

Clinical efficacy of endoscopic dilation combined with bleomycin injection for benign anastomotic stricture after rectal surgery

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Abstract

Benign anastomotic stricture is a frequent complication after rectal surgery. This study investigated the feasibility of endoscopic dilation combined with bleomycin injection for benign anastomotic stricture after rectal surgery. 31 patients who diagnosed with benign anastomotic stricture after rectal surgery were included in this study. 15 patients received simple endoscopic dilation (dilation group) and 16 patients received endoscopic dilation combined with bleomycin injection (bleomycin group). The clinical effect and adverse events were compared in the 2 groups. The strictures were managed successfully and the obstruction symptoms were relieved immediately. There were 2 minor complications in dilation group and 3 minor complications in bleomycin group. The difference was not significant between the 2 groups ($P > .05$). During the follow-up, the mean reintervention interval was 4.97 ± 1.00 months in dilation group and 7.60 ± 1.36 months in bleomycin group. The median treatment times was 4 (range 3–5) in dilation group and 2 (range 2–3) in bleomycin group. The differences in the 2 groups were significant ($P < .05$). Compared with endoscopic dilation, endoscopic dilation combined with bleomycin injection may reduce the treatment times and prolong the reintervention interval, which is a safe and effective endoscopic management for benign anastomotic stricture after rectal surgery.

Abbreviations: cm = centimeter, mins = minutes, mg = milligram, ml = milliliter, mm = millimeter, SD = standard deviation.

Keywords: benign anastomotic stricture, bleomycin, endoscopic dilation, rectal surgery

1. Introduction

Benign anastomotic stricture is one of the common complications after colorectal surgery. Low-set anastomoses, mechanical anastomosis, and other factors can promote anastomotic stricture. Influenced by these risk factors, the incidence of benign anastomotic stricture is from 5 to 30%.^[1,2] The main clinical features include dyschezia, abdominal pain, and even ileus. Patients suffer from them. At present, the effective treatments are surgery and endoscopic management. Even though the effect of surgery is remarkable, it may lead to large injury, high cost, and restenosis. Therefore, surgery is usually used for complex situations. The most common endoscopic management is dilation. After 1–3 dilations, many patients can achieve cure. But some patients are difficult to be treated, even with repeated treatment.^[3] Auxiliary ways of endoscopic dilation have been applied for improving the effect, such as steroid or mitomycin injection. Due to the limited sample size and research type, their roles remain uncertain.

Bleomycin is a common chemotherapy drug, which is used for malignant tumors. Besides, efficacy of bleomycin for healing

pterygium and hyperplastic scar have been confirmed.^[4–6] There are no studies to research the usefulness of bleomycin in gastrointestinal benign anastomotic stricture.

Therefore, a feasibility study was made to compare simple endoscopic dilation with endoscopic dilation combined with bleomycin injection. The clinical effect and adverse events were recorded.

2. Materials and Methods

2.1. Patients

Patients from Jiangsu Province Hospital, the Second Affiliated Hospital of Nanjing Medical University and Taizhou Traditional Medical Hospital between April 2014 and April 2019 were strictly selected according to standards. All patients underwent anterior resection for rectal cancer. This research followed the principles of the Declaration of Helsinki. Inclusion criteria were as follows: (1) difficulty with bowel movements, constipation or abdominal distension after anus-retained rectal operation. (2) colonoscope couldn't pass through the anastomotic

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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site. (3) the anastomotic stricture was proved benign with routine biopsies. Exclusion criteria were as follows: (1) anastomotic abscess or fistula, (2) drug allergy or a low white blood cell count, (3) severe comorbidities, such as coagulation disorders, cardiopulmonary dysfunction. We explained the advantages and disadvantages of the 2 endoscopic treatments. Patients could choose their respective therapy on an as-needed basis. Endoscopic dilation combined with bleomycin injection was not suggested if patients had the drug allergy or a low white blood cell count. This study was approved by the Ethics Committee of Jiangsu Province Hospital (2018-SR-258). Before the treatment, written informed consents were obtained from all patients.

2.2. Operation procedure

After preoperative examinations, colonoscopy was performed by skilled doctors to detect the stricture site. Patients were under conscious sedation. Before treatment, the diameter of the anastomotic site was recorded with a biopsy forcep (MTN-BF-23, Micro-Tech, Nanjing, China). The forcep was 6 millimeter (mm) in width when it was opened.^[7] Then a balloon (CRE Wireguided Balloon Dilator, Boston Scientific, Minneapolis, USA) was inserted for dilation in all patients. The diameter of the balloon was 16–20 mm. The dilation was repeated 3 times. Every time the procedure was held for 3 minutes (mins).^[8] Then 10 milliliter (ml) bleomycin (10 milligram (mg) of 1 mg/ml, Haizheng, Zhejiang, China) was injected into the anastomotic site (at the 3, 6, 9, and 12 o'clock positions) with an injection needle (INJ1-A1, Medwork GmbH, Höchststadt, Germany) in bleomycin group (shown in Fig. 1).^[9] Finally, the diameter of the anastomotic site was recorded again with the balloon.

2.3. Postoperative care and follow-up

After operation, all patients were fasted for 24 hours. If there were no related complications such as fever, abdominal pain or bloody stools, liquid diet was permitted to take. Patients were discharged when the obstruction symptoms disappeared. All patients were followed up at the outpatient department. The least follow-up period was 2 years. Patients who had obstruction symptoms recurred were admitted to the hospital and received the same endoscopic treatment again.

2.4. Statistical analysis

Statistical analyses were performed using SPSS 19.0 software (IBM, Armonk, NY, USA). Quantitative variables were expressed as mean \pm standard deviation (SD) in normal distribution and median (range) in abnormal distribution. Qualitative variables were described as frequency or percentage. Student t or analysis of variance (ANOVA) was used to compare continuous variables. Chi-squared or Fisher exact test was used to compare categorical variables. Difference between the 2 groups was considered statistically significant when the *P* value was <0.05 .

3. Results

A total of 31 patients with rectal benign anastomotic stricture were enrolled in this research, with 15 patients (10 men and 5 women) in the dilation group and 16 patients (9 men and 7 women) in the bleomycin group. All patients had history of rectal cancer operation and the lower digestive tract was rebuilt with end-to-end anastomose. The chosen patients should satisfy all inclusion criteria and eliminate every exclusion

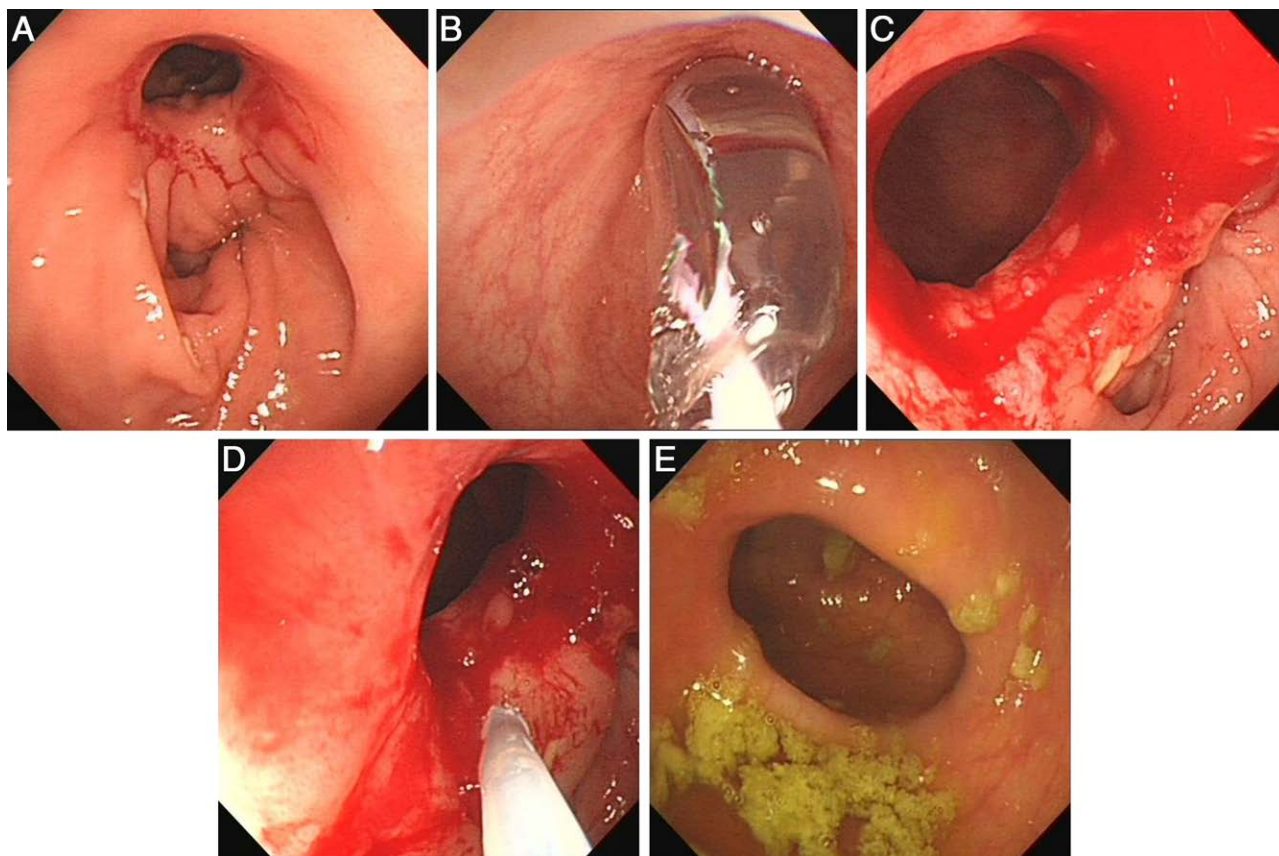


Figure 1. Endoscopic dilation combined with bleomycin injection. (a) The anastomotic stricture after rectal surgery. (b) Endoscopic dilation. (c) The anastomotic site after dilation. (d) Endoscopic bleomycin injection after dilation. (e) The anastomotic site after 1 month.

criterion. Clinical data of these patients were listed in Table 1. In dilation group, the mean age was 59.60 ± 10.55 years and the average diameter of the anastomotic site before treatment was 0.47 ± 0.14 centimeter (cm). The mean distance of the stricture site to anal verge was 6.33 ± 2.47 cm. In bleomycin group, the mean age was 60.06 ± 7.88 years and the average diameter of the anastomotic site before treatment was 0.52 ± 0.18 cm. The mean distance of the stricture site to anal verge was 5.88 ± 2.55 cm. There were no significant differences between the 2 groups in number of patients, age, gender, the diameter of the anastomotic site and the distance of anastomotic site to anal verge ($P > .05$).

All patients achieved endoscopic treatment successfully. After operation, the anastomotic site could be passed through smoothly with colonoscope and stricture symptoms were relieved soon. The mean diameter of the anastomotic site was 1.67 ± 0.15 cm in dilation group and 1.69 ± 0.17 cm in bleomycin group. The mean reintervention interval was 4.97 ± 1.00 months in dilation group and 7.60 ± 1.36 months in bleomycin group. The difference was significant ($P < .05$). When stricture recurred, the same endoscopic treatment was repeated as before. The median treatment times of bleomycin group was less than dilation group (2 vs 4, $P < .05$). There were no major complications such as perforation, massive bleeding or leakage in the 2 groups. One patient had low grade fever and 1 patient had abdominal discomfort in dilation group. Two patients had low grade fever and 1 patient had hematochezia in bleomycin group. With conventional therapy patients were discharged soon. During the follow-up, no long-term complications were observed. Local bleomycin injections didn't cause mucosa injury and systemic side effects. These results were listed in Table 2.

4. Discussion

Anastomotic stricture is one of the common complications after colorectal surgery, which includes benign stricture and

malignant stricture. The latter is usually caused by tumor relapse. The benign anastomotic stricture occurs more commonly in rectal surgery than colonic surgery because of the anastomosis method, and it has a deleterious influence on patients' life quality. The main cause of benign anastomotic stricture is hyperplastic scar.^[10] The main therapy for benign anastomotic stricture is endoscopic dilation. While some patients respond poorly to it. Repeated dilation may lead to mucosa injury and increase the incidence of perforation. Therefore, extending no-stricture period and reducing treatment times is quite essential. Endoscopic stent implantation is a solution for refractory anastomotic stricture, especially for acute obstruction. It can relieve the symptoms rapidly. But the long-term effect of stent implantation is uncertain, which is influenced by stent migration and restenosis.^[11, 12] Endoscopic incision was initially used for esophageal rings,^[13] then it has been used to treat refractory digestive tract stricture.^[14] This technology is still difficult and most primary hospitals can't carry out the operation now. In 1970s, local injection with corticosteroid was first reported to relieve gastrointestinal stricture.^[15] Researchers hoped the treatment times and the recurrence rate could be decreased by endoscopic dilation combined with corticosteroid injection. However, the results are still controversial. Some studies indicated endoscopic dilation combined with corticosteroid injection might prolong symptom-free period and decrease the dilation frequency,^[16, 17] while Hirdes *et al* revealed corticosteroid injection combined with dilation didn't prolong patency period in patients with anastomotic stricture.^[18] Therefore, further studies are needed.

Bleomycin can inhibit the transforming growth factor expression, prohibit the fibroblast proliferation and reduce the collagen generation. Excessive fibroblast proliferation and collagen generation lead to postoperative scar formation. Therefore, bleomycin has the antisthenosis effect in theory.^[4] As the analogue of bleomycin, mitomycin has been proved the value for treating benign esophageal stricture.^[19, 20] However, the efficacy of mitomycin for rectal anastomotic stricture was not satisfactory in our preliminary study, especially for refractory stricture.

Our study compared the efficacy of combination therapy with simple endoscopic dilation preliminarily. No matter in bleomycin group or dilation group, most patients develop anastomotic stricture after receiving mechanical anastomosis with staplers. It has been found that mechanical anastomoses are associated with higher levels of collagen deposition and more inflammation, which may lead to stricture formation.^[21] Besides, surgeons can control the caliber and shape of anastomoses better when they are using the hand-sewn method.^[22] The bleomycin group had the longer reintervention interval and less treatment times than dilation group. It indicated the clinical effect of combination therapy was better for benign anastomotic stricture after rectal surgery. It is possible that endoscopic dilation only tear scar tissue simply. The surrounding scar tissue will develop restenosis after a while. Bleomycin can effectively inhibit the formation of restenosis by its pharmacological role.^[4] What is more, endoscopic dilation combined with bleomycin injection did not cause any severe adverse events. Only 2 patients had low grade fever and 1 patient had hematochezia. The incidence of complications in bleomycin group was similar to that in dilation group, which might be caused by endoscopic dilation itself. During the follow-up, no other complications were observed. Local bleomycin injections didn't cause mucosa injury and systemic side effects. Of course, some limitations in our research are noted. First, this is not a randomized controlled trial. Patients choose the treatment according to their preference, which will render a selection bias. Second, the best dosage of bleomycin for treating anastomotic stricture is still uncertain. Current usage is according to previous literatures and our experience. Last but not least, endoscopic size measurements are limited. Even though we used the biopsy forcep and balloon as references, it may be still inaccuracy.

Table 1

Patient characteristics

	Dilation group (n = 15)	Bleomycin group (n = 16)	P value
Age, years, mean \pm SD	59.60 \pm 10.55	60.06 \pm 7.88	0.89
Male/femal, n	10/5	9/7	0.72
Anastomotic diameters before operation, cm, mean \pm SD	0.47 \pm 0.14	0.52 \pm 0.18	0.38
Distance to anus, cm, mean \pm SD	6.33 \pm 2.47	5.88 \pm 2.55	0.62
The kind of anastomosis			0.65
Mechanical anastomosis (stapler)	12	14	
Manual anastomosis	3	2	

SD = standard deviation.

Table 2

Treatment outcomes and follow-up.

	Dilation group (n = 15)	Bleomycin group (n = 16)	P value
Anastomotic diameter, cm, mean \pm SD			
After operation	1.67 \pm 0.15	1.69 \pm 0.17	0.81
One month later	1.57 \pm 0.09	1.64 \pm 0.15	0.13
Three months later	1.43 \pm 0.10	1.55 \pm 0.09	<0.01
reintervention interval, months, mean \pm SD	4.97 \pm 1.00	7.60 \pm 1.36	<0.01
Treatment session, median (range)	4 (3–5)	2 (2–3)	<0.01
Complication, n			1.00
Major complication	0 (0)	0 (0)	
Minor complication	2	3	
Follow-up period, months, mean \pm SD	26.90 \pm 1.70	27.21 \pm 1.85	0.63

SD = standard deviation.

In conclusion, endoscopic dilation combined with bleomycin injection is confirmed to be an effective and safe method for benign anastomotic stricture after rectal surgery. Compared with simple dilation, endoscopic dilation combined with bleomycin injection can prolong anastomosis patency period and reduce treatment times, which is especially applicable to refractory anastomotic stricture. Although the study has a small sample and short-term follow-up. Large-scale, randomized controlled trials and long-term follow-up evaluation are needed in the future. Nevertheless, the promising results of our study may open new opportunities for endoscopic treatment of anastomotic stricture.

Author contributions

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