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No survival advantage exists for patients undergoing loop ileostomy for clostridium difficile colitis

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ABSTRACT

Background: We aim to compare outcomes between loop ileostomy (LI) and total abdominal colectomy (TAC) for clostridium difficile infection (CDI) and hypothesize that LI is associated with fewer complications.

Methods: The 2011–2016 ACS-NSQIP database was queried for patients undergoing LI or TAC for CDI. Patients with high outlying age, LOS, and operative time were excluded. Statistics were performed using IBM-SPSS and NCSS PASS-11.

Results: Of 457 patients identified, 47 underwent LI. Predicted morbidity was higher in the TAC cohort (62% vs. 37%, $p < 0.001$). Patients in the LI cohort experienced fewer complications (72% vs. 87%, $p = 0.021$); however, mortality did not differ between LI (36%) and TAC (31%). Blood transfusions were more than twice as frequent in the TAC cohort (54% vs. 19%, $p < 0.001$). Four patients in the LI cohort required reoperation; however, none required colectomy.

Conclusions: No mortality difference was observed between LI and TAC. Prospective studies are required to determine the utility of LI.

Summary: An analysis of the ACS-NSQIP database was performed and demonstrates that no survival benefit exists for patients who undergo loop ileostomy for C *difficile* infection compared to those who undergo total colectomy; however, patients who undergo loop ileostomy are likely to retain their colon with low risk of requiring subsequent colectomy.

Introduction

Clostridium difficile is an increasingly common source of healthcare-acquired infection.[1] For most patients, oral or parenteral antibiotic therapies are sufficient treatment for C. *difficile* infection (CDI), and few ultimately require surgical intervention for definitive source control. An analysis of the Nationwide Inpatient Sample (2001–2010) by Halabi and colleagues demonstrated that less than 1% of patients treated for CDI during a hospital admission required surgical intervention; however, over this period, the incidence and need for surgical intervention were noted to have increased by 47% and 32%, respectively.[2] Patients who require surgical intervention often undergo a rectal-sparing total abdominal colectomy with end ileostomy (TAC). In this setting, TAC has a high mortality rate, ranging from 23 to 80%.[2–16] Compared to other indications for emergent surgery, CDI is distinguished in that it is a progressive disease, often worsening over days to weeks prior to surgical intervention. As such, alternative surgical approaches, including the formation of a loop ileostomy (LI) for antegrade therapies, are being evaluated for their safety and efficacy in this setting.

In 2011, Neal and colleagues published outcomes of 42 patients with fulminant CDI who underwent formation of a LI permitting intraoperative antegrade polyethylene glycol lavage and post-operative vancomycin flushes. This approach was associated with a significantly lower mortality rate (19%) compared to their historical cohort (50%) that underwent TAC. These findings stimulated significant discussion regarding the utility of this approach; however,

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no studies have reproduced these results.

Given the infrequent occurrence of surgical intervention for CDI, little evidence supports or refutes the safety and efficacy of LI in the treatment of CDI. In consideration of this, we aim to analyze the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database to determine the safety and efficacy of LI compared to TAC in patients who underwent surgical intervention for CDI. We hypothesize that LI is associated with lower morbidity and mortality rates compared to TAC.

Materials and methods

Database description

The American College of Surgeon National Surgical Quality Improvement Program (ACS-NSQIP) prospectively collects clinical data from patients undergoing surgery at any of several hundred participating hospitals, with most located in the United States. Data are collected by Surgical Clinical Reviewers who receive specialized training and are regularly audited for accuracy. Data are used for benchmarking purposes and serve to improve the quality of surgical care that is delivered to patients. The ICD-9-CM diagnosis coding system was utilized for years 2005–2015 whereas the 2016 database utilized the ICD-10-CM diagnosis coding system.

Study design

The 2011–2016 ACS-NSQIP database was queried for patients who underwent TAC or LI for CDI. Considering that LI for CDI was proposed as alternative to TAC in 2011 by Neal and colleagues, we limited data collection to surgeries performed during or after that year.[8] Patients were included if they had a postoperative diagnosis of "enterocolitis due to clostridium difficile" as defined by ICD-9-CM or ICD-10-CM diagnostic codes 8.45 or A04.7 in the variables named PODIAG and PODIAG10, respectively. Using CPT codes, we identified patients who underwent open (CPT 44310) or laparoscopic (CPT 44187) LI formation without a concurrent partial (CPT 44140–44147, 44160, 44204–44208) or total (CPT 44150–44158, 44210–44212) colectomy. Our TAC cohort included patients undergoing either an open (CPT 44150) or laparoscopic (CPT 44210) approach (Fig. 1). Patients who underwent exploratory laparotomy (CPT 49000) or diagnostic laparoscopy (CPT 49320) were included in the LI cohort if a LI was formed concurrently and in the absence of a colectomy. Patients who underwent exploratory laparotomy or diagnostic laparoscopy were included in the TAC cohort if a TAC was performed concurrently.

Statistical analysis

Patient demographics, perioperative variables, and postoperative outcomes were analyzed. Patients were excluded if they had high outlying (>95th percentile) length of stay (LOS, >55 days), age (>86 years), and operative time (>262 min) (Fig. 1). Descriptive statistics including Pearson's Chi-Square test, Fisher's exact test, Student T-test, and Mann-Whitney *U* test were performed using IBM SPSS v.23.0, with $\alpha = 0.05$. Descriptive statistics were reported as frequencies and continuous variables were reported as mean or median ± standard deviation (SD). A complete listing of complications and their definitions can be found in Supplemental Table 1. Preoperative probabilities of morbidity and mortality were analyzed to evaluate for potential selection bias. These probabilities are based on a logistic regression analysis of multiple patient characteristics and are included for every patient in the ACS-NSQIP database.

Power analyses were performed using NCSS PASS 11. To determine the minimum sample sizes needed to identify significant survival benefit for patients undergoing LI, five analyses were performed for varying levels of absolute risk reduction (ARR) (5%, 10%, 15%, 20%, and 25%) in patients undergoing LI. For these calculations, a fixed 30% mortality rate for patients undergoing TAC was assumed. All power analyses were performed with $\alpha = 0.05$ and $\beta = 0.20$ using a two-sided Z test with continuity correction and unpooled variance.[17]

Results

Patient characteristics

Of 457 patients, 10% underwent LI ($N = 47$) and 90% underwent TAC ($N = 410$) (Table 1). Mean age, gender and BMI did not differ between groups. Most patients in the study were Caucasian (74%), but race did not differ between groups. Most patients had ASA scores of 4 or 5 (76%) with similar distribution observed between groups. No differences in comorbid conditions were seen with regards to dyspnea, congestive heart failure, chronic obstructive pulmonary disorder, diabetes, ascites, bleeding disorder, smoking status, chronic steroid use or dialysis-dependence (Table 1). Preoperative functional status did not differ between groups as most patients in both the LI (77%) and TAC (71%) cohorts were independent prior to admission. Predicted preoperative morbidity was higher in the TAC group (62% vs. 37%, $p < 0.001$); however, predicted preoperative mortality did not differ between LI (37%) and TAC (44%) (Table 1). Mean preoperative WBC count (27.3 vs. 25.7), hematocrit (34.3 vs. 34.2), platelets (280 vs. 254), sodium (136 vs 136), creatinine (1.9 vs. 2.0), albumin (2.3 vs. 2.2), and INR (1.4 vs. 1.6) did not differ between LI and TAC cohorts, respectively (all $p > 0.05$).

Perioperative variables

Of the 47 patients who underwent LI, most were performed via a laparoscopic approach ($N = 30$, 64%) whereas nearly all the patients who underwent TAC had an open procedure ($N = 392$, 96%) ($p < 0.001$). An equivalent proportion of surgeries were classified as emergent between LI (75%) and TAC (80%). Median operative times were significantly less in patients undergoing LI (1.6 h vs. 2.2 h, $p < 0.001$) (Table 2).

Postoperative outcomes

Most patients in both the LI (72%) and TAC (87%) groups experienced at least one complication ($p = 0.021$). A similar number of patients in the LI and TAC groups experienced cardiovascular complications (15% vs. 9%), respiratory complications (47% vs. 54%), infectious complications (55% vs. 59%), thromboembolic complications (4% vs. 10%), renal failure (15% vs. 11%), and surgical site infections (2% vs. 11%), respectively. Patients who underwent TAC were more than twice as likely to receive a blood transfusion (54% vs. 19%, $p < 0.001$) (Table 3). Mean length of stay was similar between LI (19 days) and TAC (20 days) as were readmission rates (9% vs. 13%), respectively. Mortality was not significantly different between LI (36%) and TAC (31%) ($p = 0.451$) (Table 3). Annual mortality for all patients ranged from 25% (2011), 27% (2012), 33% (2013), 33% (2014), 24% (2015), and 41% (2016) ($p = 0.198$).

Reoperations and indications

Reoperation rates were similar for patients undergoing LI (9%) compared to TAC (11%). Of the four patients who required reoperation in the LI group, no patient was seen to undergo colectomy.

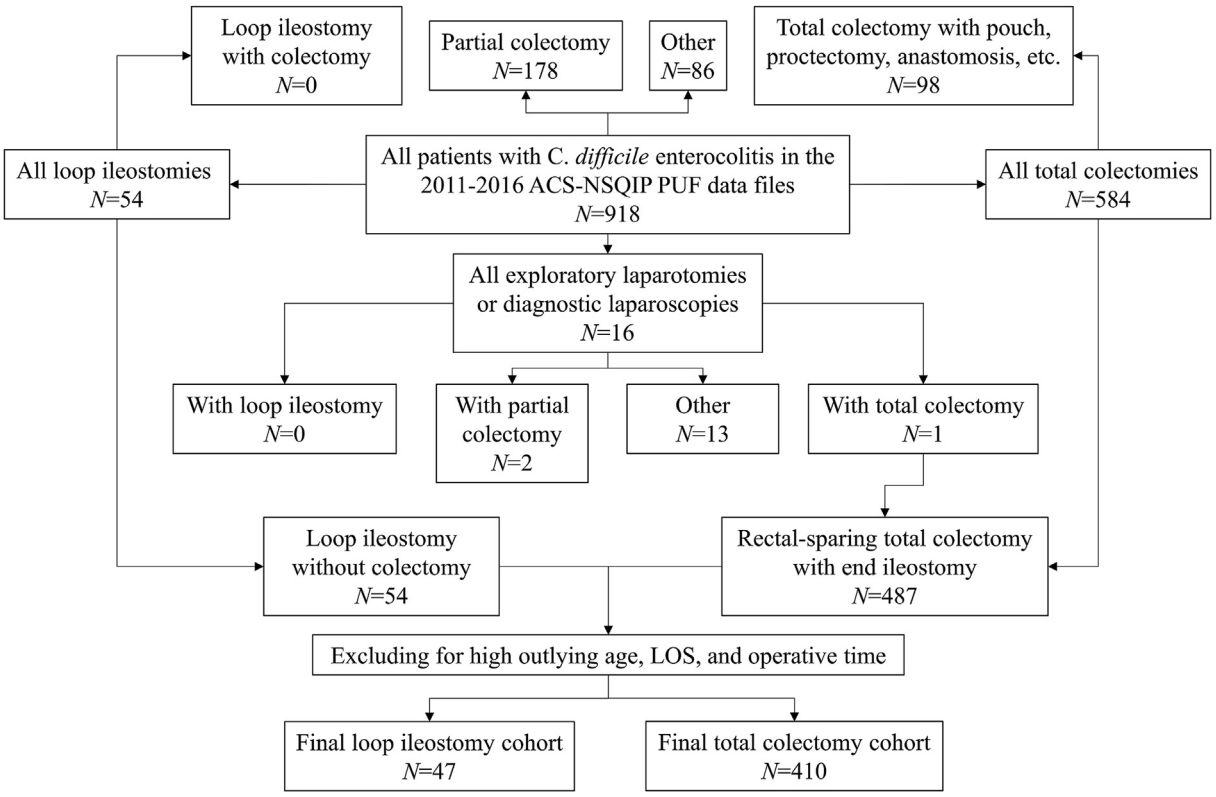

Fig. 1. Flowchart depicting the method for inclusions of patients based on CPT codes.

Table 1
Patient characteristics.

	LI		TAC		*p*-value
	N	%	*N*	%	
Total number of patients	47	10.3%	410	89.7%	N/A
Age (years, mean)	64.8 ± 14.1	N/A	65.4 ± 14.2	N/A	0.795
BMI (mean)	26.2 ± 10.6	N/A	26.5 ± 9.8	N/A	0.855
Gender					0.116
Male	15	31.9%	180	43.9%	
Female	32	68.1%	230	56.1%	
Race					0.521
Caucasian	35	81.4%	304	84.2%	
African-American	6	14.0%	50	13.9%	
Other	2	4.7%	7	1.9%	
ASA score					0.064
None assigned	1	2.1%	1	0.2%	
2	0	0%	10	2.4%	
3	14	29.8%	85	20.7%	
4	28	59.6%	235	57.3%	
5	4	8.5%	79	19.3%	
Comorbid conditions					
Dyspnea	9	19.1%	82	20.0%	0.890
CHF	3	6.4%	37	9.0%	0.785
COPD	10	21.3%	106	25.9%	0.495
Diabetes	10	21.3%	79	19.3%	0.742
Ascites	5	10.6%	54	13.2%	0.624
Bleeding disorder	6	12.8%	92	22.4%	0.126
Dialysis dependent	5	10.6%	53	12.9%	0.655
Functional status before surgery					0.420
Independent		34	77.3%	288	71.3%
Partially dependent		9	20.5%	86	21.3%
Totally dependent		1	2.3%	30	7.4%
Smoker	8	17.0%	87	21.2%	0.502
Chronic steroid use	10	21.3%	76	18.5%	0.649
Predicted preoperative morbidity	37.3% ± 16.1%	N/A	61.7% ± 14.9%	N/A	<**0.001**
Predicted preoperative mortality	37.0% ± 27.9%	N/A	44.0% ± 27.9%	N/A	0.103

Table 2
Perioperative variables.

	LI		TAC		*p*-value
	N	%	*N*	%	
Total number of patients	47	10.3%	410	89.7%	N/A
Surgical approach					<**0.001**
Open	17	36.2%	392	95.6%	
Laparoscopic	30	63.8%	18	4.4%	
Emergent surgery	35	74.5%	329	80.2%	0.352
Operative time (hours, median)	1.6 ± 0.6	N/A	2.2 ± 0.8	N/A	<**0.001**

Two of the four patients required exploratory laparotomy (both related to CDI with one indicated for compartment syndrome); however, no additional procedures were performed at that time. The third patient required tracheostomy for respiratory failure and the fourth patient underwent two separate reoperations, neither of which were recorded. Of the 43 patients who underwent reoperation after TAC, the most common procedures were exploratory laparotomy ($N = 12$) and tracheostomy ($N = 6$). The most common indications for reoperation in the TAC were hemorrhage ($N = 4$), wound dehiscence ($N = 4$) and acute respiratory failure ($N = 3$).

Power analysis

To determine the sample size needed to detect a significant difference in mortality, power analyses were calculated for varying magnitudes of ARR in mortality for patients undergoing LI using a fixed mortality rate of 30% for patients undergoing TAC. If LI-associated mortality was assumed to be 25% (ARR 5%), 15% (ARR 15%), or 5% (ARR 25%), then 1,288, 131, or 39 patients would be needed in each treatment group to detect a significant difference in mortality with 80% power, respectively (Fig. 2). Given that we had 47 patients in the LI cohort, this study would have been adequately powered to detect a difference only if mortality the observed mortality in the LI cohort was less than approximately 5% (ARR ~25%) (Fig. 2).

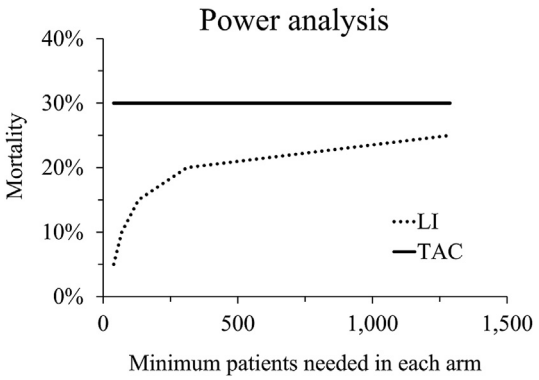

Fig. 2. Line graph depicting the number of patients in each study arm needed to adequately power a study aiming to demonstrate increased survival for LI compared to TAC. For power analyses, TAC-associated mortality rate was fixed at 30% (solid line) with varying magnitudes of absolute risk reduction associated with LI (dashed line). For all calculations $\alpha = 0.05$ and $\beta = 0.80$.

Discussion

Our analysis of the ACS-NSQIP database demonstrates that LI and TAC associated mortality rates are 36% and 31%, respectively, for patients with CDI. This difference in mortality was not found to be statistically significant; however, we did observe that blood transfusions and the occurrence of at least one complication were more common in patients who underwent TAC. Furthermore, we provide additional evidence that LI can be completed laparoscopically in most patients and that the risk of subsequent colectomy is low.

This study is distinguished in that it is the largest study to date comparing outcomes between TAC and LI in patients undergoing surgery for CDI. This study has several limitations that must be addressed. The ACS-NSQIP database does not provide information regarding antegrade lavage or antibiotic enema use. This is a

Table 3
Postoperative outcomes.

	LI		TAC		*p*-value
	N	%	*N*	%	
Total number of patients	47	10.3%	410	89.7%	N/A
Total number of complications					**0.021**
0	13	27.7%	52	12.7%	
1	11	23.4%	75	18.3%	
2	6	12.8%	76	18.5%	
≥3	17	36.2%	207	50.5%	
Cardiovascular complications					0.220
0	40	85.1%	372	90.7%	
≥1	7	14.9%	38	9.3%	
Respiratory complications					0.339
0	25	53.2%	188	45.9%	
≥1	22	46.8%	222	54.1%	
Any infectious complications					0.625
0	21	44.7%	168	41.0%	
≥1	26	55.3%	242	59.0%	
Thromboembolic complications					0.292
0	45	95.7%	371	90.5%	
≥1	2	4.3%	39	9.5%	
Surgical site infections					0.069
0	46	97.9%	367	89.5%	
≥1	1	2.1%	43	10.5%	
Renal failure	7	14.9%	46	11.2%	0.456
Transfused	9	19.1%	223	54.4%	<**0.001**
Readmitted	4	8.5%	53	13.1%	0.489
Reoperation performed	4	8.5%	43	10.5%	0.804
Length of stay (mean, days)	18.7 ± 13.4	N/A	19.6 ± 12.3	N/A	0.626
Deceased at discharge	17	36.2%	125	30.8%	0.451

significant limitation to this study given that the presumed benefit from LI is likely dependent on the postoperative usage of antegrade colonic lavage to remove toxins and kill the offending bacteria. The ACS-NSQIP only collects data pertaining to the index hospitalization, thereby preventing us from collecting information relevant to subsequent encounters. Additionally, data collected by the ACS-NSQIP is representative of only a random sampling of cases performed at participating institutions; therefore, data may not capture all patients who underwent surgery for CDI and the results of this study may not be generalizable to institutions not participating in ACS-NSQIP. Considering that this study was a retrospective analysis, it is also subject to potential selection bias. This is evidenced by our LI cohort having a lower preoperative probability of morbidity (37% vs. 62%, $p < 0.001$); however, this bias was not present to such an extent that it affected the preoperative probability of mortality between cohorts. The selection bias we observed in this study likely resulted in the inclusion of lower risk patients in the LI cohort. Approximately 20% of patients in this study were observed to have undergone surgery that was not classified as "emergent." It is therefore possible that some patients underwent surgery for chronic or smoldering CDI as opposed to fulminant CDI. Using several variables, the ACS-NSQIP does calculate the overall preoperative risk of morbidity and mortality for all patients; however, certain variables relevant to this study were not available for analysis (i.e. need for vasopressors prior to surgery) making it difficult to compare this patient population with that from other studies, further limiting our findings. Lastly, even though this study is the largest to date, it was not powered to detect a 5% difference in mortality. As our power analysis demonstrates, we would have needed several hundred patients in each group to detect such a small difference. This is also a limitation to this study considering that LI was expected to be associated with lower rates of morbidity and mortality.

Our findings do not support the initial observations made by Neal and colleagues and will further the debate regarding the comparative safety and efficacy of LI in the treatment of patients with CDI.[8] We observed no survival benefit for patients in the LI cohort. This was unexpected given that better outcomes were initially expected in the LI cohort due to selection bias. Only two other studies report comparative mortality rates between the two surgical approaches, both of which were published recently in 2017.[3,4] Ferrada and colleagues completed a retrospective multi-institution review of 98 patients, 21 of which underwent LI. In this study, unadjusted mortality did not differ between LI and TAC (24% vs. 34%, respectively); however, LI was seen to be lower risk after adjusting for reoperations (17% vs. 40%, $p = 0.002$).[4] Fashandi and colleagues also completed a retrospective single-institution review of 23 patients, 12 of which underwent LI. In this study, mortality in the LI cohort was 7% higher at 30 days and 6% higher at one year[3]; however, like our study, this difference was not statistically significant.

In our study, less than 10% of patients in the LI cohort required reoperation, and none of those patients were seen to have undergone colectomy. Granted, one patient had missing data, but even if all three patients who underwent abdominal exploration were assumed to have also undergone colectomy, the rate of colonic preservation would have still been 94%. This rate is consistent with previously reported rates, ranging from 76 to 100%.[3,4,8] Additionally, we confirm that patients undergoing TAC are at higher risk for blood transfusion.[4]

The improve survival observed by Neal and colleagues was dependent upon a large difference in mortality due to the study's small size and low power. Their colectomy-associated mortality rate of 50% is relatively high compared to other studies. A 2013 study of over 19,000 patients who underwent colectomy for CDI found that mortality was 30.7%.[2] Similarly, a 2014 study of 335 patients found colectomy-associated mortality to be 33%.[7] Several other small case series also report colectomy-associated mortality rates $\leq$36%.[5,9,11–13] If TAC-associated mortality is truly 30–35%, it weakens the claim that LI improves survival over TAC. One clinical trial (NCT01441271) aiming to compare TAC and LI, previously failed to accrue, likely due to few patients ever needing surgery for CDI. A second clinical trial (NCT02347280) is actively accruing patients and plans on enrolling 63 patients in each surgical arm. They estimate TAC-associated mortality to be 38%. This trial is powered to detect an absolute difference of 22%; therefore, if LI-associated mortality is greater than 16%, no significant difference in mortality rates will be observed.

Although LI was not associated with lower mortality, our study did demonstrate that it is safe, and can be accomplished via a laparoscopic approach most of the time. LI appears to be a viable alternative to colectomy in select patients, but it remains unclear exactly which patients are suitable for this less-invasive technique; ultimately, a prospective clinical trial will be required to determine the utility of LI in patients with CDI. Since surgical intervention is rarely warranted for CDI, and patient accrual would occur almost exclusively in the emergent setting, it is unlikely that an adequately-powered prospective study is on the horizon.

Conclusions

In summary, we show that compared to TAC, LI may not be associated with a survival advantage for patients who require surgery for CDI. We do however confirm that patients who undergo LI have high likelihood for colonic preservation and experience lower rates of transfusion compared to patients undergoing TAC. Prospective studies are required to ultimately determine the comparative safety and efficacy of LI for patients with CDI.

Conflicts of interest

All authors have nothing to disclose.

Disclosures

The authors have no financial interests to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.09.023.

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