



Does routine use of indocyanine green fluorescence angiography prevent anastomotic leaks? A retrospective cohort analysis

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ABSTRACT

Background: Insufficient perfusion to anastomoses in colorectal surgery is known to lead to complications. This study aims to evaluate whether routine use of fluorescence angiography (FA) alters the incidence of anastomotic leaks after colorectal surgery.

Methods: This was a retrospective study of 554 colorectal resections with and without the use of intraoperative fluorescence angiography. Anastomotic leak rates and whether angiography altered surgical management were the main outcomes measured.

Results: The anastomotic leak rate was found to be 1.3% both with and without use of FA ($p > 0.05$). Significantly more alterations were made to planned anastomotic site in FA group ($n = 13$, 5.6%) as compared to the group prior to use of FA in whom no alterations were made ($p < 0.05$).

Conclusions: No significant difference was found in anastomotic leak rates between the two groups studied. Routine use of fluorescence angiography significantly altered intra-operative decision-making without discernible change in clinical outcome.

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Introduction

Anastomotic leak can be a devastating complication, leading to increased length of stay, higher local recurrence, greater cost and increased mortality.^{1–3} In colorectal surgery, incidence of anastomotic leaks ranges from 1 to 19%, depending on anastomotic site as well as patient specific and operative factors.¹ Several tenets must be followed to prevent an anastomotic leak, including: aseptic technique with gentle and careful dissection, tension-free anastomosis, precise placement of sutures, appropriate staple height, and adequate blood flow to the bowel.⁴ Proper blood supply is assured through various subjective measures, including palpation of mesenteric pulses, assessment of cut edges for bleeding, and evaluation of bowel color. Other clinical adjuncts include Doppler signals, fluorescein injection, and indocyanine green fluorescence angiography.

Indocyanine green (ICG) fluorescence angiography (FA) has been used in numerous other fields, including ophthalmology, plastic

and reconstructive surgery, as well as head and neck surgery to evaluate tissue perfusion.⁵ The utilization of ICG has increased over the last few years in colorectal surgery as shown in a systematic review of the literature conducted by van den Bos et al. Ten studies were reviewed concluding the feasibility of this technique in colorectal surgery.⁶

The SPY Elite Intraoperative Perfusion Assessment System (Novadaq Technologies Inc., Bonita Springs, FL) has been used in plastic, micro-, reconstructive, gastrointestinal and cardiovascular procedures to measure tissue perfusion using ICG-FA. Unlike other systems, the SPY-Q software provides an absolute numerical value on a 0–256 gray scale representing ICG fluorescence intensity, thus providing an objective measurement to what was once a subjective assessment.

This retrospective historical cohort study aims to evaluate whether routine use of ICG-FA alters the incidence of anastomotic leak after colorectal surgery.

Materials & methods

Over the period ranging from June 2013 to June 2016, all colorectal resections at a single institution performed with intra-

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operative ICG-FA were reviewed retrospectively. Prior to creating the anastomosis, intravenous administration of 2 mL of ICG was followed by FA using the SPY Elite Imaging System. Absolute fluorescence values on the 0–256 gray-scale using SPY-Q software 60 seconds after the initial fluorescence signal were recorded in the medical record. Fluorescence values were recorded for both proximal and distal bowel segments after transection but prior to anastomosis except when performing low anterior resection (LAR) when it was not feasible to perform FA on a low-lying rectal stump *in vivo*. During LAR the splenic flexure was routinely mobilized to provide a tension-free anastomosis and the inferior mesenteric artery was ligated. Air leak test was also routinely performed.

The decision to alter the anastomotic site based on FA results was documented in the operative report. Electronic medical records were reviewed to determine whether patients suffered clinically evident anastomotic leak post-operatively, defined as anastomotic disruption evidenced by post-operative imaging or endoscopy. A historical control group consisted of colorectal resections performed by the same two surgeons without the use of FA between January 2010 and July 2013. Multiple details of patient demographics and operative factors for both groups were recorded with the primary endpoint being the rate of anastomotic leak. Confidence intervals with $\alpha = 0.05$ were compared to determine statistical significance. Institutional review board approval was granted and no funding was obtained.

Results

Three-hundred and twenty consecutive patients undergoing colorectal resection prior to the use of FA were compared to 234 consecutive patients in whom FA was utilized. As demonstrated in Table 1, there was no significant difference between the two groups in terms of demographic factors such as age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, proportion of benign and malignant disease, use of neoadjuvant chemoradiation, or history of diabetes or smoking. The groups were also similar in terms of operative factors such as operative time, estimated blood loss, proportion of emergent cases, proportion of laparoscopic or robotic cases, and proportion of patients receiving diverting ileostomies (Table 1). Furthermore, the distribution of cases and level of anastomosis was similar between the two groups as represented in Table 2.

The anastomotic leak rate was found to be 1.3% both with and without use of ICG-FA ($p > 0.05$), as described in Table 3. Secondary endpoints included mortality as well as number of alterations to the projected anastomotic site as a result of angiographic evaluation. Mortality rate was not statistically different before and

after the use of FA, at 0.6% and 0.4%, respectively ($p > 0.05$). Significantly more alterations were made to the planned anastomotic site in the FA group ($n = 13$, 5.6%) as compared to the group prior to the use of FA in whom no alterations were made by definition ($p < 0.05$). Both of these findings are represented in Table 3. Among this group of thirteen patients who had alterations made based on FA, there was no statistically significant difference in the percentage of patients with a diagnosis of malignancy (46.2%; 95% CI [19.1, 73.3%]) or in the percentage who underwent neoadjuvant treatment (15.4%; 95% CI [0, 35.0%]) when compared to the historical control group prior to FA. The level of anastomosis was not routinely documented. Of note, none of these thirteen patients suffered any complications.

There were no adverse reactions to ICG administration recorded. The mean fluorescence absolute value for all colon resections was 93.2, with a range from 34 to 253, while that of patients with anastomotic leak ranged from 50 to 100. The average absolute value when alteration was made was less than 40.

Discussion

Kingham and Pachter report a colorectal anastomotic leak rate between 1 and 19% with an acceptable leak rate ranging from 3 to 6% among experienced colorectal surgeons. The ensuing morbidity and mortality associated with anastomotic leak has multiple implications, including longer length of stay, higher costs and adverse effects on cancer recurrence.¹ In a prospective study of patients who underwent colorectal resection between 1996 and 2004, 25 out of 1417 patients (1.8%) had an anastomotic leak. Comparing patients with anastomotic leak to those without, length of hospital stay was 28 days versus 10 days and mortality rate was 32% versus 4%, respectively.⁷

Clinical judgment is still considered the most important element utilized by surgeons to avoid anastomotic leak. However, prospective studies have shown that clinical assessment of bowel perfusion lacks predictive accuracy and clinical risk assessment by the surgeon has low predictive value for development of an anastomotic dehiscence.⁸ Other adjuncts have been utilized including Doppler, fluorescein using UV Wood's lamp and ICG fluorescence angiography. ICG is an ideal molecule to use intra-operatively as it binds strongly to plasma proteins causing it to remain in the intravascular space but its short half-life of three to five minutes allows for rapid clearance and repeated usage in a single procedure. Furthermore, this molecule has an excellent safety profile with rare reported anaphylactic reactions.⁵ Spy Elite System utilizes ICG fluorescence to enable visualization of arterial inflow, venous return and tissue perfusion intra-operatively.

Table 1
Patient demographic and operative factors.

	Historical Control Group, Prior to FA (95% CI)	ICG-FA (95% CI)
Age (years)	62.5 (35.3, 89.7)	61.5 (34.6, 88.4)
BMI	28.3 (10.0, 46.6)	28.3 (15.6, 41.0)
ASA classification	2.3 (1.2, 3.4)	2.2 (1.3, 3.2)
Female	182 [56.9%; (51.4, 62.3%)]	126 [53.8% (45.7, 60.2%)]
Malignant	116 [36.3% (31.0, 41.5%)]	80 [34.2% (28.1, 40.3%)]
Diabetes	58 [18.1% (13.9, 22.3)]	38 [16.2% (11.5, 21.0)]
Smokers	51 [15.9% (11.9, 19.9)]	37 [15.8% (11.1, 20.5)]
Emergent	7 [2.2% (0.6, 3.8)]	3 [1.3% (0.0, 2.7)]
Neoadjuvant radiation	24 [7.5% (4.6, 10.4)]	16 [6.8% (3.6, 10.1)]
OR Time (min)	214.5 (116.8, 312.2)	234.9 (116.1, 353.7)
Blood Loss (mL)	127.3 (0, 495.6)	98.7 (0, 369.0)
Laparoscopic/Robotic	293 [91.6% (88.5, 96.4)]	217 [92.7% (89.4, 96.1)]
Diverting ileostomy	20 [6.3% (3.6, 8.9)]	14 [6.0% (2.9, 9.0)]

ASA: American Society of Anesthesiologists; BMI: body mass index; ICG: Indocyanine green; FA: fluorescence angiography.

Table 2
Case distribution.

	Historical Control Group, Prior to FA (95% CI)	ICG-FA (95% CI)	Alterations after ICG-FA
Right Hemicolectomy	84 [26.3% (21.4, 31.1%)]	64 [27.4% (21.6, 33.1%)]	0
Transverse Colectomy	3 [0.9% (0, 2.0%)]	3 [1.3% (0, 2.7%)]	0
Left Hemicolectomy	101 [31.6% (26.5, 36.7%)]	55 [23.5% (18.1, 28.9%)]	6
Low Anterior Resection	109 [34.1% (28.9, 39.3%)]	100 [42.7% (36.4, 49.1%)]	6
Subtotal Colectomy	10 [3.1% (1.2, 5%)]	3 [1.3% (0, 2.7%)]	0
Total Proctocolectomy with J-pouch	4 [1.3% (0, 2.5%)]	2 [0.9% (0, 2.0%)]	0
Hartmann's Reversal	9 [2.8% (1.0, 4.6%)]	7 [3.0% (0.8, 5.2%)]	1

ICG: Indocyanine green; FA: fluorescence angiography.

There have been several studies examining the utility of ICG fluorescence angiography with respect to colorectal surgery. Kudsus et al. used IC View (Pulsion Medical Systems AG, Munich, Germany), an intraoperative laser fluorescence angiography (LFA) system to assess bowel perfusion at anastomotic site. The authors conducted a matched control retrospective study (n = 402) comparing patients who underwent colorectal resections without LFA to patients who underwent colectomies with LFA. The control group had an anastomotic leak rate of 7.5% compared to 3.5% in the LFA group. Moreover, the study revealed a significantly reduced hospital stay in the LFA group.⁹

Near-infrared fluorescence angiography using PINPOINT (Novadaq, Mississauga, ON, Canada) is another system that using ICG fluorescence that has been shown to be feasible and reproducible in laparoscopic colorectal surgery. Ris et al. analyzed 30 consecutive colorectal resections using this system; a diverting ostomy was avoided in three out of six patients in part of because of the confidence imparted by the perfusion angiogram. There were no recorded anastomotic leaks.¹⁰ PILLAR II, a prospective, multi-centered clinical trial, evaluated the utility of ICG-FA using PINPOINT system for intraoperative perfusion assessment as well. A total of 139 left colectomies and low anterior resections were analyzed with FA, changing surgical plans in 11 cases. The anastomotic leak rate was 1.4% (n = 2). There were no leaks in the 11 cases that had alterations.¹¹ In addition, Ris et al. conducted a multicenter phase II trial of near-infrared imaging in elective colorectal surgery in which a total of 504 patients underwent colon resections with standard utilization of ICG-FA using the PINPOINT system. The ICG assessment resulted in a change in the site of bowel division in 29 patients (5.8%) with no subsequent leaks in these patients. The overall leak rate in this study was 2.4%, significantly lower than in participating centers in which similar operations with identical technique but without ICG technology displayed a 5.8% leak rate.¹²

In a case-matched retrospective study conducted by Kin et al., the authors sought to determine whether the use of intraoperative laser FA using SPY Imaging System affected the anastomotic leak rate in colorectal resections. One hundred seventy three pairs were analyzed and the anastomotic leak rate was found to be comparable in those who utilized intra-operative FA (7.5%) versus those who did not (6.4%) with p = 0.67. Eight patients (4.6%) underwent additional colon resection after angiographic evaluation. One anastomotic leak was recorded in this subset of patients. The authors concluded that the benefit of intraoperative fluorescence

angiography is equivocal as their data revealed no association with decreased rates of leaks, though it did alter surgical management in several cases.¹³

Lastly, Boni et al. used fluorescence angiography (KARL STORZ GmbH & Co. KG, Tuttlingen, Germany) intraoperatively to assess colonic perfusion prior to and after completion of the anastomosis in colorectal resections. A total of 107 patients were included in the study with 4 cases having alterations in the transection point based on fluorescence intensity. None of these patients suffered anastomotic leak.¹⁴ This group also looked at the impact of FA on post-operative complications and anastomotic leakage after laparoscopic LAR with total mesorectal excision (TME). Results were compared to a historical control group of 38 patients. Forty-two patients underwent a laparoscopic LAR with TME. The planned anastomotic level was changed due to hypoperfusion of the distal segment in two out of 42 patients (4.7%). Anastomotic leak rate was 0% in the FA group and 5% in historical group.¹⁵

The abovementioned studies all interpreted ICG fluorescence in a qualitative manner and therefore remain a subjective adjunct to clinical judgment. The Spy Elite System software allows for quantification of perfusion by assigning numeric values of intensity of fluorescence. As stated in a previous study conducted at this institution, the utility of these values remains to be determined and studies are scarce.¹⁶ In colorectal surgery, Foppa et al. conducted a prospective study to describe the impact of intraoperative ICG-FA using Spy-Q evaluation for small bowel ischemia and left colon resections. ICG angiography played a role in decision making in four out of 160 cases. The authors concluded that in cases of acute small bowel ischemia, resection is not warranted unless absolute values are below 19. In left colon resections, the recommended absolute unit for resection is less than 18.¹⁷

In the present study, FA was utilized to quantify bowel perfusion in 234 patients. These patients were compared to a historical group of 320 similar patients (Table 1). The leak rate before the use of SPY FA was not significantly different when compared to the leak rate with the use of SPY (Table 3), suggesting that routine use of ICG fluorescence angiographic evaluation does not independently decrease the incidence of anastomotic leak when used by experienced colorectal surgeons. There were a total of thirteen operations (5.6%) in which results of FA prompted additional bowel resection to an area of improved perfusion.

There are several limitations to this study. First, the sample size is small, albeit the largest available in assessing the SPY system. However, the exclusive use of SPY system may not reflect all modalities of FA; indeed, Kin et al. had similar findings to the present study in their qualitative assessment of SPY systems.¹³ Next, the study design is retrospective and this was not a strictly case-matched series, though patient demographic and operative factors were similar between the two groups (Table 1, Table 2). Being limited to two surgeons may reduce the generalizability of results. Furthermore, the group prior to use of FA had no changes to level of anastomosis by definition since all alterations were based on

Table 3
Endpoints before and after use of FA.

	Historical Control Group, Prior to FA	ICG-FA
Mortality	0.6% (0.0, 1.5)	0.4% (0.0, 1.3)
Alteration	0.0% (0.0, 0.0)	5.6% (2.6, 8.5)
Leak Rate	1.3% (0.0, 2.5)	1.3% (0.0, 2.7)

ICG: Indocyanine green; FA: fluorescence angiography.

subjective assessment, which may limit the significance of the higher rate of alteration found in the ICG-FA group. Lastly, the low initial anastomotic leak rate may mask the benefit of ICF-FA in populations with higher rates of anastomotic leak.

Conclusion

In this retrospective study, no significant difference was found in anastomotic leak rates between the group prior to the use of intraoperative angiography and the group utilizing fluorescence angiography. Routine use of SPY ICG-FA significantly altered intraoperative decision-making without discernible change in clinical outcome. Large, randomized control trials are needed to establish the benefit of using fluorescence angiography in colorectal surgery before its routine use can be recommended and expense justified. The clinical significance of absolute values in SPY-Q evaluation and their relationship to anastomotic leak requires further study.

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