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Evaluating the impact of infliximab use on surgical outcomes in pediatric Crohn's disease☆,☆☆,☆☆☆

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ABSTRACT

Background: The impact of infliximab (IFX) on surgical outcomes is poorly defined in pediatric Crohn's disease (CD). We evaluated our institution's experience with IFX on postoperative complications and surgical recurrence.
Methods: A retrospective review of children who underwent intestinal resection with primary anastomosis for CD from 1/2002 to 10/2014 was performed. Data collected included IFX use and surgical outcomes. Preoperative IFX use was within 3 months of surgery.
Results: Seventy-three patients were included with median age 15 years (range: 9–18). The most frequent indications for operation were obstruction (n = 26) and fistulae (n = 19). Nine patients (13%) had a surgical recurrence at a median of 2.3 years (IQR 0.7–3.5). Twenty-two patients received preoperative IFX at median of 26 days (IQR 14–46). There were 7 postoperative complications: 2 bowel obstructions, and 5 superficial wound infections. Outcomes of patients stratified by IFX were not different. When stratified by indication, refractory disease was associated with higher preoperative IFX use (IFX use 55% vs. no IFX use 28%, p = 0.027). No specific indication was associated with increased reoperation rates.
Conclusion: Pediatric CD patients treated with preoperative IFX undergo intestinal resection with primary anastomosis with acceptable morbidity. The heterogeneous approach to medical management underscores the need for guidelines to direct treatment.

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1. Background

The medical and surgical management of patients with Crohn's disease (CD) is complex and continually evolving with advances in therapy. While up to 70% of patients will require surgical intervention for treatment of Crohn's disease [1,2], the perioperative medical management plays a large role in influencing postoperative clinical course. Thus, medical and surgical therapies for Crohn's disease are closely intertwined and ideal therapy should aim to optimize both methods of treatment. Recent integration of infliximab (IFX), an anti-TNF alpha immunomodulator, into the medical regiment has positively impacted patients' clinical course through prolonged periods of remission [3–6]. Consequently, it was frequently prescribed to patients with moderate to severe Crohn's disease. However, there have been reports associating the use of IFX increasing postoperative complications [7–10].

While multiple large studies have been performed in adults to evaluate the effectiveness and complications of infliximab infusion in Crohn's disease, there is limited literature on the use of IFX in children or surgical outcomes related to IFX in children. Particularly, the effects of IFX in the perioperative and postoperative period following an intestinal resection are rarely described in the pediatric literature. To address this gap, we sought to evaluate our institutional experience with infliximab after intestinal resection in pediatric Crohn's disease. Predominantly, we aimed to evaluate postoperative surgical and wound complications as well as rate of reoperation in relation to IFX use.

2. Methods

2.1. Patient population

After institutional review board approval (H-31167), all children (≤18 years of age) with Crohn's disease who underwent initial intestinal resection with primary anastomosis at a single large referral center from January 2002 to October 2014 were included. Patients were identified through billing ICD-9 codes for Crohn's disease and chart reviews

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were conducted to confirm diagnosis of Crohn's disease via pathology reports. Patients with isolated perianal Crohn's disease, patients left in gastrointestinal discontinuity or with an enterostomy, and isolated stricturoplasties were excluded. In the majority of cases, the operative technique used was the laparoscopic approach with primarily extracorporeal stapled anastomosis through the umbilical port.

2.2. Infliximab administration

The pediatric gastroenterologist prescribed infliximab infusions to patients with moderate to severe Crohn's based on clinical criteria. When prescribed, IFX was typically administered every 8 weeks for a length of time that was to the discretion of the physician. For the purposes of our study, we defined preoperative administration of IFX use within 12 weeks of surgery as that is frequently the threshold described in literature [8,9,11]. Postoperative IFX infusion was also documented.

2.3. Study design and clinical variables of interest

This study is a retrospective chart review evaluating the impact of IFX on surgical outcomes after intestinal resection for Crohn's disease. Data collected included patient demographics, nutritional status at operation, disease details, perioperative steroid use, information on Infliximab infusion, and surgical outcomes. Nutritional status was determined through perioperative albumin and prealbumin levels. Details of the disease included location, perforating versus nonperforating disease, presenting symptoms, and indication for resection (obstruction, fistula, refractory disease). Surgical outcomes included long-term surgical recurrence defined as the need for a second surgical intervention in the same segment of bowel as the site of previous resection as well as postoperative complications. Postoperative surgical complications included superficial, deep and organ space surgical site infections, wound dehiscence, anastomotic leak, and small bowel obstruction occurring within 30-days of surgery. Long-term surgical recurrence was determined by following patients through to their most recent clinic visit.

2.4. Statistical analyses

Statistical analyses were performed using SPSS (Version 22.0, SPSS Inc., Armonk, NY). Univariate analyses were performed to evaluate the association between preoperative and postoperative IFX exposure and surgical outcomes (recurrence and postoperative complications). IFX exposure was further subdivided into four categories (preoperative IFX only, postoperative IFX only, both preoperative and postoperative IFX, and IFX-naïve). Continuous variables were analyzed using Student's t-test or Mann–Whitney-U, depending on data normality. One-way ANOVA was performed to compare means among multiple groups. Frequency distributions between categorical values were compared using χ^2-analysis. A p-value of <0.05 was deemed statistically significant.

3. Results

3.1. Patient characteristics and outcomes

Seventy-three patients met inclusion criteria at a median age of 15 years (range 9–18). 55% (n = 40) were males and mean weight at time of surgery was 47 ± 11.8 kg with median weight percentile of 10.8% (IQR 1.9–36.4). All patients underwent an intestinal resection and the most frequent resection was an ileocecectomy (n = 41). The indications for operation include obstructive symptoms (n = 35), fistulizing disease (n = 26), and refractory disease (n = 12). Sixteen patients (22%) had perforating disease identified intraoperatively. Sixty-nine patients (95%) had clinical follow-up over a median of 1.8 years (IQR 0.5–3.8). Seven patients had postoperative complications; five had superficial surgical site infections (SSI) successfully managed with antibiotics and two had small bowel obstruction managed nonoperatively. No patient developed deep/organ surgical site infection or anastomotic leak. Nine patients developed recurrence requiring a second abdominal operation at a median of 2.3 years (IQR 0.7–3.5) postoperatively.

3.2. Infliximab infusion

Twenty-four patients (33%) received preoperative IFX infusion at a median of 26 days (IQR 14–46) prior to their index operation. Twenty-six patients received postoperative IFX infusion beginning at a median time of 177 days (IQR 41–370) after surgery. The decision to place patients on postoperative IFX was determined through provider preference and indications varied among the gastroenterology providers. Twelve patients received both preoperative and postoperative IFX infusions.

3.3. Surgical outcomes stratified by infliximab exposure

Patients who received infusion of IFX prior to surgical resection (n = 22) were younger but had similar nutritional status and perioperative steroid use when compared to their counterparts who did not receive IFX (n = 51) (Table 1). Perioperative IFX did not significantly increase risk of postoperative complications nor did it decrease rate of recurrence or length of time to recurrence.

When stratified by postoperative IFX exposure, the 26 patients who received IFX after the surgery had no significant increase in long-term surgical recurrence rates (Table 2). Further subanalysis of the impact of postoperative IFX exposure in the nine patients with surgical recurrence revealed no significant difference in the time to recurrence between those who received postoperative IFX (n = 5) and those who did not (n = 4) (6.7 months (range 4.8–37) vs. 5.3 months (range 0.8–42), p = 0.456). All patients who developed a recurrence were adolescents (range 12.9–17.4 years) and most (n = 6) had obstructive etiology; none of the surgical recurrences had intraoperative identification of perforating disease at time of index resection and anastomosis.

Further evaluation of exact IFX treatment regimen revealed no differences in patient characteristics, nutritional status, or postoperative complications among the four groups (Table 3). The rate of surgical recurrence of Crohn's was equivalent among patient groups (Fig. 1).

4. Discussion

In this retrospective review of pediatric Crohn's disease, we evaluated the outcomes of children who underwent intestinal resection and analyzed surgical recurrence stratified by infliximab (IFX) use. We also assessed the possible effect of IFX use on postoperative complications. Our study revealed no significant difference in rate of surgical

Table 1
Patient characteristics, preoperative nutritional and medication status, and surgical outcomes stratified by preoperative Infliximab use.

Variables	Preoperative IFX (n = 22)	No IFX (n = 51)	p-value
Age (years), median (IQR)	15.1 (13.4–16.9)	16.8 (14.8–18)	**0.008**
Male gender, n (%)	13 (59)	27 (53)	0.628
Weight percentile at time of surgery, median (IQR)	4.43 (1.9–20.0)	14.6 (1.5–45.4)	0.418
Perioperative steroid use, n (%)	11 (50)	29 (57)	0.589
Albumin at time of operation, median (IQR)	3.9 (2.9–4.8)	3.4 (3.0–3.8)	0.176
Prealbumin at time of operation, median (IQR)	19.0 (8.6–19)	19.6 (11.1–27.1)	0.600
Perforating disease, n (%)	4 (18)	12 (24)	0.612
Postoperative complications, n (%)	2 (9)	5 (10)	0.924
Reoperation for recurrence, n (%)	2 (9)	7 (14)	0.562
Time to reoperation (years), median (range)	1.3 (0.6–2.1)	2.9 (0.3–5.0)	0.333

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