Endoscopic management of iatrogenic perforations during endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for colorectal polyps: a case series

Dimitrios Pissas, Efthymios Ypsilantis, Savvas Papagrigroriadis, Bu'Hussain Hayee and Amyn Haji

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Abstract

Background: Iatrogenic perforation during therapeutic colonoscopy, reported in up to 1% of endoscopic mucosal resections (EMRs) and up to 14% of endoscopic submucosal dissections (ESDs), has conventionally been an indication for surgery.

Aims: We present a case series of successful endoscopic management of iatrogenic colorectal perforation during EMR and ESD, demonstrating the feasibility and safety of the method.

Methods: Retrospective analysis of a database of patients undergoing EMR and ESD for colorectal polyps in a tertiary referral centre in the United Kingdom.

Results: Four cases of perforation were identified (two EMRs and two ESDs) in a series of 218 procedures (1.8%), all detected at the time of endoscopy and managed with endoscopic clips. Patients were observed in hospital and treated with antibiotics. Their median length of stay was 3 days (range 2–6 days), with no mortality or need for surgery.

Conclusion: Surgery is no longer the first choice in the management of iatrogenic perforations during EMR and ESD for colorectal polyps; in selected patients with small perforations and minimal extraluminal contamination, conservative management with application of endoscopic clips, antibiotics and close patient monitoring constitute a safe and effective treatment option, avoiding the morbidity of major surgery.

Keywords: EMR, ESD, perforation, polyp, colon, rectum

Introduction

The prevalence of adenomatous polyps detected in colonoscopy has been reported up to 25% of the general population [Giacosa *et al.* 2004], with large lesions traditionally treated surgically. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are minimally invasive, organ-sparing endoscopic techniques that increasingly replace surgery in the treatment of benign and early malignant gastrointestinal lesions. EMR is employed for the excision, *en bloc* or piecemeal, of intramucosal or superficial submucosal (sm1) neoplasms [Yoshida *et al.* 2010]. ESD is facilitated by an electrosurgical knife and offers the advantage of *en bloc* removal of larger, flat polypoid lesions, enabling more accurate histopathological assessment

and enhanced curability [Yoshida *et al.* 2010]; it is, however, technically demanding and associated with longer procedure times and increased risk of complications [Tanaka *et al.* 2010]. Both endoscopic methods are hindered by the risk of perforation, mounting to 0.3–0.5% for EMR and 4–10% for ESD [ASGE Technology *et al.* 2008], with subsequent potential risk of peritoneal tumour seeding or peritonitis, incurring mortality of up to 5% [Fatima and Rex, 2007].

Surgery has been the gold standard for colonic perforations, enabling a washout of peritoneal soiling and definitive treatment of the defect by primary repair, colonic resection or diversion; it does, however, involve surgical morbidity and prolonged

Correspondence to:
Amya Haji, MA, MBBChir, MSc, MD, FRCS
Department of Colorectal Surgery, Kings College Hospital, Denmark Hill, London SE5 9RS, UK
amynhaji@nhs.net
Dimitrios Pissas, MD, PhD
Efthymios Ypsilantis, MPhil, MSc, FRCS
Savvas Papagrigroriadis, MSc, FRCS
Bu'Hussain Hayee, BSc, MBBS, MRCP, PhD
Department of Colorectal Surgery and Endoscopy, King's College Hospital, Denmark Hill, London, UK

hospital stay [Iqbal *et al.* 2008]. Recently, there has been an increasing trend for nonsurgical treatment of perforations recognized during endoscopic procedures. In haemodynamically stable, nonimmunosuppressed patients with adequately prepared bowel and no signs of generalized peritonitis, application of endoscopic clips and antibiotic administration has been reported to favourably treat iatrogenic colonic perforations, with success rates ranging between 81.3% and 100% [Taku *et al.* 2007; Hotta *et al.* 2012; Kim *et al.* 2013; Yoon *et al.* 2013]. We present our experience of nonsurgical management of colonic perforations noted during EMR and ESD of large colorectal polyps.

Methods

A retrospective analysis was undertaken of a prospectively compiled database of patients undergoing EMR and ESD for colorectal polyps in our tertiary referral centre. All procedures were performed by one highly experienced endoscopist. Patients had bowel preparation by ingesting a mix of sodium picosulfate and magnesium citrate, and provided written informed consent. Intravenous midazolam and fentanyl were used for sedation and analgesia at titrated doses, under continuous monitoring of patients' cardiorespiratory function. Colonoscopy was performed using a single-channel lower gastrointestinal endoscope with CO₂ insufflation, and colonic irrigation with water facilitated optimal luminal views. A magnification colonoscope was used for the EMR procedures, whereas for the ESD procedures, a videoendoscope (Olympus PCF) with distal attachment was employed. The tumours were assessed by narrow band imaging and white light magnification chromoendoscopy (dye spray with 0.4% indigo carmine) according to Paris and Kudo's classifications [Kudo *et al.* 1996; Participants in the Paris Workshop, 2003]. The depth of invasion was also assessed with an endoscopic ultrasound mini-probe (Fujinon variable frequency miniprobe 75–35 mHz) at 12 and 20 Hz. Before resection, the lesions were lifted by injecting a mixed solution (hyaluronic acid, epinephrine and indigo carmine for the ESD procedures, and gelofusine, adrenaline and indigo carmine for EMRs) into the submucosal layer, using a 21-gauge injection needle. *En bloc* or piecemeal EMR was performed by snare diathermy. For ESD a transparent distal attachment cap was applied to the tip of the colonoscope and a Fujii Flush Knife® (1.5 nm + 2 nm) was employed. An ERBE V10 200D high-frequency generator was used and haemostasis was facilitated by use of Olympus Coagrasper® Haemostatic forceps.

Boston Scientific Resolution Through The Scope Endoclips® (Boston Scientific Inc., Natick, MA, USA) were used for haemostatic and tissue approximation purposes. At the end of the procedure the scar was routinely examined with magnification chromoendoscopy to ensure no residual disease was present. The presence of bowel wall perforation was confirmed by observation of mesenteric fat, intra-peritoneal organs or muscle sparing, and the defect was closed by immediate application of endoclips (described above). Patients with no complications were discharged the same day according to standard criteria and were followed up 2 days post procedure by telephone interview, whereas those with perforations were admitted for close monitoring and antibiotic treatment [computed tomography (CT), clinical criteria]. All patients had follow-up endoscopy performed at 3, 6 and 12 months.

Results

We identified four cases of perforation (two during EMR and two during ESD) during a series of 218 procedures (174 EMRs and 44 ESDs, overall perforation rate 1.8%), all detected at the time of endoscopy. There were no cases of delayed perforation in our series. The diagnosis was confirmed endoscopically and the extent of extraluminal contamination

Figure 1. (A) Circumferential lesion with type IV pit pattern. (B, C) During the EMR, a perforation was noted that was closed immediately with Boston clips. (D) Post procedure computed tomography scan showing clips inside the lumen of the rectum, small amount of perirectal fat stranding and few locules of gas at the perirectal region. EMR, endoscopic mucosal resection.

Table 1. Characteristics of four cases with perforations during therapeutic endoscopic procedures.

Patient characteristics	Case 1	Case 2	Case 3	Case 4
Age (years)	73	80	64	53
Sex	Male	Female	Female	Female
Procedure	ESD	EMR	EMR	ESD
Lesion characteristics				
Site	Upper rectum	Upper rectum	Sigmoid colon	Sigmoid colon
Lesion's size	6 × 4 cm	16 cm length	12 × 14 cm	8 cm length
Circumference	40%	100%	60%	60%
NBI (pattern)	Dense	Dense	Dense	Dense
Chromoendoscopy	Type IV	Type IV	Type IV	Type IV
Paris classification	Ila	LST granular mixed nodular	LST granular mixed nodular	LST granular homogenous
Histopathology	TVA with low grade dysplasia	TVA with low grade dysplasia	TVA with low grade dysplasia	TVA with low grade dysplasia
Perforation size	10 mm	4 mm	10 mm	2 mm
Number of clips	6	3	5	4
Length of stay	2 days	6 days	2 days	2 days
Symptoms	Free	Mild abdominal pain	Free	Free
Fever	Afebrile	One spike 38.3°C	Afebrile	Afebrile
WBC (per mm ³)	8160	15,130	6550	8400
CRP (mg/dl)	33.9	181	10.9	6.4
Antibiotic treatment*	7 days	7 days	7 days	7 days
*Total course, including oral. CRP, C reacting protein; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; LST, lateral spreading tumour; NBI, narrow band imaging; TVA, tubillovilous adenoma; WBC, white blood cells.				

was evaluated by CT (Figure 1). All four cases were managed endoscopically with primary closure of the defect with a median of four endoscopic clips per case (range 4–6, Table 1). Patients were observed in hospital and received treatment with intravenous antibiotics. The median length of hospital stay was 3 days (range 2–6 days). There was no mortality and no need for surgery. There was no evidence of stricture or recurrence at 3 and 6 months follow-up endoscopy (Figures 2 and 3). The patient and lesion characteristics and outcomes of the four perforation cases are presented in Table 1.

Discussion

Perforation is not uncommon in colonoscopic practice and the risk increases with the invasiveness of the procedure: the overall perforation risk for colonoscopy is approximately one in 1400, increasing to one in 1000 for all therapeutic procedures [Panteris *et al.* 2009]. Safe endoscopic

practice dictates recognition of factors predisposing to iatrogenic perforation during EMR and ESD, and pre procedural patient optimization to minimize the effects of perforation, should this happen. Recommended potential risk factors for perforation include the size and type of polyp, with large laterally spreading tumours (LSTs) associated with higher risk. The site of polypectomy is important, with perforations occurring more often in the right colon. The presence of fibrosis from previous biopsies or failed attempts of EMR and submucosal injection without hyaluronic acid also seem to increase the risk of perforation. Finally, the experience of the endoscopist is relevant, with higher risk for operators with less than 100 cases [Heldwein *et al.* 2005; Lee *et al.* 2012]. Recent data demonstrate that the overall perforation rate has been decreasing because of improvement in the endoscopists' skills and increased volume of procedures [Niimi *et al.* 2010].

Figure 2. (A) Lateral spreading tumour granular–mixed nodular type lesion in the sigmoid colon. (B) During the EMR, a 1 cm perforation was noted and was subsequently closed with Boston Resolution Through The Scope Endoclips®. (C) Six months follow-up flexible sigmoidoscopy after the EMR, no evidence of recurrence or stenosis.
EMR, endoscopic mucosal resection.

Figure 3. (A) A granular homogenous lateral spreading tumour in the sigmoid colon 8 cm length, occupying 60% of the circumference, tubular adenoma with low grade dysplasia. (B) A 2 mm perforation was noted, closed with four Boston Resolution Through The Scope Endoclips®. (C) Six months follow-up flexible sigmoidoscopy.

Patient optimization should emphasize adequate bowel preparation prior to the procedure to minimize the egression of faecal material into the peritoneal cavity [Damore *et al.* 1996]. Additionally, we postulate that vigorous bowel irrigation, prior to resection, using water through the colonoscope and aspiration till the achievement of a pristine bowel mucosa is also paramount, regardless of the adequacy of bowel preparation. Significant is also the use of CO₂ for insufflation as it reduces patient discomfort and promotes the absorption of leaked gas from perforation and is mandatory for ESD procedure [GETechnology Assessment Committee *et al.* 2013].

Early recognition of a perforation during an EMR or ESD procedure is crucial; late perforations, ‘delayed’ or ‘microperforations’ have been shown to be associated with higher rate of faeculent peritonitis and longer and more severe clinical course, compared with perforations identified during the procedure [Baron *et al.* 2012; Yoon *et al.* 2013]. Injection of diluted indigo carmine into the submucosa can help

determine the plane of resection and recognize deeper resection into the muscularis propria [Raju *et al.* 2011]. Sudden increase in gas flow and development of tension pneumoperitoneum also indicate signs of perforation [Ignjatovic and Jovic, 2009]. Although the rate of delayed perforation is reported to be 0.3–0.7% [Yoon *et al.* 2013], there were no cases of delayed perforation in our series. If the diagnosis is in doubt post procedure, a CT scan is the most sensitive imaging modality in establishing the diagnosis and in evaluating the extend of the peritoneal soiling [Raju *et al.* 2011].

Several devices have been developed for the endoscopic management of iatrogenic gastrointestinal perforations such as clips, tissue glues [Mutignani *et al.* 2006], covered self-expandable metal stents [Bethge *et al.* 1996] and endoscopic suturing systems [Rajan *et al.* 2012]. We prefer the use of endoscopic clips that also seem to have gained wide preference amongst endoscopists, with high immediate defect closure rates of up to 89% [Mangiavillano *et al.* 2010].

The endoscopic clipping devices that have been developed can be classified in two categories: through-the-scope clips (TTSCs) and over-the-scope clips (OTSCs) [Binmoeller *et al.* 1993]. In small perforations a single clip may be applied across the entire defect. Larger perforations may require sequential clipping starting from the periphery towards the centre of the defect [Technology Assessment Committee *et al.* 2006]. Several TTSCs are available such as Tri-Clip and Instinct clip (Cook Medical, Winston-Salem, NC), QuickClip2 (Olympus Inc., Center Valley, PA, USA), Resolution Endoclips® (Boston Scientific Inc., Natick, MA, USA). Type selection is based mostly on the endoscopist's preference and experience, and so far there are no comparative studies available. OTSCs (OVESCO, Tübingen, Germany) can achieve full-thickness closure of defects of as large as 27 mm (GE Technology Assessment Committee *et al.* 2013). An OTSC has a higher compression force and the capacity to capture a larger volume of tissue. The clip is armed on an applicator cap that is fixed on the tip of the colonoscope and can be used with a 'twin grasper' or 'anchor grasper'. The twin grasper is particularly useful to join the edges of the defect and to avoid clipping organs behind the digestive wall. Those in favour of OTSCs argue that they are more efficient than TTSCs in the closure of large defects, and on inflamed, indurated and fibrotic tissue associated with chronic fistulae [Raju, 2014]. We have limited experience of the use of OTSCs.

After endoluminal repair of colonic perforations with clips, patients are treated with broad-spectrum intravenous antibiotics and withholding of oral intake, and are closely monitored for signs or symptoms of peritonitis [Raju *et al.* 2011]. The return of appetite and of bowel function, resolution of symptoms and normalization of inflammatory markers are good indicators of successful conservative management. On the contrary, if patients develop signs of peritonitis or sepsis after endoluminal clipping of the perforation, surgical treatment is mandatory. The authors, including the main endoscopist, are colorectal surgeons but it is important to emphasize that endoscopic treatment of perforation should be done in collaboration with the surgical team.

Our series is limited by the small number of cases, but includes two patients with a 10 mm long perforation who had favourable outcome with conservative management. We conclude

that, in expert hands, the endoscopic management of colonic perforations after EMR or ESD procedures is feasible with good results, reduced cost and length of hospitalization. It requires good bowel preparation and bowel irrigation, identification of the perforation during the procedure and immediate clipping, post procedure antibiotic treatment, and close observation for signs and symptoms of peritonitis. Surgery should be the last resort in the management of failure of conservative treatment.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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