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Outcomes of ileocolic resection and right hemicolectomies for Crohn's patients in comparison with non-Crohn's patients and the impact of perioperative immunosuppressive therapy with biologics and steroids on inpatient complications

Christopher Mascarenhas, M.D.^a, Robert Nunoo, M.D.^{b,*}, Theodor Asgeirsson, M.D.^c,
Rachelle Rivera, M.D.^c, Don Kim, M.D., F.A.C.S., F.A.S.C.R.S.^{a,c},
Rebecca Hoedema, M.D., F.A.C.S., F.A.S.C.R.S.^{a,c},
Nadav Dujovny, M.D., F.A.C.S., F.A.S.C.R.S.^{a,c},
Martin Luchtefeld, M.D., F.A.C.S., F.A.S.C.R.S.^{a,c}, Alan T. Davis, Ph.D.^{d,e},
Ryan Figg, M.D., F.A.C.S.^{a,c}

^aGrand Rapids Medical Education Partners/Michigan State University, ^bGrand Rapids Medical Education Partners, ^cSpectrum Health, ^dGRMEP Research Department, ^eMichigan State University Department of Surgery, 4100 Lake Dr. SE, Suite 205, Grand Rapids, MI 49546, USA

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Abstract

BACKGROUND: The purpose of this study was to compare medication use and complication rates between Crohn's disease (CD) and non-CD patients undergoing ileocolic resections and right hemicolectomies.

METHODS: A review of patients who underwent ileocolic resections and right hemicolectomies from January 1, 2003, through December 31, 2010, was performed. Data collected included demographics and clinical information, biologics use (eg, infliximab, adalimumab), other medication use (eg, steroids), complications, and mortality.

RESULTS: There were 791 records reviewed, with 93 CD patients. There was no significant difference in major or minor complications, anastomotic leaks, operating room time, or postoperative ileus occurrence between the CD and non-CD groups ($P > .05$). Use of biologics and steroids were significantly higher among the CD patients. Mortality, age, and American Society of Anesthesiologists score were significantly higher in the non-CD group.

CONCLUSIONS: Ileocolic resections and right hemicolectomies in CD patients are not associated with an increase in complication rates even when the patients use steroids and biologics in the preoperative period. © 2012 Elsevier Inc. All rights reserved.

Crohn's disease (CD) is a chronic, relapsing transmural inflammatory disease of the gastrointestinal mucosa. It can affect any portion of the gastrointestinal tract extending from the mouth to the anus. CD most commonly affects the terminal ileum and cecum. Many different strategies have been used to treat exacerbations, maintain remission, and prevent or delay surgery in patients with CD.¹

The authors report no conflicts of interest.

* Corresponding author. Tel.: +1-616-803-5030; fax: +1-616-267-7102

E-mail address: robertnun@hotmail.com

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Despite significant strides in medical management of CD, most patients still undergo surgery.² Surgery in patients with CD is frequently a challenge because of the associated inflammatory process resulting in abscesses, fistulous tracts, dense adhesions, and strictures. Many patients are often on immunosuppressive medications including steroids, immunomodulators, and biologics. There has been some conflict in the literature as to whether, compared with patients with non-inflammatory disease, serious postoperative complications develop more frequently in patients with CD.^{2,3} The aim of this study was to determine what our local experience has been.

Methods

A review of patients who underwent ileocolic resections and/or right hemicolectomies from January 1, 2003, through December 31, 2010, was performed. Approval for this study was obtained from the Spectrum Health Institutional Review Board. Data extracted from the medical record included age, sex, operating room time, major and minor complications, length of stay, medication use (eg, steroids, biologics), mortality, American Society of Anesthesiologists (ASA) score, and estimated blood loss (EBL). Only complications and mortalities that occurred within the first 30 days were included in this study. Major complications were defined as anastomotic leak, severe anemia, portal vein thrombosis, myocardial infarction, acute renal failure, sepsis and/or pneumonia, as well as any complications requiring surgical intervention or percutaneous drain placement. Minor complications were defined as fever, hematoma, wound infection, and/or urinary tract infections. Determination of Crohn's disease status was made based on preoperative biopsy. The original biopsy slides were not reviewed for the purposes of this study.

Upon initial review of the data, it was clear that there was a large difference in age between the CD and non-CD patients because of the difference in disease process for the 2 groups of patients. To negate any bias resulting from the significant age difference between the patients in the 2 groups, a further subset analysis was performed. Fifty randomly selected patients from the non-CD group were compared with the 93 patients with CD. The process of selecting the 50 non-CD patients is described later.

Because there were no CD patients older than age 75, none of the non-CD patients from this age group were selected. By contrast, because of the low number of non-CD patients younger than age 50 ($n = 27$), all of these subjects were included in the analysis. This left the age range from 50 through 75 years of age, from which 23 subjects were selected randomly to provide an overall sample of 50 subjects in the non-CD group. Although it was anticipated that the average age in this subgroup also would be significantly higher than in the CD group, it was thought that this value would be numerically closer than found for the non-CD group as a whole.

An additional subanalysis was performed on CD patients, comparing those who received biologics versus those who did

not. No minimum dose was required for inclusion because multiple differing doses of biologic therapy were used. The half-life of infliximab in CD patients is 8 to 10 days. Most patients treated with a dose of 5 mg/kg of infliximab have detectable antibody levels at 8 weeks, but not at 12 weeks.² This was the basis for requiring fewer than 12 weeks between the last dose of biologic therapy and surgery.

Statistical analysis of the data was conducted with the Statistical Package for the Social Sciences version 18.0 (SPSS, Chicago, IL). Quantitative data are expressed as the mean \pm SD, whereas nominal data are expressed as a percentage. Comparisons between treatment groups for quantitative data were performed using the 2-tailed *t* test, and for nominal data using the Fisher exact test. Statistical significance was assessed at a *P* value of less than .05.

Results

A total of 93 patients in our study sample had CD and 698 had noninflammatory bowel disease (non-CD group). All CD patients had Crohn's disease. In the non-CD group, 368 had malignant neoplasms, 257 had benign neoplasms, and 73 had another diagnosis (eg, angiodysplasia, fistulas, radiation, ostomies). Fifty-eight CD patients had ileocolic resections and 35 had right hemicolectomies. In the non-CD group, 38 patients had ileocolic resections and 660 had right hemicolectomies. Ten patients in the CD group received stomas, and of these 2 received biologics.

The mean age of patients with CD was statistically significantly greater than for those in the non-CD group (Table 1). A significant difference also was seen in mortality and the ASA grade, which were both higher in the non-CD cohort. There was no statistically significant difference in the length of hospital stay, surgical times, or incidence of major or minor complications. The mean difference in length of stay was 1 day longer for patients with CD, whereas the mean operating room time was 7 minutes longer in patients with CD.

Because of the great difference in age between the 2 groups, a subset analysis was performed, comparing the entire CD patient group with an age-adjusted non-CD group. The selection of subjects for this age-adjusted group was described in the Methods section. The results of the comparisons between the 2 groups are depicted in Table 2. Statistically significant differences between the groups were found for less mortality and younger age, as well as greater EBL and steroid use, in the CD group when compared with the non-CD group.

Of the 93 patients with CD, 19 patients were identified who had received biologic therapy within 3 months of surgery. There was no statistically significant difference between the 2 groups for any of the variables (Table 2). The anastomotic leak rate was specifically compared between the CD and non-CD groups and no statistically significant difference was identified (10.5% vs 4.1%, respectively; $P = .27$). Length of stay was numerically

Table 1 Demographic and clinical data for the CD and non-CD groups

	Crohn's disease (n = 93)	Non-Crohn's disease (n = 698)	P value
Age, y	36.7 ± 14.0	67.2 ± 13.1	.001
Male sex	36/93 (38.7%)	347/697 (49.8%)	.04
OR time, min	134 ± 75.1	127 ± 53.8	.43
Minor complication	5/93 (5.4%)	69/698 (9.9%)	.16
Major complications	5/93 (5.4%)	28/698 (4.0%)	.58
Length of stay, d	6.7 ± 6.2	6.0 ± 6.4	.26
ASA score	2.1 ± .4	2.3 ± .6	.001
Paralytic ileus	1/93 (1.1%)	23/698 (3.3%)	.35
EBL, mL	213 ± 160	165 ± 173	.04
Steroids	46/93 (49.5%)	26/698 (3.7%)	.001
Mortality	0/93 (.0%)	39/698 (5.6%)	.01

greater in the biologics group, but this did not achieve statistical significance ($P = .08$).

Comments

Surgery for patients with CD is always concerning because of the perceived increased risk for complications. The results of our study reveal that patients with CD are no more likely to have an adverse event than patients without CD undergoing a similar procedure. This held true for CD patients versus non-CD patients, as well as for CD patients versus the age-adjusted subgroup of non-CD patients.

The major limitation of this study was the disparity in mean age between the 2 cohorts, which resulted from the non-CD patients undergoing surgery for disease processes that occur in patients more advanced in age (eg, carcinoma, polyps). It would have been ideal to have had a fully age-matched group for comparison, but this would be difficult to achieve because of the entirely different nature of the pathology of the 2 groups. In our study, age matching

would have been extremely limiting to our sample size because of the minimal degree of overlap. Our compromise was to randomly select 50 non-CD patients from a younger age range. Although the mean ages of the 2 groups still were significantly different, it is worth noting that of the 6 variables (age, sex, ASA, EBL, steroids, mortality) that were significantly different between the 2 groups in the original analysis (Table 1), only sex and ASA were not still significantly different in the second analysis, using the younger age group (Table 2). Although certainly not definitive, these results tend to support our conclusions concerning complications. In addition to this concern, no comparisons between our 2 study groups were made with regards to nutritional state, metastatic disease, fistulas, local invasion, combined resection, or use of an extended right hemicolectomy.

Tumor necrosis factor is an important cytokine mediator of inflammatory bowel disease.⁴ Biologic agents such as infliximab (Remicaide; Schering Plough, Whitehouse Station, NJ) and adalimumab (Humira; Abbott Laboratories, Abbott Park, IL) are genetically engineered chimeric monoclonal antibodies to tumor necrosis factor. Biologic agents are a highly effective therapy in the armamentarium used to treat CD.⁵

Table 2 Demographic and clinical data for the CD group and the age-adjusted, randomly selected non-CD group

	CD (n = 93)	Non-CD (n = 50)	CD with biologics (n = 19)	CD without biologics (n = 74)
Age, y	36.7 ± 14.0*	50.1 ± 14.1*	35.6 ± 14.1	37.0 ± 14.1
Male sex	36/93 (38.7%)	21/50 (42.0%)	8/19 (42.1%)	28/74 (37.8%)
OR time, min	134.1 ± 75.1	127.7 ± 45.3	122.0 ± 46.8	137.0 ± 81.0
Minor complications	5/93 (5.4%)	2/50 (4.0%)	2/19 (10.5%)	3/74 (4.1%)
Major complications	5/93 (5.4%)	0/50 (.0%)	2/19 (10.5%)	3/74 (4.1%)
Length of stay, d	6.7 ± 6.2	5.5 ± 3.5	10.2 ± 10.2	5.9 ± 4.4
ASA score	2.1 ± .4	2.2 ± .6	2.1 ± .3	2.1 ± .5
Paralytic ileus	1/93 (1.1%)	2/50 (4.0%)	1/19 (5.3%)	0/74 (.0%)
EBL, mL	213 ± 160*	134 ± 65*	158.3 ± 112.5*	228.0 ± 168.2*
Steroids	46/93 (49.5%)*	3/50 (6.0%)*	13/19 (68.4%)	33/74 (44.6%)
Mortality	0/93 (.0%)*	3/50 (6.0%)*	0/19 (.0%)	0/74 (.0%)

OR = operating room.

*Significantly different at $P < .05$.

Appau et al¹ showed that biologic therapy can cause an increased risk of postoperative sepsis, abscess formation, and readmission rates. They suggested that diverting stomas might protect against these complications. Colombel et al² and Bordeianou et al⁶ showed no increase in complication rates or conversion rates to multistep procedures in patients on biologic therapy. We have performed a subset analysis of the outcomes in our patients with CD who received biologic therapy. An analysis of our data revealed no increase in leak rates or complication rates using biologic therapy. Although the values for all 3 of these variables were higher in the biologics group, these did not achieve statistical significance.

References

1. Appau KA, Fazio VW, Shen B, et al. Use of infliximab within 3 months of ileocolonic resection is associated with adverse postoperative outcomes in Crohn's patients. *J Gastrointest Surg* 2008;12:1738–44.
2. Colombel JF, Loftus EV Jr, Tremaine WJ, et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. *Am J Gastroenterol* 2004;99:878–83.
3. Bruewer M, Utech M, Rijcken EJ, et al. Preoperative steroid administration: effect on morbidity among patients undergoing intestinal bowel resection for Crohn's disease. *World J Surg* 2003;27:1306–10.
4. Marchal L, D'Haens G, Van Assche G, et al. The risk of post-operative complications associated with infliximab therapy for Crohn's disease: a controlled cohort study. *Aliment Pharmacol Ther* 2004;19:749–54.
5. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007;369:1641–57.
6. Bordeianou L, Kunitake H, Shellito P, et al. Preoperative infliximab treatment in patients with ulcerative and indeterminate colitis does not increase rate of conversion to emergent and multistep abdominal surgery. *Int J Colorectal Dis* 2010;25:401–4.

Discussion

Dr Mathew H. Chung (Grand Rapids, MI): Only about 20% of your Crohn's patients were on biologics, so was it

independently confirmed they had Crohn's disease to start with? Why were age-matched patients not better matched? Are you planning on a bigger study, perhaps in conjunction with another large colorectal program? Were any diverting stomas done, perhaps for high steroid doses?

Dr Christopher Mascarenhas (Grand Rapids, MI): Cases were not independently pathologically reviewed. We did our best to age match the patients, but ages were very different by disease type, so this was the best we could do. A larger study may be more robust. We actually excluded all patients who had diverting ileostomies.

Dr Imran Hassan (Springfield, IL): It is very interesting as a colorectal surgeon, we always struggle with patients on biologics and steroids. Is it not likely the people who are on high-dose steroids and are sick get diverted and the ones that do not get diverted are probably not on steroids for that long and are healthier? So you have to be careful when you make any assumptions from the study that it is patient selection that determines the outcome, and you have excluded these. Secondly, do you have patients stop the biologic agent or steroids before surgery?

Dr Mascarenhas: All those patients who received biologics more than 3 weeks before the operation were excluded from our study. That is one thing we did, so anyone who is included in the biologics group had received biologics within the last 3 weeks. As far as steroid taper goes, that depends on the referring gastroenterologist, but most patients did not receive any steroid taper before surgery.

Dr William C. Cirocco (Detroit, MI): Your leak rate was 10%, which is quite high. Also, what do you do with these patients postoperatively? Who makes the decision about continuing on the immunosuppression postoperatively?

Dr Mascarenhas: Postoperatively, we leave it up to the gastroenterologists treating these patients about how quickly to taper the steroids. That is the way it has characteristically been done in our practice.