

LapLav (LAParoscopic LAVage)

A national, registry based study of clinical results and of health and well-being in patients after emergency operation for perforated diverticulitis to study implementation of laparoscopic lavage and to compare outcomes with those of resection surgery in routine use.

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1. STUDY ORGANISATION

1.1 Study planning group:

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1.2 Principal investigator: Eva Haglind

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1.4 Study secretariat

SSORG/Göteborg at Department of Surgery, Sahlgrenska University Hospital/Östra, Göteborg.

1.5 Steering committee

A planning group consisting professor Eva Haglind, post doc Mattias Prytz, MD, PhD, doctor Andreas Samuelsson, associate professor Eva Angenete, post doc Mattias Block, MD, PhD, and statistician David Bock PhD.

1.6 Scientific framework

The study is organised and performed within the framework of Scandinavian Surgical Outcomes Research Group, a network of surgeon-scientists in hospitals in Sweden and Denmark. This network started collaboration in 2008 formulating scientific questions or hypotheses, writing protocols and in the running of trials. The secretariat is situated at Sahlgrenska University Hospital, Göteborg. The website is www.ssorg.net

1.7 Writing committee

In agreement with internationally accepted guidelines for authorship members in the planning group who are active in planning, running, analysis and writing will be part of the writing committee.

Publication of results is planned for international "peer review" scientific journal.

2 PROTOCOL

Background

Diverticula of the large bowel are common; possibly around 50% of the population aged 70-80 years have diverticula. Symptoms are probably not common, and if present are unspecific. Often the diverticula are found at colonoscopy or radiologic examinations of the bowel due to other reasons¹.

Some individuals with diverticula develop an inflammation called diverticulitis, possibly 15-20%, with pain in the lower abdomen and perhaps low grade fever. This is often called uncomplicated diverticulitis. The typical case will not require any specific treatment, and recent randomized controlled trials have not found any improvement in clinical course or symptoms through hospital care, antibiotics or diets².

A small percentage develops complicated diverticulitis most often due to a perforation of the bowel that can lead to an abscess formation in close contact with the inflamed part. This can almost always be treated conservatively with antibiotics with or without percutaneous drainage. Patients with an abscess formation are treated in hospital³.

The most severe form of perforated diverticulitis is when the perforation leads to peritonitis, either purulent or fecal. Evidently these patients will be seriously ill, often septic. In Sweden the incidence is 3.5/100000 inhabitants/year. In that situation an emergency operation is considered necessary, and until recently this would consist of resection of the inflamed, perforated part of the sigmoid colon closing the rectal stump and creating a colostomy. Some have advocated resection with primary anastomosis, with or without a temporary, covering loop-ileostomy. Regardless of which type of stoma, the plan will always be to restore bowel continuity at a later stage. However in retrospective studies up to 40% of the patients will end up with a permanent stoma⁴.

Some 15 years ago a few, small case series were published, with good results of a quite new treatment concept, consisting of lavage that is cleaning the abdominal cavity from pus by using saline through a laparoscopy in combination with drainage and antibiotics⁵. The case series only included patients with perforated diverticulitis and purulent peritonitis, not patients with fecal peritonitis. One large prospective study without controls reported high success rate and that only 2% of the patients were in need of colon resection in addition to lavage. This led to the start of four randomized controlled trials (RCT's) comparing laparoscopic lavage with the standard treatment, i.e. emergency colon resection.

Three of the four trials have reported their results⁶⁻⁹. Several meta-analyses have also been published, and in short the results are that laparoscopic lavage is safe and results in a significantly lower percentage of patients in need of further surgical procedures within one year, at the cost of more infectious complications in the immediate post-operative period¹⁰⁻¹⁵. Two health economic evaluations showed lower costs for the laparoscopic lavage treatment compared with colon resection with or without a stoma^{16, 17}.

The second group of patients with perforated diverticulitis is those where the peritonitis is due to leakage of fecal content from the colon. This is an even more uncommon situation, and few systematic studies have been reported. For this situation, no new treatments have been

suggested and resection of the perforated part of the large bowel with a stoma is the norm. However, few reports of outcomes exist and possibly none on a national basis.

Aims and hypotheses

The aim of this study is to evaluate clinical results and effect on health and well-being in patients operated for perforated diverticulitis with purulent peritonitis by laparoscopic lavage in Sweden when used outside of prospective studies/trials and in comparison with the traditional treatment, i.e. colon resection with or without stoma formation.

A secondary aim is to evaluate the outcome after fecal peritonitis.

The hypothesis is that laparoscopic lavage as treatment for perforated diverticulitis with purulent peritonitis is safe, efficient and cost saving, when used in routine health care.

Primary endpoint

- need for further surgical interventions within 12 and 24 months of index surgery

Secondary endpoints

- percentage of all cases treated by laparoscopic lavage and emergency colon resection, respectively
- complications (Clavien-Dindo grade \geq IIIa) within 90 days of index surgery
- mortality (90 days and 12 months respectively)
- colon cancer diagnosis <12 months
- patient experience measured using a questionnaire 2-3 years after index surgery
- health economic analysis

For the secondary aim regarding fecal peritonitis the following endpoints will be evaluated:

- complications Clavien-Dindo \geq IIIa within 90 days of index surgery
- mortality
- need for further surgical interventions within 12 and 24 months of index surgery
- patient experience

Data retrieval

The study will be organised within SSORG and primary intention is to identify a Swedish national cohort through the National Patient Register, National Board of Health and Welfare, Sweden, linking the resulting cohort to the Death Register and to the Cancer Register, both at the National Board of Health and Welfare.

To identify the cohort, the search model for the National Patient Register will include the diagnosis classified according to international classification of diagnoses code (ICD-10) K 57 coupled with all NOMESCO codes for colon resection or laparoscopic lavage. (Appendix 1)

Based on the data retrieved from The Patient Register, the SSORG secretariat, Sahlgrenska University Hospital will contact each hospital where patients were treated with index surgery in order to retrieve data from original patient documentation (index operation and surgical care within 12 and 24 months) from which data on initial examination (type and results), technical details of index surgery, all ICD 10 and NOMESCO codes, postoperative care details such as time in intensive care unit, complications type and classification according to Clavien-Dindo, length of hospital stay, and for re-admissions ICD10 diagnosis, examinations, reoperations (NOMESCO codes), complications classified according to Clavien-Dindo. From the Death Register date of death as well as diagnosis will be retrieved and from The Cancer Register any cancer diagnosis recorded after the index surgery by ICD10 code and date.

From the Swedish Social Insurance Agency (Försäkringskassan) data on sick leave during 12 months following index surgery will be retrieved for the cohort, including all episodes, their length and diagnoses.

All patients still alive will be contacted for consent before any send-out of questionnaires, planned to occur 2-3 years after index surgery. The initial contact will be through an informative letter, followed by a phone call from a research nurse at SSORG. If the patient consents the questionnaire will be sent, including the consent form.

Data base management

The database will be administered within Göteborg University (server) and be managed by the data administrator at SSORG. Application to the Ethical Committee in Göteborg will be made as well as application to Västra Götaland “personuppgiftsombud” for permit to keep the key code at Sahlgrenska University Hospital (server).

Study design

According to previous data it can be estimated that somewhere around 350 cases per year should be registered in the national Patient Register. Using International Classification of Diagnoses (ICD)-10 codes and the Nordic Medico-Statistical Committee (NOMESCO) codes in combination with registration of “emergency” and “planned” for episodes of care, the cohort for 2016, 2017 and 2018, respectively will be identified as soon as the registry is “closed” for each year.

Using the data with personal identification codes and hospital codes, the hospitals can be contacted for information on clinical course and the collection of relevant data (described above). The reason to use hospital records is that the reporting of complications in Patient Register has been found to significantly differ compared to reporting by Case Report Forms (CRF's) in randomized controlled trials where complications are covered with a higher level of detail. Using a case report form and original patient documentation the quality of data retrieved concerning complications will improve compared with what can be found using only information in the Patient Register.

In order to study the patient experience a detailed questionnaire including functional aspects as well as experience of wellbeing and quality of life will be sent out after receiving informed consent, when 24-36 months have passed from the index operation. The individual patient will be contacted (see above) by a process that we have used in several clinical studies, resulting in a compliance of approximately 90%. The patients will first be contacted via letter followed by a telephone call. During the phone conversation, we ask for confirmation that the patient has indeed been treated for diverticulitis and ask for his/her consent to participate in the patient experience (questionnaire) part of the study.

The retrospective clinical follow-up time using hospital records for each patient is aimed at 24 months, with a questionnaire 24-36 months after index surgery. Mortality will be retrieved from the national Cause of Death Register.

In the age group dominating perforated diverticulitis, colorectal cancer is relatively common. A legitimate concern about the laparoscopic lavage treatment is that there would be a risk of missing concomitant colorectal cancer. In the trials of laparoscopic lavage an examination of the bowel as soon as possible after the index surgery was part of the protocol. In order to study risk of colorectal cancer the National Cancer register will be used to find any diagnose of colon or rectal cancer (C18 and C20) within 12 months of index surgery in the cohort.

At the time for send-out of the questionnaires patients will be identified through the national Civil Register prior to contact, in order to avoid misplaced contacts trying to reach individuals who have died, which could be stressful for remaining family.

Inclusion criteria

All patients registered in the Patient registry with ICD 10 codes K57 classified as emergency admissions and with a NOMESCO code JAH01(diagnostic laparoscopy), JFB46 (resection of sigmoid colon), JFB60 (resection of sigmoid colon, sigmoidostomy and closure of the distal stump), JFB61 (laparoscopic resection of sigmoid colon, sigmoidostomy and closure of the distal stump), JFB63 (other colon resection, colostomy and closure of the distal stump), JAK04 (laparoscopy and peritoneal lavage), JAW97 (other laparoscopic operation involving abdominal wall, mesentery, peritoneum or the omentum)

The cohort will be divided into two groups when analysing and presenting results, perforated diverticulitis with purulent peritonitis (Hinchey grade III) and perforated diverticulitis with faecal peritonitis (Hinchey grade IV) .

Exclusion criteria

Patients where hospital records reveal that the index admission was misclassified (not perforated diverticulitis) will be excluded.

No informed consent received or withdrawal of consent (questionnaire)

Hinchey I and II.

Data collection

The following information will be collected from the Patient Register:

- full personal identification
- all ICD-10 codes for index admission
- all NOMESCO codes for index admission
- date for operation
- all ICD-10 codes for all readmissions within 24 months of index
- all NOMESCO codes for all readmissions within 24 months of index admission
- dates for each re-operation
- date of admission and discharge respectively for all admissions
- hospital/s where treatment was given for index and readmissions respectively
- emergency/elective care for index and readmissions respectively.
- For each admission ACT codes
- Marital status
- Place of living according to reporting agency
- Place of living according to SCB
- Department from which the patient was discharged
- Discharged to (four categories)

From the national Register on Causes of Death the following variables will be retrieved 12 months after index operation.

age at death (years), year of death, date of death, country of birth, ICD10 code, reasons for death other than illness (Chapter 19), sex, county and town of official home, multiple causes of death (ICD 10), date of operation, operation <4 weeks of death, personal identification number, details of placement of cause/s of death, underlying causes of death (ICD10), officially not living in Sweden, nationality if not living in Sweden, date of death, sex, date of birth, age at death.

From the national Cancer Register the following information will be collected:

- Any colorectal cancer diagnosis (ICD-10) after the date of index surgery
- date of colorectal cancer diagnosis
- TNM stage (colorectal cancer as above)

External validity

External validity is ascertained by identifying the population through the national Patient Register, which has a high coverage as all caregivers in Sweden are by law requested to report to this registry. The same is true for the Cause of Death and Cancer Registries.

Patient information and informed consent

Before send out of the questionnaire, each patient still alive will receive a letter with information about the study and that a co-worker in the study will telephone the patient within a few days. In the telephone conversation the study personal will make certain that the patient has understood the written information in the letter. After this the patient is asked if he/she consents to participate. If the answer is yes the patient is further asked if she/he consents to receive the questionnaire. If the answer is yes the questionnaire is sent. In the letter containing the questionnaire a consent form is included as well as a prepaid envelope to return questionnaire and consent form to the study secretariat.

In the questionnaire contact address to the study secretariat SSORG is given and the patient is asked to call if she/he needs further information or has questions. Two weeks after send-out a thank you/remainder is sent, but after this no further active contact is taken. In the questionnaire a written consent form is included.

Retrieval of hospital records

All hospitals with patients included in the cohort from the national Patient register will be contacted in order to retrieve hospital records. No other input is expected from the hospitals.

Data collection from hospital records

The clinical record form used will collect data on details from the index surgery such as:

- Hinchey classification
- Type of surgery
- Amount of saline used when laparoscopic lavage was performed
- Primary anastomosis with/without temporary ileostomy
- Hartmann's procedure
- Loss of blood (if possible)
- Length of surgery (if possible)
- Length of stay

Further details about the index admission regarding:

- Complications, to be classified according to Clavien-Dindo
- Re-operations with NOMESCO codes

Further data on re-admission/s within 90 days regardless of reason:

- Details of operations, apart from NOMESCO codes also indication and if appropriate details described above for index surgery
- Complications after re-operations to be classified according to Clavien-Dindo (if appropriate)
- Length of stay

Further data on re-admissions after 90 days if appropriate i.e. related with the index surgery for perforated diverticulitis

- Complications to be classified according to Clavien-Dindo
- Re-operations, if any, with indication, type and NOMESCO codes
- Length of stay at readmissions

Questionnaire

Patient self-estimate of health, wellbeing and function will be assessed using a questionnaire, developed specifically for this study.

The questionnaire is based on our experience from the randomized trial DILALA and includes questions used in that trial as well as questions used in a study of functions and quality of life in a representative Swedish population. The entire questionnaire has been expert content validated and will be face-to-face validation with patients.

Most questions will be according to a clinimetric approach, such as the “Steineck concept” with questions about one symptom/function “at a time”, with separate questions on duration, intensity and severity. Some of the questions will come from questionnaires used earlier in other patients groups, whereas others will be newly constructed. Many of these questions have been used in earlier studies and trials by our group, including specific questions about bowel habits and stomas. Questions about socioeconomic details are included as well as questions on perceived wellbeing and quality of life. A few validated instruments are included in entirety such as ostomy scale, LARS (low anterior resection syndrome) score and EQ5D.

Work plan

Application to the Ethical Committee will be made during spring 2017 as well as to the “Personuppgiftsombud”.

Retrieval of the cohort of 2016 is planned during 2017, for the cohort of 2017 is planned for spring 2018, and for the cohort of 2018 during spring of 2019. A control for readmissions for the cohorts of 2016, 2017 and 2018 respectively in the Patient Register will be run in the spring of 2018, 2019 and in the spring of 2020 respectively and at each occasion a retrieval of information from the Cause of Death and Cancer Registers will be performed. Additional retrieval of hospital records as needed.

Statistical Methods and power calculation

Based on 24 months results from the DILALA trial, the proportion of patients with at least one re-operation after emergency colon resection with colostomy was approximately 70%. Assume that 25% of the patients being operated with laparoscopic lavage and 75% with colon resection with colostomy, and there is a true absolute reduction on re-operations of 10% for laparoscopic lavage compared with colon resection. With a total of 1000 evaluable patients,

there will be 80% power to detect the reduction using a two-sided test at 5% significance level.

The evaluation of the relationship between treatment and clinical and questionnaire data will be by regression analysis. The influence of confounding background factors will primarily be accounted for by adjusted analyses using multiple regression analysis but propensity score matching may as well be considered.

Data retrieval and storage

The secretariat will be in the Scandinavian Surgical Outcomes Research Group (SSORG) in the Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy at Gothenburg University and Område 2, Sahlgrenska University Hospital, Göteborg.

The key code where full personal identity is coupled with a unic study number for each patient will be kept in a server within Sahlgrenska University Hospital, with personal access for 2-3 co-workers within SSORG.

The database where variables collected from the various retrievals (Patient Register, Death register, Cancer Register, hospitals records and patient questionnaires) will be based on the study number as identification alone. This database will be kept on a server within the DAF-GU network at Gothenburg University with access for the data manager and the research nurse responsible for the study using security measures such as user name and code. The network has high security standards with automatic back-up of server data and fire walls against external violation.

Health economic evaluation

If significant differences in clinical, functional or quality of life measures between to the surgical methods are found, a health economic analysis will be performed. In the analysis data from the study will be combined with prices from the cost-per-patient system at Sveriges Kommuner och Landsting, or where appropriate, from Sahlgrenska University Hospital, in combination with sensitivity testing of results.

Ethical consideration

The study will be submitted for approval to the Regional Ethical Committee (Regionala Etiska Prövnings Nämnden), in Göteborg.

The study will be registered in the study database “clinical trials.gov”

Approval from the “Personuppgiftsombudet” at Sahlgrenska University Hospital to keep a key code.

Financing

The study will be supported by existing grants from Swedish Research Council (Eva Haglind) and ALF- grants at Sahlgrenska University Hospital (Eva Haglind)

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