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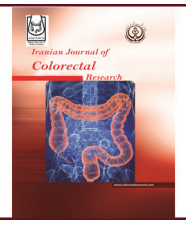

Indocyanine Green Dye Fluorescence Imaging and Colorectal Cancer Anastomotic Leak Rat; A Narrative Review

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Abstract

Anastomotic leak is a significant morbidity in colorectal surgeries. The risk factors for anastomotic leakage are multifactorial with vascularity of the bowel edge playing an important role. Indocyanine green (ICG) dye emits fluorescence and this principle is used to assess the bowel edge vascularity before anastomosis. The context of the study is that even though ICG dye has been used in colorectal cancer surgery for quite a while the evidence is not strong. Most of the data on the role of ICG dye in decreasing the anastomotic leak rate in colorectal cancer surgery comes from retrospective and few prospective trials. There are a few recently published randomized controlled trials (RCT) with contrasting outcomes in this regard. This study is a narrative review of randomized control trials and trial protocols published until 31st December 2023. PubMed, Embase, and Scopus were searched with the keywords ICG, AND Colorectal surgery, AND Anastomotic leak. Four completed RCTs were found and included in this review of all search results. Most of the included studies reported the beneficial effects of ICG on the incidence of anastomotic leak rate. To conclude, the role of ICG dye is not well established in reducing anastomotic leak rates following colorectal anastomosis, but there is growing evidence to support its use.

Keywords: Indocyanine green; Anastomotic leak; Colorectal Surgery; Anastomosis, Surgical; Fluorescence

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Introduction

Anastomotic leakage is a significant morbidity in colorectal surgeries with incidences ranging from 4 to 13% (1-3). The risk factors for anastomotic leakage are multifactorial and include vascularity of the bowel, male sex, low-lying anastomosis, neoadjuvant chemoradiation, advanced stage of tumors, blood loss during surgery, and the number of stapler cartridges fired (1). Anastomotic leakage is associated with high mortality of up to 32% in various studies (4). Vascularity of the bowel edges before the anastomosis is one of the crucial factors dictating anastomotic leak and is also under the surgeon's control (3). Insufficient vascularity may also lead to late complications such as stricture at the anastomotic site (4).

Over the past decade, various techniques have been studied that help surgeons identify the vascularity of the bowel edges before anastomosis (4). Intraoperatively, findings such as normal pinkish bowel, marginal artery pulsations, bleeding from

the cut edges, and good peristalsis suggest normal bowel vascularity. However, one study showed a low predictive value for examining bowel vascularity by surgeons, which necessitates objective methods to identify bowel vascularity (5). Indocyanine green (ICG) fluorescent dye is a technique used for the objective assessment of bowel edge perfusion.

ICG dye emits fluorescence in the presence of the infrared spectrum (750–950 nm). It was initially developed for infrared fluoroscopy by Kodak laboratories and was later adapted into medical practice (6). The ICG molecules bind to the plasma proteins, especially lipoproteins when injected into the body. When injected into tissues, ICG binds to the plasma proteins in the interstitial fluid and is carried to the lymph nodes and lymphatics, as well as into the blood. ICG molecules in the bloodstream are metabolized and excreted by the liver. Half-life is usually 3-4 minutes and depends on the liver function (7).

Various studies have assessed the role of ICG in colorectal anastomotic leak rates. ICG dye is already being used in many centers owing to its easy availability, comparatively low cost, and safety. Most evidence demonstrating the role of ICG comes from retrospective data. A few similar prospective studies and randomized control trials (RCTs) have been published but with contradictory findings. The present narrative review is a summary of evidence from various RCTs regarding the role of ICG in preventing anastomotic leaks in colorectal cancer surgery.

Evidence Acquisition

PubMed, Embase, and Scopus were searched with the keywords Indocyanine green AND Colorectal surgery AND Anastomotic leak for RCTs published until 31st December 2023. Four completed RCTs were found and included in this review of all search results. Two RCT protocols were also found, which were briefly discussed in this review.

Sample Size and Representation

The first RCT comparing ICG *vs* no ICG in reducing the anastomotic leak rate in colorectal surgery was the PILLAR 3 study by Jafari and colleagues which was a multicenter RCT from the United States of America with a minimum sample size of 400 patients for interim analysis (8). This study, designed to detect an absolute difference of 6.25% in the anastomotic leak rate between the ICG and the non-ICG arms, was stopped after a sample size of 343 patients given poor accrual, even though it was started in 2015 [Table 1] (8).

In this regard, an RCT by De Nardi and colleagues was started in 2017. This was a multicenter study from Italy with a sample size of 240 patients calculated with the power to detect 10% difference between the ICG and non-ICG groups [Table 1] (9). It was followed by the Russian multicenter FLAG RCT by Alekseev and co-workers, started in 2018 with a sample size of 377 patients calculated with an assumption of an anastomotic leak rate of 15% and 25% between the ICG and non-ICG groups [Table 1] (10). The most recently published RCT was the Japanese multicenter EssentiAL trial by Watanabe and colleagues, started in 2018 with a sample size of 839 patients with an assumed reduction in the anastomotic leak rate of at least 6% [Table 1] (11). IntAct and AVOID are two RCTs that compare the anastomotic leak rate between the ICG and the non-ICG arms in colorectal surgery and are ongoing in Europe and the Netherlands respectively [Table 1] (12, 13). There is another ongoing multicenter RCT from Finland with an unpublished protocol the ICG-COLORAR NCT03602677 study, under the accrual phase [Table 1].

Since the RCTs were conducted in the major

Table 1: Table showing the composition of patients as per gender and location of study

Study	Number of patients	Percentage of males	Percentage of females	Single/ Multicentre	Number of centres	Region of study population
PILLAR 3 trial, Jafari MD et al 2021 (8)	343	60.6% (208)	39.4% (135)	Multicenter	25	USA
De Nardi et al, 2019 (9)	240	52.5% (126)	47.5% (116)	Multicenter	3	Italy
FLAG trial, Alekseev M et al, 2019 (10)	377	48.8% (114)	51.2% (193)	Single center	1	Russia
EssenttiAL trail, Watanabe J et al, 2023 (11)	839	64.4% (540)	35.6% (2996.)	Multicenter	41	Japan
IntAct study, Armstrong G et al, protocol 2018 (12)	880*	-	-	Multicenter	25	Europe
AVOID trial, Meijer RPJ et al, protocol 2022 (13)	978*	-	-	Multicenter	-	Netherlands
ICG-COLORAL study protocol 2018	1062*	-	-	Multicenter	7	Finland

USA: United States of America; *Calculated sample size

continents of the world such as the USA, Europe, and Asia, there is a wide representation of the population. Even though the earlier studies have a smaller sample size, the most recent EssentiAL trial by Watanabe and colleagues has a good sample size as per the power with good accrual.

Study Population Characteristics

Male sex was associated with increased anastomotic leak in a few studies (1). The percentage of male patients was highest in the EssentiAL trial by Watanabe J et al (64.4%), followed by the PILLAR 3 trial by Jafari MD et al (60.6%) [Table 1]. All four RCTs have many patients with malignancies. The proportion of patients with colorectal tumors in the study by De Nardi and co-workers and in the FLAG trial by Alekseev and co-workers was around 71.3% and 91.4% respectively [Table 2]. All the patients included in the PILLAR 3 trial by Jafari and colleagues and the EssentiAL trial by Watanabe and co-workers had malignancies only.

The proportion of patients with neoadjuvant radiotherapy varied widely among all four RCTs, ranging from 6.3% to 65.3% [Table 2]. The highest proportion of patients who received neoadjuvant radiotherapy was in the PILLAR 3 trial by Jafari MD et al, with 65.3% of the study population receiving neoadjuvant radiotherapy.

The anastomotic leak rate also depends on the level of the anastomosis. The incidence of leaks increases as the level of the anastomosis goes down towards the anal canal (1). The proportion of patients with rectal tumors who require low anterior resection was 45.4% and 57.3% in the studies by De Nardi and colleagues and the FLAG trial by Alekseev and co-workers, while all the patients included in the PILLAR 3 trial by Jafari MD and co-workers and EssentiAL trials by Watanabe and co-workers had rectal tumors only [Table 2]. The proportion of low and mid-rectal tumors among rectal tumors in the PILLAR 3 trial by Jafari MD et al and EssentiAL trials by Watanabe and colleagues was 85.1% and 100%, respectively [Table 2].

ICG Dye Dose

In the study by De Nardi and colleagues, ICG dye was twice injected intravenously at a dosage of 0.3 mg/kg: before the resection of the colon and after the completion of the anastomosis to assess colonic stumps and margin perfusion (9). In the FLAG trial by Alekseev M et al, ICG dye was injected at a dose of 0.2 mg/kg after selection of the transection line (10). In the PILLAR 3 trial by Jafari MD et al, ICG was injected at a dose of 3.0±1.0 mL of a 2.5 mg/mL solution, which is approximately equivalent to 0.1 mg/kg for an adult weighing 75 kg, both for colorectal and trans-anal anastomosis (10). In the PILLAR 3 trial by Jafari MD et al, perfusion was assessed twice in colorectal anastomosis: first after ligation of the inferior mesenteric artery, and before anastomosis and the mucosal perfusion after completing the anastomosis (10). For trans-anal anastomosis, assessment was done only before anastomosis. In the EssentiAL trial by Watanabe and colleagues, patients were injected with a 12.5 mg dose of ICG before anastomosis to assess perfusion (11).

Anastomotic Technique

In the RCT by De Nardi and colleagues and the FLAG trial by Alekseev and colleagues, the Knight–Griffen circular anastomosis technique was used for colorectal anastomosis and the manual technique for coloanal anastomosis (8-10). In the PILLAR 3 study by Jafari MD et al, the anastomotic technique was not mentioned, while in the EssentiAL trial by Watanabe J et al, the technique varied among different surgeons(10, 11). However, all patients in all four RCTs underwent a pneumatic leak test at the end of the anastomosis.

Diversion Stoma

The rate of stoma varies from 21.3% in the RCT by De Nardi and colleagues et to 77.8% in the PILLAR 3 trial by Jafari and colleagues [Table 3]. The indications for diversion stoma varied in all the RCTs. In the trial by De Nardi and co-workers a protective ileostomy was performed in all patients with previous long-course neoadjuvant radio-chemotherapy, intraoperative leak on the air leak test, and anastomosis located less than 5 cm from the anal verge or coloanal anastomosis (9). In the FLAG trial by Alekseev M et al, the diversion stoma rate was 70.7%, but exact indications were not given (10). In the PILLAR 3 trial by Jafari MD et al, diversion stoma was performed at the discretion of the operating surgeon (8). There were no provisions for diversion stoma in the EssentiAL trial by Watanabe J et al, and the stoma rate was 52.7% (11).

Table 2: Table showing proportion of malignant cases, neoadjuvant radiotherapy cases and the location of tumor among the RCTs

Study	Percentage of malignant cases	Post neoadjuvant radiotherapy patients	Percentage of minimally invasive surgeries performed	Rectal tumors	Low and mid rectal tumors
PILLAR 3 trial, Jafari MD et al 2021 (8)	100%	65.3%	86.3%	100%	85.1%
De Nardi et al, 2019 (9)	71.3%	20.4%	100%	45.4%	NA
FLAG trial, Alekseev M et al, 2019 (10)	97.4%	10.3%	43.5%	57.3%	NA
EssenttiAL trail, Watanabe J et al, 2023 (11)	100%	6.3%	100%	100%	100%

Table 3: Table comparing the type of resection, diversion stoma rate and leak rates among the study population

Study	Type of resection	Percentage of diversion stoma	ICG based less/ no perfusion (%)	Leak rate in study arm (%)	Leak rate in control arm (%)	Comments
PILLAR 3 trial, Jafari MD et al 2021 (8)	Left sided colon and rectal resections	77.8%	4.6	9	9.6	No significant difference
De Nardi et al, 2019 (9)	Left sided colon and rectal resections	21.3%	11	5	9	No significant difference
FLAG trial, Alekseev M et al, 2019 (10)	Left-sided colon and rectal resections	70.8%	19.2	9.1	16.3	Significant difference
EssenttiAL trail, Watanabe J et al, 2023 (11)	Left-sided colon and rectal resections	52.7%	2.6	7.6	11.2	Significant difference but predefined value not met

Anastomotic Leak and Morbidity

In the study by De Nardi and co-workers, margin revision based on ICG fluorescence was performed for 11% of patients in the study group [Table 3]. Anastomotic leaks were detected clinically or using contrast enema before stoma closure in the postoperative period. In this study, the anastomotic leak rate was 9% in the control arm and 5% in the ICG arm. but the results were not statistically significant (14) [Table 3]. The anastomotic leak rate was 13.8% in patients without stoma and 5.8% in patients with stoma, which was not statistically significant. There were no differences in morbidity and hospital stay between the two study groups. There was no significant difference in the anastomotic leak rate when low rectal anastomosis (10%) was compared with colorectal anastomosis (4%). There was no significant difference in the anastomotic leak rate between the benign (2.9%) and malignant (8.7%) groups.

In the FLAG trial by Alekseev and colleagues, a protective ileostomy was performed in 70.8% of patients, which included all patients with low rectal anastomosis [Table 3]. The bowel transection line in view of poor blood flow on ICG florescence had to be revised in 19.2% of the patients, and all revisions were of the proximal stump only. Anastomotic leak was detected either by clinical signs or by contrast enema after 30 days of primary surgery. There was no difference in overall morbidity between the two groups. In this study, the anastomotic leak rate was 16.3% in the control arm and 9.1% in the ICG arm, which was statistically significant (10) [Table 3]. However, this trial was criticized for the unusually high leak rate in the study, which was about 16.3% and 12.1% in the non-ICG and ICG groups respectively, and which was still higher in low rectal anastomosis (10).

On subgroup analysis, the anastomotic leak rate was significant for low rectal anastomosis but not for high rectal anastomosis between the two groups (10). The significant decrease in the anastomotic leak rate in low rectal anastomosis in the ICG group was significant for grade A leaks (18.3% *vs* 6.3%) but not for grade B and C leaks. The reoperation rate was 3.7% in the ICG arm and 2.1% in the non-ICG arm, which was not statistically significant. There was no significant difference in the anastomotic leak rate between the groups with and without a positive air leak test. Reinforcement of the staple line was associated with a reduction of the anastomotic leak rate to 8.9% in the reinforced arm from 17.2% in the non-reinforced arm. Among the patients with ileostomy, there was a significant reduction in the leak rate from 21.6% in the non-ICG arm to 12% in the ICG arm. In the non-ileostomy group, there was no significant difference between the anastomotic leaks rated between the two arms.

In the PILLAR 3 trial, margin revision was required in 4.6% of the study population (8). There was no statistically significant difference in the anastomotic leak rate between the ICG arm and standard arm (9% *vs* 9.6% respectively) (8) [Table 3]. Post-operative complication rates were not statistically different between the two arms.

In the EssentiAL trial, the resection margin was revised given inadequate perfusion in two patients (11) [Table 3]. Anastomotic leak is detected based on clinical symptoms or on contrast enema in patients with diversion stoma. There was a significant difference of 4.2% in the anastomotic leak between the ICG arm and the control arm (7.6% *vs* 11.8% respectively), but this was below the study's expected reduction rate of 6% (11). There was also a significant difference in the clinically significant anastomotic leak (B+C) rate between the ICG arm and the control arm (4.7% and 8.2%). Subgroup analysis showed that the anastomotic leak rate was higher in patients with anastomosis below 5 cm and in those who received neoadjuvant therapy (11). The low rate of anastomotic leak in this study may be attributed to underreporting of grade A leaks as routine contrast enema was not performed in all cases. Variability in the rectal anastomotic technique among surgeons is another limitation of the present study.

Discussion

Most of the reviewed studies reported that ICG is

associated with lower incidence of anastomotic leak rate after colorectal surgeries. ICG fluorescence was designed as an attempt to objectively assess vascularity of the bowel edges before bowel anastomosis. Initial evidence of the role of ICG in decreasing the colorectal anastomotic leak rate comes from retrospective data. Jafari and colleagues found that ICG dye resulted in a threefold decrease in the anastomotic leak rate from retrospective data in a case-control study (14). In a systematic review of four retrospective studies and one prospective study of colorectal anastomosis patients, there was no significant difference in anastomotic leak rate with and without ICG fluoroscopy when both cancer and non-cancer indications were included (15). However, when analysis was conducted on the subgroup of patients with colorectal cancer, the difference in the anastomotic leak rate was significant (15). A meta-analysis of the same four retrospective studies reviewed by Blanco-Colino and colleagues showed an odds ratio of 0.27 favoring the ICG arm, which was clinically significant (15, 16). The above difference may also be because of the omission of one prospective study included by Blanco-Colino and co-workers and not by Shen and colleagues (15, 16) as the prospective data of the omitted study was compared with retrospective data of a different period.

In a prospective study, the anastomotic leak rate in ICG and non-ICG arms was 3.23% and 4.35%, which was not statistically significant (17). In a prospective study by Wojcik and colleagues, additional resection due to poor vascularity was required in 10.3% of the study population using ICG dye for anastomosis (18). The anastomotic leak rates in the ICG and non-ICG arms were 2.4% and 16.7% respectively, which was clinically significant (18). PILLAR 2 was a prospective single-arm study studying the role of ICG in colorectal anastomosis (19). In PILLAR 2, the resection margin was revised in 8% of the cases, and the leak rate was 1.4% (19). The low anastomotic leak rate in PILLAR 2 was attributed to the low proportion (25%) of malignant cases and the low proportion (10%) of patients who received neoadjuvant chemoradiotherapy (19). As a result of the discordant results between various retrospective and prospective studies, RCTs were conducted to identify the role of ICG in colorectal anastomosis.

As we see from the four RCTs discussed above, they give a representation of different regions of the world. The dose of ICG used in the RCTs varied from 0.3 mg/kg to 0.1 mg/kg. There were no side effects of the dye reported in any of the studies, which leads us to conclude that ICG is a very safe dye. Male sex was associated with increased anastomotic leak in a few studies (1). The reason is technical difficulty in performing the dissection and anastomosis due to deeper and narrower male pelvis anatomy, although the possibility of male sex hormones on healing is also hypothesized (1). The percentage of male patients in the four RCTs under review ranged from 48.8% to 64.4%. Neoadjuvant chemoradiotherapy is the standard care for locally advanced rectal cancers, with the focus shifting to total neoadjuvant chemotherapy to improve overall survival and organ preservation. Neoadjuvant radiotherapy is a risk factor for anastomotic leak given compromised bowel vascularity which impairs healing (1, 20). Although the EssentiAL trial is praised for its large sample size, the proportion of patients with neoadjuvant therapy is very small (6.3%), which raises doubts about the applicability of the study results in real-world scenarios. The anastomotic leak rate also depends on the level of the anastomosis. The incidence of leak increases as the level of the anastomosis goes down towards the anal canal due to unpredictable and lesser blood supply to the lower rectum when compared to the upper rectum (1). The proportion of low rectal anastomosis was higher in the studies by Jafari and colleagues and by Watanabe and co-workers which are 85.1% and 100% respectively (8, 11) .

In another RCT, there was no significant difference when benign and malignant tumors were considered and when high and low rectal anastomosis were considered, contrary to the previous studies (1, 20). The RCT by De Nardi and co-workers and the PILLAR 3 trial did not show any difference in anastomotic leak rates. The former study had a limitation of small size and hence poor power for the results. The PILLAR 3 trial is criticized for its incomplete accrual and incomplete sample size.

The FLAG trial is a positive trial to show reduction in the anastomotic leak rate, and again the results were limited to low rectal anastomosis and were predominantly for grade A leaks and not for clinically significant anastomotic leaks (Grade B and C leaks). Hence, although the FLAG trial is positive as per statistical analysis, its real-world applicability is questionable as most patients with low rectal anastomosis have a diversion stoma in clinical practice. Further, the FLAG trial is criticized for having patients with benign tumors and sigmoid colon tumors in the study population, for being a single-center study, and for conducting the randomization before the surgical procedure.

The results of PILLAR 3 trial contradict those of the FLAG trial despite enrolling patients with a higher risk of anastomoses such as a lower level of anastomosis, higher proportion of neoadjuvant radiotherapy, and greater proportion of male patients. The PILLAR 3 study by Jafari MD et al, results also contradict the previous prospective PILLAR 2 study by the same group of authors. The authors of the PILLAR 3 study claim that the low rate of anastomotic leak in the present study is owing to their greater surgical expertise in the field (10).

The EssentiAL trial, although it showed a significant difference in the anastomotic leak rate, did not reach the 6% reduction target as per the protocol. This trial

is criticized for the non-uniformity of the anastomotic technique and for not performing routine contrast enemas to detect leaks. The low rate of neoadjuvant therapy in the study population again questions the applicability of the results in the study population.

In the meta-analysis by Tang G et al., 5 RCTs (including two RCTs from China not indexed in PubMed) and 15 propensity score-matched analysis, ICG significantly reduced the anastomotic leak rate without increasing operation time or postoperative complications in colorectal surgery (17). However, the studies were heterogeneous concerning the type of study population, anastomotic technique, ICG device use, anastomotic leak definitions, and follow-up periods. In the latest metanalysis of rectal cancer surgery patients of the above-discussed four RCTs by Lucarini and colleagues, there was a reduction in the anastomotic leak rate with ICG dye from 13.9% to 9% which was statistically significant (21).

The results from the ongoing IntAct, AVOID, and ICG-COLORAL studies are awaited to throw further light on this question. As per the latest communication with the authors, the IntAct trial has completed accrual, and the preliminary results are expected to be out in June 2024. The AVOID trial has also been completed, and the results are being analyzed.

The limitations of the present study were that it is only a narrative review and no meta-analysis of the data of previous studies was done. Further, there might be a possibility of few smaller studies published in non-indexed journals which have been missed to discussed in this review. A meta-analysis of the published and forthcoming IntAct, AVOID and ICG-COLORAL studies is required to establish the exact role of the ICG dye fluorescence technique in reducing the anastomotic leak rate in colorectal malignancies.

Conclusion

The applications of ICG dye in clinical practice are continually evolving. ICG dye can be used for many purposes, such as assessment of bowel vascularity, lymph node mapping, and identification of hepatic and peritoneal metastasis in colorectal cancer. Low allergy rates, easy availability, and ease have increased the applications of ICG dye. The role of ICG dye is not well established in reducing anastomotic leak rates following colorectal anastomosis, but there is growing evidence to support its use. Anastomotic leak rate depends on standard surgical principles and a multitude of factors not just the vascularity of the bowel ends to be anastomosed.

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