Fluorescence angiography in laparoscopic low rectal and anorectal anastomoses with pinpoint perfusion imaging - a critical appraisal with specific focus on leak risk reduction

JAMES, D. R. C., et al.

Abstract

BACKGROUND AND AIMS: Anastomotic dehiscence is one of the most feared complications in colorectal surgery leading to significant morbidity and mortality. Progressively lower anastomoses are associated with a greater leak rate. One of the key factors is the perfusion of the bowel to be joined. Presently, surgeons rely on a variety subjective measures to determine anastomotic perfusion and mechanical integrity however these have shortcomings. The aim of this paper is to appraise the literature on the use of fluorescence angiography (FA) in laparoscopic rectal surgery. MATERIALS AND METHODS: A Pubmed search was undertaken using terms 'fluorescence angiography' and 'rectal surgery'. The search was expanded using the related articles function. Studies were included if they used FA specifically for rectal surgery. Outcomes of interest including anastomotic leak rate, change of operative strategy and time taken for FA were recorded. RESULTS: Eleven papers detailing the use of FA in rectal surgery are outlined demonstrating that this technique may change operative strategy and lead to a reduction in anastomotic leak rate. [...]
Fluorescence angiography in laparoscopic low rectal and anorectal anastomoses with pinpoint perfusion imaging - a critical appraisal with specific focus on leak risk reduction

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Abstract

Background and aims Anastomotic dehiscence is one of the most feared complications in colorectal surgery leading to significant morbidity and mortality. Progressively lower anastomoses are associated with a greater leak rate. One of the key factors is the perfusion of the bowel to be joined. Presently, surgeons rely on a variety of subjective measures to determine anastomotic perfusion and mechanical integrity however these have shortcomings. The aim of this paper is to appraise the literature on the use of fluorescence angiography (FA) in laparoscopic rectal surgery.

Materials and methods A PubMed search was undertaken using terms ‘fluorescence angiography’ and ‘rectal surgery’. The search was expanded using the related articles function. Studies were included if they used FA specifically for rectal surgery. Outcomes of interest including anastomotic leak rate, change of operative strategy and time taken for FA were recorded.

Results Eleven papers detailing the use of FA in rectal surgery are outlined demonstrating that this technique may change operative strategy and lead to a reduction in anastomotic leak rate.

Conclusion In this paper, we discuss assessment of colorectal blood supply using FA and how this technique holds great potential to detect insufficiently perfused bowel. In so doing, the operator can adjust their operative strategy to mitigate these affects with the aim of reducing the complications of anastomotic leak and stenosis. However, it is highlighted that there is a clear need for randomised controlled trials in order to determine this definitively.

Keywords Anastomotic leak, near infrared, indocyanine green, risk factors, low anterior resection

What does this paper add to the literature? This paper appraises the existing literature on the application of fluorescence imaging in rectal surgery and how this may aid in the prevention of anastomotic leak. This highlights the urgent need of randomised controlled trials to determine this.

Introduction

Colorectal cancer is the third most common cancer in the world and incidence is increasing [http://www.wcrf.org/int/cancer-facts-figures/data-specific_cancers/colorectal-cancer-statistics]. In conjunction with rising prevalence, screen detection of earlier disease is leading to a growth in those offered curative surgery. One third of colorectal cancer is located in the rectum and this requires the most technically demanding surgery. The main, feared complication is an anastomotic leak with the associated immediate morbidity/mortality and long-term functional disorders. Anastomotic leaks also increase the total clinical and economic burden on the healthcare system [1].

A variety of patient and tumour related factors can influence leak rates [2]. It is well established that the incidence of dehiscence increases with distally located anastomoses [3]. One of the most important factors is the blood supply to the segments of the bowel to be joined, and high tie of the inferior mesenteric artery (IMA) (proximal to the left colic artery) has been shown to be an independent predictor for anastomotic
leak [3]. While a variety of methods have been utilised to assess anastomotic integrity including mechanical patency (air leak tests and dye tests) and endoscopic assessment [4], the physical integrity of an anastomosis becomes less relevant when the bowel is hypo-perfused. Thus, determining optimal perfusion of an anastomosis is essential.

Evaluating colonic perfusion prior to resection and anastomosis can be undertaken by a variety of means. Initially, subjective assessment of perfusion by bowel inspection is undertaken. For example, operator assessment for the surrogates of a good blood supply such as tissue colour, the presence of a palpable pulse within the mesentery and the manifestation of arterial bleeding (‘flashing the artery’) following mesenteric division. These factors can be quantified by the use of a variety of technologies to determine tissue blood supply.

Scanning laser Doppler flowmetry is a technique that employs a laser beam directed at the tissue in question. Subsequent shifts in frequency from the moving erythrocytes within blood vessels are detected as a means to determine perfusion. This technique has been applied to colorectal surgery [5] and has demonstrated a reduction in perfusion following mesenteric division leading to revision in the form of further resection in two cases [5]. Visible light spectroscopy uses white light emitted from a probe adjacent/in contact with tissues and detects the changes in scattering and absorption caused by oxy- and deoxyhaemoglobin. This is detected and used to determine the oxygenation of blood within tissue capillaries and has also been used to detect colonic perfusion [6]. Similarly, near infrared spectroscopy (NIRS) detects levels of haemoglobin concentration however using light in the near infrared range. This has been used to assess anastomotic blood supply in a small pilot study and a reduction in tissue oxygenation may be associated with increased risk of anastomotic complications [7]. Even on table angiography has been described, but is impractical to carry on in a routine clinical setting. Most of the methods described above are difficult to use in the operating room, not reproducible or too expensive.

The final mode of imaging discussed and the focus of this paper is the use of fluorescence angiography (FA) with the fluorophore indocyanine green (ICG). A fluorophore is a substance that fluoresces when it is excited by light of a particular frequency. In the case of ICG, it absorbs near infrared light particularly between 800 and 810 nm and emits light at 830 nm that can be detected with a camera containing a near infrared filter [8]. Accordingly, ICG is an exogenous fluorophore that can be administered intravenously and subsequently detected with near infrared imaging within target tissues. Light in the near infrared range is able to penetrate tissues and therefore details of deeper structures otherwise not visible can be gleaned. Accordingly a greater depth of tissue can be interrogated as to its perfusion. As reviewed by Schols et al. [9], this technique has been utilised in many facets of minimally invasive surgery including biliary, colorectal, urological and endocrine surgery. It has also been used in lymph node mapping [8] which holds great promise in the development of sentinel node mapping in colorectal surgery.

**Perfusion imaging in colorectal surgery**

Numerous studies have been undertaken with the aim of investigating the effect of FA in colorectal surgery. These are summarised in Table 1. The main systems used are the Pinpoint™ system (Novadaq, Mississauga, Ontario, Canada), Firefly™ (Intuitive Surgical Inc., Sunnyvale, California, USA), SPY Elite™ Kit (LifeCell Corporation, Bridgewater, New Jersey, USA), IC-View® (Pulsion Medical Systems, Munich, Germany) and D-Light (Storz, Tuttingen, Germany). These studies represent a mix of laparoscopic [10–17] and robotic cases [18–20]. The largest study is a retrospective case controlled study including 402 patients [12]. This study included left and right-sided colonic resections and despite being limited by its retrospective nature, patients were matched between groups. The authors found that in the FA group, there was a higher incidence of the surgical plan being altered on the basis of the perfusion result. In this study, the anastomotic leak rate was lower in the FA group in the subgroups of patients over 70 and those who underwent handsewn anastomosis [12]. The study period ranged over a long period (1998–2008) and throughout this timeframe it is possible that a learning curve effect may have occurred that may have influence the lower leak rate in the later FA cohort.

Sherwington and colleagues [16] assessed anastomotic perfusion intra-lumenally, thus appraising colonic mucosa. Abnormal angiograms were noted in four out of 20 cases and two of these patients developed an anastomotic leak. Interestingly, these patients all had a negative air leak test thus reinforcing that perfusion of gastrointestinal anastomoses may be more relevant. However, as bowel mucosa is more sensitive to effects of ischaemia, it is possible that this may lead to detection of reduced perfusion to the mucosa that may not be as clinically relevant. This will need to be further explored and assessed in future trials.

Three studies utilised the Firefly™ system (Intuitive Surgical Inc.) for FA during robotic cases using da Vinci (Intuitive Surgical, Inc. Sunnyvale, California, USA). Bae et al. [18] utilised it to aid identification of...
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Study type</th>
<th>n</th>
<th>System</th>
<th>Operative procedure and design</th>
<th>Outcome and time taken for angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Kudszus</td>
<td>Retrospective Case control study</td>
<td>Control: 201</td>
<td>Laser assisted indocyanine green (ICG) angiography (IC-View® Pulsion Medical Systems)</td>
<td>Colorectal cancer resection. Case series of patients with fluorescence angiography (FA) (study) matched preceding cohort without (control). Patients matched for characteristics including age, BMI and procedure type</td>
<td>Higher rate of revision of resection margins in study group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Study: 201</td>
<td></td>
<td></td>
<td>Lower leak rate in study group</td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
<td>Time taken, mean (±SD) 6.8 ± 2.6 min</td>
</tr>
<tr>
<td>2012</td>
<td>Sherwinter</td>
<td>Observational study</td>
<td>7</td>
<td>ICG angiography (Pinpoint™ system, Novadaq)</td>
<td>Transanal FA imaging of anastomoses within 25 cm of anal verge included</td>
<td>Concludes that procedure is feasible however more study needed to link to clinical outcome</td>
</tr>
<tr>
<td>2013</td>
<td>Sherwinter</td>
<td>Observational study</td>
<td>20</td>
<td>ICG angiography (Pinpoint™ system, Novadaq)</td>
<td>Low anterior resection for benign and malignant disease. Anastomoses predicted to be &lt; 20 cm from anal verge</td>
<td>Four patients had abnormal angiogram: two had loop ileostomy and no signs leak. Two had CT confirmed leak however conservatively managed to resolution. All patients had a negative air leak test</td>
</tr>
<tr>
<td>2013</td>
<td>Bae</td>
<td>Case series</td>
<td>3</td>
<td>Laser assisted ICG angiography (Firefly™, Intuitive Surgical Inc.)</td>
<td>Robotic low anterior resection and abdominoperineal resection</td>
<td>FA enabled identification of inferior mesenteric artery and ischaemic demarcation zone on the rectum in all cases. No anastomotic leaks</td>
</tr>
<tr>
<td>2013</td>
<td>Jafari</td>
<td>Retrospective case controlled review</td>
<td>Control: 22</td>
<td>Laser assisted ICG angiography (Firefly™, Intuitive Surgical Inc.)</td>
<td>Robotic low, ultralow and intersphincteric resection. FA used at discretion of attending surgeon and decision to revise based on angiography. Air leak test performed also</td>
<td>Groups not matched for co-morbidity Three cases had site of bowel division revised following angiography and one in control group following visual assessment Four leaks in control group and one delayed leak in study group</td>
</tr>
<tr>
<td>2014</td>
<td>Ris</td>
<td>Prospective case series</td>
<td>30</td>
<td>ICG angiography (Pinpoint™ system, Novadaq)</td>
<td>Colorectal procedures for benign and malignant disease. Left and right resections. Control image taken of caecum or terminal ileum to compare</td>
<td>Successful angiogram in 29 patients Encouraged stoma avoidance in three case and no post operative leaks Time taken, median (range) 5 (3–9) min</td>
</tr>
<tr>
<td>2014</td>
<td>Ris</td>
<td>Video vignette</td>
<td>6</td>
<td>ICG angiography (Pinpoint™ system, Novadaq)</td>
<td>Video vignette demonstration of procedure in high anterior resection. six cases discussed five malignant and one diverticular</td>
<td>No anastomotic revision required No anastomotic leak undertaken</td>
</tr>
</tbody>
</table>
### Table 1 (Continued).

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Study type</th>
<th>n</th>
<th>System</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>Hellan [19]</td>
<td>Case series</td>
<td>40</td>
<td>Laser assisted ICG angiography (Firefly™, Intuitive Surgical Inc.)</td>
</tr>
<tr>
<td>2015</td>
<td>Watanabe [17]</td>
<td>Case series</td>
<td>119</td>
<td>ICG angiography (NIR camera system from Olympus Medical, Japan and Mizuho Corporation, Japan)</td>
</tr>
<tr>
<td>2015</td>
<td>Jafari [11]</td>
<td>Prospective multicentre case series</td>
<td>139 analysed, 147 enrolled</td>
<td>ICG angiography (Pinpoint™ system, Novadaq)</td>
</tr>
</tbody>
</table>

### Operative procedure and design

**2014 Hellan [19]**
- Robotic left sided colorectal resection
- Malignant: 70%. Benign 30%
- Point of transection selected and then angiography undertaken and location of division altered accordingly
- Outcome of angiogram led to change in proximal transection point in 40% of cases
- Two patients who had division point revised developed anastomotic leak
- Time taken, mean (±SD) 5.1 ± 10 min

**2014 Foppa [10]**
- Low anterior resection following chemoradiotherapy
- Reversal of Hartmann's procedure
- Both patients underwent further proximal resection on basis of reduced colonic perfusion
- No leak in either patient

**2015 Watanabe [17]**
- Patients with left sided colon or rectal cancer
- Perfusion at the rectosigmoid assessed following distal division of the specimen and classified according to degree of perfusion
- Site of bowel transection determined following angiography
- Anastomotic leak rate 5.9% and did not differ between pattern of perfusion of bowel

**2015 Jafari [11]**
- Left sided colon and rectal resections for cancer 46% (25% for rectal cancer)
- Bowel perfusion assessed at point of proximal bowel transection (serosal surface) and at completion of anastomosis intra luminaly
- Change of site of division on basis of angiography recorded
- Air leak test performed
- FA successful in 98.6% of cases
- Angiography changed surgical plan in 7.9% - no anastomotic leaks in this group
- 1.4% anastomotic leak
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the IMA alongside ischaemic demarcation of the bowel. A retrospective case-controlled review undertaken by Jafari et al. [20] of 38 patients demonstrated that FA lead to site of bowel division being altered in three cases. Four leaks occurred in the control compared to one in the study group. In their case series of 40 patients undergoing robotic left sided and rectal resections, Hellen et al. [19] reported the outcome of perfusion assessment leading to a change in point of division in 40% of cases. Anastomotic leak occurred in 2/40 cases in subjects whose site of transection had been adjusted according to the result of the angiogram. Foppa et al. [10] report outcomes in two patients. In both cases, further proximal bowel division was undertaken and no leaks were reported.

Watanabe et al. [17] utilised FA to determine site of bowel division in 119 patients. The anastomotic leak rate was 5.9% overall and did not differ between the pattern of perfusion of the colon. The PILAR II study [11] evaluates the feasibility of FA during left sided colonic resection, specifically those entailing anastomosis 5–15 cm from the anal verge. In this large multicentre series of 139 cases, FA was undertaken at two crucial points during surgery: prior to the proximal transection of the bowel and once the anastomosis was completed. The latter image was acquired intralumenally. Critically, the authors also record the operators’ intended point of transection and whether this is altered by the outcome of the angiogram. The authors report successful angiography in 98.6% of cases. Operative strategy was altered on the basis of the FA result in 7.9% of cases. The ensuing anastomotic leak rate in this study was very low at 1.4% [11]. Although it is important to note that only 25.9% of patients in this study had an anastomosis < 8 cm from the anal verge.

In work from our own group [13,14], we have demonstrated FA to be practicable when incorporated into laparoscopic colorectal surgery. It was achieved in 29/30 cases and no anastomotic leaks occurred. Importantly, it was found that use of defunctioning ileostomy was avoided in three cases following demonstration of good anastomotic perfusion [13]. We are currently analysing data on 250 prospective colorectal resections from three centres (Dublin, Geneva and Oxford), that were subjected to FA and expect to publish the results soon. These studies clearly demonstrate that this technology can be readily incorporated into clinical use in laparoscopic colorectal surgery. In terms of patient safety, ICG is safe with a very low incidence of allergic reaction (1/300 000). Furthermore, as noted in Table 1, where recorded, FA added only approximately 4–5 min to the operative procedure by an experienced team [13].

Discussion and future perspectives

Anastomotic dehiscence remains one of the most feared complications in colorectal surgery. Any benefit to patients delivered due to advances in minimally invasive surgical approaches can be instantly negated by this dreadful complication. It is evident from the existing literature, that FA holds great promise for determination of the perfusion to this critical region of the bowel. Importantly, it does not appear to have any detrimental effects to the patient.

Upon review of the literature, it is evident that there is a lack of randomised controlled data in this field. In their review, Nachiappan and colleagues [4] calculate that 600 patients would be required in each experimental arm of a study to detect a difference in anastomotic leak rate in left sided colonic surgery. We are planning a multicentre randomised controlled trial to investigate the impact of perfusion angiography on anastomotic leak rate for laparoscopic, robotic and open low anterior resection for rectal cancer. We have powered the study to detect a 33% reduction in anastomotic dehiscence in the FA group, necessitating 723 subjects in each limb. This is to be undertaken over a 5-year period across UK and European centres. We will use the Pinpoint™ system (Novadaq) as we have an extensive experience with this. Intraoperative imaging will be undertaken following division of the IMA but prior to bowel transection and subsequently transanally to assess mucosal perfusion of the completed anastomosis. It will be left to surgeon preference to alter operative strategy according the findings of the testing. The control arm will undergo the same procedure however without perfusion angiography. This proposed multicentre randomised controlled trial aims to determine whether incorporation of the technology into routine clinical practice may lead to a reduction incidence of one of the most seriously feared complications in colorectal surgery.

Conclusion

There is an urgent need of well-designed randomised control trials to assess the impact of this technology on rectal surgery and anastomotic leaks. It has the potential to alter intraoperative decision-making, enabling surgeons to modify their surgery in situ. Thus, pre-emptively avoiding the sequelae of an anastomosis between poorly perfused segments of bowel. It is feasible for this to greatly reduce the incidence of one of the most feared complications for the colorectal surgeon.
Conflict of interest

The authors have no conflicts of interest or financial ties to disclose.

References


