LOOP ILEOSTOMY CLOSURE AS A 23-HOUR STAY PROCEDURE, A MULTI-CENTER RANDOMIZED CLINICAL TRIAL

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Abstract

Rationale :
Loop ileostomy is defined by bringing a loop of small bowel out onto the surface of the skin to allow diversion of the fecal stream. It is a common procedure that is conjointly done with colorectal surgeries with the objective to protect intestinal anastomosis at high risk of leaking. Loop ileostomy closure is then performed in the months following the initial surgery when the anastomosis has healed. Often thought of as a simple procedure, it is still associated with a significant postoperative morbidity rate consisting mostly of postoperative ileus. In the CHU de Québec-Université Laval, patients are hospitalized for a median of five days until their bowels open up while no active care is given. This represents 645 days of hospitalization each year for Hôpital Saint-François d'Assise (HSFA), Hôtel-Dieu de Québec (HDQ) and Centre Hospitalier de l'Université Laval (CHUL). Hence, there is a clear need to determine if we can improve the outcomes following ileostomy closure by applying a standardized enhanced recovery pathway specific to ileostomy closure to the point where the surgery can be performed in a twenty-three hours hospitalization setting.

Objective :
The purpose of this study is to assess the safety and feasibility of ileostomy closure performed in a 23 hours hospitalization setting, using a multi-center, open-label, randomized controlled trial comparing patients being hospitalized overnight (discharged on the day after surgery) to patients being hospitalized as per the current conventional care after ileostomy closure with both groups following a standardized enhanced recovery after surgery (ERAS) pathway specific to ileostomy closure. Primary outcome will be total length of hospital stay in days and secondary outcomes, measured at 30 days, will include readmission rate, postoperative complication rate minor and severe, postoperative ileus rate, postoperative surgical site infection rate and mortality rate.

Hypothesis :
We believe patients randomized to the group 23-hour stay will have reduced total length of hospital stay compared to patients randomized to the group conventional hospitalization after ileostomy closure.

Methods :
Healthy adults (ASA I and II) undergoing elective ileostomy closure who consented to take part in the study will be enrolled in a standardized enhanced recovery pathway specific to ileostomy closure. Once surgery is completed, they will be randomized to either 23-hour stay or conventional hospitalization. Data on postoperative outcomes will be gathered prospectively until 30 days after surgery and will include total length of hospital stay in days, readmissions, postoperative complications, more precisely postoperative ileus and surgical site infections, as well as mortality.

Clinical significance :
If safety and feasibility of a fast discharge of patients is demonstrated by this study, it would then mean that patients could be discharged from hospital less than 24 hours after a loop ileostomy closure. It could potentially lower the consequences of a long hospital stay for patients, such as risks of nosocomial infections, thromboembolic events, and hospital acquired autonomy loss.

1. Background and rationale

1.1 Introduction

Loop ileostomy, defined by securing a loop of small bowel onto the surface of the skin and creating an opening to allow enteric content to be collected in an artificial outpouching system, is a procedure that is frequently done conjointly with colorectal cancer surgery. The objective is to protect distal colonic anastomoses, connections between the colon and the rectum or the anus, that are at risk of leakage in the postoperative period. Even though they do not reduce the total incidence of anastomotic leaks, they contribute in reducing the clinical consequences (1-3). Loop ileostomy are designed to be temporary and once the anastomosis has proven to have healed adequately, ileostomy closure can be scheduled. Often thought of as a simple procedure, loop ileostomy closure is associated with morbidity rates ranging from 11% to 45% (4-7). A systematic review by Chow et al. identified 48 studies including 6,107 cases of ileostomy closure (8). They found a 17.3% rate of overall morbidity with postoperative obstruction (7.2%) and surgical site infection (5.0%) being the most common complications (8). Anastomotic leak rate was found to be 1.2% while mortality rate was 0.4% (8). The average length of hospital stay in this review was 5.1 days (8).

Postoperative ileus is defined as obstipation and intolerance of oral intake due to non-mechanical factors that disrupt the normal coordinated propulsive motor activity of the gastrointestinal tract following abdominal surgery. Studies of patients treated by ileostomy closure report highly variable postoperative ileus rates, ranging from 8-32% (5-6, 8-13). Postoperative ileus is the primary reason for admission to hospital for most patients after ileostomy closure.

1.2 St. Paul's Hospital experience

St. Paul's Hospital in Vancouver and Hôpital Saint-François d'Assise in Quebec City are two tertiary care centers with similar colorectal surgical practices and patient populations. While doing a fellowship there, Dr François Letarte, senior author in this study, made a retrospective study on loop ileostomy closures in this center.

The preliminary analysis of data at St. Paul's Hospital was made through a retrospective review of all cases of ileostomy closure done at this site between January 2007 and April 2015. During that time, 496 cases of elective ileostomy closure were performed. The median length of hospital stay was four days and the median time to return of bowel function was two days. Overall morbidity rate was estimated at 26.3% with a 14.1% postoperative ileus rate and surgical site infection rate of 6.0%. The 30-day mortality rate in this series was 1.0% and the 30-day readmission rate was 6.7%.

1.3 Moving toward shorter hospital stay

In the past decade, surgeons have started to question whether keeping patients in the hospital after loop ileostomy closure is necessary. In the United Kingdom, Peacock et al. studied 4463 cases of loop ileostomy closure performed in 2013, a median length of hospital stay of five days was observed, accounting for 36 000 bed days annually (14). The majority of these patients are hospitalized until their bowel function returns while no active treatment is being performed (14). When complications occur, they are either apparent immediately after surgery or manifest themselves several days after surgery (15). Baraza et al. reviewed their hospital experience with ileostomy closure and analyzed 80 consecutive patients (16). While they found that 25% of patients experienced postoperative morbidity, over 70% of the complications were considered minor and could have been treated in an outpatient setting (16). Consistent with this assertion, the readmission rate was only 2.5% (16). Therefore, the authors concluded that there was no reason to keep patient hospitalized until their bowel function returned (16).

Joh et al. at Case Medical Center in Cleveland evaluated the role of a standardized care pathway adapted for ileostomy closure to see how it affected the outcomes (17). They were able to reduce

their length of stay to a median of two days with a readmission rate of 9.4% (17). Similarly, two other groups developed protocols where ileostomy closure patients were released from the hospital after a 23-hour observation period (18-19). Although these two studies were small case-series, they showed acceptable results with limited complications rates of less than 10% and low readmission rates of less than 5% (18-19). Finally, a pilot study of 15 patients who had ileostomy closure and were discharged from the hospital on the same day was published (20). Only two patients experienced minor complications and no readmissions were warranted (20).

1.4 Technical innovations to improve outcomes after ileostomy closure

A systematic review and meta-analysis also reviewed sutured versus stapled anastomosis for ileostomy closure and found that stapled anastomosis were less likely to present with postoperative small bowel obstruction and were associated with a decreased operating time when compared to sutured anastomosis (21). A systematic review and meta-analysis comparing purse-string closure and conventional linear closure of the wound of the ancient ileostomy site showed a 90% reduced risk of surgical site infection when using purse-string closure (22).

1.5 Reducing postoperative ileus rates

Postoperative ileus remains a significant factor affecting the length of stay after colorectal surgery. The advent of enhanced recovery after surgery programs has been advocated as a means of safely reducing the length of stay and improving the overall perioperative care for patients undergoing colectomy (17, 23-24). ERAS programs are meant to address the surgical stress response and reduce predictable complications so that the inefficiency of care can be reduced (17, 23-24). Prevention of postoperative ileus is important because this complication is a major cause of delayed discharge after abdominal surgery (25-27). A systematic review and meta-analysis performed by Adamina et al. reviewed six randomized trials on ERAS programs after colorectal surgery (24). They found that enhanced recovery pathway was associated with a shorter duration of hospital stay in patients who underwent major colorectal surgery and reduced 30-day morbidity (24). There was no effect on readmission compared to traditional care (24).

As mentioned earlier, postoperative ileus is the most frequent complication encountered in patients undergoing ileostomy closure in most studies. This was also true for the patients of St. Paul's Hospital mentioned in section 1.2 with a rate of 14.1%. One randomized controlled trial from Spain was able to significantly decrease the rate of postoperative ileus from 20% to 2.85% using preoperative stimulation of the efferent limb (27). Patients were injected a solution of normal saline and a thickening agent through the efferent limb of the ileostomy once a day for 14 days prior to surgery (27). The theory behind this intervention is that when the colon is diverted with a loop ileostomy, diversion colitis will develop in most patients (27). This could explain in part why once the ileostomy is closed and the flow of feces is re-established, patients have a tendency to experience ileus or diarrhea (27). By stimulating the efferent limb of the ileostomy and by consequence the colon prior to surgery, this could decrease the inflammation, increase absorption by the colon and reduce the time to return of bowel function (27). We believe the irrigation of the efferent limb with an enteral nutritional formula would be even more efficient to alleviate diversion colitis and remove mucous plug in the colon which could lead to decreased postoperative ileus rates and faster return of bowel function after ileostomy closure. This use of enteral nutritional formula in the distal portion of the bowel (terminal ileum/colon) is a practice derived from jejunostomy tube feeding.

1.6 Standardized enhanced recovery pathway for ileostomy closure

Recently, a standardized enhanced recovery pathway specific to ileostomy closure was developed in our center and aims to decrease length of hospital stay, readmission rate, postoperative ileus rate and postoperative complication rate. It includes early feeding and ambulation and early discharge from the hospital as soon as patients meet the pre-established criteria. For this study, preoperative efferent limb stimulation will be added to the enhanced recovery pathway. Hence, all participants of the study will be included in the enhanced recovery pathway with efferent limb stimulation.

1.7 Summary

In summary, ileostomy closure is a common procedure that is associated with significant rates of postoperative morbidity leading to long hospitalizations. However, it seems that the majority of these complications are minor and potentially preventable or avoidable. A randomized controlled trial is warranted to demonstrate the safety and feasibility of an ileostomy closure in an overnight hospitalization setting to eventually transform this procedure in a day-case surgery.

1.8 Objectives

The purpose of this study is to assess the safety and feasibility of ileostomy closure performed in a overnight surgery setting, using a multi-center, randomized controlled trial comparing patients being hospitalized overnight (discharged on the day after surgery) to patients being hospitalized as per the current conventional care after ileostomy closure with both groups following a standardized enhanced recovery pathway specific to ileostomy closure. Primary outcome will be total length of hospital stay in days and secondary outcomes, measured at 30 days, will include readmission rate, complication rate minor and severe, postoperative ileus rate, postoperative surgical site infection rate and mortality rate.

1.9 Hypothesis

We believe patients randomized to the group 23-hour stay will have reduced total length of hospital stay compared to patients randomized to the group conventional hospitalization after ileostomy closure.

2. Methods and Analysis

2.1 Study Design

This study is an open-label, randomized controlled trial designed to evaluate the safety and feasibility of ileostomy closure performed in a overnight surgery setting after undergoing a standardized enhanced recovery pathway specific to ileostomy closure. This multicenter study will be opened to other Canadian centers. Adult patients without significant comorbidities (ASA I and II) undergoing elective ileostomy closure who consented to participate in the study will be enrolled in a standardized enhanced recovery pathway specific to ileostomy closure. Right after surgery is done, they will be randomized either to the group 23-hour stay or the group conventional hospitalization. Postoperative data will be prospectively collected on a 30-day period after the surgery and will include total hospital length of stay, readmissions, postoperative complications, more precisely postoperative ileus and surgical site infections, as well as mortality.

2.2 Participants

2.2.1 Population

Data will be gathered using primary data collection strategies. This is a Canadian multi-center open-label randomized controlled trial and each center taking part in this study will be responsible

for collecting its own data and will proceed according to a pre-established standardized protocol. Surgeons and members of the research team of each center will identify patients scheduled to undergo elective ileostomy closure and then determine if they meet the inclusion criteria of the study.

2.2.2 Inclusion criteria

Patients admitted for ileostomy loop closure who meet the following criteria will be eligible to participate in the study:

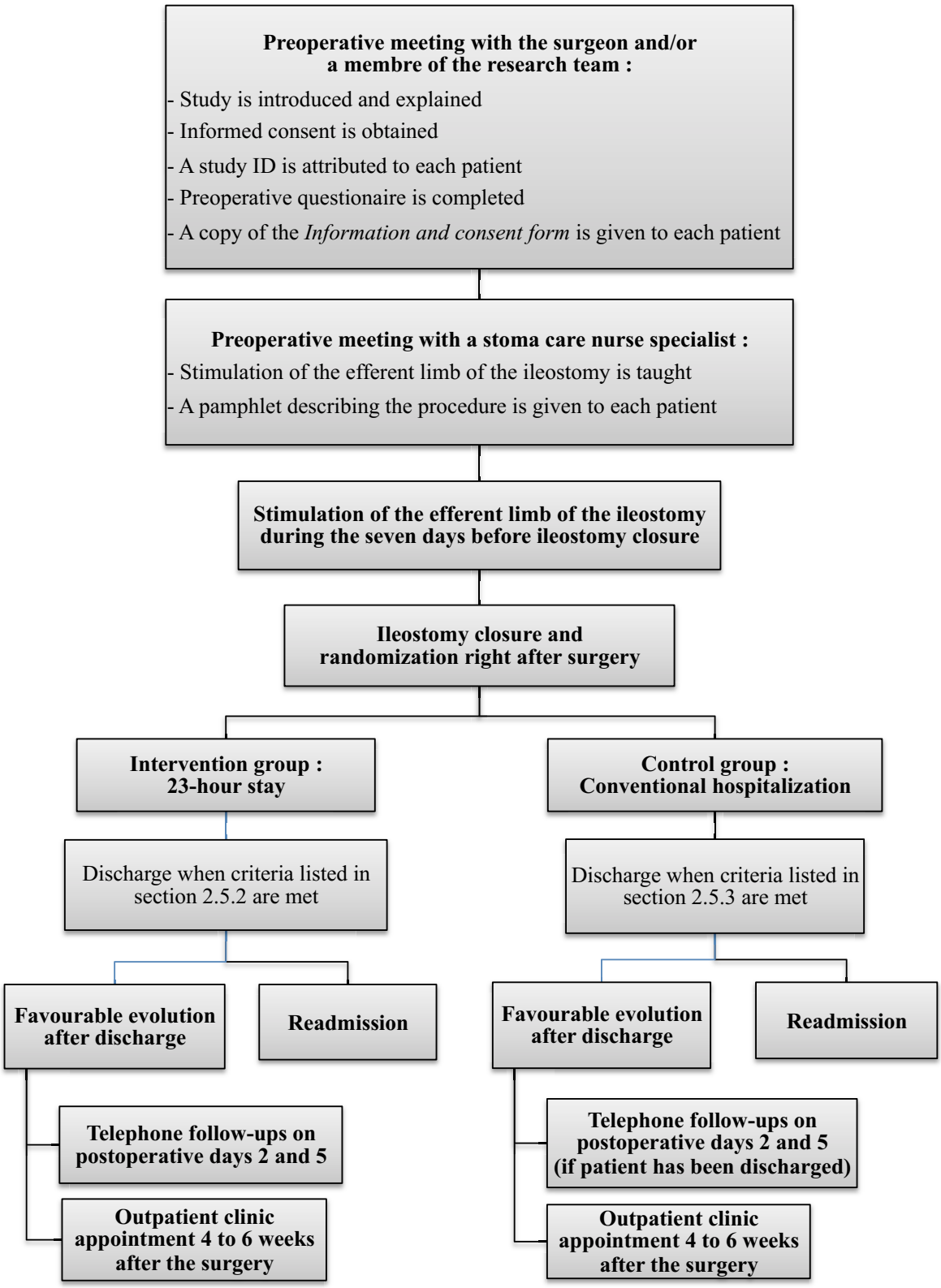
- Aged 18 years and older
- Able to provide informed consent
- ASA I and II (American Society of Anesthesiologists)
- Staying less than 50 kilometers from a hospital after surgery
- Being accompanied by an adult able to assist the patient in his recovery and to intervene in case of an emergency for the first 48 hours after surgery
- No anastomotic leak proven on preoperative water soluble enema

2.2.3 Exclusion criteria

Patients admitted for ileostomy loop closure who meet the following criteria will be excluded from the study:

- Language barrier or significant communication problem
- Immunosuppression
- Therapeutic anticoagulation
- Previous proctocolectomy
- Previous ileal pouch anal anastomosis
- Technical factors during surgery (conversion to midline laparotomy or other, at surgeon's discretion)

Figure 1. Trial timeline and visits scheduled



2.2.4 Preoperative questionnaire and teaching

Patients who are planned to undergo ileostomy closure will first meet their colorectal surgeon at an outpatient clinic appointment. As surgery is explained and consent for surgery is obtained, the surgeon (Dr Alexandre Bouchard, Dr Philippe Bouchard, Dr Sébastien Drolet, Dr Roger C. Grégoire, Dr François Letarte or Dr Claude Thibault), a resident in charge of this study (Geneviève Morin or Xavier Paré) or the research nurse (Ann Wright) will introduce and explain the study and obtain patient's consent to participate. Each patient will be attributed a study ID and will complete a preoperative questionnaire. This questionnaire will contain information on demographics such as age, gender, height, and weight. Presence of comorbidities such as diabetes, coronary artery disease, cardiac failure, renal failure, chronic obstructive pulmonary disease, and immunosuppression as well as previous abdominal surgeries will be assessed. Information regarding the initial surgery that led to the creation of the loop ileostomy will also be retrieved through the patient's medical file including date of surgery, initial pathology (neoplasia, inflammatory bowel disease, diverticular disease, colonic volvulus, trauma or other), type of surgery (anterior resection, low anterior resection, sigmoidectomy, right hemicolectomy, total colectomy, loop ileostomy alone, ileoanal reservoir or other), type of anastomosis performed (stapled or sutured), surgical approach chosen (open or laparoscopic), duration of the surgery in minutes, and use or not of pelvic radiotherapy and chemotherapy. A copy of the *Information and consent form* will be given to each participant during this meeting.

A stoma care nurse specialist will meet all patients at least seven days before their ileostomy closure to teach them how to perform the efferent limb stimulation. A pamphlet describing the procedure will also be given to them.

2.2.5 Perioperative information

Further information will be recorded at the time of the ileostomy closure. Patients will be met before the surgery in regards to stimulation of the efferent limb of the ileostomy to assess how many times it was completed during the seven days before surgery. Problems encountered and reasons for non-compliance will also be noted. Preoperative stimulation of the ileostomy has no impact on the surgical procedure or on randomization. Information regarding the ileostomy closure will be retrieved from the patient medical file in the operative note and surgical protocol. It will include date of surgery, interval between the initial surgery and ileostomy closure, duration of the surgery in minutes, presence or not of significant adhesions during surgery (based on the surgeon's opinion), need for conversion to a midline laparotomy, type of anastomosis performed (stapled or sutured), complications during the ileostomy closure (bleeding, serotomy, enterotomy, trauma to another organ), estimated blood loss in milliliters, type of skin closure (purse-string or linear), and infiltration or not of skin incision with a local anesthetic. If a surgeon decided to exclude the patient from the study due to technical factors, the reasons for this decision will be noted.

2.2.6 Postoperative information

Postoperative information will be assessed during telephone follow-ups and outpatient clinic appointment four to six weeks after the surgery using a standardized questionnaire and reviewing the patient's medical file. Data collected will include length of initial hospital stay in days, readmissions during the 30-day postoperative period, reasons for readmissions, treatment received during readmissions, length of hospital stay during readmissions in days, occurrence of complications during the 30-day postoperative period including ileus and surgical site infections, and mortality. Postoperative complications will be classified using the Clavien-Dindo classification. Hence, grade I and II complications will be considered minor and grade III and IV

complications will be considered severe. Grade V complications imply death of the patient so they will be recorded as mortality instead of complications.

2.3 Randomization

Patients included in this study will be randomized in the operating room once the surgery is completed. Patients will be randomized by a closed envelope method either to the group 23-hour stay or the group conventional hospitalisation. Randomization will be performed in a 1:1 equal allocation ratio and the sequence will be computer generated. The opaque, sealed, and sequentially numbered randomization envelopes will be mixed and distributed to participating centers according to each hospital's expected participation based on their number of ileostomy reversals performed per year. To randomize a patient, the surgeon will open the next consecutively numbered envelope.

2.4 Blinding

Due to the study design, it will be impossible to blind the patients to the intervention as it consists of either discharge the day after surgery or prolonged hospitalization. However, since randomization will occur once the surgery is completed, it ensures all patients to undergo a similar surgical procedure irrespective of their treatment arm.

2.5 Trial intervention

Difference between the intervention group and the control group will lie in whether the patient is hospitalized overnight (discharged on the day after surgery) (intervention group) or is hospitalized as per the current conventional care after ileostomy closure (control group).

2.5.1 Standardized enhanced recovery pathway specific to ileostomy closure

Patients awaiting an ileostomy closure who fit the inclusion criteria and consent to take part in the study will be submitted to a standardized enhanced recovery pathway specific to ileostomy closure including antimicrobial and thromboembolic prophylaxis at induction, controlled intraoperatively administration of volume, infiltration of all skin incisions with ten millilitres of a solution of bupivacaine 0.5% at the end of the procedure, a multimodal pain and nausea management favouring oral medication as well as early ambulation and early enteral feeding. Moreover, the surgeon will perform a stapled anastomosis and a purse-string closure of the wound. Preoperative efferent limb stimulation with an enteral nutritional formula once a day for seven days is a measure added to the enhanced recovery pathway for this study to reduce the incidence of ileus and diarrhea secondary to diversion colitis in the postoperative period. It will consist of inserting a Foley catheter in the efferent limb of the ileostomy over about ten cm and insufflating the balloon of the catheter making sure it is below the fascia. Then, 220 milliliters of an enteral nutritional formula will be injected slowly using a syringe. All participants will meet a stoma care nurse specialist at least seven days before their surgery to receive teaching on how to perform the stimulation of the efferent limb of their ileostomy. During the teaching session, a pamphlet describing the procedure will be provided to the patients and the stoma care nurse specialist will make sure the patients understand the different steps and are able to perform this intervention themselves.

2.5.2 Intervention group

Patients randomized to the group 23-hour stay will be discharged on the day after their surgery if they meet the following discharge criteria :

- Hemodynamically stable
- Temperature < 38.3 Celsius
- Alert and oriented
- Pain score < 5 (on a scale from 0 to 10)
- Tolerating oral diet without nausea or vomiting
- Passed urine
- Able to mobilize

If all the criteria are not met on the morning of the day following their surgery, patients will stay hospitalized until they are met. Moreover, even if all the discharge criteria are met, the operating surgeon will always be allowed to keep a patient hospitalized if he deems it necessary and beneficial to the patient.

Patients will be contacted by telephone on postoperative days two and five to ensure that they evolve favourably. Patients will be instructed to contact the on-call surgical resident assigned to this study at any time if they have concerns. These interventions will be under the supervision of the on-call surgeon and they will be documented by evolutive notes. Finally, an outpatient clinic appointment will be scheduled four to six weeks following the surgery.

2.5.3 Control group

Patients randomized to the group conventional hospitalization will be hospitalized as per the current conventional care after ileostomy closure. Thus, they will be discharged once they meet the criteria listed in section 2.5.2 as well as a return of bowel function. The admitting surgeon will also need to feel comfortable discharging them. If they leave before postoperative day five, these patients will also be contacted by telephone on postoperative days two and five to ensure that they evolve favourably. An outpatient clinic appointment will also be scheduled four to six weeks following the surgery.

2.6 Outcomes

The primary outcome will be total length of hospital stay and will include the number of days spent in the hospital from the time of the surgery to the time of the discharge as well as any day spent in the hospital after any readmission in the 30 days following the ileostomy closure. Secondary outcomes, at 30 days following the ileostomy closure, will include readmission rate, postoperative complication rate, minor and severe, postoperative ileus rate, postoperative surgical site infection, and mortality rate. Readmission will be defined as any unplanned consultation to an hospital in the 30-day period after surgery. Postoperative complications will include ileus, surgical site infection, bowel obstruction, anastomotic leak, pneumonia, myocardial infarction, acute kidney injury, urinary tract infection, delirium, and pseudomembranous colitis. Ileus will be defined as inability to tolerate oral intake due to nausea and/or vomiting or the need to insert a nasogastric tube by postoperative day 3 in the absence of mechanical obstruction or another indication for a nasogastric tube such as intubation.

2.7 Sample size

To estimate the mean total length of stay following elective ileostomy closure, the retrospective analysis conducted by Dr François Letarte at St. Paul's Hospital mentioned in section 1.2 was used as well previous reported outcomes of length of hospital available in the literature mentioned in section *Background and rationale*. Using these same data sources, we estimated a readmission rate of about 15% with a mean length of stay during readmission of five days. Considering these results,

we estimated the mean total length of stay following elective ileostomy closure to be 6.5 days with a standard deviation of 8.7 days. Sample size was calculated to detect a four-day decrease in mean total length of hospital stay for the intervention group with a power of 90% and a type I error of 0.05 for a multicentric study with an intraclass correlation of 0.20. Based on these specifications, a sample of 80 individuals per treatment arm and a total of 160 subjects will be necessary. Assuming an expected withdrawal rate of less than 5% during the trial, a total sample size of 168 (n = 2 x 84) subjects will be required.

2.8 Statistical analysis

Data analysis will be performed by the blinded statistician assigned to this study. Baseline characteristics of both groups will be reported. Descriptive statistics will be reported including mean, median, standard deviations, and ranges. We will use Student's *t* test, the Mann–Whitney *U* test, or analysis of variance (ANOVA) for comparing means, when appropriate. Categorical variables will be compared with the χ^2 test. Odds ratios with associated 95% confidence intervals (CI) will be calculated with logistic models for binary data (readmissions, complications). Multivariate models will include variables statistically associated with those in univariate analysis, as well as those considered to have clinical relevance in the primary outcome (total length of hospital stay). All statistics will be two-tailed and a p value < 0.05 will be deemed significant. Statistical analysis will be done with *SAS Statistical Software v.9.4 (SAS Institute, Cary, NC, USA)* for all outcomes measures using an intention to treat analysis even in the cases of crossover or non-compliance to the study protocol. For example, patients randomized to discharge at 23 hours who end up being hospitalized will still be analyzed in the intervention group.

2.9 Study limitations

A first limitation of this study results from the potential lack of compliance to the enhanced recovery pathway by the patients since the efferent limb stimulation implies significant care provided by the patient on its own. However, this will increase the external validity of the study as it will measure the effectiveness of the pathway rather than its efficacy. Also, since the randomization will occur after the surgery, compliance to preoperative protocol and surgical technique should be similar between both groups.

A second limitation will be regarding external validity. The results of this study will not be applicable to every patient undergoing ileostomy closure as the inclusion and exclusion criteria and the implications of the enhanced recovery pathway will prevent a small proportion of patients to enter the study. However, based on analysis of the cohort of patients at St. Paul's Hospital mentioned in section 1.2, the inclusion and exclusion criteria used in this study will encompass around 90% of the population of patients undergoing ileostomy closure.

Finally, readmissions will be underestimated in the control group since they will most likely stay hospitalized longer initially.

2.10 Study implications

This clinical trial will be at the forefront of emerging changes in the way patients are treated in the perioperative period for this common procedure where not much change has occurred in the past two decades. This study would be the first looking at the association of a 23-hour stay with preoperative efferent limb stimulation. The approach proposed by this trial have the potential to be adopted by other institutions around the world leading to a generalized transformation of a procedure where patients used to stay hospitalized for multiple days to a procedure where patients would go home on the following morning. This would clearly be beneficial to the patients as well as to health institutions.

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