Surgical Prevention of Anastomotic Recurrence by Excluding Mesentery in Crohn's Disease: The SuPREMe-CD Study - A Randomized Clinical Trial

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Objective: This trial aimed to provide randomized controlled data comparing Kono-S anastomosis and stapled ileocolic side-to-side anastomosis.

Background: Recently, a new antimesenteric, functional, end-to-end, hand-sewn ileocolic anastomosis (Kono-S) has shown a significant reduction in endoscopic recurrence score and surgical recurrence rate in Crohn disease (CD).

Methods: Randomized controlled trial (RCT) at a tertiary referral institution. Primary endpoint: endoscopic recurrence (ER) (Rutgeerts score $\geq$i2) after 6 months. Secondary endpoints: clinical recurrence (CR) after 12 and 24 months, ER after 18 months, and surgical recurrence (SR) after 24 months.

Results: In all, 79 ileocolic CD patients were randomized in Kono group (36) and Conventional group (43). After 6 months, 22.2% in the Kono group and 62.8% in the Conventional group presented an ER [$P < 0.001$, odds ratio (OR) 5.91]. A severe postoperative ER (Rutgeerts score $\geq$i3) was found in 13.8% of Kono versus 34.8% of Conventional group patients ($P = 0.03$, OR 3.32). CR rate was 8% in the Kono group versus 18% in the Conventional group after 12 months ($P = 0.2$), and 18% versus 30.2% after 24 months ($P = 0.04$, OR 3.47). SR rate after 24 months was 0% in the Kono group versus 4.6% in the Conventional group ($P = 0.3$). Patients with Kono-S anastomosis presented a longer time until CR than patients with side-to-side anastomosis (hazard ratio 0.36, $P = 0.037$). On binary logistic regression analysis, the Kono-S anastomosis was the only variable significantly associated with a reduced risk of ER (OR 0.19, $P < 0.001$). There were no differences in postoperative outcomes.

Conclusions: This is the first RCT comparing Kono-S anastomosis and standard anastomosis in CD. The results demonstrate a significant reduction in postoperative endoscopic and clinical recurrence rate for patients who underwent Kono-S anastomosis, and no safety issues.

ClinicalTrials.gov ID NCT02631967.

Keywords: Crohn disease, endoscopic recurrence, Kono-S anastomosis, surgical recurrence

(*Ann Surg* 2020;xx:xxx–xxx)

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Author contributions: G.L., A.R., N.I.—make substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; draft the article and revise it critically for important intellectual content; and give final approval of the version to be published. M.C.G., A.A., F.P.T., R.P.—acquisition of data, and analysis and interpretation of data. F.C., G.D.D.P., L.B.—revise critically the article for important intellectual content; and give final approval of the version to be published. All authors approved the final version of the article, including the authorship list.

Disclosure: The authors have no conflicts of interest to disclose.

ISSN: 0003-4932/16/XXXX-0001

DOI: 10.1097/SLA.0000000000003821

Crohn disease (CD) is a disabling, idiopathic, and chronic inflammatory disorder, characterized by transmural inflammation, which leads to structural bowel damage and intestinal complications such as strictures, fistulas, and abscesses, often needing surgery.[1–3]

According to the natural history of the disease, the percentage of CD patients who require surgery remains dramatically high: up to 80% of patients undergo surgical treatment, but such a treatment is not curative. In fact, the postoperative recurrence rate varies according to current definitions: clinical, endoscopic, radiological, and surgical recurrence. Endoscopic evaluation after ileocolic resection shows that in the absence of medical treatment, the postoperative endoscopic recurrence rate is about 65% to 90% within 12 months and 80% to 100% within 3 years; at the same time, the clinical recurrence without therapy is around 20% to 25% per year.[4] Another significant problem is that new drugs (ie, biologic drugs) have not changed the rate of surgical treatment of CD,[5] and, even if biologic therapy has improved disease management and short-term operative rates,[6] the long-term impact of biologic therapy on operative rates is still unknown.

Currently, there is no consensus about the best approach to prevent postsurgical recurrence of CD. From this point of view, attention has focused on: surgical techniques, in particular, the type of anastomosis (ie, end-to-end anastomosis vs side-to-side anastomosis); evaluation of patient's profile and individual risk of recurrence (ie, smoking habits, age at onset, perianal disease); and medical therapies and endoscopic monitoring to reveal early mucosal disease, as endoscopically detected disease recurrence predicts clinical recurrence.[7]

Anastomotic recurrence after intestinal resection is 1 of the most significant problems in the management of CD. To date, whether one anastomotic technique is able to reduce surgical recurrence rates over another technique is still debated.[8]

Based on the fact that anastomotic recurrences arise on the mesenteric side, a new antimesenteric, functional, end-to-end, hand-sewn ileocolic anastomosis (Kono-S) has been recently described.[9] This surgical procedure consists in transecting the bowel with a linear cutter, so that the mesentery side is located in the center of the stump after the intervening mesentery has been divided close to the bowel. Both stumps are sutured together to create a supporting column to maintain the diameter and dimension of the anastomosis. Longitudinal enterotomies are made on the antimesenteric sides of the 2 segments of the intestine. The side-to-side antimesenteric anastomosis is then performed in a transverse fashion.[9] Thanks to this procedure, Kono et al[9] concluded that the Kono-S anastomosis seems to be effective in preventing anastomotic surgical recurrence in CD. Preliminary results comparing Kono-S anastomosis with conventional surgical techniques[9] show a significant reduction in endoscopic recurrence score (mean Rutgeerts score 2.6 vs 3.4; $P = 0.008$) and surgical recurrence

rate (0% vs 15%; $P < 0.0013$), despite the fact that data were neither randomized nor controlled.

The aim of this trial was to provide randomized controlled data to compare Kono-S anastomosis and stapled ileocolic side-to-side anastomosis.

METHODS

Study Population and Study Design

In this RCT for surgical prevention of anastomotic recurrence by excluding mesentery in CD (SuPReMe-CD study), consecutive patients with ileocolic CD requiring intestinal resection for medically refractory disease or stricturing/penetrating complications were enrolled at the Tertiary Centre for Inflammatory Bowel Disease, School of Medicine Federico II, Naples, Italy, from March, 2015 to September, 2017.

The diagnosis of CD was established according to the European Crohn's and Colitis Organization (ECCO) criteria.[10] Adult (18–75 years old) subjects suffering from primary or recurrent ileocolic CD needing surgery because of stricturing disease with subocclusive symptoms, fistulizing CD, or medically refractory disease were enrolled. Patients were excluded if they had an ostomy (ileostomy or colostomy), if there was contraindication in performing subsequent endoscopy due to comorbidities or a poorly clinical state, if there was informed consent refusal, or if they were pregnant. The study was approved by Local Ethics Committee (211/15) and registered on ClinicalTrials.gov (NCT02631967). All patients provided written informed consent.

After enrollment, patients were randomly assigned in a 1:1 ratio to Kono-S anastomosis (Kono group) and stapled ileocolic side-to-side anastomosis (Conventional group) through a computer-generated randomization model (Clinical Conductor CTMS, Bio-Optronics, Inc. Rochester, NY), by controlling for the following measures: age, sex, smoking habits, disease duration, previous surgery, and CD behavior.

Surgical Technique

The Kono-S anastomosis was fashioned as previously described[11]: ileal and colonic edges were transected with a linear cutter, taking care that the mesentery was located at the center of the stump; the intervening mesentery was divided close to the bowel, to avoid any devascularization or denervation. The 2 staple lines were approximated with interrupted 3–0 vicryl, to create a kind of supporting column to maintain the anastomosis caliber. Two longitudinal enterotomies, 7 cm long, were 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 was then performed, approximating the anastomotic ends in a transverse fashion; a double layer technique was adopted, 1 layer in interrupted 3–0 vicryl, the second in running 3–0 PDS (Fig. 1A).

All surgeries were performed in laparotomy or laparoscopy, with the anastomosis done extracorporeally.

The conventional side-to-side anastomosis was performed with a double fire of a linear stapler (GIA 80) and the transverse staple line was buried in a running 3-0 vicryl suture.

Conventional Medical Treatment

Thereafter, all subjects underwent a course of metronidazole 250 mg 3 times a day for 1 month postoperatively. In case of metronidazole intolerance, the patient received 250 mg twice daily, once daily, or ceased taking the drug. However, becauser this trial is not focused on medical strategies to prevent postoperative recurrence, the postoperative treatment (no treatment vs immunomodulators vs biologics) was tailored on the basis of patient's risk profile and clinical judgment.[12,13] Enrolled patients were clinically evaluated every 3 months for 24 months, and underwent ileocolonoscopy 6 and 18 months from surgery.

Endpoints

The primary endpoint was endoscopic recurrence (Rutgeerts score[14] $\geq$i2) after 6 months. Secondary endpoints were clinical recurrence after 12 and 24 months [defined as a Crohn's Disease Activity Index (CDAI) >200], endoscopic recurrence after 18 months, and surgical recurrence after 24 months. Also, short-term outcomes (surgery duration, days to gas and/or stool, length of hospital stay) and postoperative complications were recorded.

Endoscopy

For the 6th and 18th month colonoscopies, ileocolonoscopy was performed by gastroenterologists using a conventional colonoscope (Olympus Exera CV-190), after a standard bowel cleansing with a 4-L solution of polyethilenglicole (PEG). Endoscopic

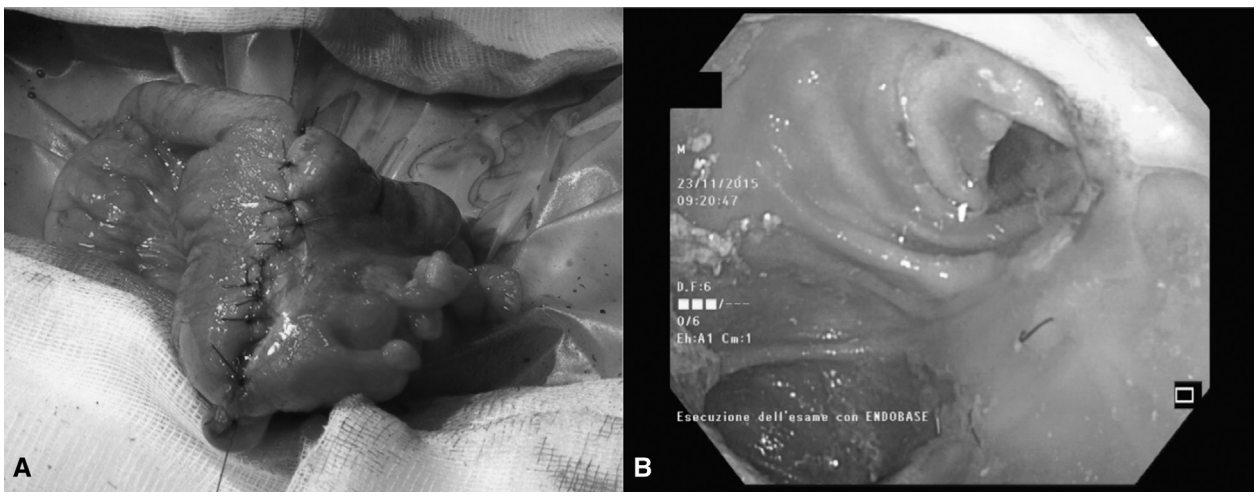


FIGURE 1. (A) Kono-S anastomosis (surgical view). (B) Kono-S anastomosis (endoscopic view showing a Rutgeerts i2 endoscopic recurrence 6 months after surgery).

remission was defined using Rutgeerts score of i0 (no lesions) or i1 (≤5 aphthous lesions); and endoscopic recurrence using i2 (>5 aphthous lesions or larger lesions confined to anastomosis), i3 (diffuse ileitis), or i4 (diffuse inflammation with large ulcers and/or anastomotic narrowing).[14] Severe endoscopic recurrence was defined when Rutgeerts score was ≥i3.[15]

Clinical and Surgical Evaluation

For clinical evaluation, the CDAI[16] was calculated 3, 6, 9, 12, 15, 18, and 24 months from surgery for all subjects. Clinical recurrence was defined as a CDAI >200. Surgical recurrence was defined as the need of re-operation in the presence of symptoms (excluding perianal disease).

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS software v.15.0, Chicago, IL) for Windows and StatsDirect statistical software (vers. 3.0). The descriptive statistics used included determination of mean values, standard deviation (SD) or median, and interquartile range (IQR) of the continuous variables, and determination of percentages and proportions of the categorical variables.

Statistical analysis was performed using chi-square, Mann–Whitney *U* test, Student *t* test, and analysis of variance, whichever was appropriate. The probability of 24-month clinical recurrence-free survival for each group was also calculated using the Kaplan-Meier method, and the curves obtained were compared using the log-rank and hazard ratio (HR) with 95% confidence interval (CI).

Binary logistic regression was used to examine the relationship between the presence of endoscopic recurrence after 6 months (Rutgeerts ≥i2) as a dependent variable and the possible predictors as independent variables. The following variables were included in the univariable analysis: male sex (yes/no), type of anastomosis (Kono-S anastomosis vs staples side-to-side anastomosis), primary vs recurrent CD, behavior (B3 vs B2), smoking habits (yes/no), disease extension >50 cm (yes/no), presence of CD localizations other than ileo-cecal disease (yes/no), type of surgery (laparoscopy vs laparotomy), postoperative exposure to biologics (yes/no), and postoperative exposure to immunomodulators (yes/no). The multivariable analysis was performed using the stepwise backward method (Wald), and it included all the variables with a $P < 0.1$ on univariable analysis. The coefficients obtained from the logistic regression analysis were expressed in terms of odds of event occurrence [odds ratio (OR)]. A *P* value of less than 0.05 was considered statistically significant.

Based on previous studies which found a reduction in endoscopic severity (Rutgeerts score) after 6 months of 0.8 points (mean Rutgeerts score 2.6 in the Kono group vs 3.4 in the Conventional group),[9] the sample size was based on an α value of 0.05 (2-sided) and 90% power. Furthermore, the sample size should consent a reduction >30% in total endoscopic recurrence when assuming a 60% to 65% endoscopic recurrence expected rate in the control group and a 30% in the case group. To allow a 10% drop-out of patients, 36 patients per group were needed (72 patients in the entire population).

RESULTS

During the study period, 37 patients with CD were randomly assigned to Kono-S anastomosis and 46 to conventional anastomosis. Four patients (4.8%) dropped out due to technical reasons (1 in the Kono group and 3 in the Conventional group needed ostomy: more specifically, 2 patients presented intra-abdominal abscesses, 1 patient had peritonitis, and 1 subject had a severe preoperative malnutrition). Therefore, a total of 79 CD patients were finally enrolled and randomized in the Kono group [36 subjects, 50% males, mean age 34 years (IQR 25–50), mean disease duration 101 months ± 88] and the Conventional group [43 subjects, 51.1% males, mean age 43 years (IQR 27–60), mean disease duration 105 months ± 89].

Table 1 shows that both groups were well-matched for baseline features. In particular, 11 (38%) and 10 (27%) patients were active smokers in the Kono and Conventional group, respectively ($P = 0.56$). Moreover, most of the patients had undergone previous surgery (52% vs 65%, respectively for the 2 groups; $P = 0.4$). CD extension was 41 cm (IQR 34–52) in the Kono group versus 48 cm (IQR 38–55) in the Conventional group ($P = 0.2$). Regarding CD behavior, fistulizing disease was found in 16 (44.4%) patients in the Kono group versus 19 (44.2%) subjects in the Conventional group ($P = 0.98$). Stricturing behavior was displayed by 15 (41.7%) and 16 (37.2%) patients in the respective groups ($P = 0.68$), whereas stricturing/fistulizing behavior was present in 5 (13.9%) and 18 (8.6%) patients, respectively ($P = 0.2$). No differences were seen in terms of patients' preoperative treatment during the 6 months before surgery.

A laparoscopic approach was used in 52.7% of cases in the Kono group and in 51.2% of cases in the Conventional group ($P = 0.8$).

Postoperative Endoscopic Recurrence

After 6 months, 8 patients in the Kono group (22.2%) and 27 patients in the Conventional group (62.8%) presented an endoscopic recurrence (Rutgeerts score ≥i2) [$P < 0.001$, OR 5.91, 95% confidence interval (CI) 2.17–16.05] (Fig. 2A). The mean Rutgeerts score (0–4) after 6 months was 0.92 ± 1.05 in the Kono group versus 2.06 ± 1.31 in the Conventional group ($P < 0.001$) (Fig. 2B). Furthermore, a severe postoperative endoscopic recurrence (Rutgeerts score ≥i3) occurred in 13.8% of Kono versus 34.8% of Conventional group ($P = 0.03$, OR 3.32, 95% CI 1.07–10.32), but none of the subjects in the Kono group presented a Rutgeerts i4 endoscopic score.

TABLE 1. Features of the study population

	Kono (n = 36)	Conventional (n = 43)	*P*
Mean age (range)	34 (25–50)	43 (27–60)	0.16
Males:females	18:18	22:21	0.84
Active smoking, n (%)	11 (38%)	10 (27%)	0.56
Mean disease duration (mos)	101 ± 88	105 ± 89	0.82
Previous surgery, n (%)	19 (52%)	28 (65%)	0.4
Behavior, n (%)			
Fistulizing	16 (44.4%)	19 (44.2%)	0.98
Stricturing	15 (41.7%)	16 (37.2%)	0.68
Stricturing/fistulising	5 (13.9%)	8 (18.6%)	0.57
CD extension, cm (range)	41 (34–52)	48 (38–55)	0.2
Type of surgery, n (%)			0.8
Open	17 (47.3%)	21 (48.8%)	
Laparoscopy	19 (52.7%)	22 (51.2%)	
Preoperative treatment, n			
5-ASA	3	4	0.8
Corticosteroids	11	11	0.62
Azathioprine	8	8	0.69
Infliximab	6	5	0.51
Adalimumab	6	8	0.82
Vedolizumab	2	7	0.13
Postoperative treatment, n			0.15
5-ASA	8	10	
Adalimumab	10	18	
Azathioprine	14	10	
Infliximab	0	1	
Metronidazole	35	42	
Ustekinumab	3	0	
Vedolizumab	1	4	

CD, Crohn disease; CI, confidence interval; OR, odds ratio; 5-ASA, mesalamine.

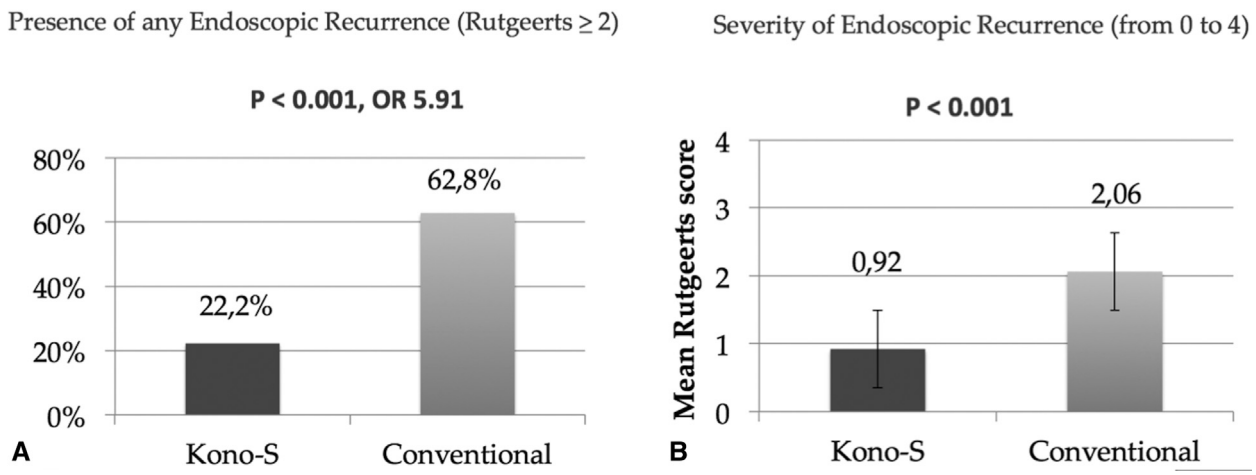


FIGURE 2. Six-month endoscopic recurrence in accordance with Rutgeerts score. (A) Percentage of patients with any endoscopic recurrence (Rutgeerts score ≥2). (B) Mean Rutgeerts score (from 0 to 4).

Figure 1B shows a case of Rutgeerts i2 endoscopic recurrence in a Kono-S anastomosis 6 months after surgery.

The 18th month colonoscopy found that an endoscopic recurrence (Rutgeerts score ≥i2) occurred in 9 patients in the Kono group (25%, including also patients with endoscopic recurrence at 6 months) and 29 in the Conventional group (67.4%, of which 27 with known endoscopic recurrence at 6 months) ($P < 0.001$, OR 6.21, 95% CI 2.31–16.69) with a mean Rutgeerts score (0–4) of 1.05 ± 1.06 in the Kono group versus 2.30 ± 1.32 in the Conventional group ($P < 0.001$) (Fig. 3A and B).

On binary logistic regression analysis, the Kono-S anastomosis was the only variable significantly associated with the reduced risk of endoscopic recurrence (OR 0.19, 95% CI 0.08–0.74, $P < 0.001$) (Table 2).

Post-operative Clinical Recurrence

After 12 months, 3 patients in the Kono group and 8 patients in the Conventional group experienced clinical recurrence (8% vs 18%, respectively; $P = 0.2$, OR 2.51, 95% CI 0.61–10.29) (Fig. 4A).

After 24 months, 4 patients in the Kono group and 13 patients in the Conventional group experienced clinical recurrence (11.1% vs 30.2%, respectively; $P = 0.04$, OR 3.47, 95% CI 1.02–11.81). On Kaplan-Meyer analysis, patients with Kono-S anastomosis presented a higher recurrence-free survival rate than patients with side-to-side anastomosis (HR 0.36, 95% CI 0.14–0.94, $P = 0.037$) (Fig. 4A and B).

Postoperative Surgical Recurrence

Surgical recurrence after 24 months occurred in only 2 patients in the Conventional group (4.6%), but none in the Kono group, although without statistical significance ($P = 0.3$, OR 4.39, 95% CI 0.20–94.62).

Postoperative Outcomes

With regards to postoperative outcomes (Fig. 5), there were no differences in terms of surgery duration (165 ± 42 minutes in the Kono group vs 163.4 ± 42.8 minutes in the Conventional group; $P = 0.8$), days to flatus (3 ± 1 vs 2.82 ± 1.08; $P = 0.4$) or stool (3 ± 1 vs 3.2 ± 1.12; $P = 0.8$), and length of hospital stay (7 ± 3 vs 7.6 ± 3.08

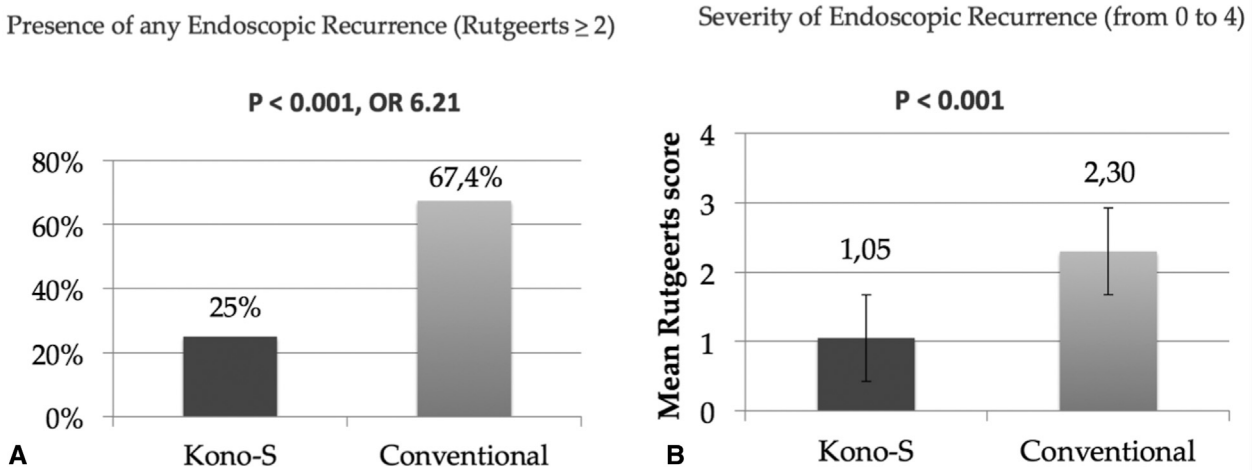


FIGURE 3. Eighteen-month endoscopic recurrence in accordance with Rutgeerts score. (A) Percentage of patients with any endoscopic recurrence (Rutgeerts score ≥2). (B) Mean Rutgeerts score (from 0 to 4).

TABLE 2. Factors associated with endoscopic recurrence at 6 months

	Univariate analysis			Binary logistic regression		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Anastomosis (Kono vs Conventional)	**0.21**	**0.09–0.75**	**<0.001**	**0.19**	**0.08–0.74**	**<0.001**
Male sex	0.89	0.7–2.1	0.7			
Previous surgery (not vs yes)	0.95	0.58–2.94	0.8			
CD behavior (fistulizing vs stricturing)	1.12	0.45–3.22	0.7			
Active smoking (yes vs not)	**1.62**	**0.8–3.1**	**0.08**	1.31	0.7–2.9	0.34
CD extension >50 cm	**2.5**	**0.5–12.4**	**0.07**	1.6	0.6–16.4	0.65
Presence of CD location other than ileo-cecal disease (yes vs not)	1.4	0.6–4.2	0.6			
Type of surgery (laparoscopy vs open)	**0.43**	**0.2–5.3**	**0.09**	0.66	0.3–3.1	0.23
Postoperative biologic (yes vs not)	1.24	0.31–4.41	0.51			
Postoperative azathioprine (yes vs not)	0.87	0.27–2.5	0.42			

Significant values have been highlighted in bold.
CD, Crohn disease; CI, confidence interval; OR, odds ratio.

days; $P = 0.3$). One case of abdominal abscess and 1 case of postoperative ileus were registered in the Kono group, whereas 1 case of anastomotic fistula, 3 cases of anastomotic bleeding, and 1 case of postoperative ileus were recorded in the Conventional group ($P = 0.6$). No anastomotic leaks were registered in the entire population. Infections (including wound infection) were found in 4 subjects in the Kono group (11.1%) versus 6 patients (13.9%) in the Conventional group ($P = 0.7$).

DISCUSSION

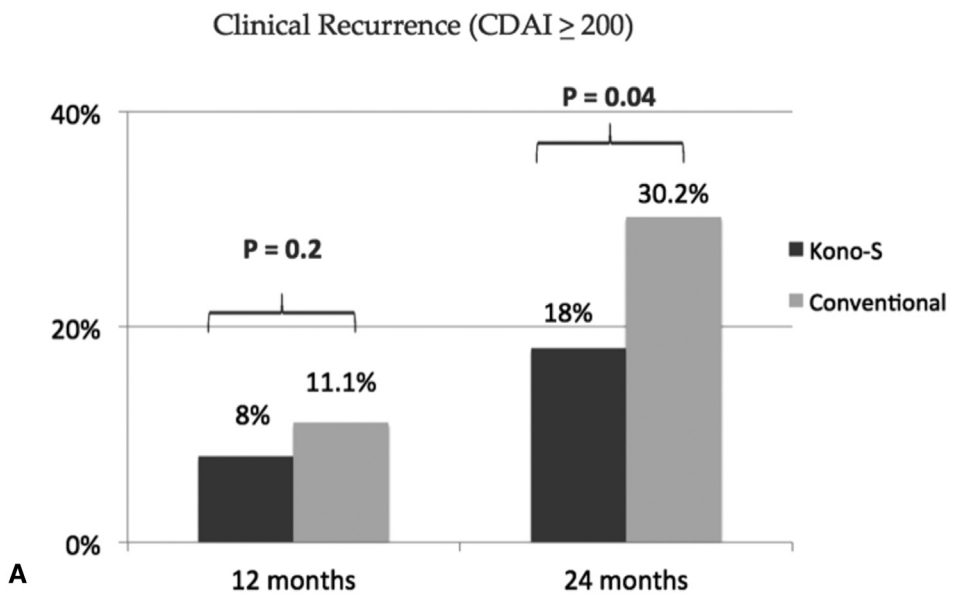
The recurrence of CD after surgery still remains a substantial problem in the management of such a condition. It seems that the triggers of anastomotic recurrence are multifactorial: some evidences have shown that the fecal stream may have a pivotal role in this, and, consequently, luminal diameter may also be involved in the occurrence of clinical and surgical recurrence, because of its close dependence on anastomotic structure. In fact, anastomotic configuration dramatically influences fecal stasis, bowel vascularization, and bacterial overgrowth. For this reason, it has been suggested that a stapled side-to-side anastomosis may prevent fecal stasis, early stricture, and ischemic damage—thanks to its larger lumen configuration, more than an end-to-end anastomosis.[11] However, no consensus in the current scientific literature has been reached about this topic.[8,17,18]

A meta-analysis by Simillis et al[18] found that end-to-end anastomosis after resection for CD may be associated with increased anastomotic leak rates (OR 4.37) than side-to-side anastomosis, with comparable anastomotic recurrence rate. These data were confirmed in a subsequent Cochrane report by Choy et al[19] and in the CAST study.[17] In contrast, a study of 141 patients by Scarpa et al[20] suggested that in the long-term, hand-sewn side-to-side anastomosis reported a significantly lower surgical recurrence rate than stapled end-to-side. Moreover, a recent meta-analysis by He et al[21] concluded that a stapled side-to-side anastomosis would appear to be the preferred procedure after ileocolic resection for CD, with reduced overall postoperative complications, especially anastomotic leak, and a decreased recurrence and re-operation rate. Indeed, Gajendran et al[22] found that 2 years after surgery, CD patients who underwent end-to-end anastomosis demonstrated better quality of life and less healthcare utilization compared with those who underwent side-to-side anastomosis. Despite this ''never-ending history,'' the ECCO recommends the stapled side-to-side anastomosis as the preferred anastomotic technique for ileocolic resection in CD.[4]

In 2011, Kono et al[9] developed a new combined stapled and hand-sewn antimesenteric functional end-to-end anastomosis (Kono-S anastomosis) to decrease surgical recurrence in CD. The authors performed Kono-S anastomosis in 69 CD patients from 2003 to 2009, and compared this group with a historical cohort of 73 CD patients who underwent conventional anastomosis from 1993 to 2003. They found significantly lower endoscopic recurrence rates in the Kono group than in the conventional one, with a lower probability of anastomotic surgical recurrence in the Kono group after 5 years (0% vs 15%; $P < 0.0013$). Therefore, no patient with the Kono-S anastomosis presented a surgical recurrence. The surgical technique and anastomotic configuration could pathophysiologically explain these results: the supporting column is able to preserve the feature and diameter of the anastomosis, and avoid distortion and stricture associated with recurrent diseases at the anastomotic site, especially on the mesenteric side which represents the original site of anastomotic CD recurrence. Further benefits of this novel surgical technique include the preservation of blood stream and innervation, both factors associated with high risk of anastomotic recurrence in CD.

In the present randomized controlled trial (RCT), we have been able to demonstrate that Kono-S anastomosis is associated with lower rate of endoscopic recurrence both after 6 months (22.2% in the Kono group and 62.8% in the Conventional group; $P < 0.001$, OR 5.91) and 18 months (25% vs 67.4%, respectively; $P < 0.001$, OR 6.21), reduced severity of endoscopic recurrence (mean Rutgeerts score after 6 months 0.92 ± 1.05 vs 2.06 ± 1.31, respectively; $P < 0.001$; and after 18 months 1.05 ± 1.06 vs 2.30 ± 1.32, respectively; $P < 0.001$), and lower rate of clinical recurrence (after 12 months: 8% vs 18%; $P = 0.2$, OR 2.51; after 24 months: 11.1% vs 30.2%; $P = 0.04$, OR 3.47), than side-to-side anastomosis. On binary logistic regression analysis, the Kono-S anastomosis was the only variable significantly associated with reduced risk of endoscopic recurrence (OR 0.19, $P < 0.001$). Furthermore, it seems that there was a trend in favor of Kono-S anastomosis in reducing surgical recurrence, although studies with longer follow-up are needed. We aim to continue with our follow-up to define this outcome.

About this last topic, in a multicentric (Japan-USA) study with a median follow-up of 65 months, Kono et al[23] found that 2 surgical anastomotic recurrences occurred in the Kono group. Kaplan-Meier analysis showed that 5 and 10 years' surgical recurrence-free survival rate was 98.6%. However, this study remains limited by its retrospective nature and comparison with a historical cohort, by differences in the study populations at the baseline, by the absence of randomization, and by significant differences in the postsurgical treatment. Similar limitations affect a more recent Kono-S versus end-to-end anastomosis comparative study by Shimada et al,[24] which



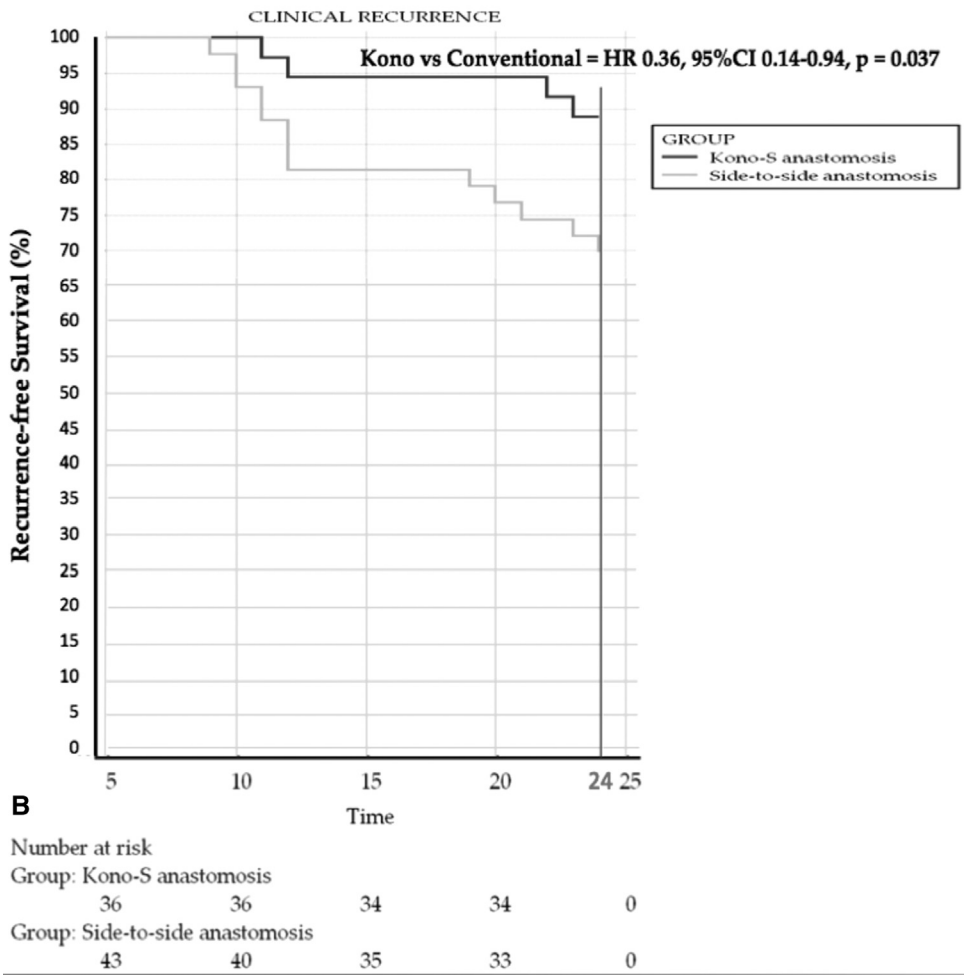
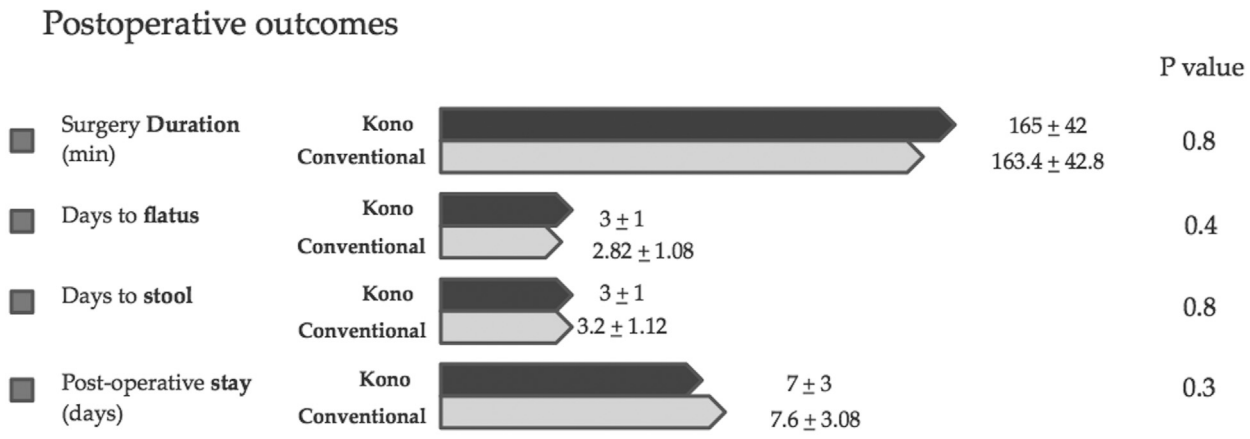


FIGURE 4. (A) Clinical recurrence (CDAI ≥200) at 12 and 24 months from surgery. (B) Probability of 24-month clinical recurrence-free survival in the study population.



	Kono (n=36)	Conventional (n=43)	p
Anastomotic fistulas, n (%)	0 (0%)	1 (2.3%)	0.9
Anastomotic bleeding, n (%)	0 (0%)	3 (6.9%)	0.3
Abdominal abscesses, n (%)	1 (2.7%)	0 (0%)	0.9
Post-operative ileum, n (%)	1 (2.7%)	1 (2.3%)	0.5
Infections, n (%)	4 (11.1%)	6 (13.9%)	0.7

FIGURE 5. Postoperative outcomes and safety of surgical techniques.

found a surgical recurrence rate of 3.4% in the Kono-S group versus 24.4% in the end-to-end group, and an increased risk of anastomotic leak in the end-to-end group (17.3%) as against the Kono-S group (5.1%). Kono-S anastomosis significantly reduced the risk of anastomotic surgical recurrence after 1 year (OR 0.14). The 5-year surgery-free survival rate on the anastomosis site with Kono-S anastomosis (95.0%) was significantly higher than that with end-to-end anastomosis (81.3%; $P < 0.001$).

About endoscopic recurrence, Kono et al[9] found that the frequency was comparable between the Kono-S group (83% after 1 year and 100% after 5 years) and the Conventional group (79% after 1 year and 100% after 5 years), although the median Rutgeerts score for the Kono-S group was less than for the Conventional group (2.6 vs 3.4; $P = 0.008$). By contrast, in the present RCT, we were able to demonstrate that the Kono-S anastomosis is not only associated with a reduced severity of endoscopic recurrence as evaluated by Rutgeerts score, but also with a reduced endoscopic recurrence rate when compared with the stapled side-to-side anastomosis (22.2% vs 62.8%; $P < 0.001$, OR 5.91). Unfortunately, the subsequent data by Kono et al[23] about endoscopic recurrence cannot be extrapolated.

Interestingly, our results showed that patients who underwent Kono-S anastomosis presented a higher recurrence-free survival rate than patients with side-to-side anastomosis (HR 0.36, 95% CI 0.14–0.94, $P = 0.037$). Previous studies comparing Kono-S anastomosis and conventional anastomoses[9,23] failed to demonstrate a relationship between anastomotic configuration and clinical recurrence. On the contrary, no role can be attributed to therapeutic postoperative prophylaxis because no differences have been observed between the 2 groups in that regard, but reduced severity of endoscopic score and, obviously, endoscopic recurrence rates predict a lower clinical recurrence rate.[25]

The role of mesentery in CD has been recently revised, especially with regards to postsurgical recurrence. In the retrospective study by Coffey et al,[26] the authors proved the clinical relevance of including mesentery in ileocolic resection for CD, showing a significantly reduced reoperation rate after excision of the mesentery (2.9% vs 40% in the close bowel resection group), and that surgical technique was an independent determinant of outcome. Although no differences have been found in the study by Coffey et al, the inclusion of a substantial part of mesentery in the specimen would mean an increased length of the resection specimen, while it is important to avoid extensive resections; excising more mesentery could compromise vascularization, leading to either the resection of more colon (another unaffected segment), or increased postoperative complication rate.[27] By contrast, the present RCT originates from the theoretical assumption of excluding the mesentery from the anastomotic rhyme, maintaining the vascularization and innervation of the bowel and reducing the rate of postsurgical recurrence that usually occurs from the mesenteric side, and avoiding (when possible) extensive ileo-colic resections.

In the present study, we cannot confirm the data by Shimada et al[24] about safety, because we found similar rates of postoperative complications in both groups, although they compared Kono-S versus end-to-end anastomosis, and not stapled side-to-side anastomosis. Nevertheless, the rates of postoperative complications found in the Kono-S group were similar to those described by Kono et al,[9,23] confirming the absolute safety of this surgical technique.

This study presents some limitations that we are well aware of. First, this is a monocentric randomized trial: although a multicentric RCT could have increased the sample size, a monocentric one limited the rates of differences among centers and is able to ''homogenize'' the data. Moreover, it is well known that most clinical and surgical recurrence occurs after 5 years, whereas this trial ended after 2 years. Long-term prospective data are needed to establish the efficacy of such a new anastomosis in reducing the long-term surgical recurrence rate. Methodologically, while patients were blinded to their

treatment arm, endoscopists were not. In a pragmatic way, it could be impossible to blind an endoscopist to anastomotic technique, because the Kono-S anastomosis configuration, even from an endoscopic view, is deeply and markedly different from the side-by-side anastomosis, and this blinding could not have given any addition to the study design. Regarding operative times, there were no differences in terms of surgery duration: we found a reduction in operative times for Kono-S anastomosis from the beginning till the end of the study: this could be explained by the progressive surgeon's knowledge and ''confidence'' about the technique. Until now, no data have been reported about mean operative times for Kono-S anastomosis, and our data cannot be compared with previous publications. Furthermore, other known risk factors for postoperative recurrence, such as smoking habits, did not reach the statistic significance in this study; probably, the study is not ''sized'' for this specific outcome, which requires a greater CD population. In our series, the rate of laparoscopic surgery was lower than that reported and recommended (about 50%).[28] However, in case of laparotomic approach, we performed a 7 to 8-cm long right flank horizontal incision (mini-laparotomy), with similar results in terms of efficacy, safety, and aesthetics as the laparoscopic cases.

CONCLUSIONS

In conclusion, this is the first RCT comparing Kono-S anastomosis and standard anastomosis in CD, which found a significant reduction in postoperative endoscopic recurrence rate, and also a dramatic decrease in the severity of endoscopic recurrence score by using the Kono-S technique, with no safety issues. Hence, the Kono-S anastomosis should be considered as a new technique in surgical management of CD in tertiary referral centers.

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