ORIGINAL CONTRIBUTION

Should Immunomodulation Therapy Alter the Surgical Management in Patients With Rectovaginal Fistula and Crohn's Disease?

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BACKGROUND: Rectovaginal fistula in Crohn's disease is challenging for both healthcare providers and patients. The impact of immunomodulation therapy on healing after surgery is unclear.

OBJECTIVE: The purpose of this study was to examine whether immunomodulation therapy impacts healing after surgery for rectovaginal fistula in Crohn's disease.

DESIGN: This was a retrospective analysis with a follow-up telephone survey.

SETTINGS: The study was conducted at two major tertiary referral centers.

PATIENTS: All of the patients who underwent rectovaginal fistula repair from 1997 to 2013 at our centers were included.

MAIN OUTCOME MEASURES: A χ^2 test and logistical regression analysis were used to study treatment outcomes according to type of procedure, recent use of immunosuppressives, and number of previous attempted repairs. Age, BMI, smoking, comorbidities, previous vaginal delivery/obstetric injury, use of probiotics, diverting stoma, and use of seton were also analyzed.

RESULTS: A total of 120 (62%) patients were contacted, and 99 (51%) of them agreed to participate in the study. Mean follow-up after surgical repair was 39 months. Procedures included advancement flap (n = 59), transvaginal repair (n = 14), muscle interposition (n = 14), episioproctotomy (n = 6), sphincteroplasty (n = 3), and other (n = 3); overall, 63% of patients experienced healing. Sixty-eight patients underwent recent immunomodulation therapy but did not exhibit statistical significance in outcome after surgical repair. In the subset of patients with fistula related to obstetric injury, a 74% (n = 26) healing rate after surgical repair was observed. Age, BMI, diabetes mellitus, use of steroids, probiotics, seton before repair, fecal diversion, and number of repairs did not affect healing.

LIMITATIONS: This was a retrospective analysis; the high volume tertiary referral inflammatory bowel disease centers studied may not be reflective of rectovaginal fistula presentation, treatment, or results in all patients, and the 3-year follow-up may not be sufficiently long.

CONCLUSIONS: Despite a relatively low success rate (63%) in healing after surgical repair of a rectovaginal fistula, the recent use of immunomodulation therapy did not negatively impact healing. However, tissue interposition techniques had the highest success rates.

KEY WORDS: Crohn's disease; Immunomodulation therapy; Rectovaginal fistula; Surgical management; Surgical outcomes.

Rectovaginal fistula (RVF) is an abnormal epithelial-lined communication from the distal rectum or anal canal to the posterior vagina, perineal body, or for which numerous treatment options exist. However, successful management continues to be challenging, with disparate success rates ranging from 30% to 90%, depending on the series.[1–5] Perianal fistula represents 54% of all fistulas in patients with Crohn's disease (CD), with the frequency of RVF being 9%.[6,7] RVF occurs in 3.5%[8] and 23.0%[9] of patients with CD involving the small and large bowel, respectively. Therefore, the frequency and severity of symptoms may be related to the large-bowel involvement.[10–13]

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Treatment options for CD-related RVF vary from medical management with immunomodulation therapy and symptom control to the need for surgery. In large controlled trials, immunomodulation therapy, specifically treatment with a monoclonal antibody, has been shown to result in significant clinical improvement of primary disease compared with placebo.[14] Monoclonal antibody therapy works by antagonizing the major inflammatory cascades to disrupt the main mechanisms of mucosal damage in CD.[14] No studies have exclusively and specifically evaluated the response of RVF to immunomodulation therapy, although some studies include patients with RVF. These studies have found a lower response rate to infliximab therapy compared with other fistula types.[15–18]

In addition, there are conflicting results regarding the influence of preoperative immunosuppressive therapy on postoperative complications after surgery in patients with CD. Patients receiving preoperative immunosuppressive may have an increased risk for surgical site infection and readmission to the hospital during the postoperative period.[19,20] Even with optimization of medical management, surgical repair of CD RVF is associated with a significant recurrence rate. In a retrospective review of 51 patients, recurrence after repair was reported to be 47% at 38.6 months.[21] Other studies have reported recurrence rates ranging from 25% to 80%.[6–23]

Success of repair may be influenced by patient comorbidities, health of the surrounding tissues, and the presence of infection and/or inflammation. Symptomatic patients may be treated in a multistep approach with medical treatment and drainage of local sepsis as the initial steps[10,24,25] before definitive surgical intervention is attempted.

In choosing an appropriate surgical treatment option, preoperative evaluation of fistula characteristics, degree of symptoms, sphincter function, anal stricture, and current active disease in the rectum and anus are important considerations. Currently, there are no evidence based, randomized, double-blind studies to support which surgical procedure should be chosen. Fistulotomy, direct repair, fibrin glue instillation, biological fistula plug, endorectal or sleeve advancement flap, episioproctotomy, and tissue/muscle interposition with or without fecal diversion have been reported as possible surgical therapies.[24,26–30]

With the increasing use of immunomodulation therapy for CD, we hypothesized that patients who had been recently treated with these medications might have a worse outcome after surgical attempt to close a CD-associated RVF. This study aimed to investigate the relationship between immunomodulators and surgical management with regard to the healing of RVF in patients with CD.

PATIENTS AND METHODS

After obtaining institutional review board approval, the authors performed a retrospective review of women with CD who underwent RVF repair between July 1997 and June 2013. Institutional review board approved prospectively maintained Colorectal surgery databases from Cleveland Clinic Foundation and Cleveland Clinic Florida were used to identify 192 patients with CD who underwent surgical repair of RVF with intent to close their RVF. The recent use of immunomodulation therapy (primarily infliximab or adalimumab), defined as within 30 days of surgical procedure, along with demographics, symptoms of RVF, healing, type of repair, time interval between last repair with intent to heal, and the use of probiotics were noted. In addition, the use of systemic steroids, azathioprine and 6-mercaptopurine were noted.

The postoperative data points of interest were healing of the fistula and relationship to the use of recent immunomodulation therapy, defined as within 30 days of surgical procedure with intent to heal RVF. All of the patients identified were mailed an information letter that described volunteer participation and the purpose of the study. The questions focused on confirming the last surgical repair with intent to heal the RVF and the occurrence of recurrence symptoms or fecal drainage through the vagina after surgical repair. Attempts were also made to contact the patients who were not followed up at our institutions. In addition, hospital medical charts were reviewed. Follow-up was defined as timing of the last surgical procedure with intent to heal RVF to the timing of telephone interview. Patients who reported persistence of symptoms that were compatible with the initial symptoms before surgical repair or current fecal drainage through the vagina at the timing of the telephone survey were reported as having failure to heal. Women who had recurrent symptoms at the time of the telephone survey but who had not gone to their surgeon for full evaluation were included in the analysis. Patients who did not agree to participate in the telephone follow-up survey or could not be reached were excluded from data analysis. No incentives for compliance were offered to the participants.

Patient data included age, BMI, comorbid conditions (diabetes mellitus, cardiac disorders, or pulmonary disease), smoking history, fecal incontinence, and local CD activity (defined as presence of active inflammation in the rectum or anal canal, anal/or perineal ulceration, or anal strictures). In addition, RVF that was associated with an obstetric injury in patients with CD was also noted. Fistula characteristics were defined as symptoms of passage of gas, fecal material, or drainage through the vagina. Fecal diversion, use of preoperative setons, type of surgical procedure performed, and number of previous surgical procedures performed were also evaluated. Fecal diversion was reversed after the surgical repair, and during the sur-

vey patients were asked about their bowel function and recurrence of symptoms after reversal. Surgical procedures were performed at the discretion of the individual surgeon with intent to heal the RVF procedures and included episioproctotomy, muscle interposition (including gracilis transposition and martius flap), placement of biological plug and fibrin glue, rectal-advancement flap, sphincteroplasty, and transvaginal repair.

The primary outcome was recurrence of RVF after surgical repair with intent to heal. Patients who received recent immunomodulation therapy before surgical repair were compared with individuals who did not; data were analyzed using the Fisher exact and χ^2 tests. The possible effects on fistula healing after surgical repair with use of preoperative seton, diverting stoma, and type of surgical procedure performed were evaluated by using the Fisher exact test. Logistic regression analysis was used to determine whether the number of attempted repairs or BMI was related to fistula healing. Differences between types of repair and primary outcome were assessed using a Kruskal–Wallis rank test. A $p \leq 0.05$ was considered statistically significant.

RESULTS

A total of 192 patients with CD RVF were identified who were surgically treated and eligible for inclusion in this study based on the medical charts; 120 patients (62%) were successfully contacted via telephone with the demographics provided. Ninety nine of the 120 women successfully contacted agreed to participate in the study, for an 82% response rate. Thus, the overall follow-up was a mean length of 39.1 ± 52.2 months. The mean age and BMI were 43.3 ± 11.9 years and 26.2 ± 5.6 kg/m^2, respectively. Preoperative patient data are described in Table 1. Commonly observed preoperative symptoms were gas per vagina (98%), drainage per vagina (97%), stool per vagina (88%), and fecal incontinence (9%). No preoperative symptoms were statistically significant with respect to the final success of surgical closure of the fistula tract ($p = 0.7$).

Table 2 lists the procedures performed. Surgical repairs performed with the intent to close the RVF included a transrectal approach with endorectal advancement flap (59.5%; 59 procedures), overlapping sphincteroplasty (3.2%; 3 procedures), fibrin glue placement (2.1%; 2 procedures), biological plug insertion (1.1%; 1 procedure), episioproctotomy (6.4%; 6 procedures), and transvaginal repair (14.1%; 14 procedures). Muscle transposition, including gracilis muscle interposition (5.3%; 5 procedures) and martius or groin flaps (9.6%; 9 procedures) were also performed. A seton was used in 43 patients before undergoing an attempted definitive surgical procedure. In this group, 24 patients observed healing after undergoing definite surgical repair ($p = 0.2$).

TABLE 1. Patient demographics

		Outcome (%)		
Demographics	*Data*	*Healed*	*Failed*	*p*
Patients, n	99	63 (63.7)	36 (36.4)	
Age, mean ± SD (years)	43.3 ± 11.9	42.3 ± 11.9	45.1 ± 12.0	0.273
BMI, mean ± SD (kg/m^2)	26.2 ± 5.7	26.3 ± 5.8	26.8 ± 6.5	0.36
Smoking, n	31	21	10	0.3
Diabetes mellitus, n (%)	6 (6.1)	4 (66.7)	2 (33.3)	0.99
Coronary artery disease, n (%)	16 (16.2)	7 (43.8)	9 (56.2)	0.13

The overall healing rate of RVF after surgical repair was 63.7%. Thirty-five women with CD also had an obstetric injury that resulted in an RVF, of whom healing was observed in 26 patients (74.3%; $p = 0.002$).

Postoperative complications <30 days after surgery occurred in 12 patients. including 2 instances of postoperative anal bleeding requiring intervention, 8 wound separations, 1 urinary tract infection, and 1 case of pneumonia. When comparing the fistula healing rate with surgical-related complications, no statistical significance was found ($p = 0.3$).

The mean number of attempted repairs that patients underwent to try to heal the RVF was 2 (range, 1–3) in the healed group and 3 (range, 1–5) in the unhealed group ($p = 0.9$). Thirty-six patients (36.3%) had a diverting stoma at the time of surgical repair, and healing occurred in 19 patients (52.7%). Patient ASA classification recorded during the timing of surgical repair had a significant association with the healing of the RVF. Specifically, ASA classification of ≥3 had a high risk of failure to heal (OR = 1.43 (95% CI, 0.94–12.26); $p = 0.03$).

Sixty-eight patients (68%) were treated with recent immunomodulation therapy for their CD (48 infliximab and 20 adalimumab). When analyzing RVF healing in patients who underwent recent biological therapy treatment followed by surgical procedure, 36.7% (25/68) did not heal in the infliximab group ($p = 0.5$), and 47.4% (9/20) did not heal in the adalimumab group ($p = 0.2$). Immunomodulation therapy did not negatively influence the surgical healing rate (Table 3). Fifty-seven patients (57%) were taking systemic steroids preoperatively, of which 38.5% (22/57) did not heal; this was not statistically significant with respect to healing after surgical repair ($p = 0.19$). A small number of patients were taking azathioprine (n = 4) and 6-mercaptopurine (n = 4), both of which did not statistically impact the healing (see Table 4 for immunosuppressant therapy outcomes).

DISCUSSION

RVF can have a significant deleterious impact on quality of life. Management of any RVF may be exceptionally challenging, and the addition of CD to the equation

TABLE 2. Types of procedures

Procedure	n	Outcome, n (%)		Biological therapy, n (%)		p
		Healed	Failed	Yes	No	
Transanal repair	1	1 (100)	0 (0)	0 (100)		
Fibrin glue placement	2	1 (50)	1 (50)	1 (50)	1 (50)	
Fibrin plug placement	1	0 (0)	1 (100)	0 (100)		
Episioproctotomy	6	2 (33)	4 (67)	3 (50)	3 (50)	
Transvaginal repair	9	8 (89)	1 (12)	5 (56)	4 (44)	
Rectal advancement flap	52	36 (69)	14 (27)	23 (44)	29 (56)	
Overlapping sphincteroplasty	3	3 (100)	0 (100)	0	3 (100)	
Gracilis transposition	5	5 (100)	0 (0)	3 (60)	2 (40)	
Martius flap	9	7 (78)	2 (22)	6 (67)	3 (33)	
Abdominoperineal resection	2	2 (100)	0 (0)	2 (100)	0	0.3

adds additional complexity to surgical decision making. Although there is no one single treatment for CD-related RVF, after maximizing medical management, surgical repair to close the fistula is considered when the symptoms are intolerable and a chance of successful closure is feasible. The choice of intervention for closure is influenced by the location of the fistula and extent of disease.[31] Currently, there are no definitive recommendations to guide the surgeon in choosing the optimal intervention that would give the best chance of success.

Biologic therapy for CD was found to be successful in management in the late 1990s; we first started using this therapy in 1997. Although the role of biological therapy in fistula disease is conflicting, a study of 218 patients with perianal fistula and CD found an overall improvement in symptoms with biological therapy as an adjuvant to surgery.[32] A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients With Fistulising Crohn's Disease II evaluated patients with CD who had fistulizing disease treated with infliximab.[33] Infliximab was reported to be effective in short-term closure of RVF, and maintenance treatment was more effective than placebo in maintaining RVF closure.[33] Another study that reported a different result involved 56 women with CD RVF.[29] They reported that healing of RVF after the first surgical repair was not affected by treatment with a biologic. Although the use of biological therapy may be an indicator of severe disease, in our study, the use of immunomodulation therapy (specifically monoclonal antibody therapy) did not improve successful closure rates or negatively impact results (Fig. 1).

We observed that the overall successful closure with surgical management of CD RVF was 63%. The successful closure of RVF in CD is reported to range from 50% to 93%.[6,34–36] Of note, advancement flap was the most common procedure performed in our study, which involved the interposition of healthy tissue. An advancement flap is considered when the rectum and anal canal have no or minimal inflammation and there is no anal canal stenosis.[6,36]

Advanced surgical procedures, such as muscle interposition, and innovations in medical research have decreased the need for proctectomy. Fürst et al[30] reported excellent short-term results with 11 of 12 healed RVFs in CD in patients who underwent gracilis transposition. Wexner et al[36] reported that 33% of CD-associated rectouretheral, rectovaginal, and pouch-vaginal fistulas successfully healed with gracilis muscle interposition. However, they reported

TABLE 3. Preoperative and operative details

Variables	Yes/no	n (%)	Healed	Unhealed	p
Seton	Yes	43 (43.4)	24 (55.8)	19 (44.2)	
	No	56 (56.6)	38 (67.9)	18 (32.1)	0.2
Stoma	Yes	36 (36.4)	19 (52.8)	17 (47.2)	
	No	63 (63.6)	44 (69.8)	19 (30.2)	0.13
Systemic steroids treatment	Yes	57 (57.6)	35 (61.4)	22 (38.6)	
	No	42 (42.4)	29 (69.1)	13 (30.9)	0.19
Biological therapy	Yes	68 (68.7)	43 (63.2)	25 (36.8)	
	No	31 (31.3)	20 (64.5)	11 (35.5)	0.5
Patients who had vaginal delivery, n		67			
RVF after obstetrical injury		35 (35.3)	26 (74.0)	9 (26.0)	0.002
Number of repairs, median (range)			2 (1–3)	3 (1–5)	0.9

RVF = rectovaginal fistula.

TABLE 4. Immunomodulation effect on rectovaginal fistula healing after surgery

Variable	n	Outcome (%)		p
		Healed	Failed	
Steroids	57	35 (61.4)	22 (38.5)	0.19
Infliximab	48	23 (47.9)	25 (36.7)	0.5
Adalimumab	20	11 (55)	9 (47.4)	0.2

that gracilis interposition failed in 4 of the 9 women with CD-associated RVF. We observed that gracilis interposition and martius flap were successful in 5 (of 5) and 7 (of 9) women with CD-associated RVF.

In our study, the types of repair varied, including muscle interposition, episioproctotomy, advancement flaps, transvaginal repair, biological plug insertion, and overlapping sphincteroplasty. Crohn's fistulas are diverse in severity and type of surgical intervention offered and may reflect the chronicity and complexity of the fistula. However, the number of attempts or the type of surgical procedure that patients underwent for repair did not statistically affect the healing rate. A limitation in this study was that the number of patients undergoing each type of surgical repair was low; nonetheless, the results suggest that rectal advancement flap seems to be an acceptable method of repair. Another problem was the assignment of treatment based on the individual preference of the surgeon. Interestingly, repair seemed most likely to be successful in women with CD and RVF secondary to childbirth injury ($p = 0.002$). In addition to overlapping sphincteroplasty as one of the procedures of choice for patients with obstetric injury related to RVF, patients underwent episioproctomy and advancement flaps at the discretion of the surgeon. These results may be attributed to the fact that fistulas may

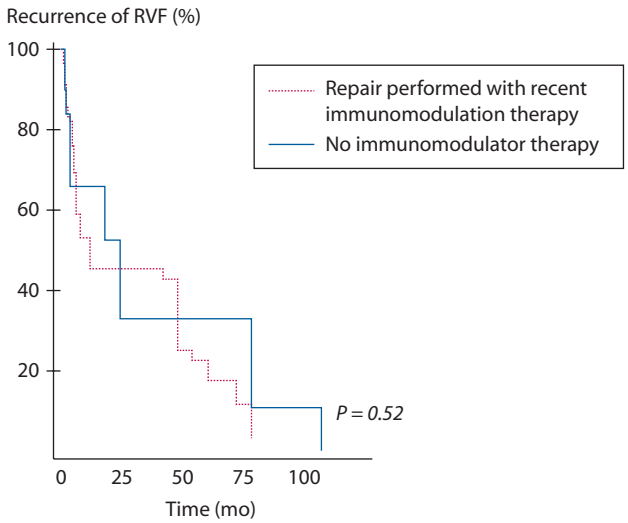

FIGURE 1. Analysis predicating the recurrence of rectovaginal fistula (RVF) after surgical repair with the intent to heal (median follow-up).

be secondary to the episiotomy rather than to the CD. The activity of the CD may be the more important factor in planning surgery.

Previous studies have indicated that preoperative seton placement for approximately 1 month before definitive surgery may reduce trapped purulence and decrease inflammation, thus leading to an improved rate of successful fistula closure.[37] However, in this study, seton drainage before surgical closure did not improve RVF closure ($p = 0.2$). In addition, fecal diversion either several weeks before surgical repair to decrease drainage and inflammation or at the time of surgical repair to eliminate stool from crossing the repair site has been suggested to improve the rate of successful surgical closure.[38] Although creating a stoma does not guarantee success, a stoma is most often considered in the most complicated cases, and this variable is difficult to control for data analysis. Nevertheless, in this study, 36% of patients had fecal diversion at the time of surgical repair, and this did not statistically improve successful RVF closure ($p = 0.13$). Although a controversial issue, currently, the decision to use a stoma is up to the judgment of the surgeon and may be influenced by the number of previous attempts, among other factors. In addition, the average number of attempted repairs in the healed versus nonhealed group did not exhibit statistical significance ($p = 0.9$). Although this result is different than what has been reported previously in the literature,[1,39] the exact algorithm to place a seton or choose a stoma may not have been the same for each patient in this study and left to the discretion of the surgeon.

There are several limitations in the current study. This is a retrospective analysis with all of the limitations of a review of surgical databases. We attempted to improve some of the data collection by individually contacting patients to verify any events since they were last cared for in our institution. Despite our attempts, follow-up was complete in only 51%. Moreover, women who had recurrent symptoms but had not gone to their surgeon for full evaluation were included in the analysis. Furthermore, we combined 2 campuses from our institution to increase the number of patients we studied; nonetheless, the denominator remained small, which may have accounted for a failure to achieve statistically significant differences. Our recurrence rate was defined as recurrence of symptoms after the last surgical repair to the telephone survey, which may underestimate the overall recurrence rate for patients who underwent multiple procedures. Although the mean number of attempted repairs in the healed group was 2 (range, 1–3) and in the unhealed group 3 (range, 1–5), this was not statistically significant. As mentioned previously, operations are performed at the discretion of the initial surgeon. Therefore, because of the low power of this study, our null hypothesis that patients recently treated with biological therapy might have a worse outcome after surgical

attempt to close a CD-associated RVF could have been rejected when it is in fact true. This study was conducted at a major tertiary referral center for CD and may not be reflective of RVF presentation, treatment, or results of treatment in all patients with CD. Lastly, the 3-year follow up may not be sufficiently long to evaluate the results. Tissue interposition techniques had the highest success rates.

CONCLUSION

Immunomodulation therapy does not negatively impact successful surgical repair, although additional studies with a larger number of patients should be conducted.

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