EASY

Early closure of temporary ileostomy - A randomized controlled trial

Early versus late reversal of the temporary ileostomy performed due to rectum resection for cancer
Project Organization:

Steering committee:
Jacob Rosenberg, professor, dr. med.
Eva Haglind, professor, dr. med.
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Adiela Correra, PhD student

Project Secretariat:
Placed at Sahlgrenska University Hospital / Östra, SE-416 85 Gothenburg, Sweden

Local investigators:
Denmark:
Herlev Hospital: Anne Kjaergaard Danielsen, PhD student
Swedish:
Göteborg: Adiela Correra, PhD students
A local investigator will be appointed at all participating hospitals.

Publishing Strategy:
The results obtained after 3 months will be a part of Anne Kjaergaard Danielsen's PhD dissertation.
The results obtained after 6 and 12 months will be a part of Adiela Correr's PhD dissertation.
Both positive and negative results will be published in internationally recognized journals. If publication in the journal type is not possible, the results will be published on the research group's website.
Co-authors according to criteria from the Vancouver group (www.icmje.org).

Data Reporting
Data are recorded locally in case report forms (CRF), which contain the exactly relevant elements, needed to investigate the study questions.
The local investigator will mail a copy of the CRF to the study secretariat in Göteborg, Sweden, and retain the original.
Randomization
Patients are randomized in blocks of a 6 after a computer-generated list and the required number of numbered envelopes will be sent out to participating departments, together with the CRF’s.

Participating centers:
The study is conducted within the framework of the Scandinavian Surgical Outcomes Research Group (SSORG) and it is expected that Swedish and Danish surgical departments within the network will participate. It will also be possible that other surgical departments may participate.

Denmark:
Herlev University Hospital
(The list is under preparation)

Sweden:
Sahlgrenska University Hospital
(The list is under preparation)
Flow chart EASY

Patients with temporary ileostomy after low anterior resection.

Assessment of post-surgical restitution
CT-scan of the rectal anastomosis 6-8 days after stoma creation

Inclusion and randomization

Randomization to control group, n=100
Assessment of surgical complications before leaving hospital

3 months (+/-2 weeks) after stoma creation:
- Assessment of surgical complications
- Quality of life (SF-36, OAS, EORTC QLQ-CR30/29)

Closure of the temporary ileostomy 8-13 days after stoma creation
Assessment of surgical complications before leaving hospital

6 months (+/-2 weeks) after stoma creation:
- Assessment of surgical complications
- Quality of life (SF-36, EORTC QLQ-CR30/29)

12 months (+/-2 weeks) after stoma creation:
- Assessment of surgical complications
- Quality of life (SF-36, EORTC QLQ-CR30/29)

Cost measurement

Randomization to intervention group, n=100

6 months (+/-2 weeks) after stoma creation:
- Assessment of surgical complications
- Quality of life (SF-36, EORTC QLQ-CR30/29)

12 months (+/-2 weeks) after stoma creation:
- Assessment of surgical complications
- Quality of life (SF-36, EORTC QLQ-CR30/29)

Cost measurement
Background:

Having a stoma is not a uniform condition, but is characterized by the fact that there are several types of stomas and several underlying causes to stoma creation. Furthermore patients are affected differently by individual psychosocial factors (1-4). Patients must adjust to a changed body image (perception of own body), changes in daily routines, changes in lifestyle, social standing (5) as well as having their sexuality influenced (6). On the other hand, construction of the stoma is also a treatment that removes disease, relieves pain and improves health status (8), whereby stoma creation can also be assigned a positive meaning (9). The impact of stoma creation may be pushed into the background by other adjacent processes, e.g. parenteral nutrition (9), complications (10), fecal incontinence (11) and cancer disease (12). Several factors also affect the individual's adaptation to life with a stoma, including age (13), socioeconomic ties (14) and sex (15). The actual stoma construction may be associated with complications, and may be of a nature so that it will ultimately affect the quality of life (10, 16-18).

Patients admitted for surgical treatment of rectal cancer are sometimes offered a low anastomosis with a simultaneous construction of a temporary ileostomy to relieve the rectal anastomosis. The temporary ileostomy prevents complications from anastomotic leaks with clinical symptoms, but not anastomotic leaks in general (19).

Several preliminary studies suggest, however, that it is possible to reduce the complication rate in selected patients by closing a temporary ileostomy within 2 weeks after creation (20).

Reversal of the temporary ileostomy is generally associated with a low mortality, regardless of time of closure (20). A retrospective study, however, had a remarkably high mortality of 1% for temporary colostomy and 5.3% for temporary ileostomy (21). Deaths were related to anastomotic leaks, sepsis, acute myocardial infarction and one patient's death was reported as of unknown reasons. Stoma reversal may cause complications requiring reoperation, and a literature review concluded, that there is wide variation from no cases to as much as 14% -17%, where the presence of inflammatory bowel disease is a risk factor per se (20).

A prospective study showed that earlier reversal of the stoma (11 days rather than 2-3 months) was not associated with increased morbidity or mortality in (22).

A small randomized study investigated the impact of early closure (9 days postoperatively) of ileostomy in 36 preoperatively selected patients. The study showed that length of hospital stay was significantly shorter in the early intervention group. However, the groups did not differ regarding time until bowel function and resumption of oral nourishment. With the controlled design in mind, the
authors concluded that early reversal of the temporary ileostomy was not associated with an increased risk of complications or mortality (23).

A randomized and controlled study of 190 patients, where the intervention group had the stoma closed after 8 days was compared to a control group, where the stoma was closed after 60 days. The study showed no significant differences in the number of complications, whereas length of hospital stay was prolonged for the late closure group. However, there were significant differences in the nature of complications, as the incidence of wound complications in the early group was higher. Patients in the late reversal group had more complications related to small bowel obstruction and medical complications (24).

Measurements of health related quality of life are increasingly demanded in the health care sector (25, 26), and is proposed as one suitable test of efficiency of clinical interventions (27). Thus it seems natural to explore the impact of stoma closure on health related quality of life.

A questionnaire survey among 76 patients with temporary stomas found that more than half of the patients were socially affected by the stoma and that 12% were completely isolated (5). A prospective study over four years on patients with cancer of the rectum showed that stoma construction generally worsens the quality of life while the closure of the stoma resulted in an increase in quality of life (28).

Pressure on the health care system is increasing, which prompts researchers also to include tools for a health economic prioritizing in treatment and nursing (29). A cost calculation may thus help to underpin professional decision making, when new treatments and methods are introduced to the health care system (30).

The aims of the study:
The study will identify differences between two different surgical operative regimes in connection with closure of a temporary protective ileostomy after treatment for cancer of the rectum. The difference between the two regimes is the period from construction of the ileostomy (first operation) to reversal of the ileostomy (second operation). The period until the of ileostomy is closed is 8-13 days for the intervention group, and the control group will have the stoma closed after a minimum of 12 weeks, according to standard clinical practice.

The differences are frequency and nature of postoperative complications and mortality, the health economic impact, and patients' health-related quality of life.
**Hypothesis:**

Primary:
Patients, who have had the temporary ileostomy closed 8 - 13 days after construction, will have fewer postoperative complications, than patients undergoing stoma reversal after a minimum of 12 weeks.

Secondary:
Cost-effectiveness analysis shows that early closure of temporary ileostomy is cost effective compared with late closure.

Patients who have normal bowel function restored earlier (corresponding to 8-13 days after surgery) will have improved health related quality of life compared with patients with normal bowel function after a minimum of 12 weeks.

**Endpoints:**

Primary:

Identification and comparison of the frequency of postoperative complications 0-12 months postoperatively

Secondary endpoints:

Registration and comparison of total costs respectively for control and intervention group 0-12 months postoperatively.

Measurement and comparison of health-related quality of life measured by SF36 3, 6 and 12 months after creation of the temporary ileostomy.

Measurement and description of the disease-specific quality of life measured by EORTC QLQ-CR29 three, six months after og12 stoma construction, if the stoma is not put back.

Measurement and description of the disease-specific quality of life of the control group as measured with Ostomy Adjustment Scale 3, 6 og12 months after stoma construction, if the stoma is not put back.
Design:
The survey is conducted as a prospective randomized controlled multicenter study of patients undergoing creation of a temporary ileostomy due to rectal cancer in Denmark and Sweden. Other participating surgical departments will be invited to participate.

The primary and secondary outcomes will be explored in all participating centers.

Approach
After construction of the ileostomy eligible patients will be included in the study (see section on inclusion) and randomized to either the intervention group, where the stoma is closed after 8-13 days, or to the control group where the stoma is closed after a minimum 12 weeks.

100 patients will be included in each group (see sample size calculation) and both groups are examined for postoperative complications at discharge, 3, 6 and 12 months after construction of the ileostomy.

The impact on patient health-related quality of life will be examined at 3, 6 and 12 months after construction of ileostomy.

Finally the health economic costs in both groups are registered and the difference is calculated.

After 3 months an analysis of complications, costs and health-related quality of life is carried out. The final analysis is conducted after 12 months for all endpoints.

Inclusion criteria:
Adult patients, who have had surgery for cancer of the rectum with construction of a temporary protective ileostomy, may be included in the study.

The first day after surgery the patient is assessed by a doctor, and it is decided whether the patient is fit for inclusion. To be included in the study patients should not have active infection or organ failure. Patients must not have any signs of anastomotic leaks. This is assured by testing for radiologic signs of anastomotic leaks with CT scanning, which is a standard examination in the department as long as the project is going on. Furthermore, patients must have had bowel function (both feces and flatus).
As such, patients are included on the basis of experienced colorectal surgeons’ assessments. Patients’ postoperative condition is documented in the form of data describing the degree of postoperative recovery. These are as follows: CRP, red blood count, nutrition, mobilization, stoma function:

When the patient is assessed fit for inclusion, the patient will be informed in writing and orally. The patient’s written consent will be obtained before the patient is included (see section on consent).

Patients are included 6-11 days after surgery, while hospitalized. Patients are randomized 6-11 days after surgery and they will be allocated to either intervention group or control group.

**Exclusion Criteria:**

- Patients on steroids
- Patients with diabetes
- Patients with language difficulties
- Patients with expected poor compliance, for example due to psychiatric disorder.

**Exclusion:**

Patients, who withdraw their commitment to participate.

**Discontinuity of trial:**

There are no foreseeable reasons for discontinuing the study.

**Sample Size**

**Calculation of primary outcome measures: Morbidity**

A randomized trial of a similar group of patients found a complication rate of 38%, (31) in patients, who had the ileostomy closed late. In this study, we have set MIREDIF to 20. Provided that the complication rate in the control group is 30% and 10% in the intervention group, 100 patients in each group would be sufficient with a power of 80% and type 1 error of 5%.

Following, we include 100 patients in each group. Excluded patients will be replaced by computer generated blocks of 6 patients until there are at least 100 patients in each group.
**Calculation of secondary endpoints: Health-related quality of life.**

Published data are available for the SF-36 measured at 3 months postoperatively in patients with temporary ileostomy created after colorectal surgery (32) with a mean of 77.73 for the SF-36's physical score and a SD of 28.30.

Accordingly, we set MIREDIF at 25 and with a type 1 error of 5% and a power of 80%, 22 patients are needed in each group.

**Registration of eligible patients:**

It must be ensured that all patients who meet inclusion criteria are included. This is registered in the screening log, which will include non-enrolled patients, and patients, who are excluded after inclusion.

Patients, who wish to leave the study will be asked, whether data, that has already been registered, can be used in the study or whether they want it to be deleted. Data will be handled according to patient decision.

**Methods:**

**Morbidity and mortality:**

Primary outcome for the study is the frequency of postoperative complications up to 12 months after creation of the stoma. Registration forms are prepared on the basis of Clavier-Dindo Classification of Surgical Complications (C-DCSC) (33, 34). C-DCSC is used to ensure that data is gathered on the basis of objective criteria. In this way the influence of personal and / or cultural conditions is minimized.

The classification score classifies complications according to the necessary treatment, which prevents an individual evaluation of the patient. Whether something is to be classified as a minor or major complication or as “severe” or “less severe”, is avoided by using the classification.

All complications are recorded in relation to type and degree, ie. each complication being treated is registered in a separate form. For the final statement the complication, with the highest classification is used.

The classification includes all complications arising during the 12 months that the investigation is progressing (33), i.e. immediately before discharge and 3, 6 and 12 months after construction of ileostomy.
Health economic costs:
The most significant costs will be registered, including outpatient contacts related to stoma surgery, and some health care services associated with municipalities and general practitioners.

Calculation of costs is made on the basis of registration of length of hospital stay, including readmissions, outpatient clinics and reoperations. Moreover we register demographic data such as education and income.

Patients' use of services from GPs and the municipal health service and their possible return to working life will be recorded. As such, we register costs associated with the use of the medical services, when contacting the GP or primary care nurse. When patients return to their former work life the societal costs are reduced, which will be identified and registered (35, 36).

Social activities will also be registered, and will contribute to a description of, when patients return to their habitual lives and activities.

Registrations are based on self-registration in a diary provided to patients at discharge, since this type of information can be difficult to access retrospectively, as patients will tend to forget or overlook visit (37, 38). Using a diary to record data relating to cost reporting is a valid method to capture events that partly take place outside of hospital, and which partly stems from the patient's daily life.

Quality of life:
The project also measures and compares health-related quality of life measured with Short Form 36 (SF36) 3, 6 and 12 months postoperatively. We also measure disease-specific quality of life in the form of European Organization for Research and Treatment of Cancer QLQ-CR30 + CR29 (EORTC QLQ-CR30 + CR29). Furthermore, we measure and describe the specific quality of life of patients with stoma (control group), which is measured with Ostomy Adjustment Scale (OAS).

Short Form 36 (SF36, general quality of life) (39) EORTC QLQ-CR29 (40, 41) and Ostomy Adjustment Scale (OAS, disease-specific quality of life) (42, 43) are all designed as convenient questionnaires designed for completion in the presence of the interviewer, self-completion and telephone completion. Furthermore, patients are also asked about demographic data in the form of education, labor market and marital status.

SF-36 was developed in a U.S. study measuring general health concepts, and the form has since been used in numerous clinical trials and population studies, and is validated in a number of interna-
tional and Danish and Swedish studies. SF-36 is a questionnaire that can be used to evaluate the person's general health status, either by self completion, or by completing it during an interview with an interviewer. It only takes about 15 to 20 minutes to complete. The questionnaire can be used to construct a generic measure of health status, which means it can be used for all age groups (aged 14 and over) and all patient groups. The questionnaire provides a measurement of a person's general health status, and explores a person's self-rated health, as well as factors aimed at measuring physical, social and mental function. The questionnaire consists of 36 questions which are divided into 8 scales that are summarized in a measure of physical health and measure of psychological health, thus giving a score of a person's overall health.

EORTC QLQ-CR29 + CR 30 (40, 41) are in the original form, developed in 1987 as cancer-specific measurement tools under the auspices of EORTC (CR30), which is an international nonprofit organization. In its current form it has been revised and now includes a general cancer-specific part (CR 30) and a more specific part against gastrointestinal symptoms (CR-29). In total there are 59 questions, which consist of functional scales, symptom-oriented scales and quality of life scale.

OAS is a questionnaire developed to assess patients' subjective adaptation to life with a stoma with a focus on physical, psychological and social changes as a result of stoma creation. It is a form with 34 questions answered on a Likert scale ranging from 1-6. This provides a possible outcome between 34 to 204 points, where a higher score indicates a better adaptation and therefore a higher health related quality of life. The form is validated and applied to patients with various stomas and can be used at different times in relation to construction of the stoma.

Both general and disease specific quality of life measured 3 months (+ / - 2 weeks), 6 months (+ / - 2 weeks) and 12 months (+ / - 2 weeks) after the construction of the temporary ileostomy. In the first survey after 3 months, it is assumed that patients in the control group has not yet had the stoma closed. OAS is only applied as long as the patient has a stoma.

The forms will be filled out in the presence of an interviewer to ensure a high response rate and to minimize problems with misunderstanding of the forms.

**The reversal of the ileostomy:**
The reversal will be performed after assessment of:

- integrity of the anastomosis evaluated by CT scan
- whether the patient has an ongoing infection
patient's general condition, as described in the separate form for postoperative recovery.

Ad 1 Patients eligible for the study undergo a computed tomography of the rectum with a water soluble contrast medium to visualize the anastomosis and possible leakage. A surgeon or a radiologist places a Foley catheter in the rectum just below the anastomosis, and instils between 300 – 500 ml of the contrast in a 5 % solution. In this way it is possible to visualize the anastomosis and any occurring leaks. The ct-scan is a standard procedure during the project-period, and will be 6-8 days after construction of the ileostomy. Evaluation of the ct-scan will be done by a surgeon and a radiologist.

Ad 2 Blood samples are examined daily, according to local standard.

Ad 3 The patient's general condition is assessed by a surgeon and it is documented in the form available in the CRF:

<table>
<thead>
<tr>
<th>Postoperative recovery</th>
<th>CRP (value listed)</th>
<th>Hemoglobin (value listed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition (tick)</td>
<td>The patient eats and drinks sufficient</td>
<td>The patient needs iv. fluid</td>
</tr>
<tr>
<td></td>
<td>The patient needs total parenteral nutrition</td>
<td>The patient needs tube feeding</td>
</tr>
<tr>
<td>Mobilization (tick)</td>
<td>Patient out of bed &gt; 6 hours / day</td>
<td>Patient out of bed &lt; 6 hours / day</td>
</tr>
<tr>
<td></td>
<td>Patient out of bed &lt; 6 hours / day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient out of bed &lt; 1 hour / day</td>
<td></td>
</tr>
<tr>
<td>Ostomy function (tick)</td>
<td>Stools _________</td>
<td>Flatus __________</td>
</tr>
</tbody>
</table>

**Timing of the closure of the ileostomy:**

Intervention Group:
The reversal of the ileostomy is done 8 to 13 days postoperatively according to the department’s standard guidelines. It is registered whether the anastomosis is hand sutured or stapled.

Control group

The reversal is done after a minimum of 12 weeks according to the department's standard guidelines.

**Stoma training in the control group:**
Patients receive stoma training according to local standard guidelines in order to handle their stoma until it is closed. This means that the patient receives standard treatment while hospitalised as well as after hospital leave, where the patient will be referred to the outpatient stoma clinic.

**Stoma training in the intervention group:**
Patients, who are having the stoma reversed early, do not receive standard care regarding handling of the stoma, as they do not need a full training course. Their training is directed towards individual needs in order to leave hospital for a few days while waiting for surgery. The training needs might for instance be emptying the pouch, changing the barrier and observing the pouch. The patient may want to go home on leave just days until closing of the stoma depending on local conditions.

**Conduct of ethics:**
Participation in the project is voluntary and patients are only included after oral and written information in order to obtain patients written consent according to the ethical standards in Denmark and Sweden. The project complies with the Helsinki Declaration II and Act 503 of 1992 on research ethics committee system, and will await approval by the local Ethics Committee before starting. The surgery is conducted on surgical departments, that are specialized in colorectal surgery. Closing of temporary ileostomies, and other medical procedures in this project are part of the department’s standard treatments. Thus, it is only the timing of the reversal, which differs from standard procedure.

Patients may at any time withdraw their consent to participate, without this having any effect on observation, treatment and nursing of the patient. The authorized healthcare professionals involved in the project will act with awareness and conscientiously, when treating the patients.
Risks and side effects of the experiment:
The surgical procedure is alike for the intervention group and the control group, and the control group is treated according to local standard guidelines. The intervention group receives exactly the same treatment and nursing as the control group, apart from the stoma training, which is adapted to individual needs.

As described earlier, previous studies do not associate earlier reversal of the ileostomy with greater risk for morbidity or mortality, as long as the patient examined by a surgeon prior to inclusion and randomization.

There are no known risks or side effects to questionnaire surveys.

It is expected that patients will experience a major improvement in quality of life related to an early reversal and return to normal bowel function. It is also expected, that the patient will resume habitual activities such as sports, work life and other social and personal activities, including an ordinary family life.

This project will contribute with final recommendations for the timing of the reversal of the temporary ileostomy in relation to morbidity and mortality. This will have major significance for the development of future clinical guidelines in the field.

This experiment will also contribute with new knowledge about health economic effects, which is used for benchmarking, when comparing health care. Furthermore, the research will provide knowledge about how life is affected when having a temporary ileostomy, which is important for the clinical care and treatment.

Science Ethical approval:
In Denmark, the project is approved by the Science Ethics committee of the Capital Region and in Sweden, the project in the same manner approved by Etiska Prövningsnämnden in Gothenburg.

Review of data monitoring:
The project was approved by the Data Inspectorate in Denmark and by Personuppgiftsombudet large Sahlgrenska Universitetssjukhuset, Västra Götaland Region in Sweden

Clinical Trials:
The project is registered at www.clinicaltrials.gov.
Financial support:
The project receives no financial support from a commercial party.

The project was initiated by the principal investigator Jacob Rosenberg, Professor, MD, who is employed and salaried by Herlev Hospital, and Anne Kjaergaard Danielsen, PhD student, who is also employed and salaried by Herlev Hospital.

Compensation to patients included in the study:
The enrolled patients will receive no compensation for their participation.

Guidelines for obtaining informed consent:
Patients who are eligible to enroll are informed orally and in writing by the local investigator. Once the patient has agreed to participate and signed the consent form, the patient is included. After inclusion the patient is randomized to the control group or the intervention group.

Information about the project will take place immediately after it is assessed that the patient is suitable for inclusion, which is after the ct-scan and after medical assessment. The written material will be handed to the patient to read prior to the oral information. The oral information will be held in an undisturbed place, either in a separate room, or if the patient is bedridden, it is ensured, that the patient agrees to be informed in the bed room. If possible, other patients will be asked to leave the room. Patients are encouraged to have a relative present, when informed about the study, and the arrival of a participating person will be awaited.

The written material is handed to the patient by a health professional appointed by the local investigator. The oral information is given by professional, appointed by the local investigator and competent to answer any questions, which might arise during the session.

After the patient is informed, he or she will have up to 24 hours of to decide whether to participate, and it is possible to withdraw the consent at any future time.

Inclusion in the project is done after receiving the patient´s written consent to participate in the project.

Patients will be randomized into the control group or the intervention group shortly after inclusion. Patients will, whatever the outcome of randomization is, be informed the closing of the ileostomy according to local procedures.
Reference List


