Indocyanine Green (ICG) Fluorescence in the Assessment of Vascularity of Anastomotic Margins in Colorectal Surgery in a Lower Middle-Income Country (LMIC) Hospital

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ABSTRACT

Background and Objective. One of the uses of indocyanine green (ICG) in the surgical field is the evaluation of the anastomotic margins in colorectal surgery. This is of particular importance because fluorescence imaging may aid in detecting vascular compromise, allowing the surgeon to change the resection margin thereby decreasing the chance of an anastomotic leak. To date, there has been no study with its use locally. This study aimed to determine whether the use of ICG can safely identify if the margins of resection are well-vascularized in patients undergoing left-sided colon or rectal surgery, which in turn may reduce anastomotic leak rates.

Methods. Through a retrospective study design, the investigators gathered data of patients who underwent left-sided colon or rectal surgery. The groups were divided into those with and without the use of ICG and a comparative data on the anastomotic leak rates were analyzed.

Results. Eighty-six (86) patients with similar patient characteristics, tumor staging, and surgical approach were compared. Both the leak rates identified during the initial hospital stay and at 30 days post-operatively were lower in those where ICG was used (p=0.035, p=0.047, respectively) than those where ICG was not used.

Conclusion. ICG fluorescence imaging may reduce the anastomotic leak rates in patients undergoing colorectal surgery.

Keywords: indocyanine green, colon, rectum, colorectal surgery, surgical anastomosis, anastomotic leak

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INTRODUCTION

Indocyanine green (ICG) is an amphiphilic substance with an acceptable safety profile that has found utility in various surgical settings. Its ability to assess blood and biliary flow allows surgeons to identify anatomical structures in real time, providing vital information that may affect intraoperative decision-making. This information may help determine anastomotic viability and adequacy of excision or may identify structures in a hostile abdomen.[1-3] Compared

to other dyes, such as isosulfan blue or patent blue dye, ICG has a better safety profile with fewer reports of anaphylactic reactions, inflammation, skin or soft tissue discoloration, and skin or fat necrosis.[1]

Several studies have shown the possible value of utilizing ICG fluorescence imaging in colorectal surgery. Studies regarding the use of ICG in sampling lymph nodes[2], determining liver metastasectomy margins[3], and identifying vital structures such as the ureters[4] have been done. Further studies, however, are required to elucidate the value of ICG for these operations.

One of the uses of ICG fluorescence imaging in colorectal surgery that has been slowly gaining ground is its effectiveness in determining the ideal resection margins for anastomosis. Studies have shown that using ICG fluorescence imaging has led to changes in determining the segment of the bowel to be anastomosed, albeit with weak evidence.[1] Likewise, it has shown a possible advantage in terms of decreasing anastomotic leaks when used on left-sided colonic and rectal resections.[1,5]

A study by Son et al. determined a time ratio, which, when reached, may predict the occurrence of anastomotic complications such as a leak or dehiscence. They measured the time from the first fluorescence increase to maximum (T_{max} = ΔT), time from first fluorescence to half of the maximum ($T½_{max}$), and its time ratio (TR= $T½_{max}/T_{max}$). A significant correlation was found with anastomotic complications with a TR of 0.6 or greater, as it meant poor perfusion in that portion of the bowel.[6]

One landmark trial, although non-randomized, was the PILLAR II trial.[5] This demonstrated the utility and feasibility of intraoperative assessment of colon and rectal perfusion using ICG. This prospective, multicenter, open-label study involved 11 centers in the United States and had 139 patients undergoing left-sided colon and rectal surgeries eligible for final analysis. They found that the use of ICG had surgical plans altered in 8% of patients, with a 1.4% overall leak rate. Of the 11 patients whose surgical plans were changed due to ICG, there were no anastomotic leaks noted.[5]

The FLAG trial, as reported by Zarodnyuk et al., included a total of 377 participants who were randomized 1:1 from an ICG group (187) and a control group (190). The authors found a decrease in anastomotic leak rate in low (4-8 cm from the anal verge, FAV) colorectal anastomoses compared to the control group (14.4% vs 25.7% p=0.04), but this difference was not observed in high (9-15 cm FAV) colorectal anastomoses (p=0.37).[7]

To date, no locally reported study has investigated the use of ICG fluorescence imaging in terms of its role in intraoperative decision-making regarding anastomotic margins and establishing a correlation with subsequent anastomotic leak rates.

OBJECTIVES

General Objective

To determine whether the use of ICG fluorescence imaging during left-sided colon or rectal resection-anastomosis is associated with a significant change in selecting the proximal line of resection.

Specific Objectives

1. To identify and record any change in the level of transection line when ICG fluorescence imaging is used during left-sided colon or rectal resection-anastomosis;
2. To identify the involved length of the additional bowel resected should a decision to resect more proximally was made;
3. To compare the 30-day anastomotic leak rate of patients following colorectal resection-anastomosis with and without the aid of ICG fluorescence imaging; and
4. To identify the adverse events associated with the use of ICG.

METHODS

Research Design

The study utilized a retrospective cohort study design.

Sampling Design and Sample Size

Using OpenEpi Version 3, this research required at least 43 subjects per group at an alpha of 0.05 and a power of 0.80. Both groups included patients who underwent left sided and rectal surgeries. The sample for both groups were retrospectively taken from the patient data recording system of the institution.

This computation was based on the results of the PILLAR II trial and its outcome on anastomotic leak rate with the use of ICG.[5] Anastomotic leak rate, in current available studies, is reported to occur in 3% to 20% of patients undergoing colorectal surgeries and depend on multiple factors such as type of surgery, radiation prior to surgery in rectal cancer cases, surgeon expertise, patient factors, and others. In the PILLAR II trial however, with the use of ICG, the anastomotic leak rate was only 1.4%.

METHODS

The sample for the control group was taken from the Integrated Surgical Information System (ISIS) of the hospital from January 2018 to September 2022. The patients who underwent either an elective left-sided colon surgery or rectal resection and anastomosis surgery, aged 18 to 75 years old, open or minimally invasive, with or without a protecting stoma, regardless of co-morbidities, were included. Patients in whom the ICG dye was used were classified under the "ICG group," and patients in whom ICG was not used under the "No ICG group." The No ICG group data was obtained in

the same years as the other group to represent the population in the same time frame and to minimize selection bias. The descriptive and outcome variables were collected from the electronic registry (Computerized Registry of Admissions and Discharges or RADISH) of the institution.

In the ICG group, any patient who had a possible hypersensitivity reaction to the ICG dye was noted and included as part of the data collection for the study. The ICG used is Diagnogreen, manufactured by Daiichi Sankyo from Tokyo, Japan, and is distributed by Zuellig Pharma. Currently, the Philippine Food and Drug Administration approval for medical use of the dye is being processed. In South Korea and Japan, this dye has been approved safe for medical and human use.

In the ICG group, the protocol was as follows: 1) prior to resection, the operating surgeon marked the bowel where he/she intended to transect (proximal and distal) in preparation for the eventual anastomosis. 2) A slow intravenous instillation of ICG was administered at 2.5 mg/ml (0.1-0.3 mg/kg). This dosing and time to assessment of perfusion protocols were both based on the recommendations of the systematic review done by Alius et al.[1] 3) After 2-5 minutes, an ICG infrared camera was used to show the features of the bowel segment of interest. 4) Perfusion to the proximal margin was identified and determined as "adequate" if there was even distribution of the dye via fluorescence angiography and "inadequate" when there was uneven or absent distribution of the dye. 5) At this point, the operating surgeon decided whether to transect the bowel at the previously marked site or to extend the proximal resection margin further. For surgical trainees, the resection margins was doubly checked by a consultant or the most senior surgeon in the team prior to any transection of bowels. 6) If the surgeon decided to extend the resection margin, this was regarded and recorded as a "change in decision." The change in the length of the proximal resection was measured from the previously marked site without the aid of the ICG to be the new margin determined after ICG. This was regarded and defined as the "change in resection margin." 7) Following resection and anastomosis, ICG fluorescence was repeated to check for the perfusion of the anastomosis and 8) Air leak test was done thereafter.

For the post operative outcomes, in-patient and 30-day outcomes were gathered from the admitted and outpatient database. All ancillary procedures or operative procedures done for the post-operative morbidities were reviewed and included in the data collection. All sensitive data relating to the privacy of the patients was removed from the data gathered.

Descriptive statistical analysis was done. An independent t-test was done to compare the demographic characteristics of both groups. The change in the resection margin in the ICG group was also noted and the mean change was determined. Anastomotic leak rates, 30-day anastomotic leak rates, and ileus rates of both groups were obtained and compared.

Ethical Considerations

This study was based on the relevant guidelines set and as specified in the Certificate of Agreement and Compliance. It was subjected to Philippine General Hospital Research Ethics Board (REB) approval prior to study commencement and modified according to the REB's requirements and recommendations.

RESULTS

From January 2018 to September 2022, 43 patients underwent left-sided surgery or rectal with resection and anastomosis in which ICG dye was used. Another 43 patients were identified based on the demographic characteristics of the ICG group. Patient demographics including age, gender, BMI, and ASA class were similar in both groups. Tumor characteristics such as tumor stage, nodal status, tumor level, exposure to preoperative chemotherapy or radiotherapy were likewise similar (Table 1).

In terms of the surgery done, there was no difference in the approach to surgery (open vs. laparoscopic vs robotic), splenic flexure mobilization, high/low ligation of inferior mesenteric artery (IMA), creation of a defunctioning stoma, level of anastomosis, blood loss, or operative time in the two groups. One patient in the ICG group was planned for a laparoscopic approach but was converted to an open surgery due to cardiopulmonary compromise during carbon dioxide insufflation (Table 2).

In the ICG group, all patients had a baseline ICG infrared imaging done. In four surgeries, there was a change in the resection margins. In these patients, an average of 3.25 cm bowel length from the originally planned margin was additionally resected. The anastomoses of all patients were checked after with ICG imaging. There was no change in anastomosis after the second ICG (Table 3).

For postoperative complications, 37.2% of patients in the No ICG group experienced either one or more morbidities following surgery, while 27.9% in the ICG group experienced at least one morbidity. There was significantly more anastomotic leak, 30-day anastomotic leak, and subsequently return to the operating room to manage these complications in the no ICG group. Post-operative ileus rates were similar in both groups (Table 4).

There were no recorded safety events associated with the use of indocyanine green.

DISCUSSION

The use of ICG in colorectal surgery has been studied and analyzed by various researchers to date. A recent systematic review by Alius et al. has summarized findings from multiple authors regarding its utility in preventing anastomotic leaks and detecting the positivity of metastatic lymph nodes.[1] In their review, they found a 25.74% change in

Table 1. Patient and Tumor Characteristics

Characteristic	No ICG (N=43)	With ICG (N=43)	p-value (<0.05)
Age in years *(Mean ±SD)*	56 (±10.3)	59 (±12.6)	0.287
Sex			
Male	24	23	0.831
Female	19	20	
BMI kg/m² *(Mean ±SD)*	23.2 (±3.1)	24.0 (±4.3)	0.296
BMI > 30, n (%)	0	2 (4.7%)	
BMI ≤ 30, n (%)	43 (100%)	41 (95.3%)	
ASA Class *(n)*			
I	4	3	0.568
II	37	37	
III	2	3	
IV	0	0	
Cancer Staging *(n)*			
T1	1	1	0.749
T2	7	8	
T3	27	27	
T4	8	7	
N0	8	16	0.064
N1	27	23	
N2	8	4	
M0	33	33	1.000
M1	10	10	
Preoperative chemotherapy *(n, %)*	21 (48.8%)	14 (32.6%)	0.127
Preoperative radiotherapy *(n, %)*	19 (44.2%)	14 (32.6%)	0.273
Tumor level			
Splenic flexure (n, %)	2 (4.7%)	0	0.603
Descending colon (n, %)	0	1 (2.3%)	
Sigmoid colon (n, %)	20 (46.5%)	24 (55.8%)	
Upper rectum (10-15cm FAV) (n, %)	2 (4.7%)	3 (7.0%)	
Mid rectum (5-10cm FAV) (n, %)	13 (30.2%)	11 (25.6%)	
Low Rectum (0-5cm FAV) (n, %)	5 (11.6%)	4 (9.3%)	

Table 2. Surgical Approach and Technique

Characteristic	No ICG (N, %) (N=43)	With ICG (N, %) (N=43)	p-value (<0.05)
Open surgery	30 (69.8%)	25 (58.1%)	0.740
Laparoscopic surgery	11 (25.6%)	15 (34.9%)	
Robotic surgery	5 (11.6%)	3 (7.0%)	
Conversion to open	0	1 (2.3%)	0.323
Splenic flexure mobilization	28 (65.1%)	25 (58.1%)	0.512
High ligation of IMA	9 (20.9%)	4 (9.3%)	0.082
Low ligation of IMA	34 (79.1%)	39 (90.7%)	
Protecting stoma	22 (51.2%)	17 (39.5%)	0.284
Level of anastomosis			
<8 cm	22 (51.2%)	14 (32.6%)	0.126
8-9 cm	7 (16.3%)	9 (20.9%)	
>10 cm	14 (32.6%)	20 (46.5%)	
Operative time *(Mean ±SD)*	352.5 (±114.5)	333.9 (±115.0)	0.464
Blood loss *(Mean ±SD)*	566.0 (±433.8)	425.1 (±385.1)	0.115

Table 3. Indocyanine Green Fluorescence before and after Transection

Characteristic	Data
Baseline ICG infrared image acquired	100%
Change to resection margin, *(n, %)*	4 (9.3%)
Distance from planned transection in cm *(Mean ±SD)*	3.25 (±0.96)
ICG infrared image after anastomosis	100%
Change in anastomosis after ICG	0%
Confirmation of vascular supply after anastomosis	100%

Table 4. Post-operative Complications

Characteristic	No ICG (N=43)	With ICG (N=43)	p-value (<0.05)
Postoperative morbidity *(n, %)*	17 (39.5%)	12 (27.9%)	
Anastomotic leak	10	3	0.035
30-day anastomotic leak	11	4	0.047
Ileus	8	8	0.135
Return to operating room	9	4	0.002

surgical decisions prompted by ICG evaluation in the study groups that included only those undergoing left colorectal surgeries. The anastomotic leak rate with ICG use was 3.75% in those that included only left-sided surgeries.

The PILLAR II trial found that with ICG, surgical plans changed in 8% of patients, with a 1.4% overall leak rate. For those patients with altered resection margins, no anastomotic leaks were noted.[5] In the succeeding PILLAR III trial done by the same group of investigators, however, it was noted that there was no significant difference in the anastomotic leak rate in those where ICG was used compared to those without it. The investigators attributed the difference in the results of their two studies to anastomotic leaks being caused by multiple factors and not just perfusion. Furthermore, it was explained that the surgeons included in their studies may have further developed the ability to assess perfusion more adequately, hence getting less benefit in the use of ICG than if the technique was used in less experienced surgeons.[8]

The FLAG trial strengthened the value of ICG utility.[7] The study found a decrease in anastomotic leak rate in low (4-8 cm from the anal verge) colorectal anastomoses in the ICG group, but not in those with high (9-15 cm FAV) colorectal anastomoses. De Nardi et al., however, found no significant difference in anastomotic leak rates, but noted that 11% of patients in the experimental group required a change in surgical resection margin following the use of ICG.[9]

In this study, we found that ICG use was associated with lower leak rates compared with those procedures for which ICG was not used. Despite the retrospective nature of this study, the patient and tumor characteristics were similar in both groups. Likewise, the mode of surgery – whether open, laparoscopic, or robotic – and some maneuvers used in the procedures showed no significant difference between the groups.

For the four patients in whom there was a change in resection margin following ICG, anastomotic leak was not noted, like the results of the PILLAR II trial. For trainees, however, the change in decision regarding the resection margin which can only be seen with the aid of ICG may help in proper identification of vascularized bowel segment, decreasing operative morbidity. In line with these findings, it may be interpreted that using ICG, at least in our setting, may provide significant benefit in decreasing leak rates.

Anastomotic leak rate in current available studies is reported to occur in 3% to 20% of patients undergoing colorectal surgeries and depend on factors such as type of surgery, radiation prior to surgery in rectal cancer cases, surgeon expertise, and patient factors.[10-13] There is no current report on leak rates locally. On our annual quality assurance reports in the last five years, anastomotic leak rate in our institution averages at approximately 10.5%.[14] While it may be impossible to decrease leak rates down to nil, the quest per institution to reduce leaks and its sequelae can never be over emphasized.

To our knowledge, this is the first study in the local setting to establish the utility of ICG in colorectal surgeries. Being in a lower middle-income country, preventing the possible added expense in terms of hospital costs in dealing with a post-operative complication, such as an anastomotic leak, justifies its use. Furthermore, preventing a leak to facilitate adjuvant treatment after surgery may prove to be an added benefit in terms of oncologic outcomes. Aside from these main possible benefits, the use of ICG may also lead to less medical cost owing to fewer days in the hospital and earlier return to work. Likewise, the mental and emotional distress to the patient because of these complications may also be reduced.

A limitation of the study, because of its retrospective nature, is the determination of resection margins prior to giving the ICG dye because of the possible heterogenous nature of the decision-making involved in choosing resection margins. Given that there are several surgeons who performed the surgeries, choosing adequacy of resection margins may have been different among them, thus possibly affecting the study results. While it is true that all surgeons in our institution are trained on the assessment of viability of bowels based on principles that are internationally proven and accepted (brisk bleeding on the bowel edges, pink mucosa with no signs of necrosis or ischemia, no signs of congestions on the bowel wall, pinkish to reddish hue of the vessel walls, etc.), there remains some subjectivity per surgeon. This factor may be controlled to a degree in a future prospective trial.

CONCLUSION AND RECOMMENDATIONS

This study showed that ICG use was associated with a decrease in anastomotic leak rates among patients who underwent colon and rectal resections. There were also no adverse events documented which may strengthen its good safety profile.

As this is retrospective non-randomized research with a relatively small sample size, co-factors and possible confounders were not controlled. A larger scale prospective randomized controlled trial using ICG may provide more information regarding its ability to decrease complication rates following colorectal surgery. Also, while it may have an effect on anastomotic complications, its other benefits in oncologic and non-oncologic surgery – lymph node identification, solid organ and peritoneal metastatic identification, ureteral identification – should be further investigated. Another study may also include aspects on how to isolate the surgeon as a variable in the decision-making in the resection margins between the ICG and no ICG groups.

Another aspect still in discussion is the cost-benefit analysis of using ICG. While there is no doubt in its ease of use, the availability and the price of the dye may not be suitable in countries where the resources may be prioritized over more important life-saving medications or equipment.

The use of ICG dye in the surgery of other organ systems may be investigated. The versatility of the dye and its use in other kinds of surgeries may mitigate the expense of its procurement.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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REFERENCES

1. Alius C, Tudor C, Badiu CD, Dascalu AM, Smarandache CG, Sabau AD, et al. Indocyanine green-enhanced colorectal surgery-between being superfluous and being a game-changer. Diagnostics (Basel). 2020 Sep;10(10):742. doi:10.3390/diagnostics10100742.
2. Emile SH, Elfeki H, Shalaby M, Sakr A, Sileri P, Laurberg S, et al. Sensitivity and specificity of indocyanine green near-infrared fluorescence imaging in detection of metastatic lymph nodes in colorectal cancer: systematic review and meta-analysis. J Surg Oncol. 2017 Nov;116(6):730–40. doi:10.1002/jso.24701.
3. Achterberg FB, Sibinga Mulder BG, Meijer RPJ, Bonsing BA, Hartgrink HH, Mieog JSD, et al. Real-time surgical margin assessment using ICG-fluorescence during laparoscopic and robot-assisted resections of colorectal liver metastases. Ann Transl Med. 2020 Nov;8(21):1448. doi:10.21037/atm-20-1999.
4. White LA, Joseph JP, Yang DY, Kelley SR, Mathis KL, Behm K, et al. Intraureteral indocyanine green augments ureteral identification and avoidance during complex robotic-assisted colorectal surgery. Colorectal Dis [Internet]. 2021 Mar;23(3):718–23. doi:10.1111/codi.15407.
5. Jafari MD, Wexner SD, Martz JE, McLemore EC, Margolin DA, Sherwinter DA, et al. Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): a multi-institutional study. J Am Coll Surg. 2015 Jan;220(1):82-92.e1. doi:10.1016/j.jamcollsurg.2014.09.015.
6. Son GM, Kwon MS, Kim Y, Kim J, Kim SH, Lee JW. Quantitative analysis of colon perfusion pattern using indocyanine green (ICG) angiography in laparoscopic colorectal surgery. Surg Endosc. 2019 May;33(5):1640–9.doi:10.1007/s00464-018-6439-y.
7. Alekseev M, Rybakov E, Shelygin Y, Chernyshov S, Zarodnyuk I. A study investigating the perfusion of colorectal anastomoses using fluorescence angiography: results of the FLAG randomized trial. Colorectal Dis. 2020 Sep;22(9):1147–53.doi:10.1111/codi.15037.
8. Jafari MD, Pigazzi A, McLemore EC, Mutch MG, Haas E, Rasheid SH, et al. Perfusion assessment in left-sided/low anterior resection (PILLAR III): A randomized, controlled, parallel, multicenter study assessing perfusion outcomes with PINPOINT near-infrared fluorescence imaging in low anterior resection. Dis Colon Rectum. 2021 Aug;64(8):995–1002. doi:10.1097/dcr.0000000000002007.
9. De Nardi P, Elmore U, Maggi G, Maggiore R, Boni L, Cassinotti E, et al. Intraoperative angiography with indocyanine green to assess anastomosis perfusion in patients undergoing laparoscopic colorectal resection: results of a multicenter randomized controlled trial. Surg Endosc. 2020Jan;34(1):53–60.doi: 10.1007/s00464-019-06730-0.
10. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg. 2007 Feb;245(2):254–8. doi:10.1097/01.sla.0000225083.27182.85.
11. Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg. 2013 Jan;148(1):65–71. doi:10.1001/2013.jamasurg.2.
12. Trencheva K, Morrissey KP, Wells M, Mancuso CA, Lee SW, Sonoda T, et al. Identifying important predictors for anastomotic leak after colon and rectal resection: prospective study on 616 patients. Ann Surg. 2013 Jan;257(1):108–13.doi:10.1097/SLA.0b013e318262a6cd.
13. Sauer R, Fietkau R, Wittekind C, Rödel C, Martus P, Hohenberger W, et al. Adjuvant vs. neoadjuvant radiochemotherapy for locally advanced rectal cancer: the German trial CAO/ARO/AIO-94. Colorectal Dis. 2003 Sep;5(5):406–15. doi:10.1046/j.1463-1318.2003.00509.x.
14. Department of Surgery Division of Colorectal Surgery, University of the Philippines – Philippine General Hospital. Annual Report. 2023. Unpublished.