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CAN FLUORESCENT ANGIOGRAPHY REDUCE THE LEAK RATE OF COLONIC ANASTOMOSES? (a meta-analysis)

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AIM: to evaluate of efficacy of fluorescence angiography (FA) in reducing the anastomotic leakage (AL) rate after colorectal surgery in meta-analysis.

SEARCH STRATEGY: PubMed were searched up to May 2019 for studies comparing fluorescence imaging with standard approach. The primary outcome measure was colorectal anastomotic leakage (AL) rate. The Newcastle-Ottawa scale was used for quality assessment. A meta-analysis with random-effects model was performed to calculate odds ratios (ORs) from the original data.

RESULTS: Two thousand four hundred and sixty-six patients from 7 non-randomized studies and 1 randomized study were included. Fluorescence imaging significantly reduced the AL rate in patients after colorectal surgery (OR 0.58; 95%CI 0.39-0.85; p=0.006) and after rectal cancer surgery (OR 0.28; 95%CI, 0.14-0.55; p=0.0002). A limitation of this meta-analysis is the inclusion of only one randomized study.

CONCLUSION: Fluorescence angiography with indocyanine green is a method of preventing of leakage of colorectal anastomosis. The results of randomized clinical trials are needed to confirm the effectiveness of this technique.

[Key words: anastomotic leakage, meta-analysis, colorectal surgery, indocyanine green]

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INTRODUCTION

Colorectal cancer is one of the most frequent oncological diseases in the world, and the incidence is growing from year to year [1]. Due to technical innovations, a better understanding of physiology and anatomy, as well as improvements in surgical technique, currently oncological results of treatment of this category of patients are improving. However, the incidence of postoperative complications and, in particular, the incidence of anastomotic leakage (AL) remains at the same level and varies from 3 to 23% [2]. This complication worsens both immediate and long-term (oncological) results of treatment [3].

According to most authors, the main causes of colorectal anastomotic leakage are poor blood supply and tension of the bowel proximal part during its formation [4]. If the latter problem is solved by mobilizing the left flexure of the colon, then determining the adequacy of blood supply to the anastomosed parts of the bowel is not an easy task. This is due to the variability of the vascular network of the left half of the colon, possible atherosclerotic lesions of the mesentery vessels in elderly patients. The standard intraoperative method of determining the adequacy of vascularization of the colon anastomosed segments is assessment by a surgeon of the intestinal wall color, ripple and the degree of bleeding from the marginal vessel at its intersection [5]. This method is quite subjective, directly depends on the surgeon's experience and is difficult to use in laparoscopic surgery.

Currently, there are clinical trials demonstrating a significant decrease in the AL incidence rate in colorectal surgery using the method of objective determination of intestinal wall perfusion – fluorescent angiography (FA) with indocyanine green [6]. This method has been used for more than half a century in various fields of medicine: plastic and hepatobiliary surgery, cardiac surgery, ophthalmology and for the last ten years has been used in colorectal surgery.

Intraoperative FA with indocyanine green is attractive for routine use due to the speed (3-5 minutes) and simplicity of its implementation, the opportunity to assess blood flow in real time [7]. Due to the use of this method in colorectal surgery, it is possible to minimize the AL risk caused by poor blood supply to the anastomosed areas of the intestine [8].

AIM

The purpose of this work is to conduct a meta-analysis of the published results of the studies of the effect of FA with indocyanine green on the AL incidence rate in colorectal surgery.

PATIENTS AND METHODS

This meta-analysis was done under recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [9].

Literature search was carried out in the electronic database of medical publications PubMed in May 2019. Anastomotic leakage, colorectal surgery, fluorescent angiography were used as the key words for the data search. The meta-analysis included only full-text comparative studies of the effect of FA with indocyanine green on the AL incidence rate in colorectal surgery.

The following publications were excluded: abstracts, non-English articles, literature reviews, the use of FA in animals, the use of FA not as a method of prevention of AL, pilot studies without comparison groups, the description of clinical cases.

The Newcastle-Ottawa scale (NOS) was used to assess the risk of bias in non-randomized comparative studies [10]. It was believed that studies with less than 6 points, had a high risk of systematic errors.

The statistical analysis was carried out using Review Manager 5.3 (The Cochrane Collaboration, Denmark). The odds ratio (OR) and coincidence interval (CI) were calculated using statistical tools for dichotomous values with respect to the AL incidence rate in the FA and the control groups.

The odds ratio was calculated using the Peto method with the construction of the Forestplot, with OR>1.0 indicating a high risk of AL in the main group, and with P<0.05 the result was considered statistically significant.

To assess heterogeneity of included in the meta-analysis studies, the criteria of χ^2 and I^2 with a null hypothesis of equal effect were used in all studies with a significance level of P=0.1 to increase the statistical power (sensitivity) of the test. Also, a funnel plot was used, with P<0.1 and I^2>50% indicating the presence of heterogeneous studies included in the meta-analysis.

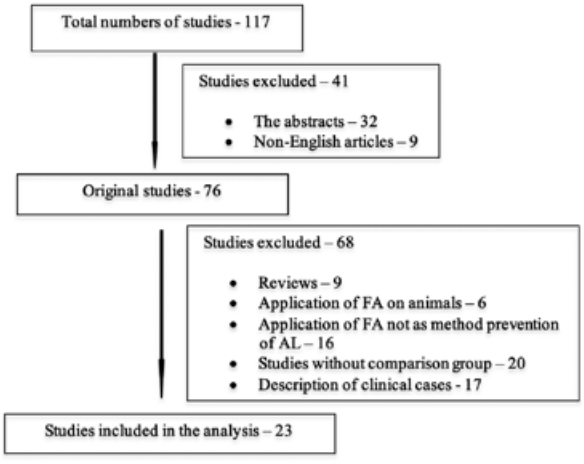

Figure 1. *Flowchart of the study selection process for meta-analysis*

RESULTS

A literature search revealed 117 studies on the use of fluorescent angiography in colorectal surgery (Fig. 1). Further, 41 non-full-text publications and non-English-language articles were excluded. Out of 76 full-text publications, 8 studies published from 2010 to 2019 were selected that fit the criteria for inclusion in this meta-analysis: seven comparative non-randomized studies, including six retrospective, and one prospective randomized study [11-18].

The characteristics of the eight studies are given in table 1. In total, the meta-analysis included 2,466 patients who underwent colon surgery with the formation of intestinal anastomosis. One thousand two hundred eighteen of those patients underwent intraoperative fluorescence angiography to determine the adequacy of blood supply to the anastomosed areas of the intestine (main group).

All the authors used the standard technique of intraoperative fluorescent angiography, which consisted of intravenous administration of 5-10 mg of indocyanine green, diluted in 1-2 ml of saline, before the formation of anastomosis. Then, after 3-5 minutes, using video endoscopic equipment, the adequacy of blood supply to the selected areas of the intestine for the formation of anastomosis was determined by fluorescence in the near-infrared light.

In case of inadequate blood supply, this part of the intestine was resected, which was considered a change in the surgery plan. A number of the authors [6,7] performed repeated fluorescence angiography after anastomosis formation in order to confirm its adequate blood supply. According to the meta-analysis of eight studies – the surgery plan change as a resection of inadequately perfused, according to the FA, was in 4.6-27.1% of cases.

The Newcastle-Ottawa scale (NOS) was used to assess the risk of bias in non-randomized trials. All papers scored 6 or more points, which indicates a low risk of systematic errors in the selected studies.

Table 1. *Characteristics of the studies included in the meta-analysis*

Author	Year	Study design	Number of patients (main: control groups)	Average age (main: control groups)	Surgery types	Surgery plan change	AL rate,% (main: control groups)	The study quality under NOS
Kudszus [3]		Retrospective	402 201:201	69:67.8	Laparoscopic and open right- and left-sided hemicolectomies, rectal resections	16.4%	3.5%:7.5%	7
Jafari [4]	2013	Retrospective	38 6:22	58:63	Robotic LRAR	19%	6%:18%	6
Kin [5]	2015	Retrospective	346 173:173	58.2:58.1	Laparoscopic and open right- and left-sided hemicolectomies, rectal resections	4.6%	7.5%:6.4%	6
Boni [6]		Retrospective	80 42:38	69:67	Laparoscopic LAR	4.7%	0%:5%	7
Kim [7]	2017	Prospective	657 310:347	57:58	Robotic rectal resections	No data	0.6%:5.2%	8
Dinallo [8]	2018	Retrospective	554 320:234	61.5:62.5	Laparoscopic and open right- and left-sided hemicolectomies, rectal resections	5.6%	1.3%:1.3%	7
Wada [9]	2018	Retrospective	149 48:101	66:67	Laparoscopic LAR	27.1%	10.4%:6.9%	6
De Nardi [10]	2019	Prospective, randomized	240 118:122	66.1:65.1	Left-sided hemicolectomies, rectal resections	11%	5%:9%	9

LAR – low anterior resection

According to the meta-analysis of the use of FA, in colorectal surgery, the AL incidence rate was from 0 to 10.4% in the main group and from 1.3 to 18.0% in the control group.

When making a Forestplot (Fig. 2) a statistically significant effect of FA on reducing the AL incidence rate OR=0.58 (95% CI, 0.39-0.85) (P=0.006) was revealed.

Among the eight studies selected for the meta-analysis, in four patients underwent rectal resections with

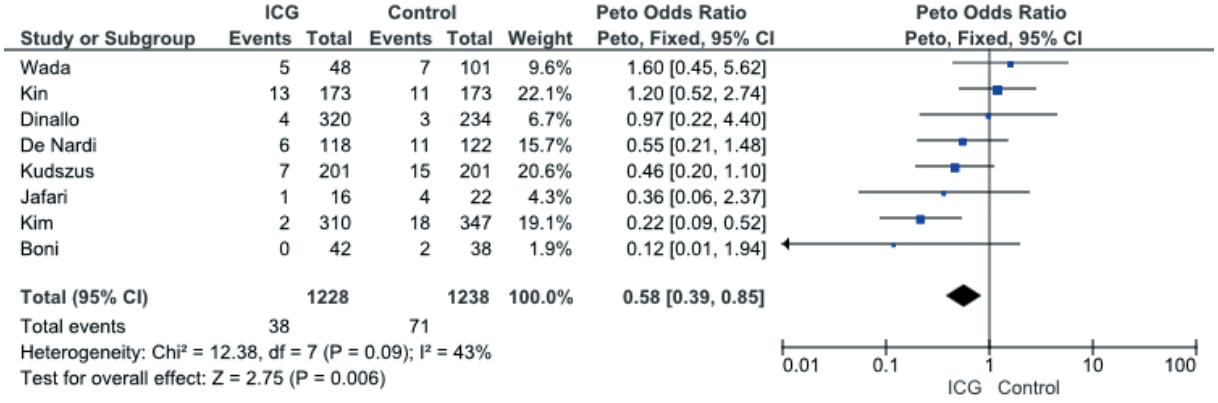

Figure 2. *Forestplot demonstrating the effect of FA on the AL incidence rate in colorectal surgery*

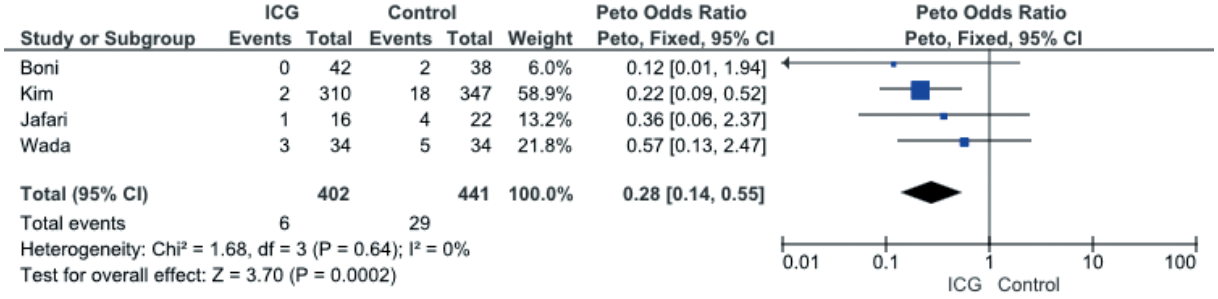

Figure 3. *Forestplot demonstrating the effect of FA on the AL incidence rate in rectal cancer surgery*

the formation of colorectal anastomoses. According to the meta-analysis of the use of FA in rectal cancer surgery, the AL incidence rate was from 0 to 10.4% in the main group and from 5 to 18% in the control group. When making a Forestplot (Fig. 3) a much more significant effect of FA on reducing the «low» anastomotic leakage incidence rate OR=0.28 (95% CI, 0.14-0.55) (P=0.0002) was revealed.

In order to assess heterogeneity of the studies included in the meta-analysis on the FA use in colorectal surgery a funnel plot was made (Fig. 4).

The indicators I^2=43% and P=0.09 indicate the absence of heterogeneity between the studies.

DISCUSSION

According to the literature, FA using indocyanine green can become a method of prevention from AL, since it allows to objectively determine the degree of adequacy of blood supply to the anastomosed areas of the intestine in colorectal surgery. Thus, in the literature review by Degett et al. [8] 10 studies on the FA influence on anastomotic colorectal leakages were analyzed.

FA was performed in 693 patients; standard surgery without this technique – in 223 patients. The AL incidence rate was significantly lower in the main group – 3.83% vs. 8.5% (P=0.005).

In another literature review by Van Den Bos et al. [6] 10 studies were also analyzed. According to them, FA was performed in 894 patients; the standard surgery without this technique – in 434 patients. The surgery plan change after FA occurred in 10.8% of patients. The AL incidence rate was significantly lower in the main group – 3.5% vs. 7.4% (P=0.002).

Recently, 2 meta-analyses of the use of FA in colorectal surgery have been published [19,20]. In a meta-analysis by Blanco-Culina et al. [19] 5 comparative randomized trials were included [11-15], while 555 patients underwent FA, and in 747 cases the adequacy of blood supply to anastomosed areas of the bowel was assessed by the traditional method. When analyzing these studies, it was shown that the use of FA in colorectal surgery does not affect the AL incidence rate – OR=0.51 (95% CI, 0.23-1.13) (P=0.1), while FA reduces the AL incidence rate in the surgery for colorectal cancer – OR=0.34 (95% CI, 0.16-0.74) (P=0.006) and rectal cancer especially – OR=0.19 (95% CI, 0.05-0.75) (P=0.02). In another meta-analysis by Shen et al. [20] 4 comparative non-randomized studies were included [11,13-15]: 569 patients underwent FA and 608 patients were included in the control group.

The meta-analysis showed the effectiveness of FA in the form of statistically significant reduction in the AL incidence rate in the treatment of colorectal cancer-OR=0.27 (95% CI, 0.13-0.53) (P=0.0002).

This meta-analysis showed the effectiveness of intraoperative fluorescent angiography in colorectal surgery and, especially, in rectal cancer surgery in the form of statistically significant reduction of the AL incidence rate in the postoperative period – OR=0.28 (95% CI, 0.14-0.55) (P=0.0002). The low level of AL in the group of patients with FA can be explained by the better blood supply to the anastomosed segments, which can be objectively determined using this technique.

The FA use led to a surgery plan change in the form of resection of an inadequately blood-supplied part of the intestine in 5-27% of cases, which could also lead to a decrease in the AL incidence rate in the main group.

This meta-analysis has the following limitations: all studies except one [18] are non-randomized, which reduces its evidence value. At the same time, in this study [18], due to the small number of patients, the FA effectiveness in the form of an AL incidence rate decrease by 5% versus 9% (P>0.05) was not proved.

It should also be noted that among the other seven non-randomized studies, in only one by Kim et al. [7] statistically significant difference in the AL incidence rate between the main and control groups was obtained – 0.6% vs. 5.2%, P=0.006.

Despite the limitations of this meta-analysis, the use of FA in surgery for colorectal cancer and, especially, in the treatment of rectal cancer looks as a promising technique that can be implemented in clinical practice for the prevention from AL.

However, in order to confirm the effectiveness of intraoperative FA, the results of randomized trials are needed.

At present in clinical trials database «clinicaltrials.gov» there is an evidence of the two randomized trials currently selecting patients – PILLAR-III (NCT02205307) and FLAG-trial (NCT03390517).

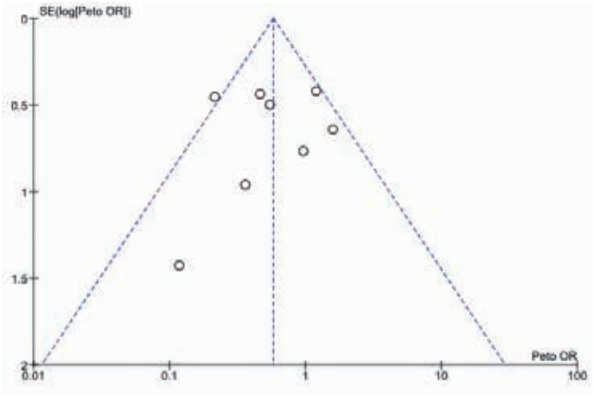

Figure 4. *Funnel plot*

Perhaps, the results of these studies will allow from the point of view of the evidence-based medicine to confirm the effectiveness of FA as a method of preventing from colorectal anastomotic leakage.

PARTICIPATION OF THE AUTHORS

Concept and design of the study by Rybakov E.G., Alekseev M.V.
Collection and processing of material by Alekseev M.V.
Statistical processing by Alekseev M.V.
Text writing by Alekseev M.V.
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The authors declare no conflicts of interest.

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