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Impact of different anastomosis methods on post-recurrence after intestinal resection for Crohn's disease: A meta-analysis

Wang ZZ *et al.* Anastomosis and Crohn's recurrence: A meta-analysis

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Abstract

BACKGROUND

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract, often requiring intestinal resection as a common treatment. However, recurrence after surgery is common. The anastomotic configuration after bowel resection appears to be associated with the recurrence of CD. Previous studies have suggested that the Kono-S anastomosis may help to reduce the recurrence rate. However, the results remain controversial. Therefore, evidence-based evidence is needed to prove the advantages of Kono-S anastomosis.

AIM

To measure the influence of anastomosis techniques on the long-term relapse rate of CD by conducting a meta-analysis.

METHODS

PubMed, Scopus, and Cochrane Library were searched until October 8, 2023. Patients who underwent intestinal resection due to CD were included. The intervention measures included Kono-S anastomosis, whereas the control group received traditional anastomosis such as end-to-end, end-to-side, and side-to-side anastomosis. Only randomized clinical trials and observational studies were included. The primary outcome measures were hospital stay post-surgery, overall postoperative complication

incidence, the proportion of Clavien-Dindo grade IIIa or higher, overall postoperative recurrence rate, and Rutgeerts score.

RESULTS

From 2011 to 2023, six articles met the inclusion and exclusion criteria. The results indicated that Kono-S anastomosis can reduce the hospital stay post-surgery of patients with CD (MD = -0.26, 95% confidence interval (CI) = [-0.42, -0.10], $P = 0.002$) than other traditional anastomosis methods. Compared to other traditional anastomosis methods, Kono-S anastomosis can significantly reduce the total recurrence rate (MD = 0.40, 95%CI = [0.17, 0.98], $P = 0.05$) and postoperative Rutgeerts score (MD = -0.81, 95%CI = [-0.96, -0.66], $P < 0.001$) in patients with CD. However, there is no significant disparity in the overall occurrence of postoperative complications and the proportion of Clavien-Dindo \geq IIIa.

CONCLUSION

Kono-S anastomosis has the potential to expedite the recuperation of CD and diminish relapse hazards; however, additional larger trials are necessary to authenticate its effectiveness.

Key Words: Kono-S; Crohn's disease; Traditional anastomosis; Postoperative recurrence; Meta-analysis

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Core Tip: There is no agreement in academic studies regarding the impact of Kono-S and traditional anastomosis on patients' recurrence after Crohn's surgery. Here, we present a primary inclusive meta-analysis exploring the effect of Kono-S and traditional

anastomosis on the recurrence of CD following surgery. The hospital stay post-surgery, the incidence of postoperative complications, the proportion of Clavien-Dindo \geq IIIa, the postoperative recurrence rate, and the Rutgeerts score were examined in patients who underwent the two techniques.

INTRODUCTION

¹ Crohn's disease (CD) is a chronic granulomatous enteritis that can affect any part of the digestive tract, with a particular predilection to the terminal ileum and cecum^[1]. The disease is characterized by clinical features, such as abdominal pain, diarrhea, weight loss, and recurrent episodes, which could result in severe malnutrition in patients^[2]. In Europe, the annual incidence rate of CD stands at 12.7 cases/100,000 individuals, while in North America, it is nearly 20.2 cases/100,000 individuals. Furthermore, the incidence rate has demonstrated a consistent upward trend in recent years^[3]. Recent research has indicated that CD pathogenesis is linked to several factors, such as genetic susceptibility, imbalanced intestinal microbial communities, environmental factors, abnormal immune regulation, and excessive expression of inflammatory mediators and cytokines^[4-6]. Despite this evidence, the pathogenesis remains unclear. Currently, there is no definitive cure for CD. Drug therapy involves mainly glucocorticoids, immunosuppressants, and other medications, yet long-term adherence proves challenging and severe side effects may occur. Consequently, surgical resection of the affected intestinal segment is required for patients with severe symptoms, significant complications, or inadequate drug response^[7,8]. Although surgical resection can efficiently manage symptoms, high postoperative recurrence rates can significantly affect patients' quality of life^[9]. Statistics show that in the absence of drug treatment, endoscopic examination following ileocolic resection reveals endoscopic recurrence in approximately 65–90% of patients within 12 months, and this proportion can increase to 80–100% within three years^[10].

Intestinal anastomosis is an essential determinant of CD recurrence after surgery^[11]. The traditional techniques of anastomosis, including ³ end-to-end anastomosis (EEA), end-to-

side anastomosis (ESA), and side-to-side anastomosis (SSA), are widely used due to their ease of operation and high repeatability^[12]. Recently, there have been several reports on a new anastomosis technique, known as Kono-S anastomosis, which aims to decrease the likelihood of postoperative recurrence in patients. This anastomosis technique excludes the mesentery from the anastomosis, limits lumen deformation, and preserves innervation and angiogenesis. It has demonstrated impressive safety and disease recurrence prevention results^[13]. In recent years, multiple small-scale randomized controlled trials and cohort studies have explored the effects of the two anastomosis techniques on the recurrence rate of CD. However, the findings are inconclusive, with some studies indicating that Kono-S anastomosis may be superior to the traditional method, whilst others revealing no significant difference between the two techniques^[12, 14, 15]. Currently, evidence-based medical data from large sample sizes to assess the impact of the two anastomosis methods on the long-term recurrence rate of CD remains insufficient. Therefore, we aimed to conduct a thorough meta-analysis of the existing research to measure the influence of both anastomosis techniques on the long-term relapse rate of CD to provide reliable, evidence-based medical evidence for clinical use. Simultaneously, we sought to clarify the application value of Kono-S anastomosis.

MATERIALS AND METHODS

Literature search

To gather additional experimental evidence, we conducted independent searches on PubMed, Embase, and Cochrane Library databases. Our selection criteria included articles with human participants, reported in English. We imposed no restrictions on publication time and type of articles. For the intervention group, we used Kono-S anastomosis whereas traditional anastomosis was used as the control group, following the PICOS scheme. The participants consisted of patients who underwent intestinal resection due to CD. We employed a combination of subject words and free words for our retrieval strategy. The search formula of the PubMed database was: (((Crohn

Disease' [Mesh]) OR ((Crohn's Enteritis) OR (Crohns Disease)) AND ((postoperative) OR (intestinal resection))) AND (((Kono-S anastomosis) OR (Kono-S Anastomosis)) OR (anastomosis)).

The following combination was used for the Embase database:

1 "crohn disease"/ exp OR "crohn disease"

2 postoperative

3 intestinal resection

4 Kono-S anastomosis

5 Kono-S Anastomosis

6 anastomosis

7 # 4 OR # 5

8 # 2 OR # 3

9 # 1 AND # 7 AND # 8

The same keywords were inserted into the Cochrane Library, which used the following search strategy:

1 MeSH descriptor: (Crohn Disease) explode all trees

2 (Kono-S anastomosis): ti, ab, kw

3 (Kono-S Anastomosis): ti, ab, kw

4 (Anastomosis): ti, ab, kw

5 # 2 OR # 3 OR # 4

6 (postoperative): ti, ab, kw

7 (intestinal resection): ti, ab, kw

8 # 6 OR # 7

9 # 1 AND # 5 AND # 8

In the field of management, the search scope is expanded through extensive cross-checking of the reference lists of all articles that meet the inclusion criteria. The search deadline for all databases was October 8, 2023. This study was conducted based on the PRISMA 2020 statement guidelines, with complete reporting of the meta-analysis data^[16].

Study selection

The primary studies' titles and abstracts were screened independently by the same two authors. Employing Cohen's kappa statistic, the authors evaluated their agreement during the initial article screening. Non-conforming and duplicate articles were excluded after reviewing the topic, abstract, and keywords. The meta-analysis applied the following criteria: a clear, comprehensive, and objective style, simple language, consistent citation, standard structure, formal register, meticulous and precise vocabulary, and grammatical accuracy.

The inclusion criteria consisted of the following: (a) studies evaluating patients who had undergone intestinal resection due to CD, (b) studies in which the intervention measure used was Kono-S anastomosis, while the control group received traditional anastomosis (including EEA, ESA, and SSA), (c) studies where relevant data for extraction were available in the results report, (d) randomized clinical trials (RCTs) and observational studies, and (e) studies evaluating the influence of Kono-S anastomosis on the occurrence of CD recurrence after intestinal resection. Review articles, letters, comments, case reports, as well as studies that did not evaluate postoperative recurrence indicators, were excluded from this analysis.

Data extraction

We examined all pertinent literature, tables, and charts and extracted relevant data as shown in Tables 1 and 2. The primary contents encompassed the following: (1) the name of the primary author, their country, publication date, and research type; (2) fundamental clinical data for patients with CD in the Kono-S anastomosis group and the traditional anastomosis group; (3) postoperative observation measures, such as the hospital stay post-surgery, total incidence of postoperative complications, Clavien-Dindo scores \geq IIIa (%), total recurrence rate, and Rutgeerts score^[17]. If further information was required, we reached out to the corresponding author of the paper for

assistance *via* email. Furthermore, any discrepancies among the reviewers were resolved through sound and sensible discussion.

Risk of bias

The Cochrane Risk Bias Assessment Tool was implemented to gauge bias risks in RCTs. The potential for bias was evaluated by examining factors, such as random sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting, and other possible sources of bias. Based on three aspects: selectivity, comparability, and outcome, the Newcastle-Ottawa Scale (NOS) score was employed to assess the quality of cohort studies. The funnel plot was utilized to assess the prospect of publication bias by analyzing the scatter points' distribution.

Statistical analysis

RevMan 5.3 was utilized to perform a meta-analysis. The odds ratio (OR) and the average difference between groups (MD) were employed as summary measures of dichotomous and continuous variables, respectively. The 95% confidence interval (CI) was applied to both methods. In cases where studies provided median and quartile ranges, the average standard deviation (SD) was calculated^[18]. Heterogeneity was evaluated using the I^2 test. If $I^2 < 50\%$ and $P > 0.1$, we ascertained that heterogeneity among the studies was low; thus, a fixed-effects model was applied. However, if $P < 0.1$ and $I^2 > 50\%$, we determined that heterogeneity among the studies was high, and a random-effects model was employed for analyzing the sources of heterogeneity. To assess publication bias, we generated funnel plots. We conducted sensitivity analyses using the one-by-one exclusion method. If there was a significant change in the I^2 value after removing an item, the study results were regarded as the origin of heterogeneity. All statistical analysis was significant at the $P < 0.05$ Level.

RESULTS

Study selection

A total of 1328 articles were collected. Among them, 215 were repetitive and therefore removed. We then analyzed the titles and abstracts of the remaining 1113 articles. Among these, 76 articles were meta-analyses, 181 were review articles, and 850 did not involve the experimental comparison of Kono-S and traditional anastomosis. Finally, we chose six articles^[15,19-23] for a full-text review, from which, we extracted all of the necessary literature data. A meta-analysis of six articles was conducted, all published between 2011 and 2023. The studies consisted of 1 randomized controlled trial and 5 retrospective cohort studies (Figure 1), collectively involving 1004 patients with CD. Among these patients, 429 underwent Kono-S anastomosis and 575 underwent traditional anastomosis (such as EEA, ESA, and SSA). Table 1 summarizes the features of the included studies.

Literature quality evaluation

The evaluation of RCT literature quality was conducted based on several criteria, such as random number generation, allocation blindness, researcher and subject blindness, result evaluation blindness, result integrity, reporting bias, and other factors. Based on the Cochrane risk bias assessment tool, the included randomized controlled study^[23] exhibited a low risk in random sequence generation; nevertheless, the blind allocation component was unclear. Minimal risk was observed in incomplete results data, as well as in selective results reporting. Furthermore, other potential bias factors meeting the requirements of this article were assessed as low risk. The literature's quality was evaluated concerning selection bias, comparability bias, and result evaluation bias according to the NOS scale. A research quality score of 9 was achieved by one paper^[15], while three papers^[19, 20, 22] received a research quality score of 8. Additionally, one paper^[21] secured a research quality score of 7. Table 3 summarizes the quality evaluation of all retrospective cohort studies. There was no disagreement between the two authors regarding the eligibility of the full-text articles (Cohen's kappa=1).

Hospital stay post-surgery

The impact of alternative anastomosis methods (Kono-S and traditional) on the hospital stay following intestinal resection for CD was evaluated using a meta-analysis. The fixed effect model indicated moderate heterogeneity among the included literature, with $I^2 = 51\%$ and $P = 0.73$. However, the use of the random effect model revealed no heterogeneity in the included studies with $I^2 = 0\%$ and $P = 0.73$. The study findings indicated that utilization of the Kono-S anastomosis approach led to a statistically significant reduction in postoperative hospitalization duration among patients with CD, as compared with traditional anastomosis methods (MD = -0.26, 95%CI = [-0.42, -0.10], $P = 0.002$), Figure 2).

Total incidence of postoperative complications

The impact of various anastomosis methods (Kono-S and traditional), post intestinal resection, on the overall incidence of postoperative complications in CD was evaluated through a meta-analysis. The analysis revealed a high degree of heterogeneity among the included literature in the fixed effect model ($I^2 = 79\%$, $P = 0.02$). Notably, even after using the random effect model, the included literature remained significantly heterogeneous ($I^2 = 79\%$, $P = 0.02$). After conducting sensitivity analysis by gradually excluding included literature, we found that Alibert, L. *et al.*'s study^[21] had the most significant impact on the outcomes, potentially serving as the primary source of heterogeneity. The findings indicated that the Kono-S anastomosis method has minimal effect on the total incidence of postoperative complications in patients with CD compared with other traditional anastomosis techniques. However, these results did not achieve statistical significance (MD = 1.00, 95%CI = [0.46, 2.20], $P = 0.99$). Further details are illustrated in Figure 3.

Proportion of Clavien-Dindo greater than IIIa

No heterogeneity was observed among the included studies, with $I^2 = 0\%$ and $P = 0.40$ under the fixed effect model. The study findings indicate that the Kono-S anastomosis method did not significantly affect the proportion of Clavien-Dindo \geq IIIa in patients

with CD, compared with other conventional anastomosis techniques (MD = 0.82, 95%CI = [0.43, 1.54], $P = 0.53$, Figure 4).

Total postoperative recurrence rate

The impact of Kono-S and traditional anastomosis methods on the overall recurrence rate of CD following intestinal resection was analyzed through a meta-analysis. The fixed effect model revealed a high level of heterogeneity amongst the included studies, with $I^2 = 76\%$ and $P = 0.002$. Subsequently, the random effect model also indicated a high level of heterogeneity among the included literature. Sensitivity analysis revealed that the studies conducted by Shimada *et al.* and Luglio *et al.*^[15,23] had the most significant influence on the results, possibly originating as the primary source of heterogeneity. The study results demonstrate that Kono-S anastomosis yields a statistically significant reduction in the total recurrence rate of patients with CD compared with other traditional anastomosis methods (MD = 0.40, 95%CI = [0.17, 0.98], $P = 0.05$, Figure 5).

Rutgeerts score

A meta-analysis indicated low heterogeneity ($I^2 = 34\%$, $P = 0.22$) using the fixed-effect model. The study results indicate that Kono-S anastomosis is a more effective method in reducing postoperative Rutgeerts scores for patients with CD compared to other conventional anastomosis techniques. This difference was statistically significant (MD = -0.81, 95%CI = [-0.96, -0.66], $P < 0.001$, Figure 6).

Evaluation of literature publication bias

A funnel plot was created for each impact indicator identified within the six included articles. Continuous variables for the length of hospital stay post-surgery and Rutgeerts score were analyzed, along with binary variables for the total incidence of postoperative complications, proportion of Clavien-Dindo \geq IIIa, and total postoperative recurrence rate. Technical abbreviations were explained upon first use. The funnel plot meta-

analysis demonstrated that hospital stay post-surgery, proportion of Clavien-Dindo \geq IIIa, and Rutgeerts score were all aligned using a vertical line. The research was evenly dispersed on both sides of the center line, creating a pyramidal dotted line range, with no evident separation phenomenon (Figure 7) (no conspicuous bias). However, the meta-analysis funnel plot of the remaining impact indicators exhibited bias, possibly due to inadequate literature included in this study.

DISCUSSION

Since its introduction by Kono *et al.* in 2003, the efficacy of the EEA technique for anti-mesenteric function has been a subject of debate. The Kono-S anastomosis procedure involves employing a linear cutter to section the intestine, after which the intestinal ends are sutured together to form a support column. Subsequently, a functional end-to-end manual suture is performed^[24,25]. Kono *et al.*^[22] posited that anastomosis effectively prevents postoperative recurrence in patients with CD. Historical data comparison revealed that the endoscopic recurrence rate of patients who underwent Kono-S anastomosis was lower than those who underwent traditional anastomosis. However, the persuasiveness of a single study is limited. Therefore, this study used meta-analysis to compare and analyze the impact of Kono-S anastomosis and traditional anastomosis on postoperative recurrence in patients with CD.

The meta-analysis results of this study showed that Kono-S anastomosis could shorten the hospital stay of patients with CD, compared with other traditional anastomosis methods (MD = -0.26, 95%CI = [-0.42, -0.10], $P = 0.002$). Notably, no heterogeneity was observed in the included literature. Many studies evaluating recurrence factors tend to overlook the postoperative hospitalization time, which can indicate the patient's recovery rate. Regarding surgical operations, Kono-S anastomosis preserves a portion of the mesenteric blood perfusion, potentially resulting in a reduction of ischemic injury at the anastomosis^[11,22]. Adequate blood supply creates favorable biological circumstances for anastomotic healing, consequently lowering the risk of early complications like anastomotic leakage and stenosis^[26]. This in turn avoids additional

surgery and extended hospital stays caused by complications. Furthermore, Kono-S anastomosis optimizes the anatomical position and three-dimensional structure of the intestinal segment, promoting swift recovery of postoperative intestinal peristalsis function, early elimination, and bowel movements in patients, and faster rehabilitation. These factors may explain why Kono-S anastomosis is advantageous for hastening the postoperative recovery of patients with CD.

Regarding postoperative complications in these patients, the number of incidences, such as intestinal obstruction, anastomotic leakage, infection, and fever were tallied for the purposes of comparing the safety of the two anastomosis methods. The outcomes indicated that the Kono-S anastomosis had no considerable impact on the overall occurrence of postoperative complications in patients with CD when compared to the traditional anastomosis method (MD = 1.00, 95%CI = [0.46, 2.20], $P = 0.99$). However, this meta-analysis has a relatively small sample size, as only 6 studies, comprising a total of 1004 patients, were included. There is some degree of uncertainty, making it necessary to interpret the results with caution. Additionally, the incidence of complications is correlated with various factors, including the surgical procedure, perioperative treatment, and the patient's underlying health condition^[27]. Therefore, due to these confounding factors, it is difficult to show the advantages and disadvantages of the two anastomosis methods just by comparing the number of complications in this study. Therefore, we further analyzed the Clavien-Dindo score, which describes the severity of complications. A higher proportion of Clavien-Dindo \geq IIIa indicates a greater number of severe complications. The study findings demonstrated that Kono-S anastomosis did not significantly impact the proportion of Clavien-Dindo \geq IIIa in patients with CD compared to other conventional methods of anastomosis (MD = 0.82, 95%CI = [0.43, 1.54], $P = 0.53$). While there were no notable variations observed in the incidence of complications or the percentage of severe cases between the groups, Kono-S anastomosis has been assessed for its safety and feasibility as a new surgical technique^[28, 29]. Further studies are required to confirm its advantages.

It is imperative to implement techniques, such as increasing the sample size, rigorous control over confounding variables, and analysis of long-term outcomes.

Regarding the postoperative recurrence rate of patients with CD, the study findings demonstrate that the Kono-S anastomosis method resulted in lower total recurrence rates compared to other traditional methods (MD = 0.40, 95%CI = [0.17, 0.98], $P = 0.05$). Endoscopic anastomotic recurrence is typically evaluated through the Rutgeerts score (\geq IIIa) at 6 to 12 months. Therefore, we performed a meta-analysis of Rutgeerts score. Our findings indicate that Kono-S anastomosis can significantly reduce Rutgeerts score in patients with CD following surgery when compared to traditional anastomosis (MD = -0.81, 95%CI = [-0.96, -0.66], $P < 0.001$). These findings align with those of a meta-analysis published in 2020, which showed that Kono-S anastomosis presents a reduced risk of recurrence in comparison to traditional anastomosis^[30]. Although the sample size for this study is limited, the outcomes are clinically significant as postoperative recurrence directly impacts patients' life quality and prognosis. On the contrary, Kono-S anastomosis could enhance healing conditions at the anastomosis site by preserving a section of mesenteric blood flow and sustaining the physiological and anatomical structure of the intestine, thus mitigating the risk of inflammation and recurrence^[31]. Conversely, Kono-S anastomosis can create a broad lumen and a supportive column at the anastomotic site, preserving a three-dimensional configuration. This is a crucial factor in preventing anastomotic stenosis^[12, 22] and preventing distortion while keeping the intestinal tract straight, which facilitates postoperative endoscopy. However, the conventional U-shaped EEA anastomosis is not suitable for endoscopic observation or balloon dilation. As a result, the Kono-S anastomosis structure surpasses the traditional EEA anastomosis structure in facilitating postoperative follow-up and treatment of anastomotic problems^[22, 32].

The limitations of this study stem from its small sample size and sole location of data collection at a single center. We anticipate the need for more studies of high quality to verify this outcome and establish the precise mechanism by which Kono-S anastomosis diminishes recurrence. It is important to recognize that the effectiveness of this surgical

approach is contingent upon rigorous regulation of operative procedures and the selection of suitable candidates. Future research must develop a uniform training program for Kono-S anastomosis and delineate the patient cohorts who can gain the maximum benefit from this technique.

CONCLUSION

To summarize, this study showed that Kono-S anastomosis is a suitable technique for patients with CD. It has proven to speed up postoperative recovery and is particularly effective in reducing long-term recurrence when compared to other conventional anastomosis methods. While this study has limitations, including a limited number of included studies and sample size, the results still provide robust support for the clinical application of Kono-S anastomosis. It is recommended that clinicians select the appropriate anastomotic technique based on the specific conditions of patients, and we anticipate further validation of the long-term efficacy of Kono-S through larger sample studies in the future.

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