Enhancing Colorectal Anastomotic Safety with Indocyanine Green Fluorescence Angiography: An update

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Abstract

Reducing anastomotic leak (AL) continues to be a main focus in colorectal research. Several new technologies have been developed with an aim to reduce this from mechanical devices to advanced imaging techniques. Fluorescence angiography (FA) with indocyanine green (ICG) in colorectal surgery is now a well-established technique and may have a role in reducing AL. By using FA, we are able to have a visual representation of perfusion which aids intraoperative decision making. The main impact is change in the level of bowel transection at the proximal side of an anastomosis and provide a more objective and confident assessment of bowel perfusion. Previous studies have shown that routine FA use is safe and reproducible. Recent results from randomized control trials and meta-analyses show that FA use reduces the rate of anastomotic leak. The main limitation of FA is its lack of ability to quantify perfusion. Novel technologies are being developed that will quantify tissue perfusion and oxygenation. Overall, FA is a safe and feasible technique which may have a role in reducing AL.

Key Words:

Fluorescence angiography, fluorescence imaging, indocyanine green, near infrared, anastomotic leak, colorectal surgery

1. Introduction

Despite advances in technology and greater precision in surgical technique, anastomotic leak (AL) continues to be the main concern for patients undergoing colorectal resectional surgery. Reported rates remain between 3-15% depending on the location of the anastomosis with higher rates for left sided or colo-rectal anastomoses [1]. Despite some variability in the exact definition of what constitutes an AL, the generally recognized grading system is that put forward by the International Study Group of Rectal Cancer[2]. It is known that AL causes an increase in patient mortality, morbidity, hospital length of stay, rates of re-operation, permanent stoma and financial burden[3]. Studies have shown that patient specific pre-operative risk factors such as obesity, smoking and chemotherapy increase the risk of AL[4,5]. A Delphi consensus by the Association of Coloproctology of Great Britain and Ireland (ACPGBI) classified risk factors into non-modifiable and modifiable[6]. Separately, identification of intra-operative factors that may pre-dispose to AL are a main focus of research. Intraoperative risk factors can be divided between patient and technical factors. Tumor size, distal location, blood loss, transfusion and duration of surgery > 4 hours have been shown to increase the rate of AL[7].

Perfusion of the anastomosis has also been shown to have an effect on healing [8,9]. This is affected by a patient’s pre-operative vasculature, the level of resection and surgical technique. One intraoperative factor which surgeons have control over is the level of colonic division and consequently the perfusion to the proximal side of an anastomosis. Several methods have been described to assess blood flow to the anastomosis. The simplest of these is a visual assessment looking for serosal discoloration, pulsatile bleeding at the cut edge of the bowel or flow from the marginal artery[10]. However, this can be inaccurate and provides no indication as to the microperfusion of the colon at the site of anastomosis.

Intra-operative fluorescence angiography (FA) has been shown to assess microperfusion of the colon though this has not been quantified[11]. This process requires the intravenous administration of the fluorophore indocyanine green (ICG) which binds to plasma lipoproteins, therefore remaining within the intravascular space until excretion in bile or urine. When ICG is excited by near infra-red light (NIR) it fluoresces. This fluorescence can be captured with an NIR camera indicating on a conventional screen the location of ICG and thus providing an estimate of tissue perfusion.

Numerous observational trials have demonstrated safety, feasibility and efficacy in assessing perfusion using ICG with promising results. This purpose of this review is to provide an update in the progress being made in this field.

2. Search strategy and selection criteria

An electronic search of PubMed, Embase and the Cochrane library was performed between 2005 and 2020 to identify the relevant literature for this review. Medical subject headings (MeSH) and text words were searched. The following search terms were used: “anastomotic leak” AND “colorectal”” AND “fluorescence angiography”, “fluorescence imaging” or “ICG”. Peer reviewed papers in the English language available in full were included. Reference lists were reviewed to include any further relevant literature. A systematic review of papers between 2015 and 2020 was performed to identify new clinical research. Comparative studies with an endpoint of anastomotic leak were included. Unmatched observational studies were excluded. These papers formed the basis for this review. Ongoing clinical trials were identified from the searched literature, ClinicalTrials.gov and ISRCTN.

3. Fluorescence Angiography in Colorectal Surgery

3.1Early Use of Fluorescence Angiography

Fluorescence angiography (FA) has been used to assess bowel perfusion in colorectal surgery for more than 15 years. It provides a more objective assessment of perfusion compared to more traditional, subjective methods described above. Perfusion remains the most important factor in the healing of bowel anastomoses.

Kudszus et al, began their series in 2003 demonstrating significantly reduced rates of anastomotic revision in the FA group compared with a retrospective matched control, 3.5% vs 7.5% respectively[12]. This showed a significant difference in the two groups and provided an important first step towards better understanding the role of FA in reducing AL. With the increased availability of CT, we can now use radiologically confirmed anastomotic leak (AL) as an endpoint rather than clinical endpoints such as reoperation.

The seminal paper by Jafari et al, the PILLAR II trial, is probably most recognized as the study which proved the feasibility and safety of FA in left-sided colonic and rectal resection[13]. This multi-centered, prospective trial recruited 139 patients across 11 centers in the USA. Importantly, this showed that FA was reproducible across sites as usable images were acquired in 98.6% cases. The use of FA changed the resection level in 6.5% cases, and there were subsequently no leaks in this group. The overall AL rate was low at 1.4% which much reduced compared to the existing literature. In 2018, Ris et al published the results of their multicenter phase II trial from 2013-2016[14]. Much larger than the trials before it, this prospective study recruited 504 patients across 3 tertiary centers. Again, this showed good usability of the technology as NIR images were obtained in all cases. The FA group had an AL rate of 2.4% against 5.8% in an historical unmatched control group. FA led to a change in surgical plan in 5.8% cases, none of which had an AL. Although their series included operations where the anticipated proximal anastomotic perfusion would be a high, such as reversal of Hartmann's or ileo-rectal anastomosis, subgroup analysis for low anterior resection (LAR) showed an AL rate of 3%. They related this to an historical group of LARs which had an AL rate of 10.7%. Although caution must be taken when using historical groups these studies showed that FA was feasible, reproducible and changed intraoperative decision making. It also suggested that its use may reduce the rate of AL.

A systematic review of 5 early studies by Blano-Colino and Epsin-Basany involved 1302 patients[15]. While based on non-randomized retrospective studies it showed a significant reduction in AL rate when FA was used in patients undergoing surgery for colorectal cancer (OR 0.35; CI 0.16-0.74; p-0.006). In particular there was significant reduction in the AL rate in a less heterogenous sub-group, patients undergoing rectal cancer resection, 1.1% FA vs 6.1% non-FA (p=0.02).

3.2 Recent Trials using Fluorescence Angiography

Since this period there have been 8 published comparative studies, two of which are randomized control trials (RCTs). There is a wide variation in these studies as some include any colonic resection and others solely low anterior resection with TME (3/8). The trial protocols did differ in their administration of ICG with doses varying widely.

2 studies specifically looked at the use of FA in patients undergoing laparoscopic LAR. In 2017 Boni et al showed a reduction in AL for LAR with TME using FA in 42 patients against a retrospective matched cohort (0% vs 5%)[16]. These results were reproduced by Mizrahi et al in 2018[17]. In this study 30 patients undergoing LAR were evaluated against a comparable historical group. 4 patients (13.3) had their surgical plan changed after FA assessment. Their study had no leaks in the FA group and 2 (6.7%) in the comparative group. These studies demonstrate that FA use may be of benefit in a patient group more at risk of AL. The authors from both studies concluded that the use of FA was safe though a randomized study was is needed.

Losurdo et al used a propensity score-matching (PSM) system in their series to try and mitigate the inherent bias from the heterogeneity within their cohort of patients undergoing laparoscopic left sided colonic or colorectal resection, including patients with handsewn coloanal anastomosis[18]. Cases converted to open were excluded. Before matching statistically fewer patients in the FA group underwent reoperation for AL. A 1:1 PSM system grouped 75 patients from each cohort. This score accounted for tumor stage, co-morbidities and baseline demographics. After matching there was a significant reduction in AL within the FA group, 9.3 vs 16.3% (p=0.058). A multicenter study by Watanabe et al used PSM in patients undergoing LAR[19]. 211 patients were matched in each group, FA and non-FA. Their study found a significant reduction in Clavien-Dindo (CD) Grade II and III anastomotic leakage.

At the time of this review there have been 2 RCTs looking at FA and AL. De Nardi et al published the first RCT in patients undergoing left sided or rectal resection[20]. In this multi-center trial 252 patients were randomized and after exclusions there were 118 patients in the study group. 11% patients in the study group had a change of surgical plan due to FA. The study did not show a significant difference in AL between groups. However, the leak rate was lower in the study group and the authors concluded that FA was a safe adjunct that was not time consuming or detrimental. Alekseev et al published the results of the FLAG trial, a second RCT focused on patients undergoing anterior rection with stapled end-to-end colorectal anastomosis[21]. They included both open and laparoscopic approaches, 380 patients were randomized. This trial demonstrated a significant reduction in the AL rate when using FA (9.1% vs 16.3% p=0.04). It is worth noting that there was a comparatively high AL rate in patients undergoing LAR without FA, 25.7% (FA group 14.4%

p=0.04). Additionally, there was a slightly higher, but non-specific, reoperation rate in the FA group (3.7% vs 2.1% p=0.38). This study demonstrates that FA has a role but that it is mainly limited to low colorectal anastomoses.

In 2020 Chan et al published a systematic review of 20 studies including the above RCTs[22]. 5498 patients were included in the meta-analysis. This showed that FA decreased AL with an odds ratio (OR) of 0.46 (95% CI 0.34-0.62; p<0.0001). Although largely based on retrospective studies a subgroup analysis of 4 prospective trials confirmed this result (OR 0.49 95% CI 0.3-0.81; p=0.005). Furthermore, this study confirmed that patients undergoing LAR for rectal cancer with colorectal anastomosis may benefit from ICG. Arezzo et al published their meta-analysis containing individual participant data from 9 trials involving 1,330 patients[23]. Their results showed a significant reduction in the rate of AL in the FA group compared with standard care 4.2% vs 11.3% respectively (p=<0.001). Additionally, risk of AL was found to be significantly lower with anastomoses <6cm from the anal verge and in patients with BMI >25.

3.3 Ongoing trials

There is only 1 current randomized control trial investigating FA and AL. The IntAct trial is a multi-center European RCT currently recruiting[24]. They aim to randomize 880 patients. This will be the largest trial of its kind and is focused on patients undergoing laparoscopic or robotic surgery for rectal cancer. An additional sub-study intervention will look at CT perfusion scanning aiming to investigate the link between pre-operative vascular anatomy and AL.

4. Challenges and Skepticism

Whilst current research is yielding promising results there are still some challenges to be overcome. Although studies produce can reproduce fluorescence, there is a broad range in the dose of ICG administered and the timing to assessment of the bowel. A recent Delphi Consensus Conference of international experts across surgical specialties, including colorectal, agreed that both dose administered and timing to assessment was important

(89.5% and 89.5% consensus)[25]. A recent review of protocols recommends a dose of 2.5mg as multiple studies have had good results at lower dosages[26]. This correlates with work undertaken in esophagogastric anastomoses[26]. Although there is a very low risk of anaphylaxis to ICG, current studies in colorectal surgery use concentrations well below that which is known to cause toxicity[27]. The European Association for Endoscopic Surgery (EAES) technology committee are preparing a consensus conference for fluorescence and we await the results of this later in 2021.

A further challenge is that whilst FA with ICG can provide a visual estimation of microperfusion, there is no standard method of quantifying this. This is perhaps the biggest hurdle at the present time. The rationale behind using FA is to be able to provide a reproducible and objective method of perfusion assessment. On the surface it may seem like ICG fulfils these criteria but in practice, the operating team still have to subjectively decide whether the fluorescent signal is strong enough to justify creation of the anastomosis or that the transection point should be revised more proximally. Recent work from Soares et al, have shown variability in users relating to specialty and experience[28]. Further, it is not known how the intensity of fluorescence correlates with microperfusion at tissue level. Several studies have modelled colonic perfusion patterns by measuring fluorescence intensity and time of onset[29,30]. This has been achieved in real time for intraoperative use[29]. A retrospective video analysis study showed that slow perfusion was an independent risk factor for AL[30]. However, parameter based models vary and are difficult to reproduce. Park et al generated an artificial intelligence (AI) model which was more accurate in retrospectively predicting the risk of AL compared with parametric models[31]. Further work is required to ascertain specific, generalizable cut off levels for intensity and time of onset that may influence intraoperative decision making.

Though FA can give an estimation of perfusion it cannot quantify oxygen delivery to the tissues. Hyperspectral imaging (HIS) uses a sensor to capture electromagnetic waves at a spectrum beyond visible light, and in greater detail. Reconstructed false color images provide a visual representation of tissue oxygen saturation. This technology is non-invasive and can accurately identify the margin of perfusion[32]. This has been shown to be comparable to FA[33]. Moreover, Clancy et al have demonstrated in patients that there is a strong correlation between high fluorescent intensity and oxygen saturation. Although, these methods require calibration and are not widely available they likely to be the main focus of tissue perfusion assessment going forward providing simultaneous optical and biological imaging patterns.

While the discussed techniques can give an estimate of perfusion at the time of anastomosis there is currently no reliable measure in the post-operative period. Recognition of patients in whom the anastomosis is failing due to ischemia may allow early intervention. Cahill et al have used an AI model to accurately identify tumors from their perfusion patterns using FA[34]. Development of this technology can lead to real-time assessment of bowel perfusion at the anastomosis. By knowing how our post-operative treatment regimen affects anastomotic perfusion we may be able to specifically tailor patient management.

Lastly, if we can reduce the rate or accurately predict AL then we can allow FA to have a greater impact on in other areas of our intraoperative decision making. Spinelli et al have used FA to guide vascular ligation when forming an ileal pouch[35]. By using FA they were able to confidently ligate the ileocolic vessels more proximally where required, giving more length for the pouch. There were no anastomotic leaks. It may be that we can make further decisions such as whether or not to create a defunctioning stoma. FA influenced this decision in a pilot by Ris et al[36]. Stomas are known to add to patient financial burden and reduce quality of life[37]. Conversely, if we can measure perfusion at the anastomosis post-operatively then we may be able to identify the patient group that benefits most from early stoma reversal which has been shown to reduce costs and increasing quality of life[38].

5. Conclusion

Fluorescence angiography in colorectal surgery is a safe and reproducible technique. There is increasingly strong evidence that the use of FA reduces the AL rate. In particular, this may be of greatest benefit in patients undergoing LAR where the AL rate is known to be the highest. Although further randomized studies are needed, we conclude that, where available, routine use of FA is not to the detriment of the patient and often influences surgical decision making. This may reduce the overall rate of AL and moderate the need for defunctioning stoma. A comprehensive protocol is required to establish a standard technique across all centers using FA. Ultimately, a way to quantify microperfusion is needed and this should be a focus of research.

Conflict of Interest

Pampiglione, T and Chand, M declare no conflict of interest

Author Statement

Pampiglione, T: Conceptualization, Methodology, Writing - original draft preparation.

Chand, M: Conceptualization, Methodology, Writing – reviewing and editing

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