



Efficacy and safety of double balloon enteroscopy in patients with Peutz-Jeghers Syndrome: Single center experience

Peutz- Jeghers sendromu olan hastalarda çift balon enteroskopinin etkinliği ve güvenliğinin değerlendirilmesi: Tek merkez deneyimi

• Mahmut YÜKSEL¹, • Bayram YEŞİL¹, • Çağdaş ERDOĞAN¹, • Alper MACİF¹,
• Dilara TURAN GÖKÇE¹, • Ferhat BACAĞSIZ¹, • İlyas TENLİK¹,
• Ömer ÖZTÜRK¹, • Derya ARI¹, • Öykü TAYFUR YÜREKLİ¹,
• Meral AKDOĞAN KAYHAN¹, • Hale GÖKCAN²

¹Division of Gastroenterology, Department of Internal Medicine, Bilkent City Hospital, Ankara, Turkey

²Division of Gastroenterology, Department of Internal Medicine, Ankara University School of Medicine, Ankara, Turkey

ABSTRACT • Background and Aims: Our understanding of the clinical outcomes of double balloon enteroscopy in individuals with Peutz-Jeghers syndrome is limited. The purpose of this study is to assess double balloon enteroscopy's effectiveness and safety in managing small intestinal polyps in Peutz-Jeghers syndrome patients. **Materials and Methods:** Data from 16 Peutz-Jeghers syndrome patients who underwent double balloon enteroscopy at our center between January 2007 and March 2020 have been collected. The study included patients with polyps larger than 1 cm in diameter. **Results:** Sixteen patients with Peutz-Jeghers syndrome underwent a total of 79 double balloon enteroscopy procedures, and a total of 469 polyps larger than 1 cm were found in 76 oral/anal double balloon enteroscopies. Over 80 polyps seen in the small intestinal segments were removed using endoscopic polypectomy during intraoperative double balloon enteroscopy. Four patients underwent intraoperative enteroscopy in addition to double balloon enteroscopy and over 200 polyps were removed via endoscopic polypectomy. A total of 19 complications which was related with procedures and anesthesia occurred either during or after the 79 double balloon enteroscopy procedures. All procedure related complications were treated with minimally invasive methods. After double balloon enteroscopy, two patients underwent surgery (one with invagination, the other with adhesion ileus). **Conclusion:** Double balloon enteroscopy can be considered a reliable and effective method in the diagnosis and long-term follow-up of patients with Peutz-Jeghers syndrome.

Key words: Double balloon enteroscopy, Peutz-Jeghers syndrome, polyp

ÖZET • Giriş ve Amaç: Peutz-Jeghers sendromlu bireylerde çift balon enteroskopinin klinik sonuçları hakkındaki bilgilerimiz sınırlıdır. Bu çalışmanın amacı, Peutz-Jeghers sendromlu hastalarda ince bağırsak poliplerinin yönetiminde çift balon enteroskopinin etkinliğini ve güvenliğini değerlendirmektir. **Gereç ve Yöntem:** Ocak 2007 ile Mart 2020 tarihleri arasında merkezimizde çift balon enteroskopi uygulanan 16 Peutz-Jeghers sendromlu hastanın verileri toplandı. Çalışmaya çapı 1 cm'den büyük polipleri olan hastalar dahil edildi. **Bulgular:** Peutz-Jeghers sendromlu 16 hastaya toplam 79 çift balon enteroskopi prosedürü uygulandı ve 76 oral/anal çift balon enteroskopide 1 cm'den büyük toplam 469 polip bulundu. İnce bağırsak segmentlerinde görülen 80'den fazla polip, intraoperatif çift balon enteroskopi sırasında endoskopik polipektomi kullanılarak çıkarıldı. Dört hastaya çift balon enteroskopiye ek olarak intraoperatif enteroskopi uygulanmış ve endoskopik polipektomi ile 200'den fazla polip çıkarılmıştır. 79 çift balon enteroskopi prosedürü sırasında veya sonrasında prosedürler ve anestezi ile ilgili toplam 19 komplikasyon meydana gelmiştir. Prosedürle ilgili tüm komplikasyonlar minimal invaziv yöntemlerle tedavi edilmiştir. Çift balon enteroskopi sonrasında iki hasta ameliyat edilmiştir (birinde invajinasyon, diğerinde adezyon ileusu). **Sonuç:** Çift balon enteroskopi, Peutz-Jeghers sendromlu hastaların tanı ve uzun dönem takibinde güvenilir ve etkili bir yöntem olarak kabul edilebilir.

Anahtar kelimeler: Çift balon enteroskopi, Peutz-Jeghers sendromu, polip

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant hereditary disease that occurs as a result of germline mutations in the *STK 11* gene which is located on chromosome 19p13.3 (1). It occurs between about 1 in 50,000 and 200,000 live births (2). Both genders are equally affected. This genetical disorder is characterized by mucocutaneous pigmentation and hamartomatous polyps in the gastrointestinal tract, especially in the small intestine. Polyps in the small intestine are most located in the jejunum (Figure 1) and less common in the duodenum and ileum. Polyps are found in the colon and stomach of 30% and 25% of patients, respectively. Polyps may cause intussusception, obstruction, bleeding, anemia, and abdominal pain (3). In addition to the gastrointestinal system, hamartomatous polyps may also be encountered in the uterus, nasal cavity, bladder, and lungs (4). Furthermore, patients with PJS carry a significantly increased risk for the development of intestinal and extraintestinal malignancies (5).

Due to the complications associated with polyps and the risk of malignancy, surveillance is recommended in people with clinical features of PJS. The main indication for small-bowel surveillance is the prevention of intussusception and emergency lap-

arotomy. If polyps are detected at the initial examination, video capsule endoscopy (VCE) is recommended every three years in symptomatic patients from 8 years of age. If only a few polyps are detected at initial examination, the surveillance can be postponed to 18 years of age (6).

Double balloon enteroscopy (DBE) was first used by Yamamoto et al. in 2001 and has since become an outstanding tool in the diagnosis and treatment of small bowel disorders. Compared to radiological methods such as magnetic resonance (MR), enterography or VCE, the most remarkable advantage of DBE is that therapeutic interventions can also be performed during the procedure (7). Recent studies have reported that polypectomy with DBE was highly diagnostic in patients with PJS (Figure 2) and, theoretically, can prevent the need for emergency interventions due to intussusception (8).

In this study, we intended to assess DBE's effectiveness and safety in managing small intestinal polyps in PJS patients.

MATERIALS and METHOD

We conducted a retrospective study including 16 patients with PJS who underwent DBE for poly-



Figure 1 Polyps in jejunum.



Figure 2 Polypectomy with snare.

ectomy between January 2007 and March 2020. Patients' data were collected from the endoscopy records and the electronic medical records. Demographic characteristics of the patients, size location and histology of the polyps, and follow-up information were recorded. Patients with polyps that were found during the procedure and were greater than 1 cm in diameter were assessed.

DBE procedure was performed with Fujinon EN-450T5 or EN-580T enteroscopes (Fujinon Inc., Saitama, Japan) under deep sedation with propofol in the presence of anesthesiologist. Intervention pathway (anterograde or retrograde) was determined based on radiological imaging [computed tomography (CT) and/or magnetic resonance imaging (MRI)]. The procedures were performed after 1 night fasting in anterograde approach and preparing for colonoscopy in retrograde approach. Marked with Indian ink to verify total enteroscopy. In addition, seeing the caecum in anterograde approach was considered as total enteroscopy verification.

The polyp size in DBE was estimated based on the width of the biopsy forceps or the diameter of the polypectomy area. Intestinal polyps with a diameter of larger than 1 cm were considered suitable for polypectomy. Polypectomy was performed with snare after adrenaline injection to the bases of the polyps (Figure 2). Polyps that were not suitable for endoscopic resection were removed by intraoperative DBE or intraoperative enteroscopy by enterotomy under operating room conditions. As indications for intraoperative endoscopic polypectomy, broad-based sessile polyps that cannot be grasped with snare, polyps whose localization is not suitable for removal with DBE, polyps larger than 6 cm, and polyps in patients with a history of ileus were determined. In these cases, it was marked with Indian ink for easy access during laparotomy.

Since the polyps were hamartomatous in patients with a diagnosis of PJS, the majority of the polyps were left in the lumen. Whereas one patient had no diagnosis, the polyps were removed for pathological analysis, and the PJS diagnosis was made using the pathology results. In addition to this, at least 1 procedure for each patient involved sending polyps to pathology. The pathology findings were all hamartomatous polyps. None of the patients' polyps were malignant.

Less than 1 cm polyps were excluded from the study. The procedures were repeated in sessions until all the polyps \geq 1 cm detected in the first procedure were removed. Surveillance was performed with radiological imaging (small bowel radiography, CT, MR) every 2-3 years as VCE not being performed due to economic reasons. When polyps in the small intestine were detected, DBE was performed for polypectomy. When polyps were detected in the stomach, duodenum and colon, polypectomy was performed with esophagogastroduodenoscopy (EGD) and colonoscopy. DBE related complications were evaluated by review of patient records and DBE report.

Ethics committee approval of the study was obtained on March 2024 by Ankara Bilkent City Hospital Medical Research Scientific Evaluation and Ethics Committee. This study was complied with the ethical guidelines of the 1975 Helsinki Declaration that was then modified in 2008.

Statistical Analysis

Statistical analyses were performed with IBM® SPSS Statistics for Windows version 26.0 software. Continuous variables are expressed as medians and ranges. Categorical variables are expressed as counts and percentages.

RESULTS

Sixteen patients with PJS who underwent DBE between January 2007 and March 2020 were in-

cluded in the study (Male/female: 9/7, Table 1). The median age of the patients was 31.4 (16 - 48) years, and the median age of diagnosis was 15 (2 - 27) years. Family history of PJS was positive in 4 patients. Eleven patients (68.75%) had a history of surgery due to complications of Peutz-Jeghers such as invagination, ileus, and malignancy prior to DBE.

A total of 79 DBE procedures (mean 5 procedures per patient) were applied to 16 patients and multiple procedures were performed together in some patients (Table 1). It was estimated that the scope was advanced 200 cm (80 - 320 cm) distally from the pylorus in anterograde approach and 120 cm (70 - 200 cm) proximally from the ileocecal valve in the retrograde approach. The median procedure

Table 1 Demographic and clinical characteristics of patients with DBE

Age, median (min-max), years	31 (16 - 48)
Age of diagnosis, median (min-max), years	15 (2 - 27)
Gender, male/female, (n)	9/7
Diagnosis (n)	16
Family history	8
Symptoms (abdominal pain/anemia/polyp prolapse)	6/1/1
Double-balloon endoscopy, total (n)	79
Oral/anal/intraoperative, n (%)	53/23/3 (67/29/4)
Procedure types (n)	16
Oral procedure	4
Oral + anal procedure	6
Oral + intraoperatively	1
Oral + anal + intraoperatively	1
Oral + intraoperative enteroscopy	2
Oral + anal + intraoperative enteroscopy	1
Oral + anal + intraoperatively + intraoperative enteroscopy	1
Procedure time for DBE	
Oral method, median (min-max) (mins)	92 (80-180)
Anal method, median (min-max) (mins)	67 (45-150)
All polyps ≥ 1 cm in diameter (n)	469
Stomach, n (%)	26 (5.5)
Duodenum, n (%)	37 (7.9)
Jejunum, n (%)	270 (57.6)
Ileum, n (%)	57 (12.1)
Colon segments, n (%)	76 (16.8)
Complications (n)	19
Procedure-related (bleeding/aspiration/focal pancreatitis)	9/1/1
Anesthesia-related (hypoxia/arrhythmia/respiratory arrest)	6/1/1
Post-DBE surgery	
Surgery/no surgery/NA*	2/11/3
Survived	
Dead/alive/NA*	2/13/1

DBE: Double balloon enteroscopy; NA:Not available

time for DBE by oral and anal approach was 92 minutes (80 - 180 minutes) and 67 minutes (45 - 150 minutes), respectively.

A total of 469 polyps \geq 1 cm were detected in 76 oral/anal DBE and polypectomy was performed with snare. 26 of these polyps (5.54%) were in the stomach, 37 of them (7.88%) were in duodenum, 270 of them (57.56%) were in jejunum, 57 of them (12.15%) were in ileum, 79 (16.84%) of them were in colon segments. More than 80 of the polyps detected in small intestine segments during 3 times of performed intraoperative DBE were removed by endoscopic polypectomy. In addition to DBE, 4 patients underwent endoscopic polypectomy with more than 200 polyps by intraoperative enteroscopy. An average of 6.17 (1 - 30) polypectomies were performed per procedure except intraoperative procedures. Complete enteroscopic procedure was performed in 10 patients (62.5%) of the 16 patients. Following the procedure, an abdominal CT scan revealed persistent polyps in 3 of these 10 patients, who had them removed with DBE polypectomy once again. In the remaining 7 cases, there were no leftover polyps found. All 10 patients completed treatment with DBE polypectomy. At 6-month intervals, abdomen contrast-enhanced CT scans were performed on all patients. If additional or new polyps were found, the DBE polypectomy procedure was repeated.

Recurrence was detected in polyps larger than 1 cm in all 16 patients during their follow-up. These recurrences were detected by imaging methods or DBE surveillance. While complete resection was achieved with DBE in 10 of 16 patients, additional interventions to DBE were performed in 6 patients (Table 1).

Of the 79 DBE procedure in 16 patients, 11 of the 19 complications were procedure-related (Table 1). None of the patients experienced severe procedure-related complications, such as perforation or

death. All procedure-related complications were managed with minimally invasive interventions.

In addition to DBE, a total of 58 EGD and 66 colonoscopy procedures were performed on these 16 patients. Polypectomy was performed on 500 polyps, 188 under EGD and 312 under colonoscopy. During these procedures, 1 patient had severe bleeding requiring surgical resection of stomach and 1 patient had colon perforation by surgically treated.

In the follow-up, 2 (12.5%) of the 16 patients required surgical intervention due to non-DBE (one with intussusception, the other with brid ileus and bleeding after endoscopic polypectomy). 2 patients were died due to reasons not related to the disease process.

DISCUSSION

Peutz-Jeghers syndrome is a rare hereditary disorder that causes hamartomatous polyps in the entire gastrointestinal tract, especially in the small intestine. These polyps can cause intussusception, obstruction, bleeding, anemia, and abdominal pain if they are not treated. When monitoring these patients, VCE is typically used to prevent intestinal blockage and intussusception. In addition, patients with PJS have an increased risk of intestinal malignancy, although not on the basis of polyps. DBE was developed in 2001, and since then, it has played a significant role in the management of PJS. The technique's ability to allow for treatment in addition to successful diagnosis is its most significant aspect. In this study, we collected the data of 16 patients with PJS who underwent DBE. The outcomes of the patients' follow-up revealed that DBE and polypectomy procedures are reliable and effective, and decreased the need for surgery. All procedure-related complications were treated with minimally invasive methods. Only two patients required surgery due to polyps after DBE procedure, and one patient developed colon cancer during the follow-up.

There is a significant risk of cancer in PJS and close to other high-risk situations where surveillance is recommended. According to a study by Van Lier et al., patients with PJS develop malignancy at an average age of 42 years, and the most common malignancy is colorectal cancer. The relative risk of cancer is 4.8-18 times higher than the general population, and the cumulative risk of cancer for life is as high as 93%. Based on these high risks, surveillance is recommended to detect malignancies in the early stage, and to remove premalignant polyps that may lead to complications (9). Although VCE and motorized spiral enteroscopy (MRE) are viable for surveillance, DBE has advantages such as direct visualization of lesions and the ability to perform therapeutic procedures when necessary. While push enteroscopy, primary surgery, and intraoperative enteroscopy have been used in the treatment of polyps of the small intestine up to 15 years, direct imaging of the small intestine with the development of VCE by DBE and the resection of polyps with snare without the need for laparotomy during the DBE procedure are performed as an alternative to laparotomy (7).

The use of DBE for the diagnosis and treatment of Peutz-Jeghers polyps was first described in 2005 by Ohmiya et al. (10). They resected polyps without bleeding and perforation with DBE in two patients with multiple polyps in the jejunum and ileum. Later studies further reported the feasibility of DBE in patients with PJS (8,11,12). In our study, we evaluated the efficacy and safety of DBE in the management of small bowel polyps in PJS. Although it was previously stated in the literature that VCE was performed for the detection of polyps before DBE, we could not use VCE as this expensive procedure is not covered by the insurance in our country. In patients who had polyps in small bowel segments that were radiologically visualized and could not be approached endoscopically or colonoscopically, DBE was performed for direct visualization of the small intestines and polyp resec-

tion. The majority of the polyps larger than 1 cm were resected during the procedure. Endoscopic and surgical polypectomy was performed via intraoperative DBE (in 3 patients), and intraoperative enteroscopy (in 4 patients) for polyps that were not considered for endoscopic removal. Although there was a higher complication rate associated with the procedure than reported in the literature (13.92% versus 7.3%), none of complications were morbid and were all treated with minimally invasive methods. The reason perforation is not among our complications could be because the polyps that were deemed endoscopically unremovable were removed intraoperatively with surgery.

Motorized spiral enteroscopy (MSE) has been postulated to ease the complexities of the standard-of-care double-balloon enteroscopy (DBE). In a study by Chan et al; MSE and DBE were compared in terms of safety and therapeutic efficacy and no significant difference was found between the two techniques in terms of technical and therapeutic efficacy (13). In the group undergoing MSE, one patient sustained a severe esophageal laceration, while another patient experienced an ileal perforation.

For Peutz-Jeghers syndrome (PJS) patients, small bowel polyps develop and result in symptoms at an early age. The efficacy and safety of balloon assisted enteroscopy were evaluated in a prospective study by Rong Li et al. A total of 242 polyps were removed in 33 patients. The complication rate was 1.8% in the polypectomy group (14). In a study by Belisha et al. evaluating the efficacy of double balloon enteroscopy in pediatric patients with PJS; 22 double balloon enteroscopies were performed in 16 patients. All polyps larger than 1 cm were removed by DBE or laparoscopy-assisted DBE and 1 patient developed pelvic abscess after the procedure (15). In our study, the complication rate was 13.92%.

PJS patients are at high risk of intussusception at a young age (50% at 20 years of age). Intussusceptions are usually caused by polyps larger than 15

mm (polyp size is most likely the most important risk factor for intussusception in the small intestine) and often lead to acute abdomen, requiring immediate surgical intervention (16). These findings support the use of endoscopic surveillance to prevent complications. Serrano et al. demonstrated that endoscopic treatment by removing small bowel hamartomas of ≥ 10 mm diameter was useful for preventing intussusceptions and the need for emergency laparotomy; this was associated with a significant decrease in the size of resected polyps as the number of sessions increased (17). In the present study, we found that only one patient had a disease-related (invagination) surgery after initiation of the DBE procedure, although 11 patients had a history of disease-related surgeries before DBE. Although our study had a retrospective design, we believe that it is valuable as it involves 16 patients with a rare disease in a single center. This

study is one of the few studies to document the implementation of the DBE method for the treatment of PJS in Turkey.

The fact that our study was retrospective, and the patients could not have VCE performed is one of its drawbacks. On the other hand, even though it is a rare disease, our study's strengths lie in the large number of patients analyzed and DBE procedures carried out.

Ethics: *This study protocol was approved by Bilkent City Hospital medical Research Scientific Evaluation and Ethics Committee on March 2024. The study was complied with The World Medical Association Declaration of Helsinki.*

Conflict of Interest: *There is no conflict of interest with any institution or person.*

Finance: *No financial support was received.*

REFERENCES

- Hemminki A, Markie D, Tomlinson I, et al. A serine / threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature*. 1998;391(6663):184-7.
- Giardiello FM, Trimbath JD. Peutz-Jeghers syndrome and managements. *Clin Gastroenterol Hepatol*. 2006;4(4):408-15.
- Gammon A, Jasperson K, Kohlmann W, Burt RW. Hamartomatous polyposis syndromes. *Best Pract Res Clin Gastroenterol*. 2009;23(2):219-31.
- Schreibman IR, Baker M, Amos C, McGarrity TJ. The hamartomatous polyposis syndromes: a clinical and molecular review. *Am J Gastroenterol*. 2005;100(2):476-90.
- Van Lier MG, Westerman AM, Wagner A, et al. High cancer risk and increased mortality in patients with Peutz-Jeghers syndrome. *Gut*. 2011;60(2):141-7.
- Beggs AD, Latchford AR, Vasen HF, et al. Peutz-Jeghers syndrome: A systematic review and recommendations for management. *Gut*. 2010;59(7):975-86.
- Yamamoto H, Kita H. Double-balloon endoscopy: From concept to reality. *Gastrointest Endosc Clin N Am*. 2006;16(2):347-61.
- Sakamoto H, Yamamoto H, Hayashi Y, et al. Nonsurgical management of small-bowel polyps in Peutz-Jeghers syndrome with extensive polypectomy by using double-balloon endoscopy. *Gastrointest Endosc*. 2011;74(2):328-33.
- van Lier MG, Wagner A, Matus-Vliegen EM, et al. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am J Gastroenterol*. 2010;105(6):1258-64; author reply 1265.
- Ohmiya N, Taguchi A, Shirai K, et al. Endoscopic resection of Peutz-Jeghers polyps throughout the small intestine at double-balloon enteroscopy without laparotomy. *Gastrointest Endosc*. 2005;61(1):140-7.
- Gao H, van Lier MG, Poley JW, Kuipers EJ, van Leerdam ME. Endoscopic therapy of small-bowel polyps by Peutz-Jeghers syndrome. *Gastrointest Endosc*. 2010;71(4):768-73.
- Ohmiya N, Nakamura M, Takenaka H, et al. Management of small-bowel polyps in Peutz-Jeghers syndrome by using enteroclysis, double-balloon enteroscopy. *Gastrointest Endosc*. 2010;72(6):1209-16.
- Chan W, Wei LK, Tan T, Hsiang LG, Kong C, Salazar E, Koay D, Khor C, Asokkumar R. Motorized spiral enteroscopy versus double-balloon enteroscopy: a case-matched study. *Gastrointest Endosc*. 2023;97(2):314-24.
- Li BR, Sun T, Li J, Zhang YS, Ning SB, Jin XW, Zhu M, Mao GP. Primary experience of small bowel polypectomy with balloon-assisted enteroscopy in young pediatric Peutz-Jeghers syndrome patients. *Eur J Pediatr*. 2020;179(4):611-7.

15. Belsha D, Urs A, Attard T, Thomson M. Effectiveness of Double-balloon Enteroscopy-facilitated Polypectomy in Pediatric Patients With Peutz-Jeghers Syndrome. *J Pediatr Gastroenterol Nutr.* 2017;65(5):500-2.
16. van Lier MG, Mathus-Vliegen EM, Wagner A, van Leerdam ME, Kuipers EJ. High cumulative risk of intussusception in patients with Peutz-Jeghers syndrome: time to update surveillance guidelines? *Am J Gastroenterol.* 2011;106(5):940-5.
17. Serrano M, Mão-de-Ferro S, Pinho R, et al. Double-balloon enteroscopy in the management of patients with Peutz-Jeghers syndrome: a retrospective cohort multicenter study. *Rev Esp Enferm Dig.* 2013;105(10):594-9.