Prehabilitation in Abdominal Surgery for Crohn's Disease: A Randomised Trial

Study Protocol

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Summary

This is a superiority randomised trial with an internal pilot, which will evaluate a 4-week prehabilitation protocol based on three interventions (exercise and protein supplementation) vs control (standard management) in people with Crohn's disease undergoing small or large bowel resection within standard care including an optimisation protocol and an enhanced-recovery protocol. The primary outcome is post-intervention change in 6-minute walking test performance.

Rationale

Prehabilitation

Prehabilitation is a multi-modal intervention aiming to improve physical function prior to major surgery, and thereby improve postoperative recovery. Protocols include endurance and

resistance exercise and typically one of more additional interventions, such as nutritional supplementation, breathing exercises and coping mechanisms. Most protocols have a duration of 4 weeks.[1]

The existing evidence base regarding prehabilitation in abdominal surgery is so far limited to cancer, vascular and bariatric surgery, and many have selected frail people as participants.[1] In pooled analyses, these trials have demonstrated decreased overall and respiratory morbidity in patients who undergo a prehabilitation protocol.[1]

Abdominal surgery for Crohn's disease

Preliminary population-based data from Sweden indicate that in contemporary care, one in four people diagnosed with Crohn's disease undergo bowel resection in the subsequent ten years, and one in five of those need another resection within 10 years after the index operation.[2] The number of patients presenting for surgery may increase over the coming years, due a growing role of surgery as an early treatment for terminal ileal disease,[3,4] and the increasing incidence of the disease worldwide.[5]

Despite the advent of minimally invasive surgery and enhanced-recovery care, bowel surgery for inflammatory bowel disease (IBD) remains associated with increased morbidity and slower recovery when compared to bowel surgery for cancer.[6,7] Furthermore, the grade of complications are more severe in IBD surgery,[7] and some 10% develop intestinal failure during the first 20 years of disease, defined as parenteral nutrition support for 12 months or more.[8]

A majority of people with Crohn's disease who need surgery have features of frailty. Over 70% in this patient group are sarcopenic,[9,10] and the degree of sarcopenia is directly related to increased postoperative morbidity in Crohn's disease.[10]

Possible causes of these additional challenges in surgery for Crohn's disease include a higher rate of malnutrition, ongoing systemic inflammation due to both sepsis and disease activity, and a high rate of immunosuppressive therapy, including glucocorticosteroid and monoclonal antibody therapy.

Prehabilitation in Crohn's disease

There is therefore a real need for novel strategies to improve outcomes in bowel surgery for Crohn's disease. No data on prehabilitation in Crohn's disease have been published. People with this diagnosis are, as a group, younger than cancer patients and often undergo a period of nutritional and pharmacological optimisation prior to surgery, lasting 4-6 weeks. Prehabilitation therefore appears to be feasible and of potential benefit in this patient group. We therefore wish to examine the feasibility and physiological effects of prehabilitation in people undergoing bowel resection for Crohn's disease.

Hypothesis

We hypothesise that an intensive, supervised 4-week prehabilitation programme in people undergoing bowel resection for Crohn's disease is feasible and results in an improvement in physical function from baseline to the week before surgery.

Participants

Adults (≥16yrs) listed for elective or expedited (within weeks) small or large intestinal resection by laparoscopy or laparotomy for Crohn's disease at Ersta Hospital, Stockholm, and McGill University Health Centre, Montréal, will be enrolled. Exclusion criteria include inability to participate in the prehabilitation programme components and operation performed through a peristomal incision alone. Patients will be offered to participate in the study at listing for surgery and randomised when written informed consent is attained.

Randomisation and stratification

Randomisation 1:1 to prehabilitation or control treatment is based on a sequence of random numbers. The sequence will be stratified for study site (Stockholm and Montréal) and gender. The sequence will be concealed by opaque envelopes.

Intervention Group

Physical exercise

Participants will perform endurance and resistance exercise and receive tailored protein supplementation to maximise anabolism.

Participants will perform exercise five times per week for 4 weeks (20 occasions). The exercise programme will be taught and supervised by clinical physiotherapists or

kinesiologists. The exercise programme consists of exercise performed in hospital once a week and at home four times per week. On days performing home-based exercise, the participant will be complete a participant diary to monitor compliance.

Table 1. Example of weekly exercise programme (repeats for a total of four weeks). The in-hospital exercise may take place on another weekday.

	Mon	Tue	Wed	Thur	Fri	Sat	Sun
Where	Home	Home	Hospital	Home	Home	Rest	Rest
What	Endurance and resistance	Endurance	Endurance and resistance	Endurance	Endurance and resistance		

The doses of endurance and resistance exercise are based on the protocol of an ongoing multi-centre study.[11] In brief, on each training occasion, endurance exercise is performed for 32 minutes on a stationary exercise bicycle (in hospital) or by jogging or brisk walking (at home) to a Borg score of 13-15. Interval training is not used.
Resistance exercise is performed three times per week, and not on two consecutive days. Two sets of 10 repetitions of elastic band loading and own body weight of six major muscle groups: leg press, chest press, abdominal crunches floor, lateral pull down, low row and step up. The participant chooses the order of endurance and resistance exercises.

Table 2. Equipment needed for exercise programme in hospital and at home (per centre)

	Hospital	Home
Exercise bicycle	1	-
Elastic bands	20+ (roll)	20+ (roll)
Steps	2	0
Exercise mats	2	0

Protein supplementation

A target dietary protein intake of 1.5-1.8 g/kg body weight in all patients will be achieved by dietary advice and, when indicated, oral nutritional supplementation of baseline diet. The baseline diet is assessed before the start of the intervention by 3-day recall, in order to

determine the supplementation needed. In participants requiring exclusive enteral nutrition, this will be dosed to reach this protein target.
In addition, participants in this group will receive whey protein within 30 min following each exercise (5 days a week) and before sleep (7 days a week) at the following doses: 20 g (body weight less or equal to 50kg), 30 g (body weight 51-80 kg) or 40 g (body weight 81 kg or more).

Control group

Participants randomised to the Control group will receive current standard care during their preoperative period. They will not receive protein supplements.

Ancillary management

All participants will undergo standard preoperative optimisation for 4-6 weeks.[12,13] In brief, corticosteroid therapy will be weaned to 10mg oral prednisolone or less (or equivalent) 4 weeks prior to surgery (when possible), monoclonal antibody therapy stopped 2-6 weeks before surgery (depending on agent) and immunomodulator therapy halted 2 weeks before surgery. To prevent disease flare, exclusive enteral nutrition is started during this time period when needed.[14,15] Ongoing weight loss is treated by oral, enteral or parenteral nutritional support with the aim to halt the weight loss by the time of surgery. Intraabdominal sepsis is treated by antibiotics and percutaneous drainage as indicated. Intensive smoking cessation is mandated. Anaemia is treated. Psychological support is provided.
All participants undergo surgery in a standard enhanced-recovery pathway.[16] This includes open and laparoscopic surgery, with epidural analgesia used for open surgery and spinal analgesia or transversus abdominis plane blocks for laparoscopic surgery.

Outcomes

Physical performance

1. Six-minute walk test (primary outcome)

The change in six-minute walk test (6MWT) performance between baseline and subsequent to the prehabilitation or control period is the primary outcome. The 6MWT is performed in a quiet 20-m corridor per standard guidelines. It is measured at baseline, after the prehabilitation (and before surgery), and 4 and 8 weeks after surgery. This measure is used as

the primary outcome due to its nearly universal use in the prehabilitation literature, with good availability of data from similar trials in other populations.

2. Timed stands test-30

In the timed stands test-30 (TST30) (also called chair stands test, sit to stand test), the participant stands and sits on a chair with arms crossed over their shoulders in rapid succession after a series of habituation stands. The number of stands performed in 30 seconds is the outcome measurement.

3. Hand grip strength

Voluntary grip dynamometry is carried out with a hydraulic hand dynamometer in the sitting position. Patients are instructed to squeeze the bulb quickly and maximally using their dominant hand. Three results are recorded, allowing 10 seconds of rest between each reading, and the highest is taken as the patients' grip strength.

4. Arm curl test

The dominant arm side is used. The subject sits on a chair, holding the weight in the hand using a suitcase grip (palm facing towards the body) with the arm extended down beside the chair. Curl the arm up through a full range of motion, gradually turning the palm up (flexion with supination). Gradually return to the starting position. The elbow must be fully bent and then fully straightened. A load of 2, 3, 4 or 5 kg is used, chosen based on individual strength. The same load is used at all measurements. The number of curls performed in 30 seconds is the outcome measurement.

Table 3. Equipment needed for measurements of physical performance (per centre)

	Number of items
Dynamometer	1
Free weights 2 kg	2
Free weights 3 kg	2
Free weights 4 kg	2
Free weights 5 kg	2

Thigh muscle area

Subjects rested in supine position for 30 min prior to scanning to prevent the influence of fluid shifts on muscle volume. No exercise or strenuous activity is completed within a

minimum of 10 h of scanning. All scans are completed at a similar time of day for each subject.

Thigh images are obtained at 200 mm proximal to lateral apex of the femur condyle of the dominant leg. Subjects are positioned in the scanner with their feet in a non-metallic foot restraint to control joint angle (and thus muscle length), compression between the legs, and compression between the legs and the scanner table. Imaging is completed in a 1.5 T scanner magnetic resonance camera (T1 vibe Dixon tra_p4_iso_W sequences). The area is calculated manually using an area tool. The mean of two independent assessors is used.

Patient-reported outcomes

The following three PROMs are collected before and after the 4-week intervention and at 4 and 8 weeks after surgery:

- EuroQoL 5D-5L: widely used health-related quality of life measure consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).
- Harvey Bradshaw Index: widely used measure of symptoms from Crohn's disease.
- Instrumental Activities of Daily Living (IADL): 8-item standardised questionnaire resulting in a score 0-8.

Additional outcomes

- **Compliance** in the intervention group is measured as the self-reported proportion of endurance and resistance exercises completed to 75% each day. Difficulties to perform exercised will be recorded, such as perianal disease, poor stamina, abdominal pain, etc.
- **Total physical activity** will be measured in both groups by a high-resolution activity tracker tracking pulse rate and physical movement.
- Postoperative **length of stay** (number of nights in hospital).
- 30-day **morbidity** including morbidity grades (Clavien-Dindo) and 30-day comprehensive complication index (CCI).
- Changes in body weight and BIA.
- Changes in circulating concentrations of the following markers of systemic inflammation: c-reactive protein, albumin.
- Changes in circulating concentrations of the following markers of metabolic health: glucose, insulin, HbA1C.

Additional data collected

- Demographic data at baseline
- Baseline Montréal classification of Crohn's disease phenotype
- Subjective Global Assessment nutritional screening at baseline

Table 4. Summary of outcome collections

	Baseline Before 4-week prehabilitation	Day(s) before surgery After 4-week prehabilitation	4 weeks postop	8 weeks postop
Physical performance outcomes (see above)	X	X	X	X
Weight, BIA	X	X	X	X
PROMs	X	X	X	X
Blood tests	X	X	X	X
Clinical outcomes			X	X

Timing

The intervention occurs in the four weeks preceding surgery. Outcomes are collected during the first 8 weeks after surgery.

Statistical considerations

We hypothesise that prehabilitation will change 6MWT performance between baseline and the day before surgery by 30 m or more, and 6MWT will not increase in the control group. An increase in 6MWT of 20 m is considered clinically significant. Several smaller studies have shown that a four-week prehabilitation programme increases 6MWT in patients undergoing colorectal cancer resection by 20-40 m with a shared standard deviation around 40 m.[17] We therefore hypothesise that 6MWT will increase by 30 (40) m in the intervention group and 0 (40) m in the control group.

6MWT and change in 6MWT is skewed, and data are therefore log-transformed for the sample size calculation. At 80% power, with a difference between groups of log 30 m and a shared standard deviation of log 40 m, 2x 39 participants (78 in total) will be studied.
Based on internal audit, approximately 40 bowel resections for Crohn's disease per year are performed each at Ersta Hospital and McGill University Health Centre. Assuming a 50% recruitment rate, 40 patients per year will be included between the two centres.
Blinding will not be feasible due to the nature of the intervention. An evaluation of health economy outcomes is beyond the scope of this trial.

Timeline

Q3 2020: Funding and ethics committee approval completed
Q1 2021: Inclusion commences at both study sites
Q1 2024: Inclusion completed at both study sites
Q2 2025: Study results disseminated through peer-reviewed journal

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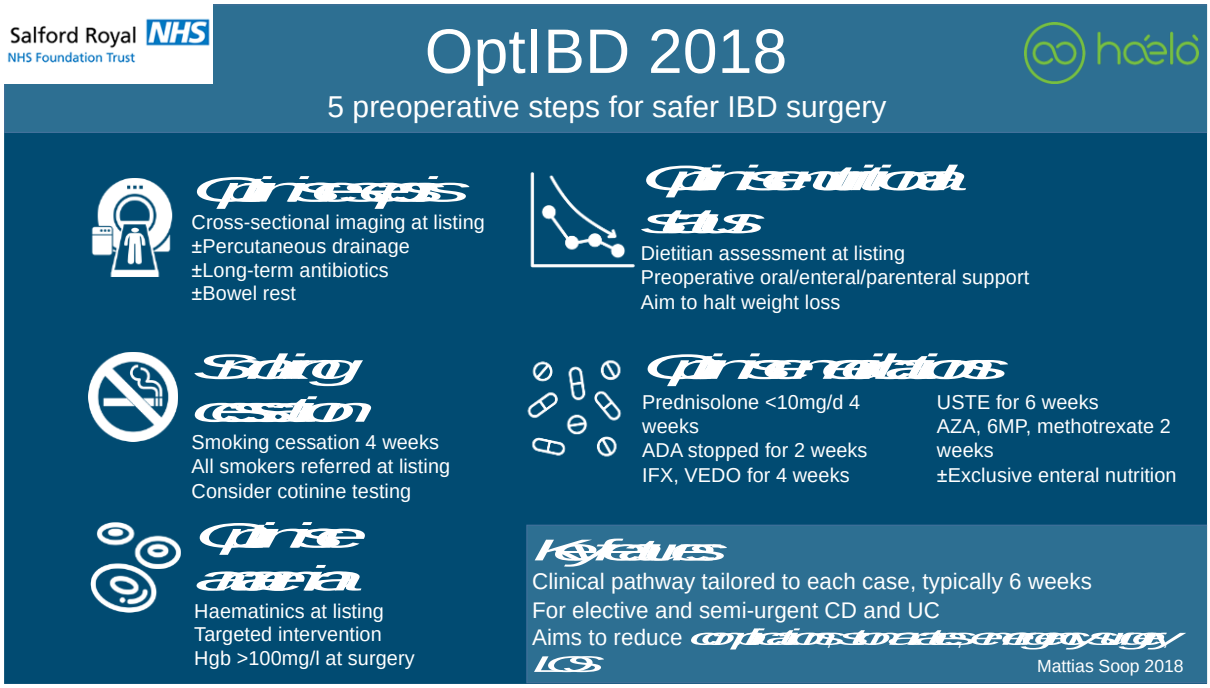

Figure 1. Summary of 4-6-week optimisation protocol for patients undergoing elective or expedited surgery for Crohn's disease.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

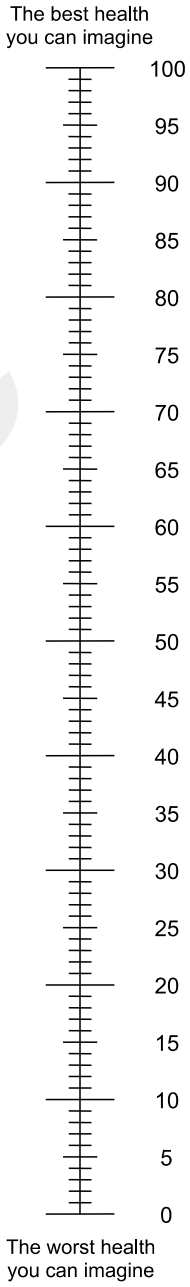

Figure 2. EuroQol EQ-5D health-related quality of life measure.

— **General well being**
(0=very well; 1=slightly below average; 2=poor; 3=very poor; 4=terrible)

— **Abdominal pain**
(0=none; 1=mild; 2=moderate; 3=severe)

— **Number of liquid stools per day**
(0=0–1 stools; 1=2–3 stools; 2=4–5 stools; 3=6–7 stools; 4=8–9 stools; 5=10+ stools)

— **Abdominal mass**
(0=none; 1=dubious; 2=definite; 3=tender)

— **Complications**
Arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissures, new fistulas, abscesses (1 point for each)

— **Total score**

Remission: HBI score <3 points.
Relapse: HBI score >7 points.

Figure 3. Harvey-Bradshaw Index of clinical activity in Crohn's disease

English version:

Please indicate whether you today feel that you can do the below activities independently or whether you need help from others to complete them:

Using the telephone	• Independent	• Need help from others
Housekeeping	• Independent	• Need help from others
Handling medications	• Independent	• Need help from others
Shopping	• Independent	• Need help from others
Doing laundry	• Independent	• Need help from others
Handling finances	• Independent	• Need help from others
Preparing food	• Independent	• Need help from others
Using transportation	• Independent	• Need help from others

Swedish version:

Vänligen kryssa i om du idag känner dig självständig eller om du behöver hjälp av andra med nedanstående aktiviteter:

Använda telefon	• Självständig	• Behöver hjälp av andra
Städa hemma	• Självständig	• Behöver hjälp av andra
Hantera mediciner	• Självständig	• Behöver hjälp av andra
Handla	• Självständig	• Behöver hjälp av andra
Tvätta kläder	• Självständig	• Behöver hjälp av andra
Hantera pengar	• Självständig	• Behöver hjälp av andra
Laga mat	• Självständig	• Behöver hjälp av andra
Resa med bil eller allmänna färdmedel	• Självständig	• Behöver hjälp av andra

Figure 4. Lawton IADL scale: the total score is the sum of independent skills (0-8)