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DOI: 10.1002/ncp.10823

CLINICAL RESEARCH

Chyme reinfusion improved outcomes after definitive surgery for small-intestinal enteroatmospheric fistula in patients with enteral nutrition

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Funding information
National Natural Science Foundation of China, Grant/Award Number: 82070579

Abstract

Purpose: In patients suffering from small-intestinal enteroatmospheric fistula who are receiving enteral nutrition (EN), although the function of the small intestine is sufficient, without chyme reinfusion (CR), disuse of the distal intestine of enteroatmospheric fistula may occur. However, CR reverses such pathological changes and have an influence on improving outcomes following definitive surgery (DS) for small-intestinal enteroatmospheric fistula. This study attempted to investigate the effect of preoperative CR in patients with EN on the outcomes after DS for small-intestinal enteroatmospheric fistula.

Methods: According to whether CR was performed between January 2012 and December 2019, patients receiving DS for small intestinal enteroatmospheric fistula were divided into the CR group and non-CR group. The effect of preoperative CR was then investigated.

Results: A total of 159 patients were finally enrolled, of which 72 patients were in the CR group and 87 patients were in the non-CR group. A total of 47 (29.56%) patients were found to have recurrent fistula after DS, the recurrent fistula rate in the CR group (multivariate odds ratio = 0.557; 95% CI, 0.351–0.842; $P = 0.019$) was lower. CR was also shown to promote postoperative recovery of bowel function (hazard ratio [HR] = 1.982; 95% CI, 1.199–3.275; $P = 0.008$), and shorten postoperative length of stay (LOS) (HR = 1.739; 95% CI, 1.233–2.453; $P = 0.002$).

Conclusion: Preoperative CR may reduce the incidence of recurrent fistula, time to return of bowel function and postoperative LOS following DS for small-intestinal enteroatmospheric fistula.

KEYWORDS
chyme reinfusion, enteral nutrition, enteroatmospheric fistula, intestinal fistula, outcomes, postoperative length of stay surgery

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INTRODUCTION

Enteroatmospheric fistula (EAF) is a type of enterocutaneous fistula (ECF), which is defined as a passage between the gastrointestinal (GI) tract and atmosphere.[1] Spontaneous closure is very rare, and definitive surgery (DS) following the formation of a frozen abdomen is often required.[1,2] Our previous study demonstrated that performing DS after ECF is a very complicated process that has a high incidence of complications, such as recurrent fistula,[3] which may be closely related to intestinal function.[3] In patients with ECF, enteral nutrition (EN) is the first choice nutrition support strategy.[1]

Chyme is a semifluid mass of partly digested food mixed that contains digestive secretions originating from the stomach. Chyme reinfusion (CR) is an EN technique that artificially re-establishes small-bowel continuity through an extracorporeal circuit of chyme, thereby mimicking definitive gastrointestinal function.[4] It improves the nutrition status, homeostasis, and liver and kidney function.[5] In patients with small-intestinal enteroatmospheric fistula who are receiving EN, although the function of the small intestine being used is sufficient, without CR, chyme rarely passes through the distal end of the fistula. As a result, similar to the physiological changes in a stoma, disuse of the distal intestine of stoma or enteroatmospheric fistula can occur. Recent studies have shown that CR can reverse the pathological changes due to disuse of the digestive tract and can improve outcomes after stoma closure in patients who have a selective temporary stoma.[6–9] In theory, intestinal function recovery following CR may have an influence on recurrent fistula rate reduction as well as the time to return of bowel function. However, such influences seem to not be taken seriously. Accordingly, this retrospective study hypothesizes that CR is associated with a reduction in the recurrent fistula rate following DS, time to return of bowel function after surgery, and postoperative hospital length of stay (LOS) in patients with small-intestinal enteroatmospheric fistula.

MATERIALS AND METHODS

This retrospective cohort study was performed at two tertiary hospitals where hundreds of patients with refractory intestinal fistula are transferred every year. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants of the study. This study was reviewed and approved by the Ethics Committee of the two hospitals.

Treatment of small-intestinal enteroatmospheric fistula and CR

Treatment of small-intestinal enteroatmospheric fistula in the present study was divided into three stages. During the first stage, infection was controlled, EN and CR were stably implemented, and a planned ventral hernia (using an epidermal skin graft) was formed. CR was performed in each patient after source control. Chyme was transferred every hour for reinfusion with an autoregulated EN pump into the downstream digestive tract via reinfusion tube (Foley tube). The hourly rate of CR was calculated by the previous hour's output, after which the reinfusion rate was adjusted for each hour.

The second stage of treatment was performed after the EN was able to be used, CR could be implemented stably, and planned ventral hernia was achieved. During the second stage, patients were transferred to their local community health service centers or local hospitals capable of continuing treatment for recuperation and physical recovery, which continued for at least 4 months.

A DS for small-intestinal enteroatmospheric fistula was performed during the third stage. When the criteria for DS were met, patients were transferred to our institution again for DS. After this stage, patients were fully recovered and discharged after successful treatment.

EN (Nutrison fiber [1.0 kcal/ml], Nutricia) was given via nasojejunal tube during the entire treatment process, for which the energy was calculated according to 30 kcal/kg. If daily defecation was >200 g, and the defecation amount was more than three times after CR, an antidiarrheal (Montmorillonite powder and Imodium) or low-dose somatostatin (1.5 mg/day) was used.

Population

From January 2012 to December 2019, patients with small-intestinal enteroatmospheric fistula who received DS were enrolled in the present study. The exclusion criteria were as follows: (1) patients younger than 18 years of age; (2) patients without EN; (3) patients with inflammatory bowel disease (IBD); (4) patients with concurrent upper gastrointestinal fistula, colon fistula, pancreatic fistula, or pancreatitis, which may influence the difficulty of the operation; and (5) patients without complete data.

During the entire treatment process, CR was recommended until DS. CR was carried out steadily when each patient was transferred to the local institute. However,

there were a considerable number of patients who refused and stopped CR at the second stage. Patients who had a cumulative duration of CR for >1 month during the second stage were placed into the CR group. The remaining patients were grouped into the non-CR group. The characteristics of the patients in the two groups were then reviewed and analyzed.

Primary outcome and secondary outcomes

Following DS, when EN (via nasointestinal tube) was resumed, all drainage tubes were removed, and no symptoms of intestinal fistula were reported, the patient was discharged with abnormality of CT scan and x-ray double-contrast small-bowel examination with urografin. After being discharged, patients were asked to resume a normal diet, and their nasointestinal tube was removed at a local hospital. Because many patients were lost to follow-up after discharge in our study, patients were followed up to hospital discharge. The primary outcome was the incidence of recurrent fistula. The secondary outcome included the following: (1) time to return of bowel function and (2) LOS after DS. Time to return of bowel function was noted by defecation after surgery.

Criteria for DS

When the criteria for DS were satisfied, patients were transferred to our institution, after which a DS was planned. The DS criteria were as follows: (1) C-reactive protein (CRP), white blood cell (WBC), and procalcitonin were normal for >1 month; (2) body mass index (BMI) $\geq$ 18 kg/m^2 with normal physical fitness; (3) hemoglobin $\geq$ 110 g/L; and (4) >4 months elapsed since first discharge from our institution.

DS for small-intestinal enteroatmospheric fistula

During DS, a lateral-lateral end anastomosis was performed in each fistula using a linear stapler (Pride Medical Inc, Jingjiang, Taizhou, Jiangsu, China). In addition, serosa and muscularis injuries were sutured using a 4-0 absorbable band (Vicryl Plus; Ethicon, Inc, San Angelo, TX). Prior to anastomosis, the digestive tract was gradually dissociated. In all cases, intraintestinal splinting was performed before abdominal closure. In addition to closure of the fistula(s), each patient received a hernia repair during the DS. Component separation technology and onlay mesh repair were used. In the procedure, a Cook Biodesign advanced tissue repair device (Cook Medical Inc, Bloomington, IN) was used. Negative pressure drainage was placed under all incisions.

Data analysis

To investigate the influence of CR on outcomes after DS, baseline data, including general patient information (sex, BMI, and age), fistula output (when patients had more than one small intestinal fistula, the output was calculated according to fistula with the greatest outflow), area of planned ventral hernia, and laboratory test results (eg, WBC count, hemoglobin, and albumin) were collected upon admission at the 3rd stage. The length from Treitz to the location of the (first) fistula and the length of the small intestine (sum of the length of the proximal and distal small intestine of fistula) were clearly investigated in the first stage of treatment using x-ray double-contrast small-bowel examination with urografin. In the third stage, the examination was conducted again, and characteristics of the fistula were re-investigated. The above fistula characteristics were collected according to data recorded in the third stage. Laboratory tests were performed every day within 7 days after DS, after which the results were collected and used for analysis. To investigate the nutrition status at the end of the first stage and the beginning of the third stage, as well as to evaluate the effect of CR on improvement of nutrition status, the BMI, and Nutritional Risk Screening (NRS) 2002 at the two time points were investigated.

All statistical analyses were performed using SPSS 26.0 software (IBM, Analytics, Armonk, NY). A Mann-Whitney *U* test was used to compare continuous variables across groups. Fisher's exact test was used to compare categorical variables. Kaplan-Meier estimates followed by a log-rank test and multivariate Cox regression analysis were used to compare effects of different methods. A *P* value of <0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics

From January 2012 to December 2019, a total of 263 eligible patients completed all three stages of treatment and received DS. Meanwhile, a total of 104 patients were excluded from this study. Of the 104 patients, 2 patients were younger than 18 years of age; 6 patients had IBD; 15 patients did not have EN; 71 patients had concurrent upper gastrointestinal fistula, colon fistula, pancreatic fistula, or pancreatitis; and 10 patients had incomplete data. A total of 159 patients were eventually enrolled in the study

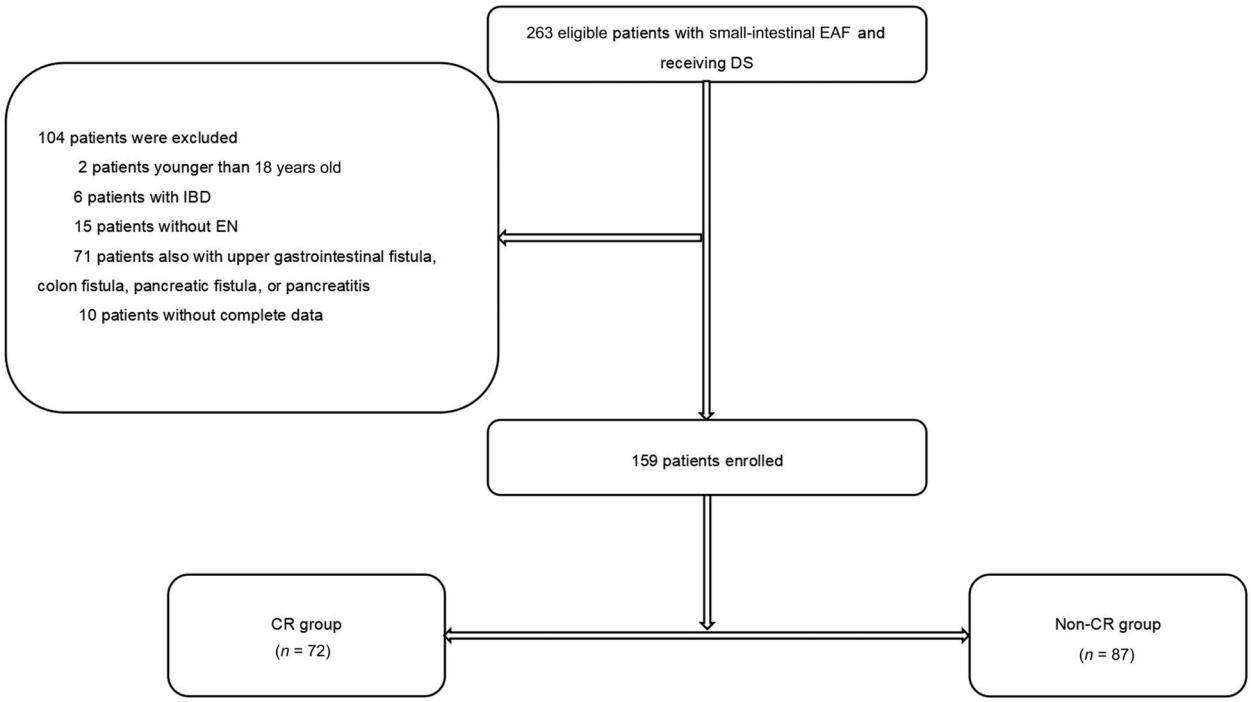

FIGURE 1 A flow chart depicting the patients and grouping. CR, chyme reinfusion; DS, definitive surgery; EAF, enteroatmospheric fistula; EN, enteral nutrition; IBD, inflammatory bowel disease

(Figure 1). Table 1 illustrates the characteristics of the 159 patients. Of the 159 patients, 72 patients (33 [45.83%] males) were in the CR group, and 87 patients (43 [49.42%] males) were in the non-CR group ($P = 0.750$). The median age was 45 years (interquartile range [IQR], 34–54.75 years) in the CR group and 48 years (IQR, 36–59 years) in the non-CR group ($P = 0.117$).

Improvement of nutrition status

The nutrition status at the end of the first stage and beginning of the third stage were then compared. The BMI (19 kg/m^2 [IQR, 18.25–20.1 kg/m^2] in the CR group vs 19 kg/m^2 [IQR, 18.25–20 kg/m2] in the non-CR group) was found to be comparable between the two groups at the beginning of the third stage. Moreover, the improvement of BMI in the CR group (3.25 kg/m^2 [IQR, 2.61–3.68] vs 2.15 kg/m^2 [IQR, 1.45–2.52] kg/m^2, $P < 0.001$) was found to be more significant.

No patients with NRS2002 had less than three points, and the percentage of patients with NRS2002 more than or equal to five points was found to be higher in the CR group (81.94% [$n = 59$] vs 63.22% [$n = 55$], $P = 0.009$), at the end of the first stage. However, after treatment in the second stage, all patients in both groups had NRS2002 less than five points. Furthermore, the percentage of patients with NRS2002 was noted to be comparable between the two groups (68.05% [$n = 49$] vs 70.11% [$n = 61$], $n = 0.780$).

Primary outcome

A total of 47 (29.56%) patients with recurrent fistula after DS were present, of which, there were 32 in the non-CR group (with recurrent fistula occurring 8 days [IQR, 7–10] after DS), and the incidence of recurrent fistula was 36.78%. Moreover, 15 of the 47 patients were in the CR group (with recurrent fistula occurring 7 days [IQR, 6–10] after DS), for which the incidence of recurrent fistula in the group was 20.83%. Multivariate logistic regression showed that the recurrent fistula rate in the CR (multivariate odds ratio [OR] = 0.557; 95% CI, 0.351–0.842; $P = 0.019$) group was lower. In addition, LOS during the second stage (multivariate OR = 1.189; 95% CI, 1.028–1.422; $P \leq 0.001$) demonstrated an increased incidence of recurrent fistula after DS (Table 2).

Only one of the 47 patients (non-CR group) died from multiple organ dysfunction syndrome. Of the remaining 46 patients, 39 underwent spontaneous closure (12 patients in the CR group and 27 patients in the non-CR group). Closure time was observed to be 39 (26–49) days after DS. In addition, seven patients received another DS 3–6 months after the first DS. Spontaneous closure was not associated with CR (univariate OR = 0.923; 95% CI, 0.197–4.330; $P = 0.919$).

TABLE 1 Patients characteristics

Clinical variables	CR group ($n = 72$)	Non-CR group ($n = 87$)	*P*
Demographic data			
Male, *n* (%)	33 (45.83)	43 (49.42)	0.652
Age, median (IQR), years	45 (34–54.75)	48 (36–59)	0.117
BMI, median (IQR), kg/m^2	19 (18.25–20.1)	19 (18.25–20)	0.710
Fistula characteristics			
Interval from fistula occurrence to admission, median (IQR), days	15 (12–19)	15 (12–19)	0.880
Length of stay in our institution for the first time, median (IQR), days	41 (34–48.75)	44 (38–50)	0.156
Required length of stay during second stage, median (IQR), months	5 (4–6)	5 (5–6)	0.124
Length from Treitz to location of (the first) fistula, mean ± SD, cm	152.64 ± 44.20	278.73 ± 33.81	<0.001
Length of small intestine, mean ± SD, cm	311.38 ± 58.79	337.01 ± 48.51	0.003
Number of fistulas (%)			0.154
1	34 (47.22)	46 (52.87)	
2	26 (36.11)	35 (40.22)	
≥3	12 (16.67)	6 (6.89)	
Output, mean ± SD, ml	1134.72 ± 367.38	610.34 ± 160.69	<0.001
Area of planed ventral hernia, median (IQR), cm^2	80.52 (59.61–0.19)	69.4 (56–84.50)	0.115
Etiology, *n* (%)			0.841
Trauma	49 (68.05)	56 (64.37%)	
Unclear perforation	2 (2.78)	2 (2.29)	
Obstruction	14 (19.44)	22 (25.29)	
Mesenteric thrombosis	7 (9.72)	7 (8.04)	
Perioperative and operative characteristics			
Hemoglobin before DS, median (IQR), g/L	127 (121–130)	121 (117–129)	0.001
Serum albumin level before DS, median (IQR), g/L	37 (35–38)	36 (34–38)	0.018
WBC before DS, median (IQR), $\times 10^9$/L	6 (5–6.4)	5.7 (5–6.3)	0.593
Duration of DS, mean ± SD, min	241.66 ± 33.52	238.85 ± 39.19	0.631
Number of anastomoses, median (IQR)	2 (1–2)	2 (1–2)	0.566
Bleeding loss during DS, median (IQR), ml	1187.50 ± 270.07	1252.87 ± 293.66	0.149
Intraoperative red blood cell transfusion, median (IQR), units, (median, IQR)	3 (3–4)	3 (3–4)	0.186
NRS2002, *n* (%)			0.780
≥3 and <5	49 (68.05)	61 (70.11)	
<3	23 (31.94)	26 (29.89)	
Postoperative characteristics			
WBC after DS , median (IQR), $\times 10^9$/L	15.1 (15–16.25)	15.5 (15–17)	0.885
CRP after DS, median (IQR), mg/L	145 (138.25–155)	143 (134–151)	0.266
Serum albumin level after DS, median (IQR), g/L	27 (23–30)	26 (21–29)	0.188
Hemoglobin level after DS, median (IQR), g/L	80 (77–90)	78 (75–86)	0.102
Postoperative red blood cell transfusion, median (IQR), units	7 (6–8)	7 (6–9)	0.140
Comorbidity, *n* (%)			
Hypertension	2 (2.78)	2 (2.29)	0.848
Diabetes mellitus	2 (2.78)	3 (3.45)	0.813
COPD	2 (2.78)	1 (1.19)	0.675

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CR, chyme reinfusion; CRP, C-reactive protein; DS, definitive surgery; NRS2002, Nutritional Risk Screening 2002; WBC, white blood cell.

TABLE 2 Logistic regression analysis of the risk factors for recurrent fistula

Clinical variables	Univariate regression			Multivariate regression		
	OR	95% CI	*P*	OR	95% CI	*P*
Male	0.665	0.328–1.305	0.229			
CR	0.452	0.221–0.926	0.030	0.557	0.351–0.842	0.019
Age	0.995	0.970–1.020	0.669			
BMI	0.839	0.645–1.091	0.190			
Interval from fistula occurrence to admission	0.959	0.887–1.036	0.289			
The length of stay in our institution for the first time	1.005	0.971–1.041	0.761			
Required length of stay during second stage	1.462	1.180–2.347	<0.001	1.189	1.028–1.422	<0.001
Length from Treitz to location of (the first) fistula	1.005	0.969–1.011	0.103			
Length of small intestine	0.991	0.985–0.997	0.004	1.000	0.993–1.008	0.906
Number of fistula	1.584	0.928–2.710	0.092	1.721	0.912–3.257	0.094
Output	0.999	0.999–1.000	0.236			
Area of planed ventral hernia	1.000	0.972-–1.001	0.069	1.016	0.998–1.034	0.085
Etiology						
Trauma	Ref					
Unclear perforation	3.375	0.451–25.244	0.236	3.096	0.247–38.777	0.381
Obstruction	1.908	0.841–4.325	0.122	1.480	0.577–3.795	0.415
Mesenteric thrombosis	4.500	1.422–14.245	0.011	4.065	0.974–16.969	0.054
Hemoglobin	0.965	0.924–1.009	0.117			
Serum albumin level	0.909	0786–1.051	0.197			
WBC	1.111	0.388–1.491	0.737			
CRP	1.000	0.298–2.904	0.910			
NRS2002 ≥3	1.976	0.889–4.405	0.095			
Duration of DS	1.007	0.998–1.017	0.138			
Number of anastomoses	1.148	0.507–1.618	0.298			
Serum albumin level after DS	0.914	0.814–1.103	0.201			
Hemoglobin after DS	0.994	0.638–1.391	0.442			
WBC after DS	1.121	0.587–2.008	0.509			
CRP after DS	1.002	0.442–1.989	0.499			
Bleeding loss during DS	1.001	1.000–1.002	0.112			
Intraoperative red blood cell transfusion	1.074	0.667–1.730	0.768			
Postoperative red blood cell transfusion	1.141	0.960–1.357	0.135			
Hypertension	2.444	0.334–17.890	0.379			
Diabetes mellitus	3.750	0.606–23.215	0.155			
COPD	1.196	0.106–13.514	0.885			

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CR, chyme reinfusion; CRP, C-reactive protein; DS, definitive surgery; NRS2002, Nutritional Risk Screening 2002; OR, odds ratio; Ref, reference; WBC, white blood cell.

Secondary outcomes

Time to return of bowel function in the CR group was found to be 7 days (IQR, 6–8), which was 9 days (IQR, 8–10) in the non-CR group. A multivariate Cox regression showed that CR promoted postoperative defecation (HR = 1.982; 95% CI, 1.199–3.275; $P = 0.008$; Table 3, Figure 2A). In addition, 18.06% ($n = 13$) of patients in the CR group and 33.33% ($n = 29$) of patients in non-CR group had time to return of bowel function ≥10 days.

TABLE 3 Cox regression analysis of the factors for defecation

Clinical variables	Univariate regression			Multivariate regression		
	HR	95% CI	*P*	HR	95% CI	*P*
Male	1.094	0.798–1.502	0.574			
CR	1.712	1.244–2.355	0.001	1.982	1.199–3.275	0.008
Age	0.997	0.986–1.008	0.525			
BMI	1.080	0.961–1.213	0.196			
Interval from fistula occurrence to admission to our institution	1.000	0.966–1.035	0.991			
Length of stay in our institution for the first time	1.009	0.991–1.028	0.338			
Required length of stay during second stage	0.781	0.651–0.936	0.008	0.737	0.611–0.887	0.001
Length from Treitz to location of (the first) fistula	1.000	0.997–1.003	0.998			
Length of small intestine	0.997	0.994–1.000	0.026	1.000	0.996–1.004	0.551
Number of fistula	0.943	0.752–1.180	0.608			
Output	1.000	1.000–1.001	0.101			
Area of planed ventral hernia	0.996	0.990–1.002	0.184			
Etiology						
Trauma	Ref					
Unclear perforation	0.906	0.33–2.470	0.847			
Obstruction	0.949	0.647–1.385	0.777			
Mesenteric thrombosis	0.797	0.448–1.421	0.442			
Hemoglobin	0.999	0.979–1.018	0.888			
Albumin	1.052	0.982–1.126	0.148			
WBC	1.109	0.698–1.386	0.387			
CRP	1.008	0.581–2.005	0.669			
NRS2002 ≥3	1.229	0.204–5.049	0.359			
Duration of DS	1.001	0.997–1.005	0.753			
Number of anastomoses	1.591	0.768–2.199	0.329			
Serum albumin level after DS	0.972	0.461–1.114	0.281			
Hemoglobin after DS	1.009	0.989–1.014	0.618			
WBC after DS	1.114	0.766–1.856	0.514			
CRP after DS	1.004	0.611–1.989	0.408			
Bleeding loss during DS	1.001	1.000–1.003	0.081	1.000	1.000–1.001	0.120
Intraoperative red blood cell transfusion	1.084	0.872–1.347	0.467			
Components separation technology + onlay mesh repair	1.536	0.511–2.046	0.729			
Postoperative red blood cell transfusion	0.999	0.917–1.089	0.986			
Hypertension	0.967	0.366–1.982	0.914			
Diabetes mellitus	0.933	0.459–1.298	0.781			
COPD	0.911	0.844–1.122	0.825			

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CR, chyme reinfusion; CRP, C-reactive protein; DS, definitive surgery; HR, hazard ratio; NRS2002, Nutritional Risk Screening 2002; Ref, reference; WBC, white blood cell.

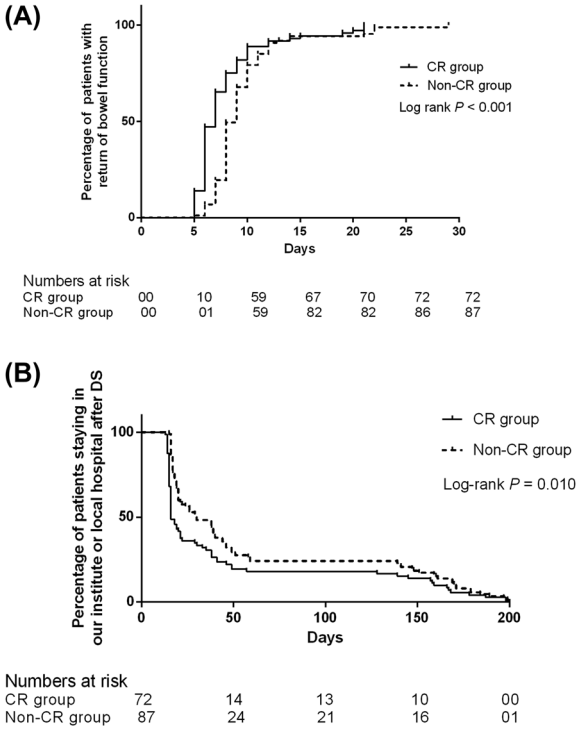

FIGURE 2 (A) A graph depicting the time to return of bowel function between the two groups; (B) a graph depicting the length of stay in hospital between the two groups. CR, chyme reinfusion

CR was not found to be an influencing factor for patients with a time to return of bowel function <10 days (multivariate OR = 2.020; 95% CI, 0.941–4.329; $P = 0.071$). Multivariate regression indicated that bleeding during DS was the only factor (OR = 0.999; 95% CI, 0.997–1.000; $P = 0.046$) associated with time to return of bowel function <10 days.

LOS after DS was noted to be 16 days (IQR, 15–41) in the CR group and 30 days (IQR, 18–59) in the non-CR group. Multivariate Cox regression indicated that CR was associated with a shortened LOS after DS (HR = 1.739; 95% CI, 1.233–2.453; $P = 0.002$; Figures 2B and 3).

Reinterventions

Complications and reinterventions are given in Table 4. In this study, four patients received a puncture and drainage, and one patient received an emergency laparotomy due to abdominal infection following recurrent fistula. The remaining 154 patients exhibited no obvious abdominal infection, of which CRP and WBC were shown to decrease more slowly in the non-CR group (Figure 4) on the seventh day after DS.

DISCUSSION

Enteroatmospheric fistula is always a high-output fistula in which a large amount of intestinal juice leaks from the fistula and cannot flow into the distal small intestine. This feature is similar to that of a temporary stoma, which may lead to a series of functional and structural changes in the bypassed intestine, including villous atrophy, smooth muscle weakness, and endocrine disturbances.[10–12] The above pathophysiologic processes may also increase risk factors for postoperative morbidity following intestinal surgery.[7] Several small-sample studies have shown that CR could reverse the pathological process caused by disuse and maintain intestinal function, thereby reducing the time to return of bowel function and decreasing the LOS.[7–9]

Few studies have focused on complications after DS for small-intestinal enteroatmospheric fistula. A small study has shown that the incidence of recurrent fistula right after surgery was 37.5% (3/8).[13] In addition, our previous study has demonstrated that patients with complicated intestinal fistula had a recurrent fistula rate of 30%.[3] Accordingly, the present study is the first to confirm the influence of CR on reducing the recurrent fistula rate (20.38% vs. 36.78%). Another novel discovery put forward by this study is that postoperative CRP and WBC on the seventh day after DS in the non-CR group were found to be higher than those in the CR group. According to the change trend of the postoperative inflammatory index, there was potential for CR to reduce the inflammatory response compared with that of non-CR.

Abdominal infection and the formation of frozen abdomen during the early treatment of small-intestinal enteroatmospheric fistula may result in severe abdominal adhesion, thus increasing the difficulty of DS as well as manipulation and bleeding loss during the procedure. Such effects have a large impact on postoperative gastrointestinal function increasing the inflammation response.[14–16] Various studies on major surgery have demonstrated an interaction between intestinal function and postoperative abdominal inflammation, which could influence the postoperative fistula rate.[3,4,14] The corresponding findings of this study suggest that a possible explanation for the influence of CR on the reduction of recurrent fistula and shortening of time to return of bowel function after DS may be due to the reduction of postoperative inflammation. In a high inflammatory response, necrosis factor-α released by mast cells inhibits the motility of the gastrointestinal tract as well as the wound healing process following intestinal anastomosis,[17] leading to the increased risk of recurrent fistula and time to return of bowel function. Furthermore, invading neutrophils can directly damage smooth muscle,[18,19] and an

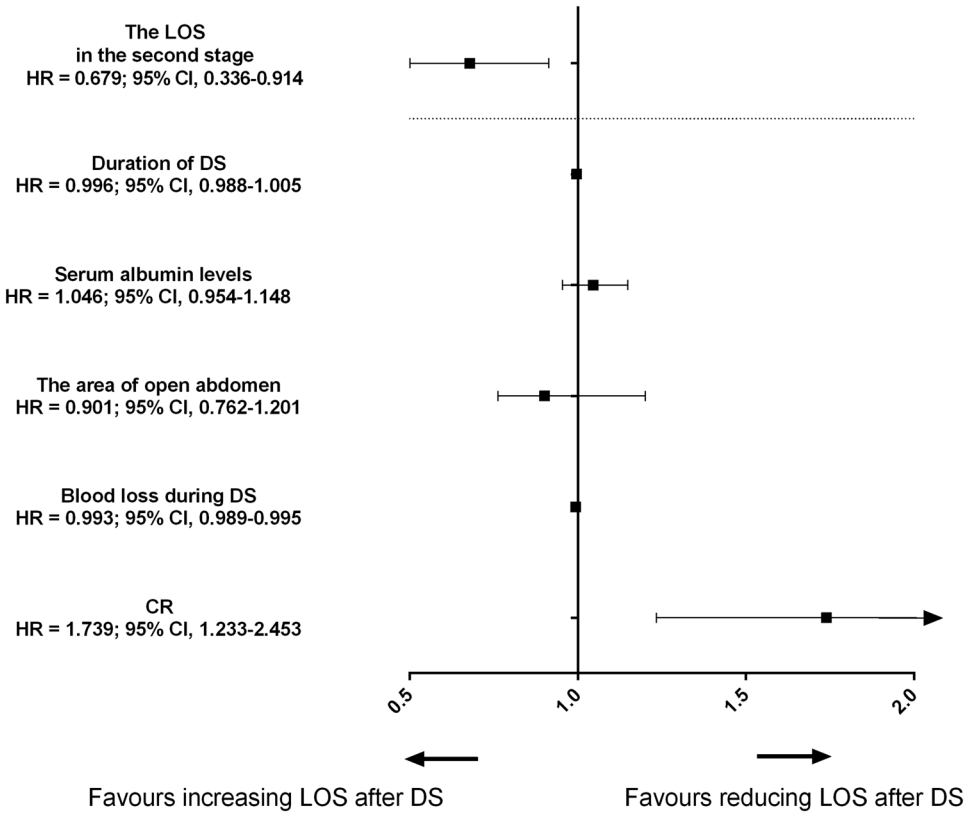

FIGURE 3 The adjusted regression analysis for reducing the length of stay (LOS) after definitive surgery (DS) for fistula. CR, chyme reinfusion; HR, hazard ratio

TABLE 4 Complications and reinterventions

	CR group	Non-CR group
Complications, n, (%)		
Recurrent fistula	15 (20.83)	32 (36.78)
Postoperative ileus	13 (18.06)	29 (33.33)
Postoperative diarrhea	0 (0)	3 (3.45)
Gastrointestinal bleeding	0 (0)	1 (1.15)
Incisional infections	22 (30.56)	26 (29.89)
Incisional hernia	12 (16.67)	18 (20.68)
Re-interventions, n, (%)		
Emergency laparotomy	0 (0)	1 (1.15)
Puncture and drainage	2 (2.78)	2 (2.29)
DS	1 (1.39)	0 (0)
DS + incisional hernia reparation	2 (2.78)	5 (5.75)
Incisional hernia reparation	10 (13.89)	13 (14.94)

Abbreviations: CR, chyme reinfusion; DS, definitive surgery.

imbalance of polarized macrophages can influence collagen deposition and tissue repair, leading to recurrent fistula.[20,21] In patients with a disused digestive tract, atrophy of the intestinal epithelium may result in an incomplete mucosal barrier, while an altered intestinal environment can aggravate the inflammatory response in critically ill patients.[22] Reversing pathological changes of long-term disuse and maintaining small-intestinal mucosa and function[7–9] may subsequently relieve the immune and inflammatory response after DS for small-intestinal enteroatmospheric fistula, a surgery that can adversely affect ill patients.[22]

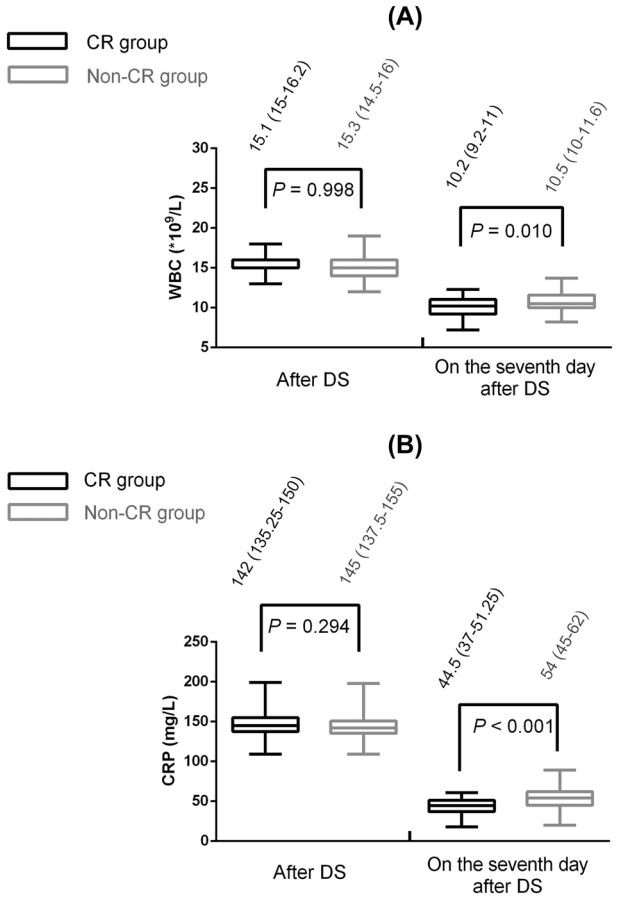

FIGURE 4 (A) The comparison of WBC between the two groups. (B) The comparison of CRP between the two groups. CR, chyme reinfusion; CRP, C-reactive protein; DS, definitive surgery; WBC, white blood cell

Other mechanisms that serve as advantages of CR for prognosis seem to have been present as well. For instance, CR has a positive influence on nutrition absorption, such as an increase in weight gain, improvement of liver profiles, and volume reduction output from proximal limb,[4,5] which may improve outcomes following DS. However, in the present study, all patient indicators were ensured to be normal before a DS could be performed (even in the non-CR group). As a result, the influences of CR on nutrition improvement may not have served as the main factors for decreasing recurrent fistula. In addition, CR can also strengthen smooth muscle tissue, in which the small intestine at the distal end of fistula becomes more robust compared with that of non-CR. Theoretically, the most direct impact of a robust intestine is that it is easier to perform anastomoses, and anastomotic patency is more optimal. Therefore, this may reduce incidence of recurrent fistula while decreasing time to return of bowel function.

This study had a few limitations. First, this was a retrospective study, hence, selection bias may have been present. The second limitation was that mechanisms of advantage of CR for prognosis were not fully explored. Accordingly, future animal experiments or randomized controlled trials (RCTs) should be performed to resolve this issue. The third limitation was that there were differences in characteristics between the two groups, and differences were mainly the length from Treitz to the location of the (first) fistula, output, serum albumin before DS, and hemoglobin before DS. Although higher concentrations of albumin and hemoglobin may lead to better outcomes, serum albumin and hemoglobin levels in the non-CR group reached as high as 36 (34–38) g/L and 121 (117–129) g/L compared with 37 (35–38) g/L and 127 (121–130) g/L in the CR group, though these differences may not have an influence. However, shorter length from Treitz to location of the (first) fistula in the CR group would lead to a higher output and worse condition. However, the findings showed the presence of a better prognosis in the CR group. To eliminate heterogeneity, propensity score matching (PSM) might be more suitable. However, after 1:1 PSM (with tolerance of 0.1), only 10 pairs were included, and this would decrease credibility of results, which may be related to a wide variety of baseline characteristics (almost 30 categories). However, the clinical situation of patients with ECF may not have been similar. Therefore, it is necessary to collect and analyze a large number of data to ascertain such problems. In addition, a multiple regression analysis was performed to compare the effects of different methods, which was also used in a large number of previous studies. In the future, an RCT should be performed. Insufficient follow-up time may have been another limitation of this study as patients with delayed fistula (recurrent fistula occurred 30 days after DS) may not be screened out. However, in patients with a longer follow-up time, none had delayed fistula.

CONCLUSION

CR prior to DS for enteroatmospheric fistula can reduce the incidence of recurrent fistula, time to return of bowel function, and hospital postoperative LOS.

CONFLICT OF INTEREST

None declared.

FINANCIAL DISCLOSURE

None declared.

AUTHOR CONTRIBUTION

Yunzhao Zhao, Weiliang Tian and Qian Huang provided research objects. Xin Xu, Shen Tao, and Risheng Zhao col-

lected and analyzed the data; Zheng Yao and Shen Tao wrote the main manuscript text; Xin Xu prepared figures. Zheng Yao designed the research. Yannian Liao reviewed the data and revised the manuscript.

DATA AVAILIBILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Liao Y, Tao S, Yao Z, et al. Chyme reinfusion improved outcomes after definitive surgery for small-intestinal enteroatmospheric fistula in patients with enteral nutrition. *Nutr Clin Pract*. 2022;1-11. https://doi.org/10.1002/ncp.10823