

Intraoperative testing of colorectal anastomosis and the incidence of anastomotic leak

A meta-analysis

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Abstract

Background: AL remains one of the most threatening complications in colorectal surgery. Significant efforts are put to understand the pathophysiological mechanisms involved in the development of leakage and to create the strategies to prevent it. We aimed to determine whether intraoperative testing of mechanical integrity and perfusion of colorectal anastomosis could reduce the incidence of AL.

Methods: A systematic review and meta-analysis of papers published before November 2019 on PubMed, Scopus, Web of Science, and Cochrane Library databases and comparing intraoperative testing of the colorectal anastomosis with standard care were conducted. Odds ratios (ORs) and 95% confidence interval (CIs) were used to assess the association between intraoperative testing and AL.

Results: A total of 23 studies totaling 7115 patients were included. Pooled analysis revealed intraoperative tests, for integrity (OR 0.52, 95% CI 0.34–0.82, $P < .001$) and perfusion (OR 0.40, 95% CI 0.22–0.752, $P < .001$) of the lower gastrointestinal tract anastomoses are associated with significantly lower AL rate.

Conclusions: Intraoperative testing for either integrity or perfusion of anastomoses both reduce the AL rate. Studies looking at the combination of these two testing methods of anastomosis, especially intraoperative endoscopy, and indocyanine green fluorescence angiography may be very promising to further reduction of the AL.

Abbreviations: AL = anastomotic leakage, CI = confidence interval, ICG-FA = indocyanine green fluorescence angiography, IOE = intraoperative endoscopy, OR = odds ratio, RCT = randomized controlled trial.

Keywords: air-leak, anastomosis insufficiency, anastomotic leak, colorectal surgery, indocyanine green fluorescence, intraoperative endoscopy, intraoperative tests, methylene blue

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Mini-abstract: An anastomotic leak (AL) is one of the most devastating postoperative complications in colorectal surgery. A systematic review and meta-analysis were conducted with the aim to assess whether intraoperative testing of mechanical integrity and perfusion of colorectal anastomosis could reduce the incidence of AL.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Anastomotic leak (AL) is one of the most serious postoperative complications in colorectal surgery because it prolongs the hospital stay, increases treatment costs, decreases the quality of life of the patient, impairs long-term outcomes in case of cancer surgery and increases postoperative morbidity and mortality.^[1–3] The reported rate of AL in colorectal surgery varies from 1.8% to 19.2% with the highest risk for low rectal anastomoses.^[4–6] Current evidence cannot fully clarify the reasons of AL in all cases, but some of the etiological factors are well known. These include poor technical construction of the stapled anastomosis when there are gaps between sutures, or anastomosis is formed under tension between the afferent and efferent loops. This may lead to an immediate or delayed AL.^[7] Similarly, insufficient blood perfusion at the anastomotic site is another well-known reason for AL.^[7,8] Therefore, some of the AL might be avoided if anastomoses were constructed in adequately perfused bowel ends and insufficiently integral anastomoses would be immediately reinforced or diverted. Historically surgeons relied on subjective parameters to avoid anastomosis formation in the poorly perfused area by judging the color of the bowel wall, bleeding from the edge of the resection margin and by the palpable pulsations of mesenteric arteries. Similarly, the integrity of the newly formed anastomosis can be evaluated by simple visual inspection. However, subjective judgment is unreliable and depends on the expertise and experience of an individual surgeon. Thus, many different tests to evaluate the anastomoses intraoperatively were created. Presently, it is still not clear whether and which tests should be used as the standard. We hypothesize that intraoperative anastomosis integrity and perfusion assessment may be associated with a reduced leak rate in patients undergoing colorectal anastomosis. We aimed to review the literature and to consolidate the current evidence on the use of various intraoperative tests to assess the colorectal anastomosis intraoperatively and to determine, whether above mentioned intraoperative tests reduce the rate of postoperative anastomotic leak.

2. Materials and methods

Our study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist.^[9,10] PRISMA and MOOSE checklists were filled according to mentioned recommendations (Supplemental digital content [Table, SDC1, <http://links.lww.com/MD/F212> and 2, <http://links.lww.com/MD/F213>]).

2.1. Eligibility criteria

Studies that compared the use of intraoperative tests evaluating the integrity and the perfusion of the anastomosis with the standard care for the assessment of anastomotic leak following lower gastrointestinal resection were eligible for inclusion. The search was restricted to human studies published in the English language only without a time limitation. Patients of any age undergoing colon or rectal resection with anastomosis were included, regardless of the operative approach, resection technique, urgency of surgery, and surgical indications (Supplemental digital content [Table, SDC3, <http://links.lww.com/MD/F214>]). An outcome measure was the rate of postoperative AL in

the control group (no intraoperative testing of anastomosis) versus the rate of postoperative AL in the experimental group (with intraoperative mechanical integrity or perfusion testing).

2.2. Information sources

Literature search was performed in PubMed, Scopus, Web of Science, and Cochrane Library online databases as suggested by Goossen et al^[11] to identify randomized controlled trials (RCT) and comparative studies analyzing the impact of various intraoperative tests on the rate of AL. The most recent search was performed in November 2019.

2.3. Literature search strategy

We used the following combination of Medical Subject Headings (MeSH) and keywords with the employment of “AND” or “OR” Boolean operators:

“Indocyanine green” OR “ICG” OR “Coloring agents” OR “Fluorescence” OR “Fluorescein angiography” OR “Fluorescent dyes” OR “Narrow Band Imaging” OR “Methylene Blue” OR “Ultrasonography” OR “Doppler” OR “Duplex” OR “Colonoscopy” OR “Endoscopy” OR “Staple line bleed” OR “Staple line bleeding” OR “Leak Test” OR “Leak Testing” OR “Spectroscopy” OR “Near-Infrared imaging” OR “Spectrum analysis” AND “Anastomotic leak” OR “Anastomotic leakage” OR “Anastomotic perfusion” OR “Anastomosis, surgical” OR “Bowel perfusion” OR “Blood supply” OR “Perfusion assessment” OR “Anastomotic dehiscence” OR “Anastomosis dehiscence” AND “Gastrointestinal Tract” OR “Lower Gastrointestinal Tract” OR “Colorectal surgery” OR “Colon surgery” OR “Rectal surgery” OR “Colorectal resection” OR “Bowel resection” AND “Intraoperative Period” OR “Intraoperative” OR “Perioperative Period” OR “Perioperative” OR “Intraoperative care” OR “Perioperative care” OR “Intraoperative procedure” OR “Perioperative procedure.”

2.4. Study selection

All titles and abstracts were independently screened for eligibility by 2 experienced reviewers using a piloted electronic database (Microsoft Excel). In the case of different opinions, the study was judged by the additional researcher. After relevant abstracts were identified, full-text articles were retrieved and re-reviewed. Letters, comments on articles, conference abstracts, short notes, meta-analyses, systematic reviews, review articles, and duplicates were manually excluded. An additional manual search of the reference lists of the included studies was performed to ensure the comprehensive search procedure. The authors of the included studies were not further contacted.

2.5. Data extraction

Finally, the following data were extracted from each study: date of publication, type of study design, study sample size, surgery-related data (access [open vs laparoscopic vs robotic], type of anastomosis [hand-sewn vs stapled], elective or emergency setting, anastomosis location), intraoperative tests used to evaluate the anastomosis and main findings of the study. Extracted data were only compared at the end of the reviewing process to reduce the selection bias.

2.6. Assessment of risk of bias

The risk of bias was assessed for each study using appropriate assessment tools. Two reviewers independently performed a duplicate outcome-specific assessment of the risk of bias for each study using the Cochrane Collaboration's tool for assessing the risk of bias.^[12] For randomized controlled trials, we used Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), for nonrandomized studies the Newcastle-Ottawa scale (≥ 7) was utilized.

2.7. Statistical analysis

Statistical analysis was performed according to the recommendations of the Cochrane Collaboration Guidelines^[10] using Review Manager Software (RevMan, version 5.3 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Data from different studies were combined to obtain a pooled (summary) odds ratio (OR) and the 95% confidence interval (CI) using the Mantel-Haenszel (M-H) method for random effects model. Between-study heterogeneity was measured by Sidik-Jonkman I^2 test. $I^2 < 50\%$ was considered to indicate low between-study heterogeneity, while 50% to 75% and $\geq 75\%$ indicated moderate and high heterogeneity, respectively. Small study effects were examined by funnel plots in order to distinguish publication bias from other causes. Sensitivity analyses were additionally performed. The sensitivity of $\geq 50\%$ was considered to be high and sensitivity of $< 50\%$ was considered low. Ninety-five percent confidence intervals for proportions were calculated according to the efficient-score method (corrected for continuity) described by Newcombe^[13] and based on the procedure outlined by Wilson.^[14]

3. Results

3.1. Search results and study characteristics

Three-thousand three-hundred and twenty-three studies were identified during the literature search. Seventy-six papers were reviewed as full-text articles. These were assessed for eligibility. Fifteen were excluded as not eligible for the inclusion: 1—review article, 3—editorial, 1—video vignette, 3—conference abstracts, 5—due to inadequate, and 1—due to overlapping data. Studies were grouped into those, which investigated the methods to test the mechanical integrity of the anastomosis ($N=41$), and those, which investigated the methods to test the perfusion of the anastomosis ($N=20$) and its' impact on AL after colonic resection with anastomosis. Twenty-three studies were selected for a meta-analysis, excluding those, lacking control group and necessary data^[15–37] (Fig. 1).

3.2. Intraoperative tests to evaluate the integrity of anastomosis

Twelve studies, involving 3787 patients, were included in the meta-analysis.^[15–26] Isolated air-leak test, intraoperative endoscopy with the air-leak test, and intraoperative endoscopy with both air-leak and blue-tinged saline tests were the methods of testing the integrity of anastomosis included in the study (Table 1). Two RCTs included showed the positive intraoperative endoscopy (IOE) test in 23% and 25% of the patients undergoing colorectal surgery.^[15,17] Both trials revealed a clear benefit of testing, as the rates of AL in the study group of 4%^[15] and

10%^[17] were significantly lower compared with the control groups 14%^[15] and 20%.^[17] Observational studies included in the meta-analysis reported a slightly lower rate of intraoperative air-leakage ranging from 1.2% to 18.8%, although detection of leaking anastomosis did not prevent from AL in some cases.^[16,18–26] The rate of AL in the study group was 0% to 10% compared with 1.5% to 12.1% in the control group. The biggest included study by Allaix et al^[18] reports that 5% of included patients had a change in a surgery plan due to positive testing. Seventy percent of these patients received protective ostomy, while 30%—reinforcement of anastomosis, with great results as none of them developed AL. AL still occurred in 2.5% of the patients without intraoperative air-leakage but was notably higher in the controls (5.8%) without any testing at all.^[18] Schmidt et al^[20] tested the integrity of the anastomoses by IOE plus air-leak followed by blue stained saline test and reported an even higher rate (10%) of AL in rectal cancer patients with normal findings at testing. From those with positive tests, the stained saline compared with the air-leakage had a higher proportion of the AL (10.4% vs 6.9%).^[20]

Lanthaler et al^[21] and Shibuya et al^[26] trials showed the most controversial results, with OR of 1.36 (95% CI, 0.24–7.74) and 2.08 (95% CI, 0.26–16.62), respectively, raising doubts about the efficacy and safety of intraoperative testing for the reduction of the AL (Fig. 2). However, these studies included fewer participants, providing only 6.9% and 5.4% of the weight on the total results of the meta-analysis. Contrarily, Yang et al^[25] and Allaix et al^[18] trials with considerable weights, (14.2% and 14.5%, respectively), showed a significant difference, 0.32 (95% CI, 0.15–0.70) and 0.42 (95% CI, 0.20–0.90), between the groups with the superiority of anastomosis integrity testing in reducing AL.^[18,25] Similarly, Beard et al^[15] and Ivanov et al^[17]—both randomized controlled trials—confirmed a greater advantage of intraoperative endoscopy and air-leak testing.^[25]

The pooled analysis with a total OR value—0.52 (95% CI, 0.34–0.82)—revealed that intraoperative tests to evaluate the integrity of anastomosis (and anastomotic reinforcement, if applicable) were associated with a lower AL rate after lower gastrointestinal tract resection. The difference was statistically significant ($P < .001$), and there was no significant heterogeneity among the studies ($\chi^2 = 9.49$; degrees of freedom = 11; $P = .58$; $I^2 = 0$). Additionally, we performed sensitivity analyses on the results of each trial and overall meta-analysis results (Supplemental Digital Content (Table, SDC 4, <http://links.lww.com/MD/F215>). Higher sensitivity was seen in RCTs compared with non-RCT trials with an exception of Lieto et al^[23] observational prospective study with a relatively high sensitivity of 0.75. Shibuya et al^[26] trial showed low sensitivity of 0.13, though the study was not excluded from the meta-analysis due to additional non-statistical input, presenting intraoperative colonoscopy as not only a method to reduce the AL, but also the one which is irreplaceable in certain cases, for example, bleeding.

3.3. Intraoperative tests to evaluate the perfusion of anastomosis

Eleven studies, involving 3328 patients, were included in the meta-analysis^[27–37] (Table 2). Included trials compared the rate of AL according to, whether intraoperative tests evaluating the perfusion of anastomosis (with anastomotic reinforcement or change in the resection margin, if applicable) were performed or not (Fig. 3). The use of indocyanine green fluorescence angiography (ICG-FA) with or without an air-leak test and its

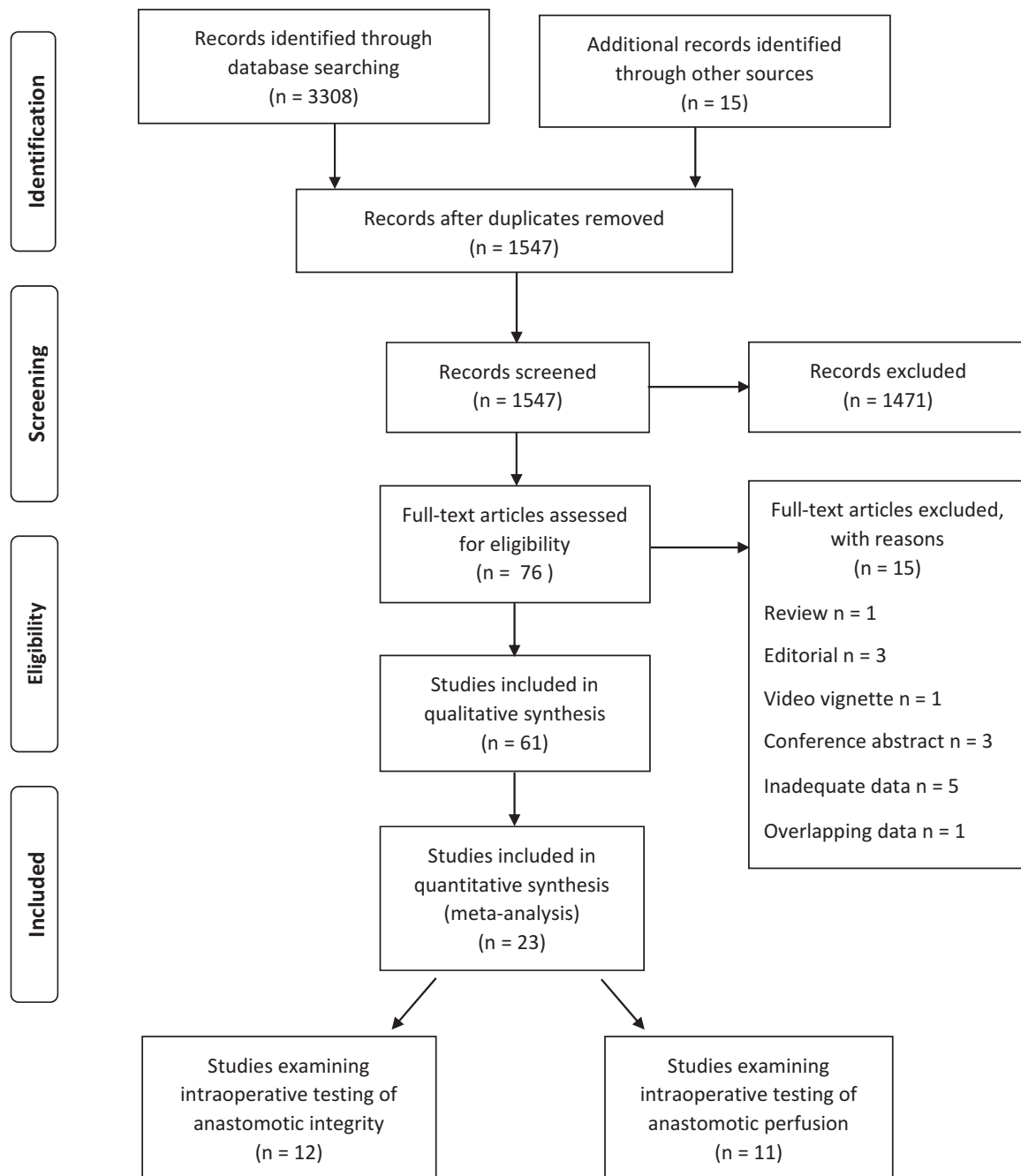


Figure 1. Flow diagram indicating selection of studies for the meta-analysis.

impact on the rate of AL were investigated. In total, these studies included 1680 patients in the control and 1648 patients in the study group undergoing colorectal surgery.

Among these trials, the rate of AL in the study group was 0% to 7.5% compared with 1.3% to 18% in the control group. 4.6% to 19% of patients had a change in the resection margin based on the results of the ICG-FA (Table 2).

The most significant input in this meta-analysis was provided by Watanabe et al.^[37] This propensity score-matched cohort study created the largest statistical weight of 16% with OR value of 0.43 (95% CI, 0.20–0.93), favoring the intraoperative assessment of anastomosis perfusion in lowering the AL rates

after lower gastrointestinal tract resections. Kin et al.^[29] and Dinallo et al.^[35] studies, though showing the equivocal effects of testing and non-testing in reducing the AL rates (1.20 [95% CI, 0.52–2.75] and 1.03 [95% CI, 0.23–4.63]), were included in the meta-analysis due to not statistical additional significance. Kin et al.^[29] trial was the first to explore the role of ICG-FA in improving outcomes in colorectal surgery. Similarly, Dinallo et al.^[35] trial presented the new North American experience.

By consolidating the available data, we could see a major decrease of the AL with the use of ICG fluorescence angiography from (6.0% (101/1680) in the control group to 2.7% (44/1648) in the study group.

Table 1
Studies investigating tests to evaluate the integrity of the anastomosis in the lower gastrointestinal tract.

Author; (publish date; study type)	Quality assessment (RoB 2.0 / Newcastle-Ottawa score)	Study group size (n)	Control group size (n)	Type of surgery (open/ laparoscopic/ robotic)	Anastomotic technique (stapled/hand-sewn/both)	Elective/ emergency surgery	Intraoperative test used	Positive test	AL rate study group	AL rate control group	P value
Beard et al ^[15] (1990; RCT)	Low risk	73	70	Open	CR; Both	Both	IOE + air-leak	25%	4%	14%	.043
Ricciardi et al ^[16] (2009)	8/9	825	173	Open/ laparoscopic	CR/ enterocolic/ enterorectal; Both	Both	IOE + air-leak	7.9%	3.8% (negative test) 7.7% (positive test)	8.1%	<.03
Ivanov et al ^[17] (2011; RCT)	Some concerns	30	30	Open/ laparoscopic	CR; Stapled	Elective	Air-leak	23%	10%	20%	n.s.
Allaix et al ^[18] (2018)	8/9	398	379	Laparoscopic	CR; Stapled	Elective	Air-leak	5%	2.5%	5.8%	.025
Sakanoue et al ^[19] (1993)	8/9	35	35	Open	CR; Stapled	Both	IOE + air-leak	5.7%	0%	11.4%	<.05
Schmidt et al ^[20] (2003)	8/9	260	36	Open	CR; Stapled	–	IOE + air-leak + blue-tinged saline	18.8%	10%	11.1%	–
Lanthalier et al ^[21] (2008)	8/9	73	49	Laparoscopic	CR; Stapled	Elective	IOE + air-leak	6.8%	5.4%	4.0%	n.s.
Li et al ^[22] (2009)	8/9	107	137	Laparoscopic	CR/enterorectal; Stapled	Elective	IOE + air-leak	2.8%	0%	1.5%	–
Lieto et al ^[23] (2011)	8/9	56	68	Open	CR; Stapled	Elective	IOE + air-leak	10.7%	3.6%	10.2%	–
Shamiyeh et al ^[24] (2012)	8/9	85	253	Laparoscopic	CR; Stapled	Elective	IOE + air-leak	2.4%	1.2%	1.6%	n.s.
Yang et al ^[25] (2017)	7/9	215	215	Open/ laparoscopic/ robotic	CR; Stapled	Elective	IOE + air-leak vs. air-leak	4.7%	4.2%	12.1%	.004
Shibuya et al ^[26] (2019)	7/9	162	23	Open/ laparoscopic	CR; Stapled	–	IOE + air-leak	1.2%	8.6%	4.3%	n.s.

AL=anastomotic leakage, CR=colorectal, IOE=intraoperative endoscopy, n.s.=non-significant.

Overall, the combined OR value was 0.40 (95% CI, 0.22–0.75), implying that the use of intraoperative ICG-FA was associated with a lower incidence of AL in the lower gastrointestinal tract anastomosis. The difference was statistically significant ($P < .001$). According to our set limits of considered heterogeneity, it could be described as low heterogeneity ($\chi^2 = 13.53$; degrees of freedom = 10; $P = .20$; $I^2 = 26$).

Similarly, we calculated sensitivities for experimental groups (Supplemental Digital Content [Table, SDC 5, <http://links.lww.com/MD/F216>]). Starker et al,^[33] Kudszus et al,^[27] and Dinallo et al^[35] studies showed the highest, while Watanabe et al,^[37] Kin et al,^[29] and Kim et al^[30]—the lowest (or not expressible)

sensitivity values. Moreover, 1.00 sensitivity can be considered as false positive. Nevertheless, the latter studies were included in the meta-analysis due to the above mentioned non-statistical contribution. The overall sensitivity was 0.69.

3.4. Assessment of publication bias

We performed the funnel plot analysis for the outcomes and observed no obvious asymmetry (Fig. 4). We concluded that overall, there was no evidence of significant bias about these outcomes in the included trials and our results can be described as statistically reliable.

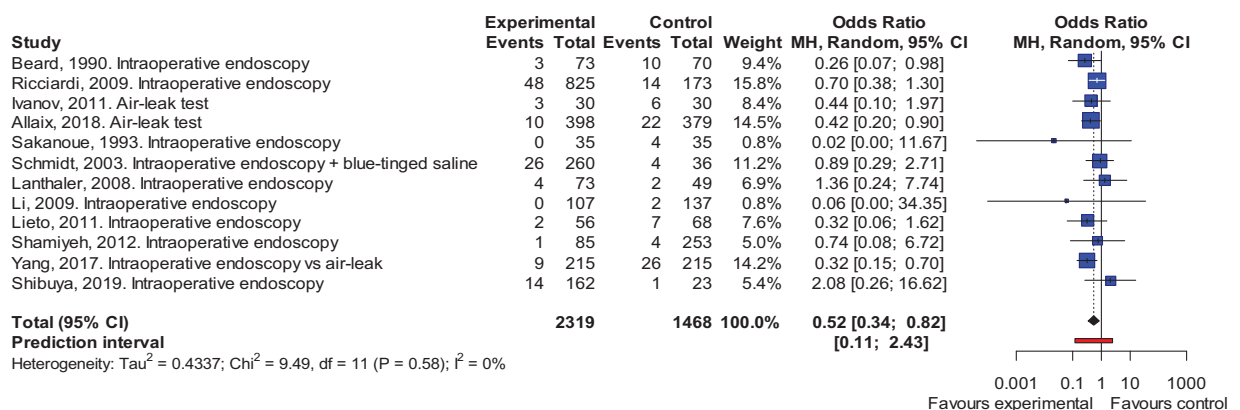


Figure 2. Forest plot showing odds ratios (OR) for AL following lower gastrointestinal surgery in experimental (intraoperative testing of anastomosis integrity and anastomosis reinforcement, if applicable) versus control (non-testing) group. AL=anastomotic leakage.

Table 2
Studies investigating tests to evaluate the perfusion of the anastomoses in the lower gastrointestinal tract.

Author; (publish date; study type)	Quality assessment (Rob 2.0 /Newcastle-Ottawa score)	Study group size (n)	Control group size (n)	Type of surgery (open/laparoscopic/robotic)	Anastomotic technique (stapled/hand-sewn/both)	Elective/emergency surgery	Intraoperative test used	Positive test	AL rate study group	AL rate control group	P value
Kudszus et al ^[27] (2010)	8/9	201	201	Both	Entero-colic/colo-colic/CR; Both	Both	ICG-FA	13.9%	3.5%	7.5%	-
Jafari et al ^[28] (2013)	8/9	16	22	Robotic	CR; Stapled	Elective	ICG-FA + air-leak	19%	6%	18%	-
Kin et al ^[29] (2015)	9/9	173	173	Open/ Laparoscopic	Colo-colic/CR/Colo-anal; stapled	Elective	ICG-FA	4.6%	7.5%	6.4%	n.s.
Kim et al ^[30] (2017)	7/9	310	347	Robotic	CR; Both	-	ICG-FA + air-leak	-	0.6%	5.2%	.006
Boni et al ^[31] (2017)	9/9	42	38	Laparoscopic	CR/ Colo-anal; Both	Elective	ICG-FA	4.7%	0%	5.3%	n.s.
Mizrahi et al ^[32] (2018)	8/9	30	30	Laparoscopic	CR/Colo-anal; Stapled	Elective	ICG-FA	13.3%	0%	6.7%	n.s.
Starker et al ^[33] (2018)	8/9	238	109	Open / Laparoscopic	Entero-colic/ Colo-colic/ CR; -	Elective	ICG-FA	4.6%	0.8%	5.5%	.004
Brescia et al ^[34] (2018)	9/9	75	107	Laparoscopic	Entero-colic/ Colo-colic/ CR; Stapled	Elective	ICG-FA	6.6%	0%	5.6%	.03
Dinallo et al ^[35] (2019)	7/9	234	320	Open/ Laparoscopic/ Robotic	Entero-colic/ Colo-colic/ CR; -	-	ICG-FA + air-leak	5.6%	1.3%	1.3%	n.s.
de Nardi et al ^[36] (2019; RCT)	Low risk	118	122	Laparoscopic	CR, colo-anal; Stapled/manual	-	ICG-FA + air-leak	11%	5%	9%	n.s.
Watanabe et al ^[37] (2019)	7/9	211	211	Laparoscopic	CR; Stapled	Elective	ICG-FA	5.7%	4.7%	10.4%	.042

AL = anastomotic leakage, CR = colorectal, IOE = intraoperative endoscopy, ICG-FA = indocyanine green fluorescence angiography, n.s. = non-significant.

4. Discussion

This systematic review and meta-analysis found that intraoperative testing of the mechanical integrity and the perfusion of anastomosis are significantly associated with a reduced rate of postoperative AL following colorectal surgery.

4.1. Tests to evaluate the mechanical integrity of the anastomosis

Overall, any of the above-mentioned methods can identify some leaking anastomosis intraoperatively. Unfortunately, some AL still occur even after reinforcement. This is especially true in cases of stapled leaking anastomoses, where reconstruction or diversion is the safer method of action. Negative intraoperative

tests reduce the risk but do not completely prevent AL. There is also a lack of studies with properly selected controls to conclusively answer what is the real benefit of each test and which is the best. Air-leak and methylene blue tests through the Foley catheter are cheaper and easier to perform compared with IOE.^[38] Moreover, some clinicians warn of the danger of powerful air insufflation using IOE, causing mechanical disruption of the staple lines, thus creating a high false-positive air-leak rate and even increasing the rate of AL itself.^[19] However, the mean of the maximal pressure during IOE in humans is about only 42 mmHg, while at least 2-fold higher pressure is necessary to cause the leakage in experimental large animal studies.^[39] Also, only IOE can identify some other—rare, but threatening intraoperative complications as intensive anastomotic suture-line bleeding or others.^[34] Therefore, technically more challenging

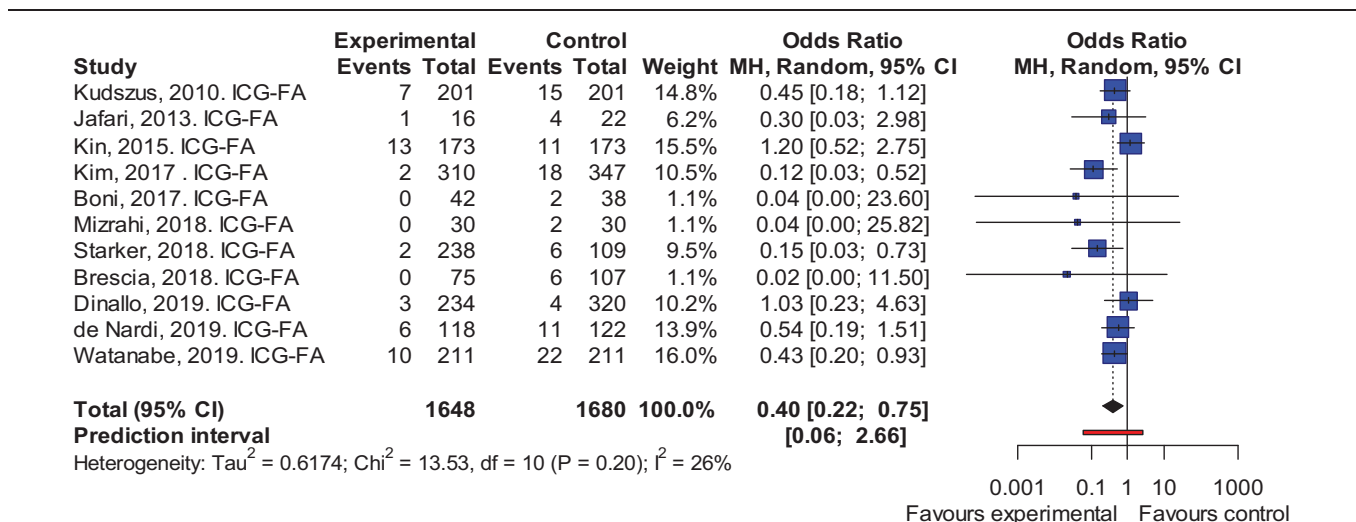


Figure 3. Forest plot showing odds ratios (OR) for AL following lower gastrointestinal surgery in experimental (intraoperative testing of anastomosis perfusion and anastomosis reinforcement or change in the resection margin, if applicable) versus control (non-testing) group. AL = anastomotic leakage.

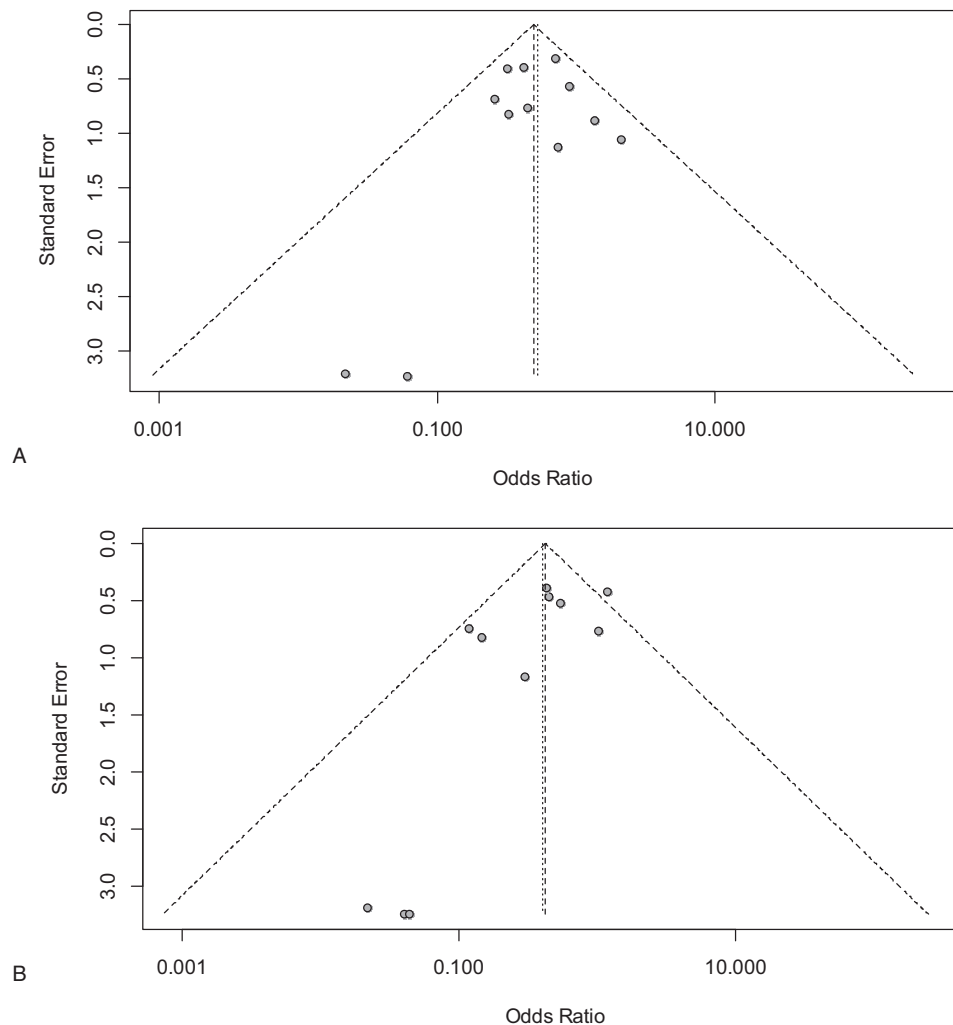


Figure 4. Funnel plots for visual inspection of publication bias. Each point represents a standardized comparison of a separate study, comparing the outcome effect (odds ratio) with the standard error. (A) Intraoperative testing of the anastomosis integrity compared with the control group; (B) intraoperative testing of the anastomosis perfusion compared with the control group.

and more expensive IOE may be a better alternative to air-leak and methylene blue tests.

4.2. Tests to evaluate the perfusion of the anastomosis

We identified 11 studies that have a control group and directly analyzed the impact of ICG-FA testing on the rate of AL.^[27–37] This technique creates the possibility to identify high-risk patients who may benefit from a change in the surgical plan, where the anastomotic technique is tailored to the individual patient or even delayed by creating ostomies. However, the main drawback of application of ICG-FA in colorectal surgery is a lack of objective criteria to determine sufficient or insufficient perfusion. Some attempts to create an objective system exist. For instance, Protyniak et al^[40] proposed a technique that measures the color intensity of the bowel during the ICG-FA, while Wada et al^[41] suggested to measure how fast the color intensity reaches its maximum. Until these techniques are standardized, more and higher quality evidence from a larger scale studies is necessary. Further research to develop exact quantitative parameters, which would describe a threshold of adequate perfusion, below which

most of the anastomoses will leak, has to be established to adopt ICG-FA in routine clinical practice.

4.3. Strengths of the study

We performed a comprehensive search of the topic and quality assessment of the trial methodology according to the recommendations of the Cochrane Collaboration. Only trials with a control group were included in the meta-analysis. The number of participants was comparatively large. All studies were looking at colonic or rectal resections with primary anastomosis. All results were statistically significant with not significant or low heterogeneity among the studies. There was no evidence of significant selection or outcome bias in the included trials.

4.4. Limitations

Most of the studies were retrospective, only a few were observational prospective, and only 2 RCTs in the anastomosis integrity testing group and 1 RCT in the anastomosis perfusion testing group were included. We did not include non-English

trials due to resource constraints and lack of policy relevance outside English-speaking countries. This could have hindered the efforts to avoid bias in review and meta-analysis. Moreover, due to low numbers of RCTs we mixed them together with other study types. Also, some of the studies showed relatively low sensitivity, though were not excluded due to additional non-statistical input. Trials looking both at resections due to colorectal cancer, and, at benign colorectal surgery were included. The studies examining both open and laparoscopic (or robotic) colorectal resections were included, which may affect the outcomes between the trials. The effect of the surgeon's experience and surgical methods (emergency vs elective, hand-sewn vs stapled anastomosis) on the procedure outcomes is also a concern. Intraoperative tests included different techniques for integrity testing (intraoperative endoscopy with the air-leak test, with or without blue-tinged saline, or air-leak test alone) and perfusion testing (ICG-FA with or without air-leak test), giving additional limitations to the meta-analysis. The study has not looked at the combination of mechanical integrity and perfusion tests. Therefore, prospective randomized controlled trials comparing combined use of intraoperative testing methods in colorectal anastomosis are necessary in the future. Our ongoing study investigates mechanical integrity by air-leak and methylene blue in combination with vascular perfusion evaluation by ICG-FA and its impact on AL.^[42]

5. Conclusions

Intraoperative testing of both the integrity and the perfusion of anastomosis may reduce the rate of AL following lower gastrointestinal tract resections. Intraoperative endoscopy might be the best available test to check the integrity of anastomosis as it can also reveal other anastomosis-related complications, such as bleeding. ICG-FA seems to be the best method to evaluate perfusion of the anastomosis in the nearest future. Studies examining the combination of both mechanical integrity (intraoperative endoscopy) and perfusion (ICG-FA) tests, preventing the occurrence of the same complication through different pathways, may be very promising to further reduction of the postoperative anastomotic leaks.

Author contributions

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References

- [1] Li Y-W, Lian P, Huang B, et al. Very early colorectal anastomotic leakage within 5 post-operative days: a more severe subtype needs relaparotomy. *Sci Rep* 2017;7:39936.
- [2] Carboni F, Valle M, Federici O, et al. Esophagojejunal anastomosis leakage after total gastrectomy for esophagogastric junction adenocarcinoma: options of treatment. *J Gastrointest Oncol* 2016;7:515–22.
- [3] Wang S, Liu J, Wang S, et al. Adverse effects of anastomotic leakage on local recurrence and survival after curative anterior resection for rectal cancer: a systematic review and meta-analysis. *World J Surg* 2017; 41:277–84.
- [4] Gessler B, Eriksson O, Angenete E. Diagnosis, treatment, and consequences of anastomotic leakage in colorectal surgery. *Int J Colorectal Dis* 2017;32:549–56.
- [5] Pacheco PE, Hill SM, Henriques SM, et al. The novel use of intraoperative laser-induced fluorescence of indocyanine green tissue angiography for evaluation of the gastric conduit in esophageal reconstructive surgery. *Am J Surg* 2013;205:349–52. discussion 352–353.
- [6] Phillips BR. Reducing gastrointestinal anastomotic leak rates: review of challenges and solutions. *Open Access Surg* 2016;2016:9–14.
- [7] van Praagh JB, de Goffau MC, Bakker IS, et al. Intestinal microbiota and anastomotic leakage of stapled colorectal anastomoses: a pilot study. *Surg Endosc* 2016;30:2259–65.
- [8] Sparreboom CL, Wu Z-Q, Ji J-F, et al. Integrated approach to colorectal anastomotic leakage: communication, infection and healing disturbances. *World J Gastroenterol* 2016;22:7226–35.
- [9] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg Lond Engl* 2010;8:336–41.
- [10] Stroup DF. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000;283:2008–12.
- [11] Goossen K, Tenckhoff S, Probst P, et al. Optimal literature search for systematic reviews in surgery. *Langenbecks Arch Surg* 2018;403: 119–29.
- [12] Clarke M, Horton R. Bringing it all together: Lancet-Cochrane collaborate on systematic reviews. *Lancet* 2001;357:1728.
- [13] Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 1998;17: 857–72.
- [14] Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 1927;22:209–12.
- [15] Beard JD, Nicholson ML, Sayers RD, et al. Intraoperative air testing of colorectal anastomoses: a prospective, randomized trial. *Br J Surg* 1990;77:1095–7.
- [16] Ricciardi R, Roberts PL, Marcello PW, et al. Anastomotic leak testing after colorectal resection what are the data? *Arch Surg* 2009;144: 407–11.
- [17] Ivanov D, Cvijanović R, Gvozdenović L. Intraoperative air testing of colorectal anastomoses. *Srp Arh Celok Lek* 2011;139:333–8.
- [18] Allaix ME, Lena A, Degiuli M, et al. Intraoperative air leak test reduces the rate of postoperative anastomotic leak: analysis of 777 laparoscopic left-sided colon resections. *Surg Endosc* 2019;33:1592–9.
- [19] Sakanoue Y, Nakao K, Shoji Y, et al. Intraoperative colonoscopy. *Surg Endosc* 1993;7:84–7.
- [20] Schmidt O, Merkel S, Hohenberger W. Anastomotic leakage after low rectal stapler anastomosis: significance of intraoperative anastomotic testing. *Eur J Surg Oncol* 2003;29:239–43.
- [21] Lanthaler M, Biebl M, Mittermair R, et al. Intraoperative colonoscopy for anastomosis assessment in laparoscopically assisted left-sided colon resection: is it worthwhile? *J Laparoendosc Adv Surg Tech A* 2008; 18:27–31.
- [22] Li VKM, Wexner SD, Pulido N, et al. Use of routine intraoperative endoscopy in elective laparoscopic colorectal surgery: can it further avoid anastomotic failure? *Surg Endosc Interv Tech* 2009;23:2459–65.
- [23] Lieto E, Orditura M, Castellano P, et al. Endoscopic intraoperative anastomotic testing may avoid early gastrointestinal anastomotic complications. a prospective study. *J Gastrointest Surg* 2011;15: 145–52.

- [24] Shamiyeh A, Szabo K, Wayand WU, et al. Intraoperative endoscopy for the assessment of circular-stapled anastomosis in laparoscopic colon surgery. *Surg Laparosc Endosc Percutan Tech* 2012;22:65–7.
- [25] Yang SY, Han J, Han YD, et al. Intraoperative colonoscopy for the assessment and prevention of anastomotic leakage in low anterior resection for rectal cancer. *Int J Colorectal Dis* 2017;32:709–14.
- [26] Shibuya N, Matsuda T, Yamashita K, et al. Clinical significance of intraoperative colonoscopy for anastomotic assessment in rectal cancer surgery. *Anticancer Res* 2019;39:5761–5.
- [27] Kudzus S, Roesel C, Schachtrupp A, et al. Intraoperative laser fluorescence angiography in colorectal surgery: a noninvasive analysis to reduce the rate of anastomotic leakage. *Langenbecks Arch Surg* 2010;395:1025–30.
- [28] Jafari MD, Lee KH, Halabi WJ, et al. The use of indocyanine green fluorescence to assess anastomotic perfusion during robotic assisted laparoscopic rectal surgery. *Surg Endosc Interv Tech* 2013;27:3003–8.
- [29] Kin C, Vo H, Welton L, et al. Equivocal effect of intraoperative fluorescence angiography on colorectal anastomotic leaks. *Dis Colon Rectum* 2015;58:582–7.
- [30] Kim JC, Lee JL, Park SH. Interpretative guidelines and possible indications for indocyanine green fluorescence imaging in robot-assisted sphincter-saving operations. *Dis Colon Rectum* 2017;60:376–84.
- [31] Boni L, Fingerhut A, Marzorati A, et al. Indocyanine green fluorescence angiography during laparoscopic low anterior resection: results of a case-matched study. *Surg Endosc* 2017;31:1836–40.
- [32] Mizrahi I, Abu-Gazala M, Rickles AS, et al. Indocyanine green fluorescence angiography during low anterior resection for low rectal cancer: results of a comparative cohort study. *Tech Coloproctol* 2018;22:535–40.
- [33] Starker PM, Chinn B. Using outcomes data to justify instituting new technology: a single institution's experience. *Surg Endosc Interv Tech* 2018;32:1586–92.
- [34] Brescia A, Pezzatini M, Romeo G, et al. Indocyanine green fluorescence angiography: a new ERAS item. *Updat Surg* 2018;70:427–32.
- [35] Dinallo AM, Kolarsick P, Boyan WP, et al. Does routine use of indocyanine green fluorescence angiography prevent anastomotic leaks? A retrospective cohort analysis. *Am J Surg* 2019;218:136–9.
- [36] De Nardi P, Elmore U, Maggi G, 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* 2019;34:53–60.
- [37] Watanabe J, Ishibe A, Suwa Y, et al. Indocyanine green fluorescence imaging to reduce the risk of anastomotic leakage in laparoscopic low anterior resection for rectal cancer: a propensity score-matched cohort study. *Surg Endosc* 2019;34:202–8.
- [38] Smith S, McGeehin W, Kozol RA, et al. The efficacy of intraoperative methylene blue enemas to assess the integrity of a colonic anastomosis. *BMC Surg* 2007;7:15.
- [39] Kryzauskas M, Degutyte A, Abeciunas V, et al. Experimental study of mechanical integrity testing in stapled large bowel: methylene blue leak test is not inferior to air-leak test. *Visc Med* doi:10.1159/000510660.
- [40] Protyniak B, Dinallo AM, Boyan WP Jr, et al. Intraoperative indocyanine green fluorescence angiography—an objective evaluation of anastomotic perfusion in colorectal surgery. *Am Surg* 2015;81:580–4.
- [41] Wada T, Kawada K, Takahashi R, et al. ICG fluorescence imaging for quantitative evaluation of colonic perfusion in laparoscopic colorectal surgery. *Surg Endosc* 2017;31:4184–93.
- [42] Kryzauskas M, Poskus E, Dulskas A, et al. The problem of colorectal anastomosis safety. *Medicine (Madr)* 2020;99:e18560.