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"**Re**section of the **me**sentery vs Kono-S **a**nastomosis in preventing **su**rgical **re**currence for primary Crohn Disease: the **REMEASURE** prospective, randomized, controlled trial"

Clinical Trial. Gov number NCT07164209

Remeasure study protocol + statistic

Sincerely

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REsection of the **ME**sentery vs **A**nastomotic configuration and **SU**rgical **Re**currence.

REMEASURE Trial in Crohn's Disease V2.1

Resection of the mesentery with functional end-to-end anastomosis vs Kono-S anastomosis in preventing relapse after ileocolic resection for primary Crohn's Disease.
A prospective, monocentric, randomized trial.

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Background

Crohn's disease (CD) is an Inflammatory Bowel Disease (IBD), with a relapsing and remitting course, and with an annual incidence of 3–25 per 100000 inhabitants. Over 80% of patients with CD will require a surgical procedure due to abdominal complications within 15 years from diagnosis, and 50% of them will require reoperation for recurrent intestinal disease in the next 15 years[1,2].

The gold standard surgical treatment of CD patients, as reported by latest ECCO, ECCO-ESCP, and SICCR guidelines, is based on laparoscopic approach, bowel resection without microscopically disease-free margins, and stapled side-to-side anastomosis[3-5]. However, two novelties have recently appeared in the field of CD surgery, both aimed to improve long-term surgical recurrence: the inclusion of the mesentery in the resection of a diseased bowel loop, and a new anastomotic configuration to leave the mesentery far from the anastomotic margins[6,7].

At present, the incidence and prevalence, clinical significance, surgical implications, and role in surgical recurrence of mesentery thickening and enlarged lymph nodes are completely unknown. Crohn's disease has been thought to originate in the gut lumen, and thus the medical treatment tends to focus on mucosal inflammation. Surgical treatment is based on the resection of the diseased bowel but, unlike cancer surgery, the removal of the mesentery and associated lymph nodes is not considered essential for adequate treatment[8]. Since a thickened mesentery often bleeds heavily when divided, a common approach among surgeons has been to disconnect it flush with the intestine and to leave it retained. Furthermore, no long-term benefits in terms of recurrence have been reported after mesentery removal. However, recent data suggest that margin positivity and reoperation rates can be substantially reduced if resection is guided by mesenteric based strategies[9,10]. The mesenteric organ is a single structural entity spanning the gut from duodenojejunal flexure to mesorectum; it is now recognized that this histological overlap is the true intestinal hilum, where blood vessels enter or leave. At the intersection between the intestine and the mesentery, the mesenteric mesothelium continues onto the intestine and contributes to the cellular component of the outer layer, the serosa. From the serosa, connective tissue separations extend into underlying muscle and submucosa, meaning that the mesenteric and intestinal connective tissue are contiguous[9,10]. Crohn himself was the first to document mesenteric abnormalities, noting that mesenteric fat often advances over the intestinal surface[11]. Nowadays, the mesentery has been proposed as a separate organ, with a role in systemic inflammation. Visceral tissue plays an important role in immunoregulation and may

function as a pro-inflammatory agent; adipocytes release molecules like adiponectin and leptin are implicated in the production of pro and anti-inflammatory cytokines. Fibrocytes also play a central role in the development of systemic inflammation. In pathological states involving mesenteric inflammation (including CD) circulating fibrocytes levels are elevated, secreting cytokines, favoring antigen presentation and enhancing the production of metalloproteinases[12]. The most evident link between the mesentery and Crohn's disease is the macroscopic phenomenon of "fat wrapping" or "creeping fat," where mesenteric fat is inflamed and extends beyond its normal anatomical distribution over the surface of the contiguous intestine. Fat wrapping is a typical and constant finding in Crohn's disease, and is absent in all other forms of intestinal inflammation. The degree of fat wrapping seems to correlate with the severity of intestinal inflammation in the contiguous intestine. Furthermore, some patient presents with extensive lymph nodes enlargement throughout the mesentery tributary of a diseased segment. The reason of this phenomenon and its pathological rule are nowadays completely unknown. In consideration of the above-mentioned evidences, we could target the CD therapy also on the mesentery. At present there are no drugs specifically designed to act on the mesentery, so that the only target-therapy is surgical removal. Mesenteric division in CD is challenging because of bleeding that may be difficult to contro[7,9,13]. Excision of the mesentery is associated with an increased lymphatic tissue removal; this may reduce the immunological stimulation, resulting in improved post-operative outcomes. It may also reduce the recruitment of fibroblasts which subsequently migrate to the intestinal surface[8]. Coffey et al. reported the first retrospective study demonstrating the clinical relevance of including the mesentery in ileocolic resection for CD. The authors analyzed the rate of surgical recurrence after inclusion of the mesentery during ileocolic resection for CD, by comparing two cohorts of patients: cohort A (30 patients who underwent classical ileocolic resection close to the bowel) and cohort B (34 patients in which the affected mesentery was fully dissected and partially excised). As a result, cumulative reoperation rate for CD recurrence were 40% and 2,9% in cohort A and B respectively. In addition, intestinal length and margin positivity rates were both reduced, while nodal yield was increased, following mesenteric resection[7].

With the same intent of reducing surgical recurrence rate after ileocolic resection of CD, Kono et al. published in 2011 a paper concerning a new technique of an anti-mesenteric, functional end-to-end anastomosis (EEA), called Kono-S anastomosis[6]. After the bowel and the corresponding mesentery have been mobilized, ileal and colonic edges are transected with a linear cutter, with the mesentery

located at the center of the stump; the intervening mesentery is divided close to the bowel, to avoid any devascularization or denervation. The 2 staple lines are approximated to create a kind of supporting column to maintain the anastomosis caliber. Two longitudinal enterotomies, 7 cm long, are made at the antimesenteric side of the 2 bowel stumps, starting from 1 cm from the staple line. A hand-sewn, side-to-side, antimesenteric anastomosis is then performed, approximating the anastomotic ends in a transverse fashion. The endoscopic recurrence rate has been reported to be lower with Kono anastomosis than with conventional EEA, and two studies showed a 5-year surgical anastomotic recurrence rate was 1.8%, during a median follow-up of 65 months (range, 43–138 months)[14,15]. Shimada et al. published in 2019 a retrospective trial showing that the Kono anastomosis was associated with a low risk of recurrence after 1 year. Kono anastomosis was reported to be superior in terms of anastomotic recurrence at 5 years, using Kaplan–Meyer analysis, as well as having a lower anastomotic leakage rate[16]. The first RCT comparing Kono-S anastomosis and standard anastomosis in CD has been recently published. The authors found a significant reduction in postoperative endoscopic recurrence rate, and also a decrease in the severity of endoscopic recurrence score, in favor of the Kono-S technique comparing to a conventional side-to-side anastomosis, performed with a double fire of a linear stapler, and with the transverse staple line buried in a running suture[15]. Despite some peculiarities in terms of suturing, the Kono anastomosis is a functional, end- to-end anastomosis which keeps the mesentery distant from the mucosal sutures but leaving in situ the mesentery regardless of its characteristics. In the study by Luglio et al., it was compared with a standard side-to-side anastomosis, but without mesentery removal[15].

In conclusion, since the two surgical techniques are similar, and share the same pathophysiological rational in terms of relapse, the aim of this Troial is to verify if the manual Kono-S anastomosis, with mesentery preservation but exclusion form the anastomosis, has the same efficacy as a stapled, antimesenteric, functional end-to-end anastomosis performed after mesentery removal.

Aim of the study

Aim of the present study is to compare an antimesenteric, stapled, functional end-to-end, ileo-colic anastomosis with removal of the mesentery versus the manual, functional end-to-end, ileo-colic Kono-S anastomosis with mesentery preservation, in terms of peri-operative safety and efficacy in preventing endoscopic recurrence after ileocolic resection for Crohn Disease

Type of the study

Experimental

Design of the study

Prospective, randomized, controlled clinical trial

Target population and setting

Patients presenting with ileocolic primary Crohn disease either not suitable for medical treatment or with contraindications for therapy i.e: occlusion, abscess, contraindications to the use of biologics.

Enrollment:

Inclusion Criteria

- Patients > 18 years
- Informed consent

Exclusion Criteria

- Older than 70
- Recurrent disease, previous surgery for CD
- Clinicians or patients not willing to maintain a drug washout for six months
- Emergency surgery

Endpoints

Primary endpoint: endoscopic recurrence (ER) (Rutgeerts score i2 or greater) after 6 months (see table Rutgeerts score). All patients will maintain a drug washout for six months.

Secondary endpoints: postoperative complications, clinical recurrence* (CR) after 12 months, ER after 18 months, surgical recurrence (SR) after 24 months.

(*) Clinical recurrence: recurrence of disease with bio-humoral alterations (PCR, Calproctectin) or symptoms that require hospitalization or resumption of medical therapy according the Harvey Bradshaw Index and according to the treating physician assessment.

Rutgeerts' score

score	Endoscopic findings
Rutgeerts i0	**Absence of any lesion at the site of anastomosis and in the neo-terminal ileum**
Rutgeerts i1	**>= 5 aphthous ulcers (< 5 mm)** **> 5 aphthous ulcers with normal mucosa**
Rutgeerts i2	**Between the lesions, or skip lesions, or lesions confined to the ileocolic anastomosis**
Rutgeerts i3	**Diffuse neo-terminal ileitis with diffusely inflamed mucosa**
Rutgeerts i4	**Diffuse neo-terminal ileitis with large ulcers (<= 5 mm), nodules and/or narrowing**

Methods

Patients who meet inclusion criteria will be randomized between two surgical procedures:
The excision of the mesentery and ileocolic anastomosis (group A) and the Kono-S anastomosis (group B) after ileocolic or ileo-cecal resection. The operation could be performed with open or laparoscopic approach. Two videos will be provided showing the anastomotic techniques in order to improve standardization among the contributing Centers.

1) Excision of the mesentery: the mesentery is fully dissected and excised to the limit of macroscopic "fat wrapping", where mesenteric fat is inflamed and extends beyond its normal anatomical distribution over the surface of the contiguous intestine. A functional, end-to-end, stapled anastomosis between colon and ileum is than performed (the functional end-to-end is a latero-lateral, antiperistaltic, antimesenteric anastomosis, which has a similar, final configuration of the Kono-S).
2) Kono-S anastomosis: the mesentery is not removed but cutted close to the bowel. The bowel is then divided transversely by placing a linear stapler perpendicular to the intestinal lumen and the mesentery. The corners of the two staple lines are reinforced and the two stumps are approximated using 5–7 sutures to create the column. If the caliber of the two intestinal segments differs significantly, the sutures should be spaced to evenly distribute the surplus tissue of the larger segment, in order to achieve good approximation and stable support for the anastomosis. To create the anastomosis, an antimesenteric longitudinal enterotomy (or colostomy) is performed on each stump to allow a transverse lumen of 7 cm in diameter for the small bowel or closer to 8 cm for the colon. In this way the supporting column is located immediately behind the posterior wall of the anastomosis providing a rigid and stable support to prevent mechanical deformation and functional constriction of the lumen of the anastomosis.

Study Design for a Randomized Trial

The aim of the study is to determine wheather the two therapies have the same efficacy; therefore, we are in the framework of No Difference Testing. [17] [18]

Based on previous literature the expected reduction rate of 6 months for endoscopic recurrence after Kono anastomosis was 25% in order to be more conservative (45% after resection of the mesentery group and 20% in the Kono group), and a value of 0.05 (1-sided) and 75% power was estimated a sample size of 70 patients.

After enrollment, patients will be randomly assigned in a 1 : 1 ratio between Kono anastomosis and resection of the mesentery, by controlling for age, sex, smoking habits, and other health related quantities, including the origin from different centers will be taken into account.
The two Groups will be compared for safety in terms of perioperative characteristics and postoperative complications. Continuous variables will be analysed using a two-tailed, unpaired, Student's t-test, and proportions will be compared using two-tailed, Fisher's exact or chi-square test, where appropriate. Since multiple tests will be performed, a suitable p–value correction will be used, such as Bonferroni correction. A model-based approach for the multivariate analysis, setting the presence of postoperative complications as dependent variable will be performed, a binary logistic regression will be used, with all the variables significant at the univariate level as predictors. The greatest emphasis will be on the dummy variable encoding the different treatments (for example 1 = "Kono anastomosis", 0 = "Resection of the mesentery"). In this context, the equivalence may be evaluated in two ways: 1 • the associated coefficient of the regression is not significant from a statistical point view. • the Odds Ratio (OR) associated to the corresponding coefficient is close to 1 (and in particular the 95% confidence interval contains 1), meaning that changing the type of treatment does not affect the probability postoperative complications.
Endoscopic, clinical, and surgical recurrences will be analyzed using the time-to-event estimates of the Kaplan-Meier function, and compared for univariate analysis with the Log-rank test. Cox proportional hazard regression analysis will be used to set up a predictive model simultaneously exploring the effects of the independent variables on recurrences in relation to time. Significance will be considered for p-value inferior to 0.05.

Data collection

Data will prospectively be collected using a web-based, dedicated, REDCup database. A local study manager will be identified for each participating center, and a dedicated REDCup username and password will be assigned. The completeness and congruity of the data will be checked periodically by the study's Scientific Committee. The Scientific Committee will refer to the local managers for any request for clarification.

Duration of the study

24 months

Ethical consideration

The study will be performed according to the institutional guidelines and to the ethical standards of the Helsinki Declaration and the formal approval by the ethical Committee of each participant.

Funding

No funds needed

Data collections:

REDCup for REMEASURE trial database and CRF

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