Editorial

Indocyanine green fluorescence angiography during laparoscopic rectal surgery

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Advances in medical equipment and surgical techniques have enabled surgeons to offer patients better oncological and clinical outcomes after colorectal resections. However, anastomotic leakage remains one of the most serious postoperative complications in rectal surgery. The rate of anastomotic leakage after rectal surgery has been reported at 6% to 14% (1-4). In particular, low anastomoses have a considerably higher risk of leakage compared to intraperitoneal ones (1,2). Anastomotic leakage results in increased length of hospital stay, health care cost, morbidity, and mortality rates (3,4). In addition, anastomotic leakage has been found to negatively impact prognosis on local recurrence and cancer specific survival (5).

There are many risk factors related to anastomotic leakage. Risk factors can be categorized as patient-related, disease-related, and intraoperative-related. Patient-related risk factors include gender, body mass index (BMI), nutrition, and American Society of Anesthesiologists (ASA) score (1-3,6). Disease-related factors include level of anastomosis, neoadjuvant therapy, and tumor size (1,2,6). These risk factors may be beyond the influence of the surgeons. Conversely, intraoperative-related factors including blood perfusion to the anastomotic tissue, tension on the anastomosis, operative time, blood loss, and number of stapler firings (2,6-8), can be controlled by the surgeons. Among these factors, blood perfusion is thought to be an important factor for avoiding anastomotic leakage. Adequate blood supply is crucial for successful healing, and avoidance of intestinal ischemia and necrosis (6-8). Anastomotic leakage and stricture may be attributed to inadequate perfusion of anastomotic tissue.

Accurate determination of the resection margin of the viable bowel may help to reduce anastomotic leakage. The selection of an optimal site for anastomosis has been dependent on the surgeons' gross inspection. Intestinal microperfusion and viability is usually estimated intraoperatively from clinical parameters, such as color of the bowel wall, presence of bowel peristalsis, bleeding from the edges of the bowel, and palpable pulsations of mesenteric arteries. However, this assessment is subjective and based on the surgeons' experience. Karliczek *et al.* (9) evaluated the accuracy of the surgeons' gross inspection for anastomotic leakage occurrence in a prospective clinical study. The surgeons' ability to predict anastomotic leakage appeared to be low in gastrointestinal surgery, with a sensitivity of 61.3% and a specificity of 88.5%. Thus, objective and reliable intraoperative methods to assess bowel viability are required.

There are several different intraoperative assessment of anastomotic microperfusion, such as Doppler technology, tissue oxygen tension, and oxygen spectroscopy (10,11). However, due to equipment cost, complex maneuvers, lack of reproducibility, and the need for a specialist, these techniques have thus far been experimental and have not achieved widespread clinical acceptance. In recent years, indocyanine green fluorescence angiography (ICG-FA) has proved useful in assessing real-time microperfusion intraoperatively and can apply to open, laparoscopic, and robotic surgery.

ICG is a sterile, anionic, water-soluble, tricarbocyanine

compound dye that serves as an optical contrast agent. It absorbs near-infrared (NIR) light at 800–810 nm and emits it at a slightly longer wavelength of 830 nm. Following intravenous injection, ICG rapidly and extensively binds to plasma proteins, and is confined to the intravascular compartment. It is cleared by the liver in 3 to 5 minutes and excreted via the bile within 10–15 minutes. ICG has been safely used clinically in many countries for over 30 years. ICG exhibits a low toxicity with few adverse events (12,13). However, ICG contains sodium iodide and therefore should be used with care in patients with an iodine allergy. Special camera filters are necessary to visualize the ICG fluorescence. The light needed for the excitation of the fluorescence is generated by a near infrared light source which is attached directly to a camera. This camera allows the absorption of the ICG fluorescence to be recorded in real time. ICG-FA is suitable for use as an intraoperative imaging tool, and has been associated with improved outcomes in coronary, transplant, plastic surgery, and a number of other surgical procedures (14). ICG-FA was validated for assessing bowel microperfusion in a pig ischemia model (15). The fluorescence intensity was directly correlated with tissue perfusion, and ICG-FA could effectively detect the demarcation between ischemic and vascular areas.

There are several recent articles which describe the usefulness of ICG-FA for colorectal surgery with first report published by Kudszus *et al.* (16). They reported that ICG-FA led to a change of the initially planned proximal transection line in 13.9% (28/201) of cases. ICG-FA significantly reduced anastomotic leakage rate in colorectal surgery by 4% compared to a historical control group (3.5% *vs.* 7.5%). ICG-FA during colorectal surgery has also been described in other non-randomized studies (17-22). Jafari *et al.* (17) reported the results of a multi-institutional prospective single armed study, PILLAR-II that assessed the feasibility and utility of ICG-FA in left-sided colorectal resections. In this study, ICG-FA obtained successful imaging in 98.6% (137/139) of cases. The overall anastomotic leakage rate was 1.4% (2/139). ICG-FA led to change in the surgical plan in 8% (11/139) of cases, with most changes occurring at the time of transection of the proximal margin due to hypoperfusion, and no anastomotic leakage occurred in these patients. However, the height of anastomosis from the anal verge was higher than or equal to 8 cm in 74.1% (103/139) of cases and this study did not focus on total mesorectal excision (TME).

There are very few articles focused on the use of ICG-FA during rectal surgery with TME, which has a higher risk of leakage compared to colon surgery, and the rate of diverting stoma is higher (18,19). Boni *et al.* focused on rectal surgery with TME and reported that ICG-FA was safe and effective. ICG-FA influenced the surgical strategy in 4.7% (2/42) of cases and there was no anastomotic leakage (0/42) in low rectal cancer resection. Gröne *et al.* (18) also reported that the overall anastomotic leakage rate was 5.6 % (1/18) in low rectal and anorectal anastomoses.

Most of the studies were focused on the change in surgical decision making, however there are a few studies that have reported on the reduction in anastomotic leakage rate (16,20,21). Boni *et al.* reported that the anastomotic leakage rate was 0% and 5.2% in the ICG-FA group and historical control group, respectively. A recent systematic review showed that ICG-FA of colorectal anastomosis was associated with a significantly lower risk of anastomotic leakage compared with a control group without ICG-FA (3.8% *vs.* 7.6%; P=0.0055) (20). Only one retrospective case-matched study by Kin *et al.* (21) revealed that there was no difference in anastomotic leakage rate in colorectal resection between the ICG-FA group and control group. The authors acknowledged several limitations of their study such as the retrospective nature of the study, selection bias and the small sample size.

There are several limitations of ICG-FA. First, the surgeons' assessment of the intensity of perfusion is subjective. One study attempted to evaluate the fluorescence intensity by a five step score ("1" indicating no uptake and "5" indicating maximal uptake) but this assessment did not clearly show any conclusion regarding the predictive value of an abnormal ICG-FA (19). Another study aimed to quantify the fluorescence intensity level by using specially designed software that calculated the steepness of the light emission curve (pixel intensity per second) in order to achieve a more objective perfusion assessment (16). Unfortunately, this study did not lead to a cut-off value to quantify the fluorescence intensity, which is needed to minimize observational variability between surgeons. The ideal time to perfusion after injection of ICG is unknown. Kawada *et al.* (22) reported that the median time to perfusion was 35 seconds. However, the association between the time and poor perfusion is unclear. Therefore, ICG-FA remains subjective until more objective cut-off levels for sufficient perfusion are established.

Secondly, ICG-FA can be influenced by various conditions, such as distance, surrounding lighting, the dose of ICG injection and the effect of repeated ICG injections.

The distance between the tip of the camera and subject, and the operating room lighting may affect the fluorescence intensity (23). The optimal dose of ICG injection prior to assessment is unknown. The fluorescence intensity of ICG is almost linearly increased with concentration within a low concentration range, while the fluorescence intensity peaks and subsequently decreases at a higher concentration, a phenomenon known as the 'quenching effect', and is an important consideration (23). This effect cannot be controlled by the surgeon and lower concentrations are recommended to avoid this problem. However, the dose of ICG varies according to the studies. The effect of repeated injections of ICG is unknown and has not been investigated (24).

In conclusion, ICG-FA enables the surgeon to ensure sufficient blood supply to the anastomosis. ICG-FA is easily reproducible, cost effective, incurs little additional time, and has limited adverse effects. ICG-FA may prevent anastomotic leakage in patients undergoing colorectal surgery. However, no randomized controlled trials have been published and the present studies lack a high level of evidence therefore the clinical benefit of ICG-FA is inconclusive. A large, randomized, controlled trial, PILLAR-III, could determine if ICG-FA would have a positive impact on anastomotic leakage rate in rectal surgery.

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References

1. Pommergaard HC, Gessler B, Burcharth J, et al. Preoperative risk factors for anastomotic leakage after resection for colorectal cancer: a systematic review and meta-analysis. Colorectal Dis 2014;16:662-71.
2. Qu H, Liu Y, Bi DS. Clinical risk factors for anastomotic leakage after laparoscopic anterior resection for rectal cancer: a systematic review and meta-analysis. Surg Endosc 2015;29:3608-17.
3. Kang CY, Halabi WJ, Chaudhry OO, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg 2013;148:65-71.
4. Snijders HS, Wouters MW, van Leersum NJ, et al. Meta-analysis of the risk for anastomotic leakage, the postoperative mortality caused by leakage in relation to the overall postoperative mortality. Eur J Surg Oncol 2012;38:1013-9.
5. Mirnezami A, Mirnezami R, Chandrakumaran K, et al. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 2011;253:890-9.
6. Kingham TP, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. J Am Coll Surg 2009;208:269-78.
7. Foster ME, Brennan SS, Morgan A, et al. Colonic ischaemia and anastomotic healing. Eur Surg Res 1985;17:133-9.
8. Thompson SK, Chang EY, Jobe BA. Clinical review: Healing in gastrointestinal anastomoses, part I. Microsurgery 2006;26:131-6.
9. Karliczek A, Harlaar NJ, Zeebregts CJ, et al. Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. Int J Colorectal Dis 2009;24:569-76.
10. Urbanavičius L, Pattyn P, de Putte DV, et al. How to assess intestinal viability during surgery: A review of techniques. World J Gastrointest Surg 2011;3:59-69.

11. Nachiappan S, Askari A, Currie A, et al. Intraoperative assessment of colorectal anastomotic integrity: a systematic review. Surg Endosc 2014;28:2513-30.
12. Benya R, Quintana J, Brundage B. Adverse reactions to indocyanine green: a case report and a review of the literature. Cathet Cardiovasc Diagn 1989;17:231-3.
13. Hope-Ross M, Yannuzzi LA, Gragoudas ES, et al. Adverse reactions due to indocyanine green. Ophthalmology 1994;101:529-33.
14. Alander JT, Kaartinen I, Laakso A, et al. A review of indocyanine green fluorescent imaging in surgery. Int J Biomed Imaging 2012;2012:940585.
15. Diana M, Noll E, Diemunsch P, et al. Enhanced-reality video fluorescence: a real-time assessment of intestinal viability. Ann Surg 2014;259:700-7.
16. Kudszus S, Roesel C, Schachtrupp A, et al. Intraoperative laser fluorescence angiography in colorectal surgery: a noninvasive analysis to reduce the rate of anastomotic leakage. Langenbecks Arch Surg 2010;395:1025-30.
17. Jafari MD, Wexner SD, Martz JE, et al. Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): a multi-institutional study. J Am Coll Surg 2015;220:82-92.e1.
18. Gröne J, Koch D, Kreis ME. Impact of intraoperative microperfusion assessment with Pinpoint Perfusion Imaging on surgical management of laparoscopic low rectal and anorectal anastomoses. Colorectal Dis 2015;17 Suppl 3:22-8.
19. Sherwinter DA, Gallagher J, Donkar T. Intra-operative transanal near infrared imaging of colorectal anastomotic perfusion: a feasibility study. Colorectal Dis 2013;15:91-6.
20. Degett TH, Andersen HS, Gögenur I. Indocyanine green fluorescence angiography for intraoperative assessment of gastrointestinal anastomotic perfusion: a systematic review of clinical trials. Langenbecks Arch Surg 2016;401:767-75.
21. Kin C, Vo H, Welton L, et al. Equivocal effect of intraoperative fluorescence angiography on colorectal anastomotic leaks. Dis Colon Rectum 2015;58:582-7.
22. Kawada K, Hasegawa S, Wada T, et al. Evaluation of intestinal perfusion by ICG fluorescence imaging in laparoscopic colorectal surgery with DST anastomosis. Surg Endosc 2016. [Epub ahead of print].
23. Miwa M. The principle of ICG fluorescence mode. Open Surg Oncol J 2010;2:26-8.
24. Diana M, Halvax P, Dallemagne B, et al. Real-time navigation by fluorescence-based enhanced reality for precise estimation of future anastomotic site in digestive surgery. Surg Endosc 2014;28:3108-18.

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