Protocol

Diverticulitis – **la**paroscopic **la**vage vs resection (Hartman procedure) for acute diverticulitis with peritonitis

DILALA trial

A trial within the Scandinavian Surgical Network for Clinical Trials

Version 10

COMMITTEES

Protocol committee: The Scandinavian Surgical Outcomes Research Group (SSORG)

Steering committee: Protocol committee plus the local investigator for each participating centre

Writing committee: Those members of the protocol and steering committees who actively work and fulfil established criteria for "authorship" as well as doctoral/post.doc students actively working with the trial.

COORDINATING CENTRE

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

Principal Investigator: Eva Haglind, MD, adj. Professor of Surgery

Deputy Principal Investigator: Jacob Rosenberg, MD, Professor of Surgery

Post-doc: Eva Angenete, MD, PhD

Doctoral student: Anders Thornell, MD

PROTOCOL SUMMARY

All patients with suspected acute diverticulitis for whom an emergency operation has been decided are primarily included. The operation starts with a diagnostic laparoscopy in all patients. Patients with Hinchey I-II diverticulitis, if operated on, undergo only laparoscopy and are not a part of the trial. Patients with Hinchey IV diverticulitis are converted to open surgery and resection according to Hartman (all). Patients with Hinchey III are randomized between

A) laparoscopic lavage and drainage

B) open resection with closure of the rectum and colostomy (Hartman's procedure). Primary endpoint is of the re-operation rate within 12 months from index surgery. Secondary end-points include clinical variables, quality of life and health economy analyses.

INTRODUCTION

Diverticula of the colon are a common finding increasing with age (1). Most patients are non-symptomatic, and the finding of diverticula is mostly "by chance" when colonoscopy is performed for other reasons. Inflammation of colonic diverticula, i.e. diverticulitis, is a well know clinical situation (2), which it is often possible to treat conservatively (without surgery) with GI rest with or without antibiotics. However, in a small number of patients, the inflammation is more serious, presenting with peritonitis with or without perforation (3).

Diverticulitis has been classified according to severity by Hinchey in grades I – IV, where IV represents obvious leakage of faecal content into the abdominal cavity (4). In Hinchey III – IV, i.e. peritonitis with signs of perforation of the colon and/or large abdominal mass as a sign of abscess formation, the traditional treatment has been an emergency operation, with resection of the affected segment of colon, most often the sigmoid, closure of the rectum and diversion (colostomy), i.e. a classic Hartman's procedure (5-8). A less common alternative is a colon resection with primary anastomosis (7). The number of patients with diverticulitis treated by emergency surgery varies between different centres.

At the Sahlgrenska University Hospital, Göteborg a retrospective study including all patients with a combination of ICD 10 codes K572, K573 and emergency admittance and a surgical procedure between 1 January 2003 and 30 June 2008. There were 4-5 emergency operations per year and 100 000 inhabitants and the total number of patients was 110. The mortality was 5% during the primary hospitalization. Two more patients died during a later hospital stay. In that study the mean age at the time of the first emergency operation was 65 (range 32-98) years. The mean length of hospital stay was 17 (range 1-111) days for the first hospitalisation. The dominating primary procedure was a Hartman's resection, only 21% were operated with a primary anastomosis. The mean number of procedures during the primary hospitalisation was 1,3 (range 1-10). Re-admission occurred one or more times in 50% of the patients, and the mean number of re-admission was 1 i.e. many patients were re-admitted several times. A total of 42 patients underwent one or more (range 1-8) re-operations at a later hospitalisation. Re-admissions and re-operations were either emergency or planned, the latter in order to re-establish bowel continuity. However 25 patients with a colostomy and who survived the initial hospitalisation, were never considered/did not want a re-operation for re-establishing the bowel continuity (17). Thus, even in a recent study, with a comparatively "low" mortality, the suffering, morbidity and resource consumption is high as a result of complicated diverticulosis.

During the last few years several reports of the results of a new principle for the emergency surgery for complicated diverticulitis have been published. The alternative treatment modality reported is laparoscopy, lavage and drainage (9-16). So far only case series (9-13, 16) have been reported. Only one of these is prospective (14) and none of the studies are controlled. A recent review of the literature summarised the results (15). Compared with historical data the results are in favour of the laparoscopic approach (15). However, as none of the studies was

controlled, this does not warrant any changes in the routine treatment of complicated diverticulitis.

The aim of this trial is to compare the traditional open emergency resection and colostomy (Hartman's procedure) with laparoscopic lavage and drainage, for diverticulitis Hinchey grade III, in terns of effects on re-operation rate and other clinical outcome variables.

STUDY DESIGN

This design is
randomized,
international,
multi-center
study comparing laparoscopic lavage and drainage with conventional sigmoid resection for diverticulitis Hinchey grade III. The design involves all consecutive patients with diverticulitis for whom an emergency operation has been decided upon.

Patients will be accrued from the hospitals represented in the SSORG. Surgical departments with interest in the treatment of perforated acute diverticulitis, where emergency abdominal surgery is performed and laparoscopy is a routine procedure, are welcome to join in the trial.

The initial step is laparoscopy and for those with Hinchey grade III randomization 1:1 to either of the two procedures: laparoscopic lavage and drainage or Hartman's procedure by open surgery. The initial laparoscopies will be reviewed to ensure that the Hinchey classification has been uniformely used in all participating centres. Elective resection of the colon at a later stage is not routine. Instead later resection should only occur if deemed necessary as an emergency procedure, during a renewed attack of complicated diverticulitis (18,19) or to treat complications to the diverticulitis (such as fistulas, stricture of the colon).

For patients with Hinchey grade IV all patients are treated with open surgery and Hartman's procedure, and excluded from the comparison.

The trial will be stratified according to hospital.

ENDPOINTS

Primary end-point:

Re-operation within 12 months of emergency operation.

Secondary end-points:

Re-admission

Postoperative infections, wound or deep infection (abscess formation)

Postoperative thrombosis

Other complications

Hernia

Bowel obstruction, requiring hospitalisation or operation

Total length of hospital stay (for diverticulitis and complications) during 12 months

Quality of life

Health economy analysis

Re-operation during primary hospitalisation

Mortality within 30 days of primary operation

Mortality within 12 months

Permanent stoma (stoma at 12 months postoperatively)

Re-admissions and re-operations registrered in including hospital database at 24 months.

ETHICS

The trial must be approved by the appropriate ethics committee for each participating institution prior to entry into the study. In Sweden the coordinating centre (Sahlgrenska University Hospital) has applied for all Swedish participating centres and the trial was approved (EPN/Göteborg Dnr 378-09).

In Denmark professor Jacob Rosenberg has applied for all Danish participating centres and the trial was approved (Region Hovedstaden CVR/SE 29190623, Protokol nr H-4 2009-088).

In Norway dr Esther Kuhry will apply fort St Olav's hospital, Trondheim.

Eligible patients or a relative should be informed in person by the treating surgeon and receive written information about the trial. Informed consent should be obtained from each patient/relative according to the guidelines of the ethical committee, prior to randomization into the study. Patients remain free to withdraw their consent to participate in the study at will and at any time without giving their reasons.

In Sweden the Ethical Committee has approved for the trial to include patients unable to give informed consent. In such cases a relative should be informed and also have written information, however the relative cannot consent. The patient can then be included. After the procedure the patient should be informed as soon as his/her condition allows this, and the patient can then either consent or refuse further participation.

ELIGIBILITY

Inclusion: criteria

Patients

* with suspected acute diverticulitis with intra-abdominal fluid or gas on CT or a simple X-ray of the abdomen
* a decision by the surgeon to perform emergency surgery
* possible to operate in regard to concomitant disease
*giving informed consent to participate (in Sweden also patients unable to give informed consent due to the emergent situation, see above)

Exclusion: criteria

Not possible to operate due to concomitant disease

Participation in other randomized trials in conflict with the protocol and end-points of the DILALA trial

RANDOMIZATION

Randomization will be 1:1 to laparoscopic or conventional operation, performed by closed envelope system in each participating hospital and will take place after the initial diagnostic laparoscopy has established perforated diverticulitis Hinchey grade III to be present, i.e. during operation. Randomization will be balanced and stratified by hospital.

When patients are not subjected to the treatment modality as randomized, data will be analyzed on an "intention to treat basis" (once randomized, patients will not be excluded or change groups because of conversion or type of surgery).

Patients who do not consent to participation or are excluded should be treated by open surgery and Hartman's procedure.

Randomization: criteria

Perforated diverticulitis Hinchey grade III at diagnostic laparoscopy

Exclusion from randomization: criteria

Hinchey grade I - II at laparoscopy i.e. no free fluid/pus in the abdomen – no further surgical procedure.

Hinchey grade IV at laparoscopy, i.e. gross faecal contamination will be converted to open surgical procedure with resection and stoma formation.

Other pathology than perforated diverticulitis, for example perforated appendicitis or stomach ulcer.

Exclusion after randomization

Withdrawn consent

Cancer diagnosed in resected specimen (only possible in randomised to Hartmann's procedure)

Cancer diagnosed at colonoscopy after initial episode

Intention to treat

All patients randomised in accordance with randomization criteria and not excluded correctly after randomization (criteria for this see above) will be analysed in group of randomisation. This means that patients randomised to laparoscopic lavage and converted to open surgery will be analysed in the "laparoscopic lavage group".

Grade	
I	Diverticulitis with a phlegmonous or a pericolic abscess.
II	Diverticulitis with a pelvic abscess or a retroperitoneal abscess.
III	Diverticulitis with diffuse/generalized purulent peritonitis.
IV	Diverticulitis with faecal peritonitis.

External validity

All patients with suspected acute diverticulitis for whom an emergency operation has been decided upon, should be registered in the "screening log" at each participating centre. Thus

patients who do not meet the inclusion criteria, as well as patients excluded after randomization, should be registered concerning date, hospital patient identification number, gender, age, ASA class, type of operations, and Hinchey grade. The reason for non-inclusion or exclusion should always be noted.

PRE- AND PERI-OPERATIVE CARE & EXAMINATIONS

CT of the abdomen showing signs of diverticulitis including fluid or perforation
Haemoglobin
Leucocytes
CRP
Body temperature
ASA classification

Patients should all be given antibiotics before start of the operation, the same regimen regardless of randomisation, and according to the routine in each participating hospital. Patients included in this trial cannot be included in other randomised trials in conflict with the protocol and end-points of the DILALA trial.

SURGICAL PROCEDURE

1 Laparoscopy including all four quadrants of the abdomen, to ascertain that pathology other than perforated diverticulitis is not present. A recording of this laparoscopy should be made, and a copy (un-identified) sent to the secretariat.
2 If Hinchey grade I-II – no further surgical procedures, only diagnostic laparoscopy and the operation is ended.
3 If Hinchey grade IV – conversion to open surgery followed by sigmoid resection, closure of the rectum/sigmoid colon and colostomy
4 If Hinchey grade III randomisation 1:1 between
   A) laparoscopic lavage and drainge
   B) open surgery, sigmoid resection, closure of the rectum/sigmoid and colostomy

<u>Open surgery</u>

All patients undergoing open procedure, either due to Hinchey IV or because of randomisation or non-consent, should be operated by removal of obvious faecal contamination and thereafter a resection of the inflamed part of the colon, most commonly the

sigmoid colon including the perforation, with a diverting colostomy (Hartman's procedure. A passive drainage should be placed in the pelvis for all patients and left in place for at least 24 hours.

Laparoscopic surgery

All patients should receive lavage with no less than 3 l of saline of body temperature, or more until return of clear fluid by suction and followed by a passive drainage placed in the pelvis and left in place for at least 24 h.

The same principle for removing the drainage should be used for both arms of the trial. These include body temperature <38.0, drainage fluid of a serous nature, volume < 200 ml/24 hours.

HISTOPATHOLOGY

All resected specimens should undergo histological examination, giving details about amount and severity of inflammation, yes/no as to perforation, yes/no to cancer and length of resection given in cm.

POST-OPERATIVE TREATMENT

Continued antibiotics according to local routines, the same principles for all patients with diverticulitis. Changes of antibiotics should be noted in the CRF, including the reasons for change and total time for systemic as well as oral antibiotics.

FOLLOW-UP

The day before discharge the patient should fill out the quality of life forms.

Minimum clinical follow-up at 6-12 weeks, 6 months and 12 months after the index surgery.

All patients should undergo a work up of the colon by colonoscopy, virtual radio-colonography or traditional radiological double barium enema as soon as clinically safe and always within 12 months.

Patients who undergo a second operation to re-establish bowel continuity (closure of the colostomy and re-anastomosis of the colon/rectum) will undergo a clinical follow-up at 6-12 weeks after this procedure, regardless of the basic routine of follow-up at 6 and 12 months after the index= the emergency operation. This means that for some patients the total follow-up will be more than 12 months.

The follow up should include
clinical control,
haemoglobin,
LPK,
CRP,
stoma yes/no.
re-admittance/s (separate CRF): date, ICD 10 code, length of hospital stay
re-operation/s (separate CRF): date, type of procedure (emergency/planned, type of operation),
Radiologic follow up as needed, date and type should be noted.
Patient reported quality of life by questionnaires post operatively before discharge from hospital, at 6 months and at 12 months. SF 36, EuroQol, EORTC C30 and C38 are in part included, specific questions about bowel symptoms, hernia, bowel related episodes requiring re-admittance and re-operation, socio-economic status, stoma care and ADL.

RECURRENT DISEASE

See above. It is adamant to report recurrences resulting in either re-admittance or re-operation. In the follow-up CRFs, questions about symptoms attributed to diverticulitis, are included.

DATA COLLECTION

A CRF should be filled in for the operation (by the surgeon), for the hospitalisation period (nurse) and for each follow-up visit (surgeon). The initial laparoscopy before randomization should be recorded, if possible, and in an un-identified form sent to the trial secretariat. For each episode of re-admittance and re-operation new CRFs are filled in. The questionnaires filled out by the patients are returned to the trial coordinating centre at Sahlgrenska University Hospital, all coded. The de-codification can only be performed by the local investigator at the hospital where the patient was included. The data base will be stored within the Sahlgrenska University Hospital IT system, using the security system inherent. The data base will be kept on a server within the hospital system and will be registered with “personuppgiftsombudet” for Sahlgrenska University Hospital.
Data can only be analysed or copied from the database by decision of the principal investigator and the deputy principal investigator together. All such decisions should be discussed by the steering committee.

SAFTEY COMMITTEE

At the point where half the intended accrual has been reached a group of independent scientists, who are not directly involved in the trial, will discuss the following variables: re-operations, re-admission, postoperative infections, postoperative thrombosis and other complications, cancer diagnosis and compare the findings in the two groups with the safety view. The committee will be asked to suggest to the steering committee whether the trial should continue or stop. The results as such will not be made apparent to or discussed by the trial steering committee at this point.

STATISTICAL CONSIDERATIONS

In a Swedish retrospective material from one large hospital (5.5 years, n=110) we found 40% renewed hospitalisation with re-operation for the same disease, many of which were stoma closures. The only prospective study of the laparoscopic lavage operation so far reported (7 years, n=92) had a 1% occurrence of further surgery after the initial episode, whereas the other seven studies, all retrospective, varied between 0% and 100% reoperation, all of which were colon resections. A reduction of the need for further operations to 10% of the patients in the group that has undergone laparoscopy and lavage is regarded as interesting. With alfa = 0.05, statistical power at 80% this would mean 32 patients in each group. In view of the relatively complicated flow chart for the trial and that all procedures are emergency surgery, the inclusion is set to 80 randomised patients (40 + 40).

ORGANIZATION

The trial secretariat function including data collection and the data base will be situated in the Sahlgrenska Academy, Gothenburg University/ Sahlgrenska University Hospital, Göteborg. In each participating hospital a local investigator will be responsible for the inclusion, the control of the internal validity, the data collection and participate in the steering committee. The trial has been registered in the British registry (ISRCTN) for clinical trials. There will be no publication, apart from presentation of the protocol and number of inclusions, during the inclusion part of the trial. The steering committee decides if an interim analysis should be made. Any analyses of results prior to full inclusion must be decided by the PI and deputy PI together. A plan for data analyses will be made by the steering committee well in advance of reaching full accrual into the trial. After reaching accrual, all analyses, results and conclusions will be discussed in the steering committee, as will any publication issues.

LITERATURE

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Appendices

CRF operation

hospitalisation

follow up visit

re-admission

re-operation