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Do medications affect outcomes in pelvic pouch construction?

Amy L. Lightner

Division of Colon and Rectal Surgery, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, USA

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ABSTRACT

Ileal pouch anal anastomosis is the preferred operation for restoration of intestinal continuity in patients with ulcerative colitis due to favorable functional outcomes and quality of life. However, up to 30% can develop postoperative complications, of which pelvic sepsis is the most dreaded due to impaired pouch function and increased rates of pouch failure. Several modifiable risk factors are associated with postoperative pelvic sepsis including obesity, poor nutritional status, anemia, and immunosuppressive therapy. While the evidence regarding the effect of immunosuppressive therapy on adverse postoperative outcomes is controversial, there is mounting data to suggest the operation performed at the time of immunosuppression exposure is critical for subsequent pouch outcomes. This has resulted in an increased number of pouches being performed as a modified 2-stage or 3-stage approach, a conservative yet safe approach to avoid potential deleterious effects of immunosuppression at the critical step of pouch formation.

Introduction

Proctocolectomy with ileal pouch anal anastomosis (IPAA) remains the procedure of choice for restoration of intestinal continuity in patients with ulcerative colitis (UC). IPAA allows at risk tissue to be removed while maintaining favorable long-term functional outcomes and quality of life.[1,2] Although less than 30% of patients experience short-term postoperative morbidity following IPAA,[3–5] up to 15% of pouches will ultimately fail due to technical or inflammatory complications.[1,2,6–8] The resulting permanent stoma is devastating for some patients as it may adversely affect body image and quality of life.

The leading cause of pouch failure is pelvic sepsis, reported in 5%–25%[4,9–11] of patients. Pelvic sepsis is most often a result of a pouch anastomotic leak or a leak from the blind limb of the J pouch reported in 6.5%–15% of patients.[1] A leak may manifest as a peri-pouch abscess, dehiscence of the staple line, fistula, or chronic sinus tract, all of which lead to peripouch inflammation and eventual scarring. Unfortunately, this chronic inflammation can result in pelvic fibrosis and decreased distensibility of the pouch, ultimately resulting in poor function. This eventually culminates in an increased risk of pouch failure which can reach up to 40% at 10 years.[12]

Thus, prevention of pelvic sepsis following IPAA is of critical importance to optimize long-term pouch function. Several modifiable risk factors for pelvic sepsis following IPAA have been identified including increased body mass index,[13] anemia,[14] poor nutritional status,[15] and immunosuppresssion.[16–19] Fortunately, in pouch surgery, the operation can be staged in order to avoid pouch construction under suboptimal conditions. As such, it is increasingly important to understand which patients are at highest risk of postoperative complications and best served with a modified 2-stage or 3-stage approach. In an era of a rapidly expanding repertoire of immunosuppressive agents used to treat UC, the focus of this discussion is to highlight the association of immunosuppression and adverse postoperative outcomes.

Corticosteroids

Corticosteroids have been used to treat UC since 1955 when Truelove and Witts showed that oral cortisone effectively induced remission in patients with active UC.[20] While both single series and population based studies have clearly demonstrated the efficacy of corticosteroids,[21,22] many UC patients become steroid dependent,[23] and corticosteroids have significant number of side effects including osteoporosis, cataract formation, and growth retardation in children.[24] In addition, corticosteroids are a concern in the perioperative period since it well established that corticosteroids impair wound healing[25,26] and increase the risk of infectious complications[27] in non IBD surgery. Animal studies have even demonstrated that high doses of corticosteroids negatively impact anastomotic healing.[28] While the literature of post IPAA outcomes is limited by its retrospective design, there is now a significant body of literature reporting data on post IPAA outcomes in the setting of preoperative corticosteroid exposure.

Several large series have reported postoperative overall and septic complications following IPAA in the setting of variable dosages and durations of corticosteroids. Despite many studies of relatively similar design, the data remains controversial with some reporting no

E-mail address: Lightner.amy@mayo.edu

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association of corticosteroids on adverse postoperative complications, and others reporting increased risk of postoperative complications at doses >20 mg,[16,29] >40 mg,[29–31] or in combination with anti-TNF therapy.[32] While it is difficult to account for other patient factors contributing to increased disease severity, many studies did include a multivariable analysis (Table 1).

When synthesizing the data regarding corticosteroids, it seems those at highest risk are patients taking >20 mg daily, those on corticosteroids longer than two months, and those on combination immunosuppression with biologic therapy. In these patients, pouch formation should be delayed until a second stage, either as a modified 2-stage or 3-stage approach. This allows for an adequate window to taper off corticosteroid therapy before performing the IPAA under improved conditions. Less clear is the strategy for patients on <20 mg of corticosteroids or those who only receive 3–5 days inpatient of IV hydrocortisone. In the absence of other risk factors for a complication, it is reasonable to consider a 2-stage approach, although, in the current era these patients are mostly likely to have additional risk factors for a post IPAA complication, or at least have been exposed to biologic therapy within the prior 12 weeks.

Anti-TNF

The advent of biologic therapy for the treatment of IBD commenced in 1998 when the Federal Drug Administration (FDA) approved infliximab for the treatment of moderate to severe Crohn's disease (CD). Infliximab was later FDA approved in 2005 for moderate to severe UC. Since, biologics have replaced corticosteroids as the cornerstone of medical management, especially with an increased adoption of a top down treatment approach. While it remains uncertain if the increased use of biologics has resulted in a decreased rate of colectomy,[33,34] an increasing number of UC patients are certainly exposed to anti-TNFs by the time of surgical consultation. Because one third of patients will have a primary loss of response and another one third develop a secondary loss of response to infliximab, may have been exposed to multiple anti-TNF therapies (infliximab, adalimumab, certolizumab pegol, golimumab) by the time they reach the decision to undergo surgical intervention for medically refractory disease.

The most well studied anti-TNF with regard to postoperative outcomes is infliximab. Numerous studies, both in the form of retrospective reviews and meta-analyses have now reported on postoperative outcomes and, more specifically, pouch related septic complications in the setting of infliximab. Unfortunately, the data is conflicting, with some reporting an increased rate of complications while other report no increased risk of infectious complications (Table 2). This may be due to a number of limitations: variable duration of anti-TNF exposure, variable time from last dose of anti-TNF to surgery, and significant heterogeneity with regard to additional patient risk factors. For example, the elimination half-life of infliximab is between 7 and 18.5 days[35]; by 12 weeks (4.5 half-lives), most patients should have undetectable levels of infliximab. Therefore, when studies gather data on patients exposed to infliximab up to a year prior to surgery, the findings are likely to be unaffected by infliximab. It would be useful if future studies reported events along a continuum from the time of last biologic exposure to more accurately reflect the true effects of the anti-TNF therapy.

However, even in similar study design and primary outcome, the data remains controversial in similar study design across some of the largest IBD referral centers. In the study by Selvasekar et al of 301 patients from Mayo Clinic, the odds ratio for an infectious complication was 3.5 on multivariable analysis; anastomotic leaks ($p = 0.02$), pouch-specific ($p = 0.01$) and infectious complications ($p < 0.01$) complications were more common in the infliximab exposed patients.[36] Similarly, the odds ratio for postoperative sepsis in the Mor et al paper of 523 patients from Cleveland Clinic was 13.8 in the infliximab exposed cohort.[18] In addition, in a paper encompassing results from three large IBD referral centers, preoperative exposure to anti-TNF combined with corticosteroids increased the rate of anastomotic leaks following proctocolectomy and IPAA (OR 5.82; $p = 0.011$). This increased risk of anastomotic leak was not noted in those who underwent a completion proctectomy and IPAA, underscoring the safety in a staged approach with colectomy first. Contrasting these findings are the results from the largest series by Zittan et al from Mount Sinai Hospital in Toronto which reported no increased risk of posteroperative leaks, even when comparing those who had been operated on within 15 days or 31–180 days.[37] Similarly, meta-analyses also report conflicting results, despite similar analysis.[38–40] Interestingly, in one meta-analysis by Selvaggi et al, an important comment was made: many studies mix operations included in the analysis to include both subtotal colectomy and IPAA which likely dilutes the detrimental effect of anti-TNF on patients who underwent IPAA. Regardless of all these aforementioned limitations and exhausting attempt to definitively answer if anti-TNF increases peripouch sepsis, there is enough literature arguing the likely increased rates of pouch complications in the setting of anti-TNF therapy to recommend a 3 stage approach to patients exposed to anti-TNF therapy. The consequence of peripouch sepsis and worsened pouch outcomes is not worth saving one extra operation.

Vedolizumab

Similar to the anti-TNF data, the findings of postoperative complications in the setting of vedolizumab exposure are also controversial. The initial study suggesting the potential for an increased risk of postoperative complications in vedolizumab treated IBD patients was a retrospective review from Mayo Clinic comparing 94 vedolizumab

Table 1
Postoperative outcomes with corticosteroids.

Author	Journal	Year	Study design	Dose of corticosteroids (mg)	*n*	Postoperative outcomes	Significant increase with corticosteroids
Ziv[47]	DCR	1996	Retrospective/Cleveland Clinic	>20, <20, none	661	30-day post op sepsis and sepsis related reoperation	No
Heuschen[30]	Ann Surg	2002	Retrospective/Germany	>40, <40, none	706	Pouch related septic complications	Yes, high dose
Mahadevan[31]	Inflamm Bowel Dis	2002	Retrospective/UCSF	>40, <40, none	216	<30 day postop complications	Yes, high dose
Lake[48]	J Gastrointest Surg	2004	Retrospective/USC	>20, <20, none	100	30-day post op infectious complications	No
Lim[29]	DCR	2007	Retrospective/Leeds, UK	>40, >20, <20, none	445	30-day post op septic complications	Yes, increased as dose increased
Ferrante[16]	Inflamm Bowel Dis	2009	Retrospective/Leuven	>20 for >2 months	141	30-day post op infectious complications	Yes
Sahami[32]	JCC	2016	Retrospective/multi-center	>20, or >20+ant-TNF	640	30-day anastomotic leak	No, unless combined with anti-TNF

Table 2
Postoperative outcomes with anti-TNF.

Author	Journal	Year	Study design	*n*	Duration of anti-TNF exposure	Postoperative outcomes	Increased with anti-TNF
Schluender[49]	DCR	2007	Retrospective/Cedars	151	1–12 months	Postoperative complications	No
Selvasekar[36]	J Am Coll Surg	2007	Retrospective/Mayo	301	6 moths	Postoperative pouch related and infectious complications	Yes
Mor[18]	Dis Colon Rectum	2008	Retrospective/Cleveland	523	4–37 weeks	Postoperative complications	Yes
Kunitake[50]	J Gastrointest Surg	2008	Retrospective/Boston	413	12 weeks	Postoperative complications	No
Ferrante[16]	Inflamm Bowel Dis	2009	Retrospective/Leuven	141	12 weeks	Postoperative infectious complications	No
Yang[39,40]	Aliment Pharmacol Ther	2010	Meta-analysis	706	Variable	30-day post op sepsis and sepsis related reoperation	Yes
Gainsbury[51]	J Gastrointest Surg	2011	Retrospective/Boston	81	12 weeks	30-day post op infectious complications	No
Bregnbak[52]	J Crohns Colitis	2012	Retrospective/Denmark	71	12 weeks	30-day post op infectious complications	No
Yang[39]	Aliment Pharmacol Ther	2012	Meta-analysis	2933	Variable	Total, infectious, noninfectious complications	No
Eshuis[53]	J Crohns Colitis	2013	Retrospective/Amsterdam	72	Up to one year	30-day post op septic complications	No
Gu[54]	Dis Colon Rectum	2013	Retrospective/Cleveland	581	12 weeks	30-day and 1 year post op septic complications	Yes
Bregnbak[52]	J Crohns Colitis	2012	Retrospective/Denmark	71	12 weeks	30-day postoperative complications	No
Nørgård[55]	Aliment Pharmacol Ther	2013	Populational/Denmark	199	12 weeks	30-day anastomotic leak	No
Selvaggi[38]	Inflamm Bowel Dis	2015	Meta-analysis	630	<12 weeks, >3 doses	30-day peripouch septic complications	Yes
Zittan[37]	Inflamm Bowel Dis	2016	Retrospective/Mount Sinai	773	<15 days, 15–30 days, 31–180 days	30-day anastomotic leak	No
Kulaylat[56]	JAMA Surg	2017	Claim data, United States	2476	<90 days	90-day post op complications	Yes

treated patients to 126 anti-TNF treated patients and 172 non biologic patients undergoing a major abdominal operation for IBD.[41] The rate of all postoperative complications was significantly higher in the vedolizumab treated cohort as compared to anti-TNF or no biologic therapy (53% vs 28% vs 33%; $p < 0.001$), and on multivariable analysis, vedolizumab was an independent predictor of postoperative infectious complications when compared to the anti-TNF ($p < 0.01$) and no biologic ($p < 0.01$) cohorts. However, this report included both UC and CD patients, and there were too few patients to look at pouch outcomes specifically. A subsequent multi-center retrospective review confirmed these findings of increased risk of postoperative infections in the setting of vedolizumab exposure on multivariable analysis ($p < 0.01$),[42] but other centers have not found the same increased risk.[43]

The first study reporting outcomes in UC patients alone was from Leuven. The group compared 34 patients who received vedolizumab within 16 weeks of colectomy to 60 patients who received anti-TNF therapy within 8 weeks of surgery, 32 who received moderate to high dose prednisone, and 71 who received no therapy at the time of colectomy. The group reported that there was no association of vedolizumab with short-term postoperative infectious complications at the time of colectomy or subsequent pouch formation. Interestingly, however, only three patients underwent total proctocolectomy with IPAA in the vedolizumab group making it difficult to assess infectious complications after pouch formation in the setting of vedolizumab.[14] Only pouch construction at the first stage was associated with an increased risk of postoperative complications. Thus, the authors recommended pouch construction should be delayed until the second step of the operation in order to minimize postoperative morbidity.[14]

Another retrospective series from Mayo Clinic investigating the effect of vedolizumab in UC patients alone ($N = 88$ vedolizumab, $N = 62$ anti-TNF) found a significant increase in superficial surgical site infection ($p = 0.047$) in vedolizumab treated patients, but there was no significant increased risk of overall 30-day infectious complications. Importantly, there was a higher rate of intra-abdominal peripouch abscesses following IPAA in the vedolizumab treated patients as compared to anti-TNF patients.[44] Therefore, similar to the concluding statements made by the Leuven group, the Mayo group also recommended a 3-stage IPAA or modified 2-stage IPAA in vedolizumab treated UC patients (Table 3).

Utility of serum drug levels

To date, three studies have looked at the association of preoperative serum drug levels and the relationship with postoperative complications. The first by Lau et al looked at the relation of serum anti-TNF levels and postoperative complications in 94 UC patients and 123 Crohn's patients. While the authors found higher rates of postoperative morbidity ($p = 0.047$) and hospital readmissions ($p = 0.04$) in the ≥ 8 μg/mL compared to <3 μg/mL group when looking at Crohn's patients, there was no association of increased postoperative complications with increasing serum anti-TNF levels in UC patients.[17] A subsequent prospective study of 214 Crohn's patients undergoing an ileocecal resection found no difference in complications based on serum trough levels; UC patients were not included in the analysis.[45]

A recent abstract of serum vedolizumab levels also found no association of serum drug levels and postoperative complications.[46] Due to small patient numbers (18 CD, 14 UC, 3 indeterminate colitis), all diagnoses were combined so it is difficult to see if levels would be helpful in one diagnosis versus the other. In addition, there is little understanding as to what serum vedolizumab levels indicate with regard to receptor saturation and tissue level effects, thereby limiting the utility in drawing serum levels. Overall, it does not seem as though serum levels of biologics are useful in predicting postoperative complications in UC patients, and are therefore unlikely to be helpful in guiding the timing of surgery.

Table 3
Postoperative outcomes with vedolizumab.

Author	Journal	Year	Study design	CD/UC/Both	Patients exposed vedo	Postoperative outcomes	Significant increase with vedolizumab
Lightner[41]	JCC	2017	Retrospective single-center/Mayo Clinic	Both	94	30-day post op infectious complications	yes
Lightner[42]	Inflamm Bowel Dis	2018	Retrospective multicenter	Both	146	30-day post op infectious complications	yes
Yamada[43]	Am J Gastroenter	2017	Retrospective single-center/U of Chicago	Both	64	30-day post op infectious complications	no
Lightner[44]	IBD	2017	Retrospective single-center/Mayo Clinic	UC	88	30-day post op infectious complications	yes
Ferrante[14]	JCC	2017	Retrospective single-center/Leuven	UC	34	30-day post op infectious complications	no

Conclusions

While the evidence surrounding perioperative exposure to immunosuppression and postoperative complications remains controversial, there is enough data to suggest increased risk of postoperative complications in the setting of high dose corticosteroids, anti-TNF therapy, and vedolizumab to support a modified 2-stage or 3-stage approach for IPAA. The consequences are too great for long-term function not to take a conservative approach at the time of pouch construction. Future research efforts could focus on the window between immunosuppressive exposure and surgery, serum drug levels and postoperative complications, and the effect of combination immunosuppression. Until we have more detailed information which allows for a complex algorithm of which patient should receive which IPAA approach, it is safe to 3-stage immunosuppressed patients in order to avoid an increased risk of post IPAA complications.

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