Original Article

Intraoperative angiography with indocyanine green injection for precise localization and resection of small bowel bleeding

Jun Kawachi,[1] Hidemitsu Ogino,[2] Rai Shimoyama,[1] Chikamasa Ichita,[3] Naoko Isogai,[1] Takaaki Murata,[1] Katsunori Miyake,[1] Tomoki Nishida,[1] Ryuta Fukai,[1] and Hiroyuki Kashiwagi[1]

[1]Department of Surgery, Shonan Kamakura General Hospital, Kamakura, [2]Department of Surgery, Narita Tomisato Tokushukai Hospital, Tomisato, and [3]Gastroenterology Center, Shonan Kamakura General Hospital, Kamakura, Japan

Aim: Bleeding in the small bowel rarely occurs, and its treatment is challenging. Surgery is sometimes required in unstable patients; however, intraoperative identification of the bleeding site is extremely difficult. Many methods have been reported, but no standard strategy has been established yet. Here, we aimed to assess the safety and feasibility of intraoperative angiography with indocyanine green staining to accurately identify small bowel bleeding sites.

Methods: This retrospective study analyzed contrast-enhanced computed tomography images of patients (n = 8) with small bowel extravasation who underwent surgery. If extravasation or other vessel abnormalities that were potential bleeding sites were detected on intraoperative angiography, a microcatheter was placed as close as possible to the extravasation site. Laparotomy was carried out, and 3–5 mL indocyanine green was injected through the microcatheter. The green-stained segment of the small bowel was resected.

Results: Seven of the eight patients had positive angiographic findings and underwent bowel resection. The eighth patient had no abnormalities and hence did not undergo laparotomy. The rate of hemostatic success among the resected cases was 85.7% (six of seven cases). The resected specimens showed pathologic features in six of the seven patients (85.7%), all of whom achieved hemostasis. One patient had pneumonia and congestive heart failure that required longer hospital stay, but no mortality occurred.

Conclusions: Intraoperative angiography with indocyanine green injection, followed by resection for massive small bowel bleeding is effective. This can be a therapeutic option for hemodynamically unstable patients.

Key words: Indocyanine green, intraoperative angiography, small bowel bleeding

INTRODUCTION

AMONG ALL CASES of gastrointestinal (GI) bleeding, 5% originate from the small bowel.[1] If a patient is hemodynamically stable, minimally invasive techniques, such as balloon endoscopy or video capsule endoscopy, are effective in treating obscure GI bleeding.[2–4] However, these are not useful in emergency settings, especially for unstable patients. Such patients require emergency transarterial embolization (TAE) or surgical removal of the bleeding site. Intraoperative bleeding site localization is challenging, but necessary; an excessively wide resection can cause severe disability, and missing the exact site can lead to recurrent bleeding.

The methods for detecting small bowel bleeding include intraoperative enteroscopy, preoperative computed tomography (CT)-guided percutaneous needle localization, and intraoperative angiography with dye injection. However, no standard strategy has yet been established because the availability of physicians, drugs, and medical equipment differs considerably among various medical institutions. Indocyanine green (ICG) dye is widely used for several clinical purposes, including liver function testing, surgical navigation,

Corresponding: Jun Kawachi, MD, Department of Surgery, Shonan Kamakura General Hospital, 1370-1 Okamoto, Kamakura, Kanagawa, Japan. E-mail: jkawachi@d7.dion.ne.jp.
Received 11 Apr, 2020; accepted 30 Jun, 2020
Funding information
No funding information provided.

and evaluation of the blood supply to organs; however, to the best of our knowledge, only one case report has mentioned its use for managing small bowel bleeding.[5] In this study, we evaluated the efficacy and safety of intraoperative angiography with ICG injection in locating the site of massive small bowel bleeding.

METHODS

FROM JANUARY 2009 to December 2018, eight patients (mean age, 65.1 years; range, 18–89 years; five men and three women) were admitted to our hospital for massive small bowel bleeding (Table 1). We obtained data from the patient files and laboratory records. Details regarding the preoperative, intraoperative, and postoperative clinical course were summarized. Patients who presented with massive hematochezia and/or melena underwent contrast-enhanced CT according to a standard algorithm for managing massive lower gastrointestinal bleeding (Fig. 1). If extravasation from the small bowel was observed (Fig. 2), the patient was transferred to the hybrid operating room. Under general anesthesia, a 4-Fr sheath was introduced into the common femoral artery and a catheter was placed in the superior mesenteric artery. If extravasation (Fig. 3) or other findings, including abnormally running vessels or early venous drainage, were observed, a microcatheter was placed as close to the bleeding site as possible.

For laparotomy, a midline incision was made and 3–5 mL ICG, as gauged by the surgeon, was injected through the microcatheter, followed by resection of the green-stained region (Fig. 3, Movie S1) and functional end-to-end anastomosis. If there were no remarkable angiographic findings, the surgery was stopped.

RESULTS

DURING THE 9 -year study period, eight patients (mean age, 65.1 [range, 18–89] years; four men and three women) were admitted to our hospital for massive small bowel bleeding (Table 1). Six of the patients had vital signs suggestive of shock, including low blood pressure or tachycardia. Extravasation of contrast media on enhanced CT was observed in all patients. Four patients had diabetes mellitus, four were taking antithrombotic drugs, three were taking oral methylprednisolone, and three were on hemodialysis. Seven patients (case nos. 1–7) showed extravasation, early venous drainage, or abnormally running vessels on intraoperative angiography, and small bowel resection was carried out after ICG injection. Patient no. 8 had no notable angiographic findings, and the surgery was terminated; the patient had no recurrent bleeding post-discharge. The average time from CT to surgery was 124.5 (49–174) min. The average operative time including angiography was 115.6 (70–211) min. In total, 10.3 and 5.8 units of red blood cells and fresh frozen plasma were required, respectively. Only one patient needed platelet concentrates of 20 units.

Six of seven patients who underwent bowel resection (case nos. 1, 3, 4, 5, 6, and 7) had pathological findings in the resected specimens (85.7%) (Table 2), and achieved recurrence-free hemostasis. The pathological findings were arteriovenous malformation in two patients, and angiodysplasia, diverticulum, ulcer, and vasculitis in one patient each. Patient 2 underwent bowel resection because the angiographic findings revealed abnormally running vessels, but no pathological features were detected in the resected specimen. In this patient, the

Table 1. Patient data of eight subjects with small bowel bleeding

No.	Age (years)	Sex	Medical history	Medication	BP (mmHg), HR (/min)
1	67	M	DM HD	Antiplatelet	148/78, 69
2	74	F	DM HD	PSL	150/80, 69
3	78	M	–	–	80/63, 90
4	18	M	–	–	80/32, 94
5	73	M	DM OMI	Double antiplatelet	120/82, 119
6	67	M	DM HD AP	Double antiplatelet	72/51, 87
7	55	F	SLE	PSL, antiplatelet, anticoagulant	80/62,102
8	89	F	UC	PSL	109/78,102
Average	65.1				

–, not available; AP, angina pectoris; BP, blood pressure; DM, diabetes mellitus; F, female; HD, hemodialysis for chronic renal failure; HR, heart rate; M, male; OMI, old myocardial infarction; PSL, prednisolone; SLE, systemic lupus erythematosus; UC, ulcerative colitis.

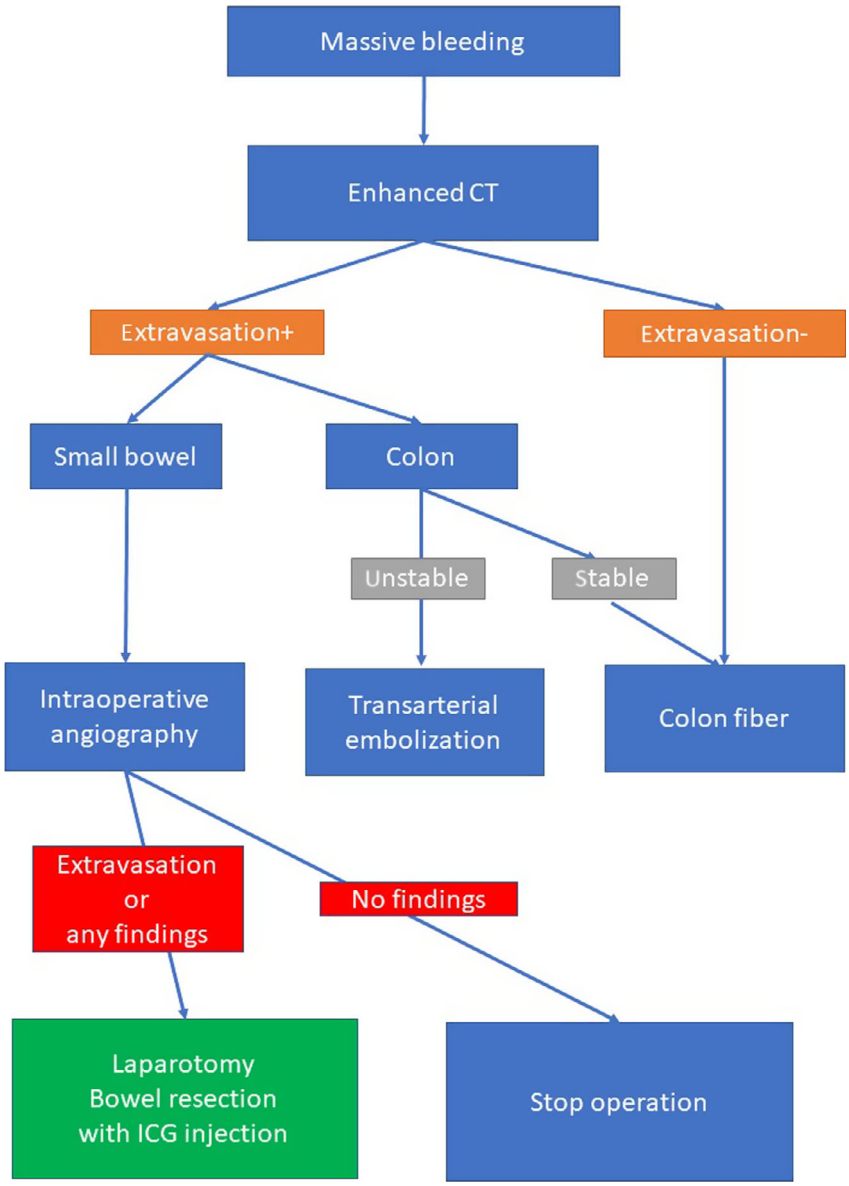

Fig. 1. Algorithm for massive lower gastrointestinal bleeding. CT, computed tomography; ICG, indocyanine green.

bleeding stopped after only one episode of recurrent bleeding, without any treatment. The cause of bleeding was unknown. Overall, the hemostatic success rate was 85.7% (six of seven cases). All patients were discharged without any complications, except for one high-risk patient (case no. 7) who had pneumonia and congestive heart failure and required prolonged hospitalization. The complication rate was 12.5% (1/8). The mean resected bowel length was 35.3 (range, 4–90) cm. The mortality rate was zero.

DISCUSSION

IN THIS STUDY, we used ICG to identify the bleeding sites in the small bowel. The bleeding origin could be identified in the resected specimen in six of the seven patients who underwent bowel resection. In the eighth patient, no abnormal angiographic findings were observed.

Small bowel bleeding can occasionally be quite significant and require emergency treatment. For obscure GI bleeding, balloon endoscopy or capsule endoscopy have

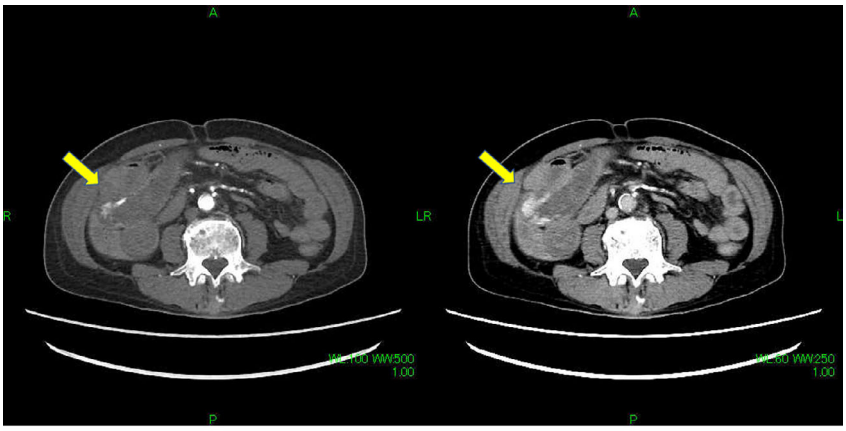

Fig. 2. Contrast-enhanced computed tomography (A, early phase; B, delayed phase) for detection of small bowel bleeding. The contrast blush of the small bowel (arrow) in the early phase spreads in the delayed phase.

Fig. 3. Extravasation to the small bowel on angiography (A) and injection of indocyanine green (B, before injection; C, after injection). Arrow indicates the extravasation site.

been reportedly effective, but they cannot be used in unstable patients. Nusbaum and Baum reported that extravasation from the GI tract was detectable using angiography if the bleeding rate exceeded 0.5 mL/min.[6] For GI bleeding, TAE with a gelatin sponge, a coil, alcohol, or n-butyl-2-cyanoacrylate has been effective, with technical and clinical success rates of 89%–100% and 68%–91%, respectively, but with bowel ischemia occurring in 4.6%–10% of cases.[7–10]

The American Society of Gastrointestinal Endoscopy guidelines for small bowel bleeding recommend TAE for unstable patients or patients with brisk bleeding.[11] The guidelines also state that the management of massive bleeding should be coordinated with surgery and interventional radiology. We adopted the same indication for angiography, but utilized additional resection after angiography instead of embolization. There are no randomized studies comparing surgery with TAE for small bowel bleeding, but surgery has

Table 2. Patient outcomes among eight subjects with small bowel bleeding

No.	Hemostasis	Angiographic findings	Pathological findings	Length of specimen (cm)	Time from CT to operation (min)	Operative time (min)	RBC	FFP	PC	Discharge POD
1	Success	Early venous drainage	Angiodysplasia	90	145	211	6	4	–	10
2	Rebleed	Abnormally running vessel	No region	50	176	177	6	–	–	16
3	Success	Extravasation	Diverticulum	29	116	95	12	10	–	25
4	Success	Early venous drainage	AVM	4	49	143	16	6	–	10
5	Success	Early venous drainage	AVM	16	174	80	12	8	–	17
6	Success	Extravasation	Vasculitis	50	122	79	16	6	–	10
7	Success	Extravasation	Ulcer	8	88	70	8	6	20	176
8	No treatment	–	–	–	126	70	6	6	–	19
Average				35.3	124.5	115.6	10.3	5.8	2.5	35.3

AVM, arteriovenous malformation; CT, computed tomography; FFP, fresh frozen plasma; PC, platelet concentrates; POD, post operative day; RBC, red blood cell.

the advantage of obtaining pathology samples, including masses or tumors.

In the emergent setting, we adopt a CT-first approach (Fig. 1) to massive bleeding. If extravasation from the small bowel is observed, the patient is taken to the operating room for intraoperative angiography. Intraoperative identification of the precise bleeding site is difficult. The localization methods include preoperative clipping using balloon endoscopy, preoperative dye injection, CT-guided needle placement,[12,13] and intraoperative enteroscopy.[14,15] Puncturing from the surface poses the risk of injury to other organs. Intraoperative enteroscopy requires enterotomy and the use of a disinfected endoscope in the operative field. Another option is intraoperative angiography followed by resection. The marking methods used for the identification during angiography include guidewire placement,[16] Tc-labelled red blood cell injection,[17] and methylene blue dye injection through a microcatheter.[18–20] Guidewire localization, which surgeons accomplish using their hands, after laparotomy can be difficult, especially in patients with a fat-rich mesentery, and Tc-labelled red blood cells could be unavailable in an emergency setting. Therefore, methylene blue injection has become the preferred method.

Methylene blue had been widely used for chromoendoscopy.[21,22] However, its popularity is declining due to the recent widespread adoption of narrow band imaging for endoscopy and its association with DNA damage.[23,24] Indocyanine green has been used for preoperatively evaluating liver function before liver resection, especially in East Asian countries.[25] It has also been used for surgical navigation[26,27] and assessing organ blood perfusion during fluorescence imaging.[28,29] Hence, ICG might be a better choice for angiography than methylene blue, because it is safer and more easily available. To the best of our knowledge, the advantages of ICG have been reported in only one case, which involved a small bowel arteriovenous malformation.[5] Our report shows that ICG is also effective in other diseases that can cause massive GI bleeding.

The average time from the CT scan to surgery was long (124.5 min). Currently, this interval is decreasing from historical durations. We should shorten the time required to complete consultation at the emergency room, staff and hybrid room preparation, general anesthesia induction, and stabilization of the patient.

In this study, the resection length was quite short in some cases (case nos. 4 and 7). If the extravasation is clearly visible and the microcatheter can be inserted as distally as possible, shorter lengths of bowel can be resected, making the surgery less invasive.

We undertook intraoperative angiography with ICG injection in a hybrid operating room, but it can also be carried

out in separate rooms for angiography and surgery. Although our procedures were directly visualized and the surgery was open, fluorescence imaging and laparoscopic surgery could be possible in the future.

The limitation of intraoperative angiography with ICG is that it does not allow for therapeutic intervention when angiographic abnormalities are not found. In this study, we detected the bleeding site in seven of the eight patients. In the patient with no detectable bleeding on angiography (case no. 8), we assumed that hemostasis had occurred while the patient was being transferred from the emergency room to the operating room. Moreover, we had one case of negative resection with no pathological findings in the resected specimen (case no. 2). In this case, the finding of abnormally running vessels on angiography was equivocal. The threshold for a positive angiographic finding should be strict. Recurrent bleeding is possible in such cases, which often necessitates repeat angiography. If this occurs, local anesthesia can be considered for angiography, followed by general anesthesia for bowel resection.

In conclusion, intraoperative angiography with ICG injection can be a feasible method for identifying the sites of massive small bowel bleeding, thereby enabling resection. This can be a therapeutic option for hemodynamically unstable patients. Unlike coiling TAE, the unstable patient would not need to be transferred to the operating room in the case of treatment failure. Moreover, it has the advantage of obtaining pathological findings, which can lead to a correct diagnosis. The use of local anesthesia for angiography before laparotomy with general anesthesia should be considered. Laparoscopy is an option that can be used in the future as well.

DISCLOSURE

Approval of research protocol: This retrospective study was approved by the ethics committee of Shonan Kamakura General Hospital.
Informed consent: The requirement for obtaining informed consent from patients was waived due to the study's retrospective nature. Patients were allowed to withdraw from the study whenever they wished.
Registry and the registration no. of the study: N/A.
Animal studies: N/A.
Conflict of interest: None.

DATA AVAILABILITY STATEMENT

All data are available on request.

REFERENCES

1 Briley CA Jr, Jackson DC, Johnsrude IS, Mills SR. Acute gastrointestinal hemorrhage of small-bowel origin. Radiology 1980; 136: 317–9.
2 Shishido T, Oka S, Tanaka S *et al*. Outcome of patients who have undergone total enteroscopy for obscure gastrointestinal bleeding. World J. Gastroenterol. 2012; 18: 666–72.
3 Sun B, Rajan E, Cheng S *et al*. Diagnostic yield and therapeutic impact of double-balloon enteroscopy in a large cohort of patients with obscure gastrointestinal bleeding. Am. J. Gastroenterol. 2006; 101: 2011–5.
4 Ohmiya N, Yano T, Yamamoto H *et al*. Diagnosis and treatment of obscure GI bleeding at double balloon endoscopy. Gastrointest. Endosc. 2007; 66: S72–S77.
5 Ono H, Kusano M, Kawamata F *et al*. Intraoperative localization of arteriovenous malformation of a jejunum with combined use of angiographic methods and indocyanine green injection: Report of a new technique. Int. J. Surg. Case Rep. 2016; 29: 137–40.
6 Nusbaum M, Baum S. Radiographic demonstration of unknown sites of gastrointestinal bleeding. Surg. Forum. 1963; 14: 374–5.
7 d'Othee BJ, Surapaneni P, Rabkin D, Nasser I, Clouse M. Microcoil embolization for acute lower gastrointestinal bleeding. Cardiovasc. Intervent. Radiol. 2006; 29: 49–58.
8 Koh DC, Luchtefeld MA, Kim DG *et al*. Efficacy of transarterial embolization as definitive treatment in lower gastrointestinal bleeding. Colorectal. Dis. 2009; 11: 53–9.
9 Murata S, Onozawa S, Nakazawa K *et al*. Glue embolization for endoscopically unmanageable gastrointestinal haemorrhage. Hepatogastroenterology. 2012; 59: 1126–30.
10 Hur S, Jae HJ, Lee M, Kim HC, Chung JW. Safety and efficacy of transcatheter arterial embolization for lower gastrointestinal bleeding: a single-center experience with 112 patients. J. Vasc. Interv. Radiol. 2014; 25: 10–9.
11 ASGE Standards of Practice Committee, Gurudu SR, Bruining DH *et al*. The role of endoscopy in the management of suspected small-bowel bleeding. Gastrointest. Endosc. 2017; 85: 22–31.
12 Heiss P, Feuerbach S, Iesalnieks I *et al*. Obscure gastrointestinal bleeding: preoperative CT-guided percutaneous needle localization of the bleeding small bowel segment. J. Vasc. Interv. Radiol. 2009; 20: 533–6.
13 Martinez JC, Thomas JL, Lukaszczyk JJ. Single incision laparoscopic surgery approach for obscure small intestine bleeding localized by CT guided percutaneous injection of methylene blue. Int. J. Surg. Case Rep. 2014; 5: 1082–5.
14 Lau WY, Wong SY, Yuen WK, Wong KK. Intraoperative enteroscopy for bleeding angiodysplasias of small intestine. Surg. Gynecol. Obstet. 1989; 168: 341–4.

15 Weaver GA, Bordley JT, Olson JE. Management of bleeding angiodysplasia of the upper small intestine. J. Clin. Gastroenterol. 1985; 7: 145–51.
16 Unal B, Kutlu R, Aydin C, Kayaalp C. Preoperative angiographic guidewire localization of the bleeding small bowel segment. Surg. Laparosc. Endosc. Percutan. Tech. 2011; 21: e97–e99.
17 Saito K, Koizumi K, Goto Y, Yamamoto K, Abe K. Localization of small bowel bleeding by arterial injection of Tc-99m-labeled RBC. Ann. Nucl. Med. 1999; 13: 191–4.
18 Fogler R, Golembe E. Methylene blue injection. An intraoperative guide in small bowel resection for arteriovenous malformation. Arch. Surg. 1978; 113: 194–5.
19 Mazziotti MV, Muldowney S, Darcy M, Hackett BP, Skinner MA. Intraoperative localization of small intestinal bleeding in an infant by methylene blue injection: a case report. J. Pediatr. Surg. 1998; 33: 754–5.
20 Mukai M, Ibusuki K, Gotoh T *et al*. Intraoperative fluoroscopic detection of an occult jejunal arteriovenous malformation. J. Laparoendosc. Adv. Surg. Tech. A. 2006; 16: 45–7.
21 Kiesslich R, Fritsch J, Holtmann M *et al*. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003; 124: 880–8.
22 Taghavi SA, Membari ME, Eshraghian A, Dehghani SM, Hamidpour L, Khademalhoseini F. Comparison of chromoendoscopy and conventional endoscopy in the detection of premalignant gastric lesions. Can. J. Gastroenterol. 2009; 23: 105–8.
23 Davies J, Burke D, Olliver JR, Hardie LJ, Wild CP, Routledge MN. Methylene blue but not indigo carmine causes DNA damage to colonocytes in vitro and in vivo at concentrations used in clinical chromoendoscopy. Gut 2007; 56: 155–6.
24 Hiraku Y, Goto H, Kohno M, Kawanishi S, Murata M. Metal-mediated oxidative DNA damage induced by methylene blue. Biochim. Biophys. Acta. 2014; 1840: 2776–82.
25 Makuuchi M, Kosuge T, Takayama T *et al*. Surgery for small liver cancers. Semin. Surg. Oncol. 1993; 9: 298–304.
26 Desiderio J, Trastulli S, Gemini A *et al*. Fluorescence image-guided lymphadenectomy using indocyanine green and near infrared technology in robotic gastrectomy. Chin. J. Cancer Res. 2018; 30: 568–70.
27 Ishizawa T, Saiura A. Fluorescence imaging for minimally invasive cancer surgery. Surg. Oncol. Clin. N. Am. 2019; 28: 45–60.
28 Santi C, Casali L, Franzini C, Rollo A, Violi V. Applications of indocyanine green-enhanced fluorescence in laparoscopic colorectal resections. Updates Surg. 2019; 71: 83–8.
29 Ishige F, Nabeya Y, Hoshino I *et al*. Quantitative assessment of the blood perfusion of the gastric conduit by indocyanine green imaging. J. Surg. Res. 2019; 234: 303–10.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Movie S1. The ileal surface changes to green after injection of indocyanine green l.