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Double-balloon enteroscopy: The diagnosis and management of small bowel diseases

İnce barsak hastalıklarının tanı ve tedavisinde çift balon enteroskopi

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Background/aims: *Double-balloon enteroscopy is a novel endoscopic technique developed to investigate small bowel diseases. The aim of this study was to evaluate the diagnostic and therapeutic impact of double-balloon enteroscopy in patients with suspected or documented small bowel disease who were referred to our tertiary center, which was the first to introduce the double-balloon enteroscopy system in Turkey.* ***Methods:*** *This is a single-center prospective study. A total of 216 double-balloon enteroscopy procedures (168 antegrade, 48 retrograde) were done in 188 patients who were referred to our center for suspected small bowel disease. The main outcome measurements were complications, insertion depth and duration, and diagnostic and therapeutic rates.* ***Results:*** *Indications included obscure gastrointestinal system bleeding, iron deficiency anemia, abnormality on radiographic evaluation, abdominal pain, diarrhea, and suspected celiac disease. A diagnosis was established in 130 (69%) patients. The most common pathologic findings included angiodysplasias (29%), ulcerations (16%) and Crohn's disease (9%). Mean time±standard deviation to perform the examination using the antegrade route was 116.4±7.17 min, and the average±standard deviation insertion length was 310.65±90.3 cm (beyond the pylorus). Therapeutic interventions were performed in 66 patients (56 angiodysplasias, 4 ulcers, 4 strictures, and 2 polyps), and the success rate was 97%. No serious complication was observed, although pancreatitis occurred in 6 of 48 (12.5%) patients who were followed up for post-procedure pancreatic enzyme levels.* ***Conclusions:*** *Our prospective analysis suggests that double-balloon enteroscopy is a feasible and useful technique for the diagnosis as well as treatment of small intestinal disorders.*

Key words: Double balloon enteroscopy

Amaç: *Çift balon enteroskopi ince barsak görüntülenmesi için geliştirilen yeni bir tekniktir. Bu çalışmanın amacı ince barsak hastalığı olan veya ince barsak patolojisinden şüphelenilen hastalarda çift balon enteroskopinin tanı ve tedavideki önemini değerlendirmektir.* ***Metod:*** *Bu tek merkezli prospektif bir çalışmadır. Toplam 216 çift balon enteroskopi işlemi (168 antegrad, 48 retrograd) ince barsak patolojisi düşünülen 188 hastaya yapıldı. Komplikasyon, işlem süresi, gidilen mesafe, tanı ve tedavi oranları değerlendirilmiştir.* ***Bulgular:*** *Endikasyonlar obscure gastrointestinal sistem kanaması, demir eksikliği anemisi, radyolojik tetkiklerde anormallik, karın ağrısı, ishal ve çölyak hastalığı idi. 130 (%69) hastaya tanı konuldu. En sık rastlanan patolojik bulgu angiodisplazi (29), ülser (%16) ve Crohn's hastalığıdır (%9). Ortalama işlem süresi antegrad olarak 116.4±7.17 dk, ve ortalama pilordan sonra ilerleme mesafesi 310.65±90.3 cm idi. Tedavi edici girişim 66 hastaya yapıldı (56 angiodisplazi, 4 ülser, 4 striktür, ve 2 polip), %97 başarı sağlandı. Ciddi komplikasyon olmadı, ancak işlem sonrası pankreas enzim takibi yapılan 48 hastanın 6'sında (%12.5) pankreatit gelişti.* ***Sonuç:*** *Çift balon enteroskopi ince barsak hastalıkları tanısında uygulanabilir yararlı bir yöntemdir.*

Anahtar kelimeler: Çift balon enteroskopi

INTRODUCTION

The small bowel remains a partially visible area of the gastrointestinal (GI) tract and often requires intraoperative endoscopy or explorative laparoscopy or laparotomy (1,3). In the last decade, capsule endoscopy (CE) was actually considered the method of choice for starting the diagnostic work-up in patients with small bowel pathology (4-6). However, CE is limited by the fact that biopsies cannot be taken and interventional endoscopic procedures cannot be carried out (7, 8).

Double balloon enteroscopy (DBE), first described by Yamamoto et al. (9) in 2001, is a new endoscopy

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device designed to examine the small bowel. Initial experience reports DBE as a safe and feasible endoscopic technique with an important clinical impact on the diagnosis, treatment and management of small bowel disorders (10-13).

The aim of this study was to prospectively determine the indications and the diagnostic and therapeutic impact of DBE in patients with known or suspected small bowel disorders.

MATERIALS AND METHODS

Patients

Between March 2006 and August 2009, 188 consecutive patients (mean age±SD 53.21±13.99 years, 64 women and 124 men) with suspected small bowel disease referred to Yeditepe University Hospital underwent DBE. Indications included the following: obscure GI system bleeding (OGIB) (80), iron deficiency anemia (42), abnormalities on radiographic evaluation (24) (obstruction, polyp or intestinal wall thickening on computerized tomography [CT] or enteroclysis), abdominal pain (18), diarrhea (16), and suspected celiac disease with negative gastroscopy (8).

All patients had already undergone upper and lower gastrointestinal endoscopy one or more times. Before referral for DBE, radiographic or angiographic evaluation of the GI system or CE had been performed in 138 patients (24 CE, 88 CT, 8 angiographies, 6 radionuclide scanning, and 12 enteroclysis). In the remaining 50 patients, DBE was performed as an adjunctive tool to gastroscopy and colonoscopy. Repeated DBE examinations using the same route in the same patient were not included in the total sum.

The procedure and its risks were explained to all patients, and informed consent was obtained prior to the procedure, including consent to the endoscopic treatment. The data collected included age, sex, insertion length, procedure duration, indication of DBE, and diagnosis.

The choice of sedation was made at the discretion of the anesthesiologist. Conscious sedation with midazolam and meperidine, monitored anesthesia with propofol or general anesthesia was preferred according to the patients' cardiovascular risk status.

The Double-Balloon Technique

Double balloon endoscopy (DBE) was carried out using a Fujinon high resolution enteroscope (EN-450P5/20) with a working length of 200 cm and an outer diameter of 8.5 mm and a flexible overtube with a length of 140 cm and an outer diameter of 12 mm. The working channel of the enteroscope was 2.2 mm in diameter. Two latex balloons are attached separately to the tip of the enteroscope and scope, and are inflated and deflated with air from a pressure-controlled pump system (PB-10) (14). Olive oil measuring 10-20 ml was injected into the space between the enteroscope and the overtube as a lubricant to reduce friction. The procedure was performed using the technique described by Yamamato et al. (9). Additionally, in the last 76 peroral procedures, we used a so-called P-tube (Figure 1), another overtube reaching from the mouth to the upper esophagus, to reduce oropharyngeal complications (15).

The procedure was performed either by mouth or rectum, depending on the likely location of the pathology. If a diagnosis was not obtained with the primary access route, the alternative route was used. When both the antegrade and retrograde procedures were performed, Indian ink was used to mark the maximum insertion point. Fluoroscopy was used mostly at the beginning of the learning curve of DBE. Advancement of the instrument was measured by counting the number of full 40 cm advancement sequences carried out after the reference point established by initial full-length insertion of the endoscope (16).

All patients underwent DBE after an overnight fast. Additionally, patients who underwent retrograde DBE used standard colon lavage solution the day before as for colonoscopy.

The duration of the procedure was limited by effective diagnosis or treatment and the patients' vital signs recorded by the anesthesiologist. On the other hand, the procedure was stopped when the

Figure 1. P-tube.

pathologic area could not be reached in 130 minutes (min). All of the patients were followed-up for complications during the endoscopy procedure and at least for four hours after the procedure in the recovery room.

Statistical Analyses

Data were collected into a statistical software package (SPSS 15 for Windows) and were expressed as means, with SD of the mean calculated when appropriate. Differences between means were analyzed by one way ANOVA test, and the $\chi 2$ test was used to compare the prevalences between groups. A value of $p<0.05$ was regarded as identifying significance.

RESULTS

Demographic Data

A total of 216 DBE procedures (168 antegrade, 48 retrograde) were performed in 188 patients. The patients' average age±SD was 53.21±13.99 years, and there were 64 women and 124 men.

Technical Performance

All procedures were carried out by one doctor, one anesthesiologist and two nurses assisting for interventions such as biopsy and polypectomy. The procedure was terminated when a suspicious lesion (tumor, obstruction, etc.) was reached. Eighteen patients who had tattooing with Indian ink during the initial procedure to confirm small bowel examination underwent both antegrade and retrograde route. Panenteroscopy was completed successfully in 16 of these 18 patients (89%). The cecum was reached in one session in 8 (5%) of the 168 antegrade processes, and the average insertion length±SD was 540.6±42.4 cm in these patients. Thus, panenteroscopy was successful in 24 patients (13%). The terminal ileum could not to be intubated in 2 (4%) of 48 retrograde DBEs.

Mean time±SD to perform the examination using the antegrade and retrograde route was 116.4±7.17 and 113.12±9.64 min, respectively. The procedure was terminated in 44 (23%) of 188 patients after 130 min although no pathologic lesion could be detected (44 antegrade, 12 retrograde routes). The average insertion length±SD was 310.65±90.3 cm (beyond the pylorus) for peroral DBE and 166.8±80.2 cm (beyond the ileocecal valve) for anal DBE.

Fluoroscopic guidance was only used in 38 (17%) procedures to correct loops (30 (14%) of them were carried out at the beginning of the learning curve) and in some therapeutic procedures. After the first 30 procedures, fluoroscopic guidance was no longer used to correct loops.

Conscious sedation with midazolam and meperidine was used in the first 8 patients without the presence of an anesthesiologist. After these experiences, monitored anesthesia with propofol (320±60 mg) and midazolam (5.2±1.8 mg) was used during all 48 retrograde procedures and 150 antegrade DBEs, or general anesthesia was preferred in 10 patients according to the patients' cardiopulmonary risk status. If the anesthesiologist could not decide whether intubation could be done easily in case of emergency, general anesthesia was preferred.

Endoscopic Findings

A diagnosis was established in 130 (69%) of 188 patients. The most common finding was angiodysplasias (AGD), diagnosed in 56 patients (30%) who were referred for OGIB (32 patients) and iron deficiency anemia (24 patients). The second most common lesion was ulcer, which was observed in 30 patients (16%) who were referred for OBIB, and all of them had a history of nonsteroidal anti-inflammatory drugs (28 patients) and diarrhea (2 patients). On the other hand, Crohn's disease was diagnosed in 16 patients (6 patients with suspicious lesions on radiologic examination, 8 with chronic abdominal pain and 2 with chronic diarrhea). Gastrointestinal stromal tumor (GIST) was detected in 14 patients (7%): 10 of them with OGIB, 6 with iron deficiency anemia. Small bowel stricture, adenocancer, lipoma, and polyposis were also diagnosed during the procedure (Table 1). In 58 (30%) patients, no small bowel lesion could be detected (in 2 patients ileocecal intubation was not successful using the retrograde route, in 44 patients the procedure was terminated after 130 min as no lesion was found, and in 12 patients, a second procedure using the alternative route could not be performed due to financial problems).

One hundred thirty-eight patients had a small bowel investigation (CE, CT, radionuclide scan or angiography), with 78 of them (55%) having an identified lesion prior to DBE, and in these patients the duration of the procedure was significantly shorter than in those 50 patients without any prior small bowel examination (106.4±7.17 vs. 127±6.15 min; p=0.02). The diagnostic yield of the procedure was higher in patients with identified

Table 1. Indications for the double-balloon enteroscopy and endoscopic findings

Indications	Endoscopic findings	n	Therapeutic impacts
Obscure bleeding	Angiodysplasia	32	Endoscopic treatment
(n: 80)	Ulcer	28	Endoscopic and medical treatment
	GIST	10	Surgical treatment
	No lesion identified	6	
	Lipoma	2	Surgical treatment
	Malignant tumor	2	Surgical treatment
Iron deficiency anemia	Angiodysplasia	24	Endoscopic treatment
(n: 42)	No lesion identified	12	
	GIST	4	Surgical treatment
	Malignant tumor	2	Surgical treatment
Abdominal pain	No lesion identified	8	
(n: 18)	Crohn's disease	8	Medical treatment
	Foreign body	2	Endoscopic treatment
Diarrhea	No lesion identified	12	
(n: 16)	Ulcer	2	Medical treatment
	Crohn's disease	2	Medical treatment
Abnormalities on	No lesion	14	
radiographic	Crohn's disease (stricture)	6	Endoscopic and medical treatment
evaluation	Stricture	2	Endoscopic treatment
(n: 24)	Polyposis	2	Endoscopic treatment
Suspected celiac disease	No lesion identified	6	
(n: 8)	Gluten enteropathy	2	Dietary measures

Table 2. The clinical guidance and impact of other procedures before the double-balloon enteroscopy

Status before the DBE			***Duration of DBE (min)***	**Diagnostic yield of DBE**
Patients with an established diagnosis (78 patients)	*Capsule endoscopy* *Computerized tomography* *Angiography* *Nuclide scan* *Enteroclysis*	*(n:24, D:16)** *(n:88, D:54)** *(n:8, D:0)** *(n:6, D:0)** *(n:12, D:6)**	106.4±7.17	64/76 (84%)
Patients without a diagnosis (50 patients)			127±6.15	36/50 (72%)
Significance			p = 0.02	χ^2=1.37;p= 0.24

(*): n = total number of patients who underwent the procedure, D = number of patients with an established diagnosis prior to DBE.

lesions prior to DBE, but this did not reach statistical significance [64/76 (84%) *vs.* 36/50 (72%), p=NS (Table 2)].

Additionally, a diagnosis could only be established via DBE in 12 patients with CE, in 28 patients with CT, in 8 patients with angiography, and in 6 patients with radionuclide scan and enteroclysis, in whom no diagnosis could be established prior to DBE procedure. In contrast to this finding, no lesions were detected during DBE in 8 patients having CE for OGIB or anemia and diagnosed to have AGD.

Therapeutic Procedures

Fifty-six patients with AGD and 4 patients with bleeding ulcers underwent heater probe and/or argon laser coagulation. The same intervention had to be repeated for the second and third time in 18 and 8 patients with AGD and ongoing bleeding, respectively. Two of these patients had to undergo surgical laparotomy to stop the bleeding. In 2 patients, 4 small bowel polyps were polypectomized. In 2 patients referred for unexplained abdominal pain, a bezoar was noticed in the distal jejunum and extracted using basket catheter. In 4 patients with strictures due to Crohn's disease, balloon dilatations were performed safely.

Complications

No complications other than mild abdominal pain were observed after 48 retrograde procedures. In the first 46 antegrade procedures in which an additional overtube was not used, 6 patients (13%) had oral bleeding, 1 patient (2%) had a broken tooth, 14 patients (30%) complained of a sore throat, and 1 patient (2%) experienced respiratory depres-

sion due to aspiration, had to be hospitalized and was discharged after 2 days. In the following 122 antegrade procedures, an additional overtube (P-tube) (15) was used, and this significantly reduced oropharyngeal complications like sore throat and bleeding (p=0.01 for both) (Table 3).

After the first 36 antegrade procedures, we noticed that some patients developed pancreatic-type abdominal pain; thus, before and after the following 48 antegrade and 8 retrograde DBEs, we began to follow-up the amylase and lipase levels. It was observed that 6 patients (12.5%) developed acute pancreatitis as a complication, but none of the 8 patients undergoing anal DBE. These patients who were diagnosed as pancreatitis are shown in Table 4, and these data were analyzed as the issue of another study (17).

A 65-year-old patient with intestinal strictures after radiotherapy for metastatic pelvic malignancy experienced respiratory depression, which was immediately treated medically, but she died after 24 hours due to cardiovascular collapse. An autopsy revealed that she had died due to her primary metastatic disease and not to any complication of the procedure (Table 3). However, we think that the deep sedation during the procedure might have had a hastening effect on the fatal outcome due to the primary disease.

DISCUSSION

Double balloon endoscopy (DBE) is a relatively novel technique, which was introduced in 2003 and is spreading to other countries. Our tertiary referral center was the first to introduce the DBE procedure in our country. In our series, OGIB was the most common indication (41%) followed by iron deficiency anemia (21%), and the most commonly detected lesion was AGD (29%) followed by ulcers (16%) of varying etiology. In accordance with recent studies (18,19), most of the AGDs (92%) were observed in the first 180 cm, a finding that underlines the importance of first investigating the jejunum with antegrade approach in patients referred for OGIB.

A diagnosis could be established in 69% of our patients and in 31%, therapeutic interventions were performed. Fifty-six patients with AGD and four patients with bleeding ulcers underwent heater probe and/or argon laser coagulation. Bleeding could not be stopped with DBE in only two patients, and these patients underwent laparotomy and re-

Table 3. Complications of double-balloon enteroscopy

	Complications		**P value**	*Treatment*
	Before P-tube (n=46)	**After P-tube (n=122)**		
Sore throat*	14 (31%)	2 (2%)	*P=0.01*	Self-limited
Bleeding from oral cavity*	6 (13%)	0	*P=0.01*	Self-limited
Aspiration*	1	0		Hospitalization
Broken tooth	1	0		Referral to dentist
Abdominal pain**	12/48 (25 %)			Hospitalization
Pancreatitis**	6/48 (12.5%)			Hospitalization
Death***	1/216 (0.4%)			

* Complications amendable via the use of P-tube.
** The last 48 of 84 antegrade procedures were followed-up using the visual analogue scale for abdominal pain; amylase and lipase levels in these patients were determined before and after the procedure.
*** One patient died 24 hours after the retrograde procedure and an autopsy revealed that this was unrelated to DBE.

Table 4. The endoscopic characteristics of patients with pancreatitis and hyperamylasemia

	Indications	**Clinical findings**	**Endoscopic findings**	**Endoscopic treatment**
Patient 1	Anemia	Pancreatitis	Angiodysplasia	Argon laser
Patient 2	Obscure bleeding	Hyperamylasemia	Angiodysplasia	Argon laser
Patient 3	Anemia	Pancreatitis	Ulcer	Biopsy
Patient 4	Obscure bleeding	Pancreatitis	Angiodysplasia	Argon laser
Patient 5	Anemia	Hyperamylasemia	No lesion	No treatment
Patient 6	Obscure bleeding	Pancreatitis	Angiodysplasia	Argon laser
Patient 7	Stricture	Hyperamylasemia	Crohn's disease	Biopsy
Patient 8	Anemia	Pancreatitis	Ulcer	Biopsy
Patient 9	Anemia	Hyperamylasemia	Ulcer	Biopsy
Patient10	Obscure bleeding	Hyperamylasemia	Angiodysplasia	Argon laser
Patient11	Abdominal pain	Pancreatitis	Crohn's disease	Biopsy
Patient 12	Obscure bleeding	Hyperamylasemia	Angiodysplasia	Argon laser

section. Successful balloon dilatations and polypectomy were performed in six patients without any complications. Thus, in our series, the overall diagnostic and therapeutic yield of DBE was 69% and 97%, respectively, and this shows that DBE allows the diagnosis and treatment of small intestinal diseases at a relatively high rate.

Even the experienced gastroenterologist has a learning curve for new procedures. We had to use fluoroscopic guidance only in the first 30 patients, and in accordance with previous studies, this may be accepted as a sufficient number during the learning curve (19, 20).

The DBE is actually more time consuming than other endoscopic procedures, which typically takes about 2 hours (h), and a longer duration often means patient intolerance and tendency towards complications. Conscious sedation with midazolam and meperidine was used in the first eight patients without the presence of an anesthesiologist, and this was a very uncomfortable experience for both the patients and physicians. Thus, after these, monitored anesthesia with propofol and midazolam was used during all the 48 retrograde procedures and 150 antegrade DBEs, while general anesthesia was preferred in 10 patients. However, we performed no statistical comparisons between the different anesthesia groups according to related complications, as most of them belonged to the propofol + midazolam group and just a minority to the other two groups. Nevertheless, it seems reasonable to prefer monitored anesthesia with propofol and midazolam for a comfortable procedure.

Panenteroscopy in one session is very difficult, and reaching the duodenum with retrograde approach has never been reported. In our series, the cecum was reached in only 5% of patients, a success rate similar to previous studies (18-21). Identification of lesions and/or their locations prior to DBE is useful to determine the antegrade or retrograde approach, but except for significantly reducing the duration of DBE, this did not significantly increase its diagnostic yield. CE is commonly used prior to DBE, but eight patients diagnosed to have GIST after DBE were reported to have normal CEs. In favor of this, it was previously reported in some relatively small studies that lesions smaller than 3 cm could be overlooked during CE (7, 22-24). For this reason, we think that ongoing symptoms despite a negative CE should be regarded as an indication for subsequent DBE. Additionally, we think that a cost-effect analysis from large series about using radiologic examinations or CE in different patient subgroups prior to DBE would be appropriate.

Retrograde procedures caused no complications in our series. However, regarding our experience, the enhanced flexibility of the enteroscope compared to usual colonoscopes caused easier looping and difficulties in reaching the cecum, but inflating the balloons in the sigmoid, descending and transverse colon made the ileal intubation easier.

Antegrade procedures most commonly caused oropharyngeal complications. To improve this condition, we used a second overtube (P-tube, Figure 1) extending from the mouth to the upper esophagus (15). Before the application of the P-tube in the first 46 patients, the rate of oropharyngeal complications was 43%, and one patient experienced respiratory problems due to aspiration. After introducing the P-tube, the rate of oropharyngeal complications significantly decreased, and only two patients had a sore throat due to difficulty during placement of the P-tube.

After emerging reports about post-procedure pancreatitis, we also followed-up the pancreatic enzyme levels in 56 patients, 48 of them undergoing antegrade DBEs. None of the eight patients undergoing retrograde DBE showed elevations of pancreatic enzymes, whereas enzyme elevations were observed in 12 of the 48 patients (25%), six of them being hospitalized due to frank pancreatitis after antegrade DBEs. Honda et al. (25), who reported their experience with 13 patients, found that six of them (46%) developed pancreatic enzyme elevations and one developed acute pancreatitis, but this finding and its implications are addressed in a separate study.

In conclusion, DBE is a safe invasive endoscopic technique, with most of its complications being self-limited. Particularly, we did not observe any complications after retrograde DBE, but after antegrade DBE, pancreatitis seems to be an important complication that deserves further investigation. Although it is practically difficult to examine the whole small intestine in only one session, most of it can be investigated, and the procedure is well tolerated when using appropriate anesthesia with propofol and midazolam. In light of our study, the advantages of DBE might be listed as high diagnostic and therapeutic yield, and as a matter of fact, in contrast to CE or radiologic examinations, it allows the performance of a variety of treat-

ments including argon plasma coagulation, coagulation biopsy (hot biopsy), balloon dilatation, and polypectomy. Thus, this underlines the importance of DBE as most of these therapeutic procedures are alternatives to surgical treatments.

We think that DBE has opened a new era in the diagnosis and treatment of small intestinal diseases, most of them having been overlooked in the past with conventional techniques. Although future studies and meta-analyses will help us to create a clear-cut outline of the diagnostic and therapeutic impact of DBE, we believe that it must be kept in mind as the first diagnostic procedure in case of OGIB and for treating established AGDs.

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