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Safety and Efficacy of Infusional Perioperative Tacrolimus Therapy in Crohn's Disease Patients Undergoing Intestinal Resection

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Keywords
Crohn's disease · Tacrolimus · Postoperative complications · Inflammatory bowel disease · Calcineurin inhibitor

Abstract
Introduction: Perioperative optimization of Crohn's disease (CD) patients is mandatory in order to ensure favorable outcomes and limit perioperative morbidity such as anastomosis-related complications. The use of perioperative tacrolimus may offer beneficial inflammatory control and improve postoperative outcome. However, it also may exhibit unwanted effects of immunosuppression on infectious complications and wound healing. ***Methods:*** This is a single-center, retrospective study of CD patients undergoing intestinal resection between 2009 and 2018. Characteristics of CD patients receiving infusional perioperative tacrolimus or not were systematically evaluated and exploratively compared. To investigate the impact of tacrolimus and other predictors on postoperative infectious complications, simple regression with a threshold of $p < 0.05$ was used. Significant predictors of the simple regression analysis, as well as tacrolimus, were then included into multiple logistic regression. ***Results:*** This analysis included 30 patients (34.88%) having received tacrolimus perioperatively and 56 patients (65.12%) that were not treated with tacrolimus. In median, 1 mg/day of tacrolimus was given intravenously for 11 days. Adverse events occurred in 3 patients (10%). The most common adverse events were headache and paresthesia. Tacrolimus showed no significant correlation to postoperative infectious complications. Furthermore, multiple regression analysis found no significant effect of tacrolimus on postoperative infectious complications when controlling for previously identified confounders. ***Conclusion:*** Administration of tacrolimus showed no negative impact on postoperative infectious complications in the study cohort, indicating safety of perioperative tacrolimus therapy. By describing in detail our study population of patients receiving perioperative tacrolimus, we provide data guiding future prospective studies.

Introduction

Despite the growing number of immunosuppressive agents available to treat Crohn's Disease (CD) patients, many of these patients require surgery at one point [1–3].

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Approximately 20–30% of the patients with CD, undergoing intestinal resection, develop at least one postoperative complication [4, 5]. The most feared complications are intra-abdominal septic complications, which include anastomosis leakage, enterocutaneous fistula and intra-abdominal abscess [6]. Studies have identified many risk factors for the occurrence of these postoperative complications, such as low albumin level, preoperative abscesses and previous resections [6]. Nonetheless, there is ongoing controversy regarding postoperative complications among patients treated with immunosuppressive therapy. It is well known that preoperative steroids can trigger postoperative complications [5, 6]. However, data are inconsistent when use of biologicals is investigated. Multiple studies, including a Cochrane review, found that preoperative anti-TNF therapy was in fact associated with a higher risk of morbidity after surgery for ileocolonic CD [7–9]. In contrast, more recent work from the REMIND group and the PUCCINI trial affirmed that preoperative anti-TNF therapy was not associated with an elevated risk of postoperative complications [5, 10]. On the contrary of possible negative outcomes, it is pathophysiologically plausible that luminal inflammatory control with immunosuppressive therapies could even be beneficial for the perioperative course of patients with CD undergoing intestinal resection. Hypothetically, immunosuppressive agents could have positive impact on the inflammatory status of the anastomosis and prevent the occurrence of postoperative anastomosis-related complications. For CD patients in need of urgent surgery, our department uses perioperative tacrolimus to control the luminal disease activity, in order to improve the postoperative outcome and delay disease recurrence.

Tacrolimus (FK 506) was isolated from *Streptomyces tsukubaensis* and used as an immunosuppressant in transplant patients [11]. As a calcineurin inhibitor, its immunomodulatory action is based on the ability to disrupt T-cell activation and cytokine expression, with 100 times higher potency than cyclosporine [12]. Tacrolimus exhibits a rapid onset, reaching peak blood concentrations within 0.5–4 h, similar to cyclosporine A, though with a tendency to act slightly faster [13]. Additionally, both tacrolimus and cyclosporine A have low oral bioavailability, requiring oral doses approximately 4 times higher than intravenous administration. The half-life of tacrolimus ranges between 4 and 40 h, depending on liver function, which is comparable to that of vyclosporine A [13]. Both drugs are mostly metabolized through the liver [14]. Rat models showed that after 48 h around 80% of tacrolimus is eliminated through the bile [14]. In the context of inflammatory bowel disease (IBD), much lower doses are administered. Yamatoto et al. [15] conducted a small observational study in patients with ulcerative colitis, demonstrating that orally administered tacrolimus at a dosage of 0.1 mg/kg achieved target blood levels of 10–15 ng/mL within 2–5 days.

The perioperative use of tacrolimus for inflammatory control in patients with CD is not mandated by national or international guidelines but extrapolated from studies on use of long- and short-term effects of tacrolimus as an immunosuppressant in patients with IBD. For instance, two RCTs using oral tacrolimus showed clinical response in patients with CU within 2 weeks [16, 17]. Interestingly, there were also significant short-term effects of tacrolimus on the secondary endpoint, the endoscopic mucosal healing, compared to Placebo [16]. In CD, positive effects of tacrolimus have been reported in observational studies [18–20]. Yet, there is only one RCT which revealed benefits of oral tacrolimus on the healing of perianal fistula in Crohn's patients within 4 weeks [21]. Moreover, experimental studies using mouse models indicate that tacrolimus might have beneficial effects on the healing of postoperative intestinal anastomosis [22, 23]. To our knowledge, no study on the use of perioperative tacrolimus in patients with CD has been performed yet. For this reason, the aim of this study is to systematically analyze our experience with tacrolimus in this setting, providing safety data and a detailed description of our study population and the tacrolimus protocol. Thereby, we add further evidence in the discussion of perioperative immunosuppression therapy in patients with CD.

Material and Methods

Study Design

This retrospective study included CD patients that received an intestinal resection between January 2009 and December 2018 at the University Hospital Marburg. A total of 97 cases were identified through database research by search terms "Crohn's Disease" and "intestinal resection." Eight patients appeared twice as they received a second surgery within the 10-year time frame. Of those patients, only the first resection was included in the analysis, resulting in 89 cases. Three patients had to be excluded as surgery was unrelated to the diagnosis of CD. Eighty-six patients were included into further study work-up. The study was approved as a retrospective observational analysis by the Ethics Committee of the University of Marburg. Digital and analog health records

were screened for relevant data, which were excerpted in pseudonymous form and then transformed into a data table based on Excel (Microsoft).

Definition of Study Parameters

Five groups of parameters were excerpted and documented: patient characteristics and inflammatory treatment, data on the surgical procedure itself, postoperative outcome, tacrolimus-related data and data on the clinical course after surgery. Preoperative data included patient characteristics such as age, sex, body mass index, serum albumin, and nicotine use. Preexisting conditions were documented and transformed into the Charlson-Comorbidity index, using an electronic calculator [24]. Preoperative ASA scale according to the American Society of Anesthesiologists was documented [25]. CD characteristics were documented according to the Montreal classification at time of admission for surgery [26]. Inflammatory activity at admission was assessed using serum CRP and clinical symptoms with regard to abdominal pain, diarrhea, and extraintestinal manifestations. Preoperative complications were grouped into intra-abdominal abscesses, intra-abdominal fistulae, intestinal stenoses, and preoperative sepsis/SIRS. Medication use within 8 weeks prior surgery was classified into aminosalicylates, immunosuppressives (azathioprine, 6-mercaptopurine, methotrexate), steroids, biologicals (infliximab, adalimumab, ustekinumab, and vedolizumab), and antibiotic therapy. Topical therapies were excluded from analysis. Concerning surgery, urgency was evaluated based on anesthesia protocols (elective, urgent within 6 h, and emergency). From a technical perspective, all ileocecal resections were executed as hand-sewn side-to-side anastomoses. Unexpected intraoperative adverse events included intraoperative bleeding and organ injury [4]. Further, we accessed the need for intraoperative blood transfusion. From pathology reports, inflammation in the resection margins as well as presence of epithelioid-like granulomas were documented. Concerning the postoperative phase, our standard therapy is as follows: For left-sided colon resections, a suction drain is placed, while no drains are used for small bowel or right-sided colon resections unless intraoperatively indicated. Patients are closely monitored with blood counts checked 4 h post-surgery and full laboratories on the 4th postoperative day. Clinical abnormalities prompt more frequent testing. Nasogastric tubes are removed on day 1, oral intake begins on the day of surgery, and drains are removed by day 7. Metronidazole is administered for 4 weeks, initially intravenously and then orally once tolerated. Regarding postoperative complications, we investigated infectious and noninfectious complications. Infectious complications were grouped into anastomosis-related complications (intrabdominal abscesses and fistulae, as well as anastomotic insufficiencies) and non-anastomosis-related infections (sepsis, wound infection, infectious ascites, peritonitis, and other infections such as pneumonia and urinary tract infection). Regarding noninfectious complications, we evaluated specific conditions such as postoperative ileus (POI), intra-abdominal bleeding and postoperative diarrhea. POI was defined as a modified version of Vather's et al. [27] definition by presence of one of these terms in medical records: intestinal atonia, intestinal paralysis, delay in oral feeding, nausea and vomiting, inflated abdomen, paralytic ileus. A period of 4 days has been suggested as a normal time frame for reestablishing oral feeding [27]. As our dataset did not permit the identification of the exact start day of oral feeding, the time interval before oral feeding was reintroduced was not used for defining POI.

Following a suggestion from Wolthuis et al. [28], POI was classified as prolonged POI (PPOI) if a gastric tube was placed, which then constituted a major complication. In general, postoperative complications were grouped according to the Clavien-Dindo-classification (CDC) into major (CDC >2) and minor complications (CDC ≤2) [29]. In case more than one complication was documented, the more severe one was included into data analysis. In case a noninfectious and an infectious complication were documented, the case was counted as an infectious complication. Only complications that developed in the postoperative setting were counted as postoperative, excluding instances of, e.g., sepsis that had already existed before surgery. Tacrolimus-related data included duration, dosing, mode of application, serum levels, side effects, and instances when tacrolimus was either paused or terminated. Recurrence of disease was evaluated based on case documentation in an interval of 2 years following surgery. Here, necessity of hospital admission due to clinical symptoms (abdominal pain, fistula, abscesses, stenosis, ileus) or for in-hospital work-up prior to a change in therapy (usually intensifying therapy) were assessed as postoperative, in-hospital recurrence. Independently of this clinical endpoint, digital files of endoscopic images were evaluated for postoperative endoscopic recurrence. Colonoscopies within a time frame of 2 years after surgery were included, and only cases after ileocecal resection were included. Here, blinded analysis by an experienced endoscopist according to the Rutgeerts score was performed [30].

Table 1. Tacrolimus data

Details of application	Use of tacrolimus
	yes (n = 30)
Tacrolimus doses, mg/day	
Median	1.00
Maximum	25.00
Minimum	0.70
Percentile 25	1.00
Percentile 50	1.00
Percentile 75	1.00
Missing data	0
Tacrolimus doses without outlier, mg/day	
Mean	1.12
Median	1.00
SD	0.76
Minimum	0.70
Maximum	5.00
Number of patients with Tacrolimus blood level estimation, n (%)	
No	23 (76.7)
Yes	7 (23.3)
Tacrolimus blood level, µg/L	
Mean	32.65
SD	44.54
Median	12.00
Maximum	120.43
Minimum	3.35
Missing data	23
Tacrolimus – total duration of application in days	
Mean	11
SD	5
Median	11
Maximum	24
Minimum	1
Missing data	0

Course of treatment	n (%)
Changing of dosage	
No	27 (90.0%)
Yes	3 (10.0%)
Reason for changing	
Unknown	2 (6.7%)
Adverse events	1 (3.3%)
Pausing the application	
No	28 (93.3%)
Yes	2 (6.7%)
Reason for pausing	
Unknown	0 (0%)
Infection	2 (6.7%)
Cancelling the application	
No	29 (96.7%)
Yes	1 (3.3%)
Reason for cancelling	
Unknown	0 (0%)
Infection	1 (3.3%)
Adverse events	
No	26 (86.7%)
Yes	3 (10.0%)
Feeling of inner warmness	1 (3.3%)
Paresthesia	2 (6.7%)
Nausea	1 (3.3%)
Headache	2 (6.7%)

Definition of Outcome

The study parameters were grouped into patients receiving perioperative tacrolimus and those not receiving tacrolimus. These two groups were exploratively compared. However, the primary aim of this study was to investigate if the perioperative use of tacrolimus (binary independent variable) shows an effect on the postoperative infectious complications (binary dependent variable) under the control of confounders. Due to the small range in doses and the limited sample size, binary scaling of tacrolimus was reasonable. After screening the data for the incidence of postoperative anastomosis leakage, we decided that the occurrence of these complications is not high enough to allow feasible statistical analysis. As a result, we decided to examine the impact of tacrolimus on the overall postoperative, infectious complications, having in mind that immunosuppressive therapy could lead to infections. Through this strategy, we aimed to provide safety data for further studies.

Statistical Analysis

Exploratory group comparisons based on nominal or ordinal variables were analyzed by Pearson's chi-squared tests. For expected frequencies smaller than five, we used the Fisher's exact Test. Continuous variables were evaluated for normal distribution graphically and by the Kolmogorov-Smirnov test. In the case of normal distribution, variables were analyzed by parametric tests, such as the t test. Otherwise, nonparametric tests, such as the Mann-Whitney U test, were used.

The impact of tacrolimus on the postoperative infectious complications was analyzed by multiple logistic regression. Potentially relevant predictors were identified by simple logistic regression. Those predictors with a significance level of $p < 0.05$ were then included in the multiple logistic regression analysis. To avoid overfitting, the number of predictors was limited to one per five events, resulting in three predictors for each model [31]. In order to explore the effects of all eight predictors identified in the simple regression analysis, we built six models each including tacrolimus and two other predictors. With this strategy, we aimed to investigate the impact of tacrolimus on postoperative infectious complications under the control of other cofounders, keeping possible suppressor effects of other independent variables in mind [32]. The fitting of the models was evaluated using Nagelkerke-R^2 (R^2[N]), Akaike's Information Criterion (AIC), and Hosmer-Lemeshow Test (HL-Test) [32, 33]. All our models were investigated for required assumptions, such as multicollinearity, outlier effects, independence, and linearity [32]. Statistical analysis was performed in cooperation with the Institute for Medical Bioinformatics and Biostatistics of the University of Marburg using SPSS (28.0.1.0) and *R* (*R*-4.3.0).

Results

Tacrolimus Therapy

Tacrolimus was given with a median dosage of 1 mg/day (Table 1). However, individual doses ranged from 0.7 to 25 mg/day. Due to the high range, we used a scatter plot to analyze the data points in detail. Hereby, the patient with a high dose of 25 mg/day was identified as an outlier. Calculation was repeated excluding this outlier, showing a mean dosage of 1.12 mg/day, close to the median of 1 mg/day. Tacrolimus was applied continuously using a 24-h perfusor, with a median dose of 1 mg delivered in 50 mL of NaCl at a median infusion rate of 2 mL per hour (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000542443). The perioperative duration of application was in median 11 days. In 7 patients (23.3%), serum tacrolimus levels were measured, with a median level of 12 µg/L. Two patients showed markedly higher levels: 1 patient with 120 µg/L and another with 66.9 µg/L. Upon further review of the data, it was found that the latter patient was the one that received an unusually high tacrolimus dose of 25 mg. This patient also experienced a postoperative wound infection and tacrolimus-associated side effects, including flushing. In total, 3 patients (10%) reported adverse events, which were documented as directly related to the tacrolimus therapy. These included headaches, paresthesia, nausea, and a feeling of inner warmness. In three cases (10%) the tacrolimus dosage was adapted, in two cases the therapy had to be temporarily interrupted (6.7%) and in one case, the therapy was cancelled completely (3.3%). The reported reasons for these adaptions were either adverse events related to the drug itself or infections in general, yet in other cases the reasons remained unknown.

Exploratory Group Comparison of Tacrolimus-Treated versus Untreated Patients

Of all 86 MC patients with intestinal resection in our dataset, 30 received tacrolimus perioperatively, and 56 did not (34.9% versus 65.1%). These two groups were analyzed for significant differences, according to patient characteristics and inflammatory treatment, data on the surgical procedure itself, postoperative outcome and data on the clinical course after surgery.

Patient characteristics and inflammatory treatment: With regard to the Montreal classification (Table 2) almost all patients that received tacrolimus had penetrating disease (B3: 96.7%, vs. 67.9%; $p = 0.002$) with a significant higher percentage of abscesses and fistulae (50.0% and 73.3% vs. 28.6% and 39.3%; $p = 0.049$ and $p = 0.003$, respectively). In general, patients in the tacrolimus group were significantly more often symptomatic (83.3% vs. 55.4%; $p = 0.010$) and fulfilled significantly more often the sepsis/SIRS criteria (23.3% vs. 3.6%; $p = 0.008$). CRP levels were significantly higher in the tacrolimus group ($p = 0.001$). Especially, very high CRP levels (>300 mg/L) were more often seen in the tacrolimus group (online suppl. Table 2). Patients in the tacrolimus group had a significantly lower percentage of patients receiving infliximab (13.3% vs 51.8%; $p < 0.001$; Table 3) Further, the use of high doses of prednisone within 8 weeks prior to surgery (≥20 mg per day) was significantly more prevalent in the tacrolimus group ($p < 0.001$). Perioperative use of antibiotics was associated significantly with tacrolimus application ($p = 0.002$). In the tacrolimus group, steroid use decreased from 70% preoperatively to 53.3% postoperatively (delta of 16.7%). In the no-tacrolimus group, the percentage decreased from 48.2% to 30.4% (delta of 17.8%; Table 3; online suppl. Table 3).

Surgery and intraoperative treatment: 93% of all patients received an ileocecal resection. Patients that required emergency surgery were significantly more often treated with tacrolimus than those patients that

Table 2. Baseline patient characteristics

	Use of tacrolimus			*p* value
	no (*n* = 56)	yes (*n* = 30)	total (*n* = 86)	
Sex, *n* (%)				
Female	27 (48.2)	12 (40.0)	39 (45.3)	0.466
Male	29 (51.8)	18 (60.0)	47 (54.7)	
Age at hospital admission, years				
Mean	39	36	38	0.452
SD	15	14	14	
Median	39	33	39	
Maximum	75	65	75	
Minimum	16	16	16	
Age at initial MC diagnosis, years				
Mean	31	29	30	0.402
SD	14	13	13	
Median	24	23	24	
Maximum	75	57	75	
Minimum	12	13	12	
Nicotine use, *n* (%)				
No	33 (58.9)	22 (73.3)	55 (64.0)	0.185
Yes	23 (41.1)	8 (26.7)	31 (36.0)	
ASA, *n* (%)				
1	4 (7.1)	2 (6.7)	6 (7.0)	0.690
2	31 (55.4)	15 (50.0)	46 (53.5)	
3	10 (17.9)	9 (30.0)	19 (22.1)	
4	3 (5.4)	2 (6.7)	5 (5.8)	
Previous intestinal resection, *n* (%)				
No	50 (89.3)	26 (86.7)	76 (88.4)	0.734
Yes	6 (10.7)	4 (13.3)	10 (11.6)	
Previous abdominal surgery, *n* (%)				
No	35 (62.5)	17 (56.7)	52 (60.5)	0.598
Yes	21 (37.5)	13 (43.3)	34 (39.5)	
Symptomatic, *n* (%)				
No	22 (39.3)	4 (13.3)	26 (30.2)	0.010*
Yes	31 (55.4)	25 (83.3)	56 (65.1)	
Abscesses, preoperative, *n* (%)				
No	40 (71.4)	15 (50.0)	55 (64.0)	0.049*
Yes	16 (28.6)	15 (50.0)	31 (36.0)	
Fistula, preoperative, *n* (%)				
No	34 (60.7)	8 (26.7)	42(48.8)	0.003*
Yes	22 (39.3)	22 (73.3)	44 (51.2)	
Stenosis, preoperative, *n* (%)				
No	21 (37.5)	15 (50.0)	36 (41.9)	0.263
Yes	35 (62.5)	15 (50.0)	50 (58.1)	
Sepsis/SIRS preoperative, *n* (%)				
No	54 (96.4)	23 (76.7)	77 (89.5)	0.008*
Yes	2 (3.6)	7 (23.3)	9 (10.5)	
Montreal: age at diagnosis, *n* (%)				
A1	3 (5.4)	3 (10.0)	6 (7.0)	0.737
A2	41 (73.2)	20 (66.7)	61 (70.9)	
A3	11 (19.6)	6 (20.0)	17 (19.8)	

Table 2 (continued)

	Use of tacrolimus			*p* value
	no (*n* = 56)	yes (*n* = 30)	total (*n* = 86)	
Montreal: location, *n* (%)				
L1	46 (82.1)	22 (73.3)	68 (79.1)	0.647
L2	4 (7.1)	3 (10.0)	7 (8.1)	
L3	6 (10.7)	5 (16.7)	11 (12.8)	
Montreal: location L4, *n* (%)				
No	56 (100.0)	30 (100.0)	86 (100.0)	
Yes	0	0	0	
Montreal: behavior, *n* (%)				
B1	0	0	0	0.002*
B2	18 (32.1)	1 (3.3)	19 (22.1)	
B3	38 (67.9)	29 (96.7)	67 (77.9)	
Montreal: perianal disease, *n* (%)				
No	53 (94.6)	30 (100.0)	83 (96.5)	0.549
Yes	3 (5.4)	0	3 (3.5)	
BMI, kg/m^2				
Mean	23.69	23.12	23.48	0.776
SD	4.91	4.28	4.67	
Median	23.14	23.33	23.15	
Maximum	35.34	34.57	35.34	
Minimum	15.17	16.07	15.17	
Missing data	3	0	3	
CRP at admission, mg/L				
Mean	63	120	85	0.001*
SD	92	126	109	
Median	16	82	38	
Maximum	310	416	416	
Minimum	0	10	0	
Missing data	12	2	14	
Albumin at admission, g/L				
Mean	34	34	34	0.309
SD	9	5	8	
Median	37	33	35	
Maximum	46	45	46	
Minimum	10	28	10	
Missing data	25	12	37	

ASA, American Society of Anesthesiologists Criteria; BMI, body mass index; CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome. *Significant variable to the <0.05 level.

went into surgery electively (64% vs. 26%; $p = 0.012$; Table 4).

Postoperative outcome: Overall, 34.9% of our population showed at least one of the observed postoperative complications, and 17.4% of patients had at least one infectious complication without significant differences between the groups ($p = 0.466$ and $p = 0.647$; Table 5). On detail analysis, amongst infectious complications wound infections were most frequent with 8.1%. The rate of anastomotic failures was low, both in the tacrolimus group (0%) and in the no-tacrolimus group (3.6%; $p = 0.540$). For noninfectious complications POI was most frequent (16.3%; 3.5% with a prolonged course). At a very low event rate, intra-abdominal fluid collection was found significantly different between tacrolimus-treated and untreated patients was ($p = 0.040$). In regards to the surgical outcome, death events after surgery were recorded once in the no-tacrolimus

Table 3. Anti-inflammatory and antibiotic treatment

	Use of tacrolimus						p values
	no (*n* = 56)		yes (*n* = 30)		total (*n* = 86)		
Aminosalicylate preoperative							
No	48	(85.7%)	26	(86.7%)	74	(86.0%)	1.000
Yes	8	(14.3%)	4	(13.3%)	12	(14.0%)	
Mesalazine preoperative							
No	48	(85.7%)	26	(86.7%)	74	(86.0%)	1.000
Yes	8	(14.3%)	4	(13.3%)	12	(14.0%)	
Sulfasalazine preoperative							
No	56	(100.0%)	30	(100.0%)	86	(100.0%)	
Yes	0	(0.0%)	0	(0.0%)	0	(0.0%)	
Immunosuppression preoperative							
No	32	(57.1%)	19	(63.3%)	51	(59.3%)	0.578
Yes	24	(42.9%)	11	(36.7%)	35	(40.7%)	
Metothrexate preoperative							
No	54	(96.4%)	29	(96.7%)	83	(96.5%)	1.000
Yes	2	(3.6%)	1	(3.3%)	3	(3.5%)	
Azathioprine preoperative							
No	35	(62.5%)	20	(66.7%)	55	(64.0%)	0.701
Yes	21	(37.5%)	10	(33.3%)	31	(36.0%)	
Mercaptopurine preoperative							
No	55	(98.2%)	30	(100.0%)	85	(98.8%)	1.000
Yes	1	(1.8%)	0	(0.0%)	1	(1.2%)	
Biologicals preoperative							
No	17	(30.4%)	22	(73.3%)	39	(45.3%)	<0.001*
Yes	39	(69.6%)	8	(26.7%)	47	(54.7%)	
Adalimumab preoperative							
No	46	(82.1%)	28	(93.3%)	74	(86.0%)	0.202
Yes	10	(17.9%)	2	(6.7%)	12	(14.0%)	
Vedolizumab preoperative							
No	55	(98.2%)	29	(96.7%)	84	(97.7%)	1.000
Yes	1	(1.8%)	1	(3.3%)	2	(2.3%)	
Ustekinumab preoperative							
No	56	(100.0%)	29	(96.7%)	85	(98.8%)	0.349
Yes	0	(0.0%)	1	(3.3%)	1	(1.2%)	
Infliximab preoperative							
No	27	(48.2%)	26	(86.7%)	53	(61.6%)	<0.001*
Yes	29	(51.8%)	4	(13.3%)	33	(38.4%)	
Steroids preoperative							
No	26	(46.4%)	9	(30.0%)	35	(40.7%)	0.139
Yes	30	(53.6%)	21	(70.0%)	51	(59.3%)	
Prednisolone preoperative							
No	29	(51.8%)	9	(30.0%)	38	(44.2%)	0.053
Yes	27	(48.2%)	21	(70.0%)	48	(55.8%)	
Prednisolone ≥20 mg/day preoperative							
No	45	(80.4%)	13	(43.3%)	58	(67.4%)	<0.001*
Yes	11	(19.6%)	17	(56.7%)	28	(32.6%)	
Budesonide preoperative							
No	47	(83.9%)	24	(80.0%)	71	(82.6%)	0.647
Yes	9	(16.1%)	6	(20.0%)	15	(17.4%)	
Antibiotics preoperative							
No	28	(50.0%)	5	(16.7%)	33	(38.4%)	0.002*
Yes	28	(50.0%)	25	(83.3%)	53	(61.6%)	

*Significant variable to the <0.05 level.

group, but not in the tacrolimus group. Revision surgery was needed once in both groups. Involvement of intensive or intermediate care was recorded in 21.4% of the untreated patients and 53.3% of the tacrolimus-treated patients ($p = 0.003$). Mean duration of the hospital stay was 14 ± 9 days in the no-tacrolimus group and 21 ± 12 days in the tacrolimus group ($p < 0.001$). Prednisolone and hydrocortisone were applied significantly more often in patients with tacrolimus therapy in the postoperative period ($p = 0.037$ and $p = 0.007$, respectively). At discharge, only antibiotics were significantly more often continued in patients with tacrolimus ($p = 0.007$; online suppl. Table 4).

Clinical course after surgery: In the 2 years clinical course post-surgery, 17 (19.8%) patients were readmitted in our hospital due to a disease recurrence; however, there is no significant difference between patients with or without tacrolimus therapy (Table 6). Postoperative endoscopy in this 2-year period was performed in 17 patients (19.8%) with a mean duration of 0.88 years (SD = 0.52) from the discharge until the endoscopy date. Rutgeerts score was evaluated in all endoscopies, revealing most patients showed an endoscopic recurrence, defined as i2 ($n = 6$), i3 ($n = 3$), or i4 ($n = 4$) [34], yet no significant differences between the tacrolimus and no-tacrolimus group were found.

Regression Analysis of Tacrolimus on the Postoperative Infectious Complications

Table 7 shows the independent variables, which had a significant impact on postoperative, infectious complications in simple regression. These variables were then integrated together with tacrolimus into six multiple regression models (Table 8). Throughout all six models, as well as in simple correlation analysis ($p = 0.767$; online suppl. Table 5), tacrolimus showed no significant influence on postoperative infectious complications, even

Table 4. Surgery and intraoperative treatment

	Use of tacrolimus						*p* value
	no (*n* = 56)		yes (*n* = 30)		total (*n* = 86)		
Type of surgery							
No Ileocecal resection	4	(7.1%)	2	(6.7%)	6	(7.0%)	1.000
Ileocecal resection	52	(92.9%)	28	(93.3%)	80	(93.0%)	
Urgency							
Elective	45	(80.4%)	16	(53.3%)	61	(70.9%)	0.012*
Urgent (within 6 h)	1	(1.8%)	1	(3.3%)	2	(2.3%)	
Emergent	5	(8.9%)	9	(30.0%)	14	(16.3%)	
Unexpected intraoperative adverse events							
No	53	(94.6%)	30	(100.0%)	83	(96.5%)	0.549
Yes	3	(5.4%)	0	(0.0%)	3	(3.5%)	
Perioperative blood transfusion							
No	49	(87.5%)	26	(86.7%)	75	(87.2%)	1.000
Yes	1	(1.8%)	0	(0.0%)	1	(1.2%)	
Stoma							
No	51	(91.1%)	27	(90.0%)	78	(90.7%)	1.000
Yes	5	(8.9%)	3	(10.0%)	8	(9.3%)	
Histology: inflammation at resection margins							
No inflammation	48	(85.7%)	25	(83.3%)	73	(84.9%)	0.564
One margin inflammation	8	(14.3%)	4	(13.3%)	12	(14.0%)	
Both margins inflammation	0	(0.0%)	1	(3.3%)	1	(1.2%)	
Granulomas in resection sample							
No	47	(83.9%)	26	(86.7%)	73	(84.9%)	1.000
Yes	9	(16.1%)	4	(13.3%)	13	(15.1%)	

*Significant variable to the <0.05 level.

under the control of other independent variables. All models showed no significant *p* values in the HL-test, indicating a good fit of the models. No evidence of strong multicolinearity between the variables could be found, shown by a low variance inflation factor (online suppl. Table 6). CRP at admission, ASA ≥3, sex and stoma formation were independent risk-factors for the occurrence of postoperative, infectious complications in multiple regression analysis. The urgency of surgery was found to be a significant predictor in model six, yet not in model one under the control of stoma formation and tacrolimus.

Discussion

In this single-center study, we found no negative effect of tacrolimus on postoperative infectious complications neither in simple correlation, nor in multiple regression analysis, indicating safety of perioperative tacrolimus therapy. To our knowledge, this is the first study that has investigated the perioperative use of intravenous tacrolimus on the postoperative outcome in patients with CD. There are only few small observational studies analyzing the effect of tacrolimus on postoperative complications in IBD patients. Although they did not find any negative impact of tacrolimus on the postoperative outcome, these studies were of smaller sample size than ours, focused on patients with ulcerative Colitis and did not use multiple regression with control of confounders [35, 36]. Here, our study contributes data on immunosuppressive tacrolimus therapy in a perioperative setting. In our study population, the rate of postoperative complications (32.8%) was comparable to other studies [4, 5]. Frequency of postoperative anastomosis leakage was lower in our study population (3.6%, Table 5) than in published cohorts, with reported incidences of postoperative intra-abdominal septic complications ranging from 8 to 13% [6, 37–39].

Table 5. Postoperative outcome

	Use of tacrolimus						*p* value
	no (*n* = 56)		yes (*n* = 30)		total (*n* = 86)		
Total number of complications							
No	38	(67.9%)	18	(60.0%)	56	(65.1%)	0.466
Yes	18	(32.1%)	12	(40.0%)	30	(34.9%)	
Infectious complications							
No	47	(83.9%)	24	(80.0%)	71	(82.6%)	0.647
Yes	9	(16.1%)	6	(20.0%)	15	(17.4%)	
Minor (CDC ≤2)							
No	50	(89.3%)	25	(83.3%)	75	(87.2%)	0.504
Yes	6	(10.7%)	5	(16.7%)	11	(12.8%)	
Major (CDC >2)							
No	52	(92.9%)	29	(96.7%)	81	(94.2%)	0.654
Yes	4	(7.1%)	1	(3.3%)	5	(5.8%)	
Wound infection							
No	52	(92.9%)	27	(90.0%)	79	(91.9%)	0.691
Yes	4	(7.1%)	3	(10.0%)	7	(8.1%)	
Sepsis							
No	55	(98.2%)	30	(100.0%)	85	(98.8%)	1.000
Yes	1	(1.8%)	0	(0.0%)	1	(1.2%)	
Abscess							
No	55	(98.2%)	29	(96.7%)	84	(97.7%)	1.000
Yes	1	(1.8%)	1	(3.3%)	2	(2.3%)	
Fistula							
No	56	(100.0%)	29	(96.7%)	85	(98.8%)	0.349
Yes	0	(0.0%)	1	(3.3%)	1	(1.2%)	
Anastomotic leakage							
No	54	(96.4%)	30	(100.0%)	84	(97.7%)	0.540
Yes	2	(3.6%)	0	(0.0%)	2	(2.3%)	
Other infections							
No	53	(94.6%)	28	(93.3%)	81	(94.2%)	1.000
Yes	3	(5.4%)	2	(6.7%)	5	(5.8%)	
Noninfectious complications							
No	45	(80.4%)	21	(70.0%)	66	(76.7%)	0.279
Yes	11	(19.6%)	9	(30.0%)	20	(23.3%)	
Minor (CDC ≤2)							
No	46	(82.1%)	22	(73.3%)	68	(79.1%)	0.339
Yes	10	(17.9%)	8	(26.7%)	18	(20.9%)	
Major (CDC >2)							
No	55	(98.2%)	28	(93.3%)	83	(96.5%)	0.278
Yes	1	(1.8%)	2	(6.7%)	3	(3.5%)	
Postoperative ileus (POI)							
No	47	(83.9%)	25	(83.3%)	72	(83.7%)	1.000
Yes	9	(16.1%)	5	(16.7%)	14	(16.3%)	
Prolonged postoperative ileus (PPOI)							
No	55	(98.2%)	28	(93.3%)	83	(96.5%)	0.278
Yes	1	(1.8%)	2	(6.7%)	3	(3.5%)	
Intra-abdominal bleeding							
No	55	(98.2%)	30	(100.0%)	85	(98.8%)	1.000
Yes	1	(1.8%)	0	(0.0%)	1	(1.2%)	
Intra-abdominal fluid collection							
No	56	(100.0%)	27	(90.0%)	83	(96.5%)	0.040*
Yes	0	(0.0%)	3	(10.0%)	3	(3.5%)	
Diarrhea							
No	54	(96.4%)	30	(100.0%)	84	(97.7%)	0.540
Yes	2	(3.6%)	0	(0.0%)	2	(2.3%)	

Table 5 (continued)

	Use of tacrolimus						*p* value
	no (*n* = 56)		yes (*n* = 30)		total (*n* = 86)		
Wound dehiscence							
No	56	(100.0%)	29	(96.7%)	85	(98.8%)	0.349
Yes	0	(0.0%)	1	(3.3%)	1	(1.2%)	
Death post-surgery							
No	55	(98.2%)	30	(100.0%)	85	(98.8%)	1.000
Yes	1	(1.8%)	0	(0.0%)	1	(1.2%)	
Revision surgery							
No	55	(98.2%)	29	(96.7%)	84	(97.7%)	1.000
Yes	1	(1.8%)	1	(3.3%)	2	(2.3%)	
Intermediate/intensive care							
No	44	(78.6%)	14	(46.7%)	58	(67.4%)	0.003*
Yes	12	(21.4%)	16	(53.3%)	28	(32.6%)	
Total duration of hospital stay, days							
Mean	14		21		17		<0.001*
SD	9		12		11		
Median	11		20		12		
Maximum	50		74		74		
Minimum	4		9		4		
Missing	0		0		0		
Preoperative duration of hospital stay, days							
Mean	3		8		5		0.002*
SD	6		12		9		
Median	1		5		1		
Maximum	28		60		60		
Minimum	0		0		0		
Missing	0		0		0		
Postoperative duration of hospital stay, days							
Mean	11		13		12		0.008*
SD	6		6		6		
Median	9		11		10		
Maximum	36		31		36		
Minimum	3	8		3			
Missing	0		0		0		

CDC, Clavien-Dindo classification; SD, standard deviation. *Significant variable to the <0.05 level.

Besides multiple regression analysis, a strength of this study is the detailed description of patients receiving tacrolimus and those who did not, as well as analyzing the tacrolimus therapy protocol in depth. In summary, tacrolimus was more often used in sicker patients with a complicated, inflammatory active disease, who were more often treated with steroids. We could not identify any signs of tacrolimus having a large positive or negative impact on the postoperative outcome, as well as on the further postoperative course. The absence of a worse outcome in a sicker study sub-cohort (that received tacrolimus) supports the safety of tacrolimus therapy and might indicate beneficial efficacy. However, this is rather hypothetical and would need verification in a prospective study.

Further, perioperative tacrolimus might be particularly helpful in patients on steroids with a highly inflammatory disease phenotype. RCTs have shown that tacrolimus could be effective in steroid-dependent or steroid-refractory patients with IBD [17]. Thus, tacrolimus might exert beneficial efficacy by allowing reduction of steroid treatment perioperatively, as steroids have a well-documented negative impact on postoperative complications [6, 7]. In our analysis, both groups

Table 6. Data on the clinical course post-surgery

	Use of tacrolimus			*p* value
	no (*n* = 56)	yes (*n* = 30)	total (*n* = 86)	
Disease recurrence with hospitalization				
No	44 (78.6%)	24 (80.0%)	68 (79.1%)	1.000
Yes	11 (19.6%)	6 (20.0%)	17 (19.8%)	
Endoscopy data				
No	46 (82.1%)	22 (73.3%)	68 (79.1%)	0.256
Yes	9 (16.1%)	8 (26.7%)	17 (19.8%)	
Years until endoscopy				
Mean	0.89	0.87	0.88	0.963
SD	0.58	0.49	0.52	
Median	0.90	0.75	0.83	
Maximum	1.86	1.61	1.86	
Minimum	0.22	0.20	0.20	
Missing data	47	22	69	
Rutgeers-score				
i0	3	1	4	0.733
i1	1	0	1	
i2	3	3	6	
i3	1	2	3	
i4	1	2	3	

Table 7. Significant variables to the <0.05 level in simple regression

Variables	*p* value	OR	95% CI
Sepsis preoperative	0.035	4.800	1.113–20.700
ASA ≥3	0.015	4.700	1.342–16.456
Urgency	0.018	2.190	1.142–4.197
Stoma	0.003	11.333	2.340–54.901
CRP at admission	0.007	1.007	1.002–1.012
Sex	0.04	4.114	1.069–15.839
Postoperative duration of hospital stay, days	<0.001	1.276	1.116–1.459
Intermediate (IMC)/intensive care (IC)	0.004	5.889	1.775–19.538

OR, odds ratio; CI, confidence interval.

showed similar reduction of steroid use from pre- to postoperative phase. However, the tacrolimus group showed more complicated disease behavior and higher preoperative use of steroids. This suggests that tacrolimus may indeed help reduce the need for continued steroid therapy even in more complex cases. We suggest that tacrolimus may help manage steroid-dependent cases, particularly in those with less controlled luminal inflammation and elevated CRP levels. Further research is required to determine the long-term clinical significance of this finding.

In our cohort, tacrolimus was less often administered in patients previously treated with infliximab, probably due to concerns about combining potent immunosuppressants. Only 6 of 30 patients in the tacrolimus group had received anti-TNF therapy, compared to 39 of 56 in the no-tacrolimus group. This pattern was not seen with other agents like Ustekinumab, Vedolizumab,

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Table 8. Multiple regression

Variables	Model 1			Model 2			Model 3			Model 4			Model 5			Model 6		
	p value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI
Tacrolimus	0.764	1.235	0.311–4.901	0.551	0.628	0.136–2.905	0.659	1.344	0.361–4.998	0.205	0.377	0.083–1.704	0.277	0.449	0.106–1.903	0.954	0.958	0.233–4.114
Sepsis preoperative													0.644	1.582	0.226–11.060			
ASA ≥3							0.046[b]	3.794	1.027–14.013									
Urgency	0.140	1.761	0.831–3.733													0.046[b]	2.193	1.015–4.738
Stoma	0.012[b]	8.445	1.602–44.519															
CRP at admission										0.005[c]	1.008	1.002–1.014	0.010[b]	1.007	1.002–1.013			
Sex							0.041[b]	5.422	1.071–27.453	0.059[a]	4.239	0.945–19.008				0.023[b]	6.539	1.294–33.053
Postoperative duration of hospital stay				0.004[c]	1.262	1.076–1.479												
IMC/IC				0.653	1.484	0.266–8.291												

Fitting	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
AIC	69.328	64.311	66.020	66.105	70.027	68.851
R^2(N)	0.230	0.393	0.235	0.260	0.186	0.239
HL-Test (*p* value)	0.787	0.333	0.684	0.501	0.560	0.640
Missing data	9	0	10	14	14	9

AIC, Akaike's Information Criterion; R^2(N), Nagelkerkes R^2; HL-Test, Hosmer-Lemeshow Test; OR, odds ratio; CI, confidence interval. [a]$p < 0.1$; [b]$p < 0.05$; [c]$p < 0.01$.

or Azathioprine. We propose that the decision to add tacrolimus to an ongoing infliximab therapy should be based on the luminal disease activity and therefore on the immunosuppressive efficacy of infliximab therapy in an individual patient. In a patient whose luminal disease activity is clearly not controlled (based on e.g., high CRP levels), concomitant tacrolimus therapy in addition to infliximab might be beneficial.

In published literature, CRP was identified as a predictor for postoperative intra-abdominal-septic complications [40]. Further, high CRP levels correlated well with effective response to immunosuppressive therapy in CD [41]. In our study, models 4 and 5 (Table 8) show lower *p* values, a reduced odds ratio, and tighter confidence intervals for tacrolimus, indicating a potential trend toward reducing postoperative infectious complications. This effect may be linked to CRP, a highly significant predictor in both models. A new model calculation was conducted using an interaction term between tacrolimus and CRP to evaluate the potential moderating effect of CRP on the relationship between tacrolimus and postoperative infectious complications (online suppl. Table 7). However, this effect did not achieve statistical significance. Given the study's small sample size, there is a high likelihood of a Type II error. In larger cohorts, this effect might be significant.

After outlier exclusion, the tacrolimus dosage in our population was comparable to the dose used in other studies (see online suppl. Table 8 for dose distribution) [19, 42]. Documented adverse events occurred comparably rare and were of low severity [18, 20]. As a caveat, frequency of tacrolimus serum level measurements, as recommended in other studies [16, 17], was low. Regarding the outliers, our results show that a high tacrolimus dosage, likely due to a dosing error, led to elevated blood levels. In these cases, adverse events and postoperative infectious complications occurred, yet they were of low severity. However, it is also possible that these complications were related to the overall higher severity of the patient's conditions (elevated CRP, high-dose steroid therapy, ICU admission). These findings highlight the need for close tacrolimus monitoring, especially in complex cases.

Cost analysis is a relevant factor in guiding therapeutic decisions. The most important cost factor in both groups was length of hospital stay. Patients in the tacrolimus group stayed in mean 21 days in hospital (range = 9–74 days; standard deviation [SD] = 12 days), whereas no-Tac patients stayed 14 days (range = 4–50 days; SD = 9 days). Cost of one hospital day has been calculated as EUR 1,048 (for 2022 at a hospital with >1,000 beds [43]). This would result in a total cost for the hospital stay of EUR 22,000 in the Tac group and EUR 14,600 in the no-Tac group. However, due to a more severe disease course in the tacrolimus group, which directly affects the length of hospital stay and consequently the overall costs, group comparison of mean expenses is biased. Nevertheless, tacrolimus itself is costly; one ampulla of tacrolimus with 5 mg cost EUR 61.92. As perfusor therapy requires 1 ampulla per day in a normal clinical setting (irrespective of the final dosage, which was mostly 1 mg/day), the total course of tacrolimus therapy for a mean of 11 days costs EUR 681.

There are several limitations of this study. First, due to the the small sample size and the limited number of infectious postoperative complications, we were not able to enter all significant variables into one multiple regression model, which might have shown different results. Moreover, the small sample size only allows the detection of larger effects of tacrolimus on postoperative infectious complications [32]. Second, results from explorative group comparison have to be interpreted with caution, due to the heterogeneity of the groups and because we did not control for multiple testing. Lastly, there is always the possibility of omitted variable bias in retrospective studies.

Conclusion

Despite the limitations of this small observational study, we provide safety data and a detailed analysis of perioperative variables characterizing the use of tacrolimus in patients with CD in need of urgent intestinal resection.

Statement of Ethics

The study was reviewed and approved on July 31 (2020) as a retrospective observational analysis by the Ethics Committee of the University of Marburg. There were no ethical or professional objections to the project. As this is a purely retrospective analysis using strictly anonymized and routinely collected patient data, the Ethics Committee approved our protocol without requiring individual patient consent for the retrospective analysis (Identification code: EK_MR_31_07_20_bauer).

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Conceptualization and writing – original draft preparation: C.B. and M.B.; methodology and visualization: C.B., M.B., and N.S.; software and formal analysis: M.B. and N.S.; investigation: D.B., M.A., J.G., C.B., and N.K.; writing – review and editing, D.B. and T.G.; supervision: D.B., T.G., and C.B.; all authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Due to considerations of privacy, the data from this study are not publicly accessible but are kept in pseudonymous form and are available from the corresponding author (Christian Bauer and Maximilian Beck), upon reasonable request.

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