijs een alvleesklier schade betekent. Het verminderen van het totale risico op acute pancreatitis na dunne darm endoscopie, zou mogelijk zijn door het gebruik van de juiste moderne enteroscopie techniek. De relatie tussen het optreden van hyperamylasemia en acute pancreatitis blijft nog steeds onduidelijk en vraagt verder onderzoek.

General discussion and future perspectives

Until the end of the 20th century the small bowel was considered to be the "black box" for gastroenterologists. In this thesis the current diagnostic and therapeutic options, and safety, of modern device-assisted enteroscopy for endoscopic access of the small bowel are presented. The findings from the included studies provide useful information about feasibility and safety of DAE in evaluation of the small bowel. In these included studies comparing these different enteroscopy techniques, most comparative parameters (depth of insertion, complications, diagnostic yield, and therapeutic yield) were comparable among DBE, SBE, and SE. With regard to complete visualization, we could not show noninferiority; whether SBE is inferior, equivalent or even superior compared with DBE remains an open question. According to other presented studies the rate of complete enteroscopy seems to be superior for DBE, compared to SBE and SE [28]. Because these results do not indicate an increase in diagnostic or therapeutic yield, the clinical impact of complete enteroscopy remains controversial. To our opinion the diagnostic yield is the most important parameter and if the first enteroscopy attempt results in a diagnosis, it may be reasonable to withdraw the enteroscope from this end point of the insertion. Therefore, complete small bowel visualization should only be preserved for patients with a need for examination of the entire small intestine. Future prospective studies are needed to answer the question in which patients complete bowel visualization is required.

The choice of DAE method should be based on availability, physicians' experience and clinical implications. Therefore we advise in centers who access to both systems -SBE and DBE- to use the SBE for diagnostic- or therapeutic procedures in patients with high suspicion of a significant lesion in "proximal" part of small bowel, as it is easier to use respect to DBE, avoiding attaching the enteroscope balloon to the distal tip of the scope encountered and the requirement of inflating and deflating two balloons. Future studies comparing DBE and SBE techniques should include total of preparation and procedure time, which are especially relevant for the daily clinical routine.

It is our opinion that the measurement of insertion depths is highly dependent on the endoscopist's subjective evaluation, and some authors consider that it is easy to overestimate the insertion depth and record exaggerated data [29]. The method used for estimation of DBE (first described by May et al. [30]) insertion depth has been validated in post-mortem pig intestines with a mean deviation of 10%. This measurement of insertion depth is recently also validated in the in vivo porcine model during progression and withdrawal [31]. Until now there are no studies that evaluated the validity of the insertion depths of SBE and SE. Complete visualization of the small bowel is an objective parameter, that seems to be superior for DBE comparing to SBE or SE [28]. Knowing all these facts (higher rate of complete visualization in favor of DBE, validated measurement methods for DBE and NOT for SBE or SE) we presume that the "real time" insertion

of DBE in the small bowel deeper is comparing to the SBE or SE. Therefore we suggest that the DBE procedure can be reserved for patients with the need for deep insertion of the "distal" part of the small bowel, or for patients who require complete evaluation of the small bowel. We would also advise that in patients with a high clinical suspicion on small bowel pathology, who underwent a negative and / or incomplete SBE or SE, to consider a DBE procedure. Future prospective studies might help us in answering the question if the diagnostic yield increases after repeating the enteroscopy with the DBE in patients with a negative and / or incomplete SBE or SE. Secondly, prospective in vivo animal studies validating insertion methods for SBE and SE are necessary tho answer the ongoing discussion about insertion depths.

This thesis makes clear that future randomized, controlled trials with larger numbers of patients are needed to work out the further subtleties of every single modern enteroscopy method.

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Chapter 11

Dankwoord

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Dankwoord

Het sollicitatiegesprek die ik in Eramus MC in augustus 2005 aanging was bedoeld om direct te solliciteren naar een opleidingsplek tot MDL-arts. Ik werkte in AZ Klina in België als assistent in opleiding tot internist, maar wilde graag een MDL-arts worden en terug naar Nederland. Het gesprek verliep goed en er werd mij ook meteen een opleidingsplek en mogelijkheid tot promotie aangeboden. Eindelijk is het zover, mijn proefschrift is afgerond en weet dat dit werk niet tot stand had kunnen komen zonder de hulp van vele mensen.

Allereerst wil ik daarom mijn co-promotor **Peter Mensink** bedanken voor het feit dat dit boekje er is. Beste Peter in een periode dat ik qua wetenschappelijk onderzoek weinig gemotiveerd was, kwam je bij mij met de mogelijkheid om bij jou te kunnen promoveren over het onderwerp enteroscopieën in de dunne darm. Je had data voor me klaar liggen en ook had je mooie ideeën zodat ik er meteen aan kon beginnen. Met jouw enthousiasme wist je mij altijd te motiveren waardoor ik met plezier dit onderzoek heb verricht. Ik vond het heel prettig dat ik je laagdrempelig kon benaderen bij vragen en dat je tijd voor me maakte wanneer ik die nodig had. Ik wil je eveneens bedanken voor je begeleiding bij het aanleren van verschillende enteroscopie technieken. Ik ben blij dat we nu dicht bij elkaar wonen en kijk uit naar meer contact en samenwerking in de toekomst.

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Alle MDL artsen in het Erasmus MC, in het bijzonder **Rob de Man en Henk van Buuren**. Beste Rob, ik ben je dankbaar dat je me in het begin van mijn opleiding begeleid en gestimuleerd heb bij het uitvoeren van wetenschappelijke onderzoek. Beste Henk, dank voor je hulp en adviezen bij de tot standkoming van directe percutane endoscopische jejunostomie manuscript.

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Alle maten van de Maatschap Interne geneeskunde / MDL van het ZGT en in het bijzonder mijn collega's MDL artsen **Rolf, Ton, Andries en Peter.** Beste collega's dank voor het creëren van een inspirerende werkomgeving en een gezellige werksfeer. Beste **Rolf,** jij was toch wel diegene die meest geïnteersseerd was hoe het met mijn proefschrift verliep en ook diegene die me vaak stimuleerde om dit af te ronden. Ik wil je hiervoor in het bijzonder bedanken.

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Curriculum vitae

De auteur van dit proefschrift werd geboren op 7 juni 1977 te Enschede. Na het behalen van het V.W.O. eindexamen aan het Stedelijk Lyceum in Enschede werd in 1996, ten gevolge van uitloting, gestart met de studie Geneeskunde in Antwerpen. Hier haalde hij in 2000 zijn kandidaats examen met onderscheiding, gevolgd door het arts examen in 2004 met grote onderscheiding. In oktober 2004 tot 2005 werkte hij in 1 jaar in Brasschaat (B) als assistent in opleiding tot internist (opleider dr. J. Teuwen). In 2005 werd hij aangenomen voor de opleiding Maag-, Darm en Leverziekten (Prof dr E.J. Kuipers, Dr R.A. de Man) in Erasmus MC en maakte hij de overstap naar Rotterdam. In november 2005 startte hij aan zijn resterende vooropleiding interne geneeskunde in het het St Franciscus Gasthuis te Rotterdam (drs A. Rietveld). Hierna werkte hij 4 jaar als MDL arts in opleiding in het Erasmus Medisch Centrum te Rotterdam (dr R.A. de Man, opleider). Op 1 november 2010 werd hij geregistreerd als MDL arts. Sinds 1 februari 2011 werkt hij als MDL arts in het ZGT te Almelo en Hengelo. Gedurende de vervolgopleiding tot MDL-arts was er een belangstelling voor de dunne darm diagnostiek met enteroscopieën. Tevens werd onderzoek verricht uitmondend in dit proefschrift (promotor Prof. dr. E.J. Kuipers). Hij is gehuwd met Zehre Yuksel en samen hebben zij twee zonen Ali Haydar en Riza Efe.

List of publications

1. Hyperamylasemia and pancreatitis following spiral enteroscopy. Teshima CW, Aktas H, Kuipers EJ, Mensink PB. Can J Gastroenterol. 2012 Sep;26(9):603-6.
2. Single- versus double-balloon enteroscopy: the evidence base: Comment on Endoscopy essentials, Small-bowel endoscopy.Lenz P, Domagk D, Mensink P, Aktas H, Bretthauer M. Endoscopy. 2012 Aug;44(8):799
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