Akershus Universitetssykehus

Scandinavian Diverticulitis Trial – SCANDIV

A randomized prospective multicenter trial

Laparoscopic lavage vs. primary resection as treatment for perforated diverticulitis

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Abstract

Background: Acute diverticulitis is a common disease in the western world. Perforation of the acute diverticulitis with peritonitis is a feared complication and standard treatment (primary sigmoid resection such as Hartmann`s procedure) still has unsatisfactory results. Both mortality and morbidity are quite high. Several trials have reported a lower mortality and morbidity when acute perforated diverticulitis is treated with laparoscopic lavage instead of radical surgery. However, there are no randomized controlled trials supporting these observations.

Methods: We wish to conduct a randomized multicenter trial in Scandinavia in order to compare primary sigmoid resection with laparoscopic lavage as treatment for acute perforated diverticulitis. All patients presenting with suspicion of perforated diverticulitis will be offered inclusion in the trial if CT scan confirms clinical findings. We intend to include 150 patients divided in two arms over a period of 2 years. Main end-point is severe postoperative complications within 90-days. We will further look at long term morbidity, quality of life and cost effectiveness.

Discussion: Our project will give a scientific base for decision-making and correct treatment for perforated diverticulitis. Several main hospitals in Scandinavia have decided to participate in this trial and others have shown interest to join as well.

Abstract amendment 18th October 2015 (Long term follow-up): After the publication of the primary results of this trial in JAMA (October 6, 2015; Vol 314, No 13) we decided to prolong follow up from originally planned one year to 10 years.

Background

Diverticulosis is most commonly found in the western world where approximately 30% of those aged above 50 and more than 65% of the population above 70 years have this condition. Around 10-25% of individuals with diverticulosis develop diverticulitis and among these patients, approximately 15-20% experience severe complications such as formation of abscess, fistula, obstruction or perforation (1).
The term "perforated diverticulitis" is usually used to describe Hinchey stage III and IV. This condition requires surgical treatment.

Table 1. Hinchey classification of complicated diverticulitis (2)

Hinchey grade	Findings
I	Pericolic abscess
IIA	Distant abscess amendable to percutaneous drainage
IIB	Complex abscess associated with fistula
III	Generalized purulent peritonitis
IV	Faecal peritonitis

In 1921 Henry Hartmann described an operation method for recto-sigmoid cancer that consisted of tumour resection, closure of the remaining rectum and a terminal colostomy (3). In the 1950's this procedure, also referred as Hartmann's operation, was described as treatment for acute diverticulitis (4). This operation still is the most common treatment of perforated diverticulitis in Scandinavia. There are several disadvantages associated with Hartmann's operation. The mortality rate is 10-25% and morbidity rate is 30-50% (5,6,7). Colostomy is inconvenient for the patients and stoma complications are very common. In addition a secondary stoma reversal procedure is needed. According to some reports reversal of the colostomy should be possible for most of these patients but in reality more than 30% of them never get their stoma reversed (8,9).
Several alternative strategies for treatment of perforated diverticulitis have been described. Some authors have claimed that sigmoid resection and primary anastomosis with or without a defunctioning proximal stoma will lead to lower mortality, but until now no randomized trials comparing this procedure with Hartmann's operation have been published. All existing materials have the weakness of historical controls or a considerably degree of selection bias. The mortality for patients with generalized peritonitis does not differ significantly in these trials (5,6).
Recently the treatment of perforated diverticulitis by means of peritoneal lavage has been described and several series have reported surprisingly low mortality rates for patients with generalized purulent peritonitis (10,11,12,13). The recently published prospective multicenter series by Meyers and colleagues included 100 patients with perforated diverticulitis (10). All of those who didn't have faecal peritonitis (n=92) were treated with laparoscopic peritoneal lavage in addition to intravenous antibiotics. They reported a mortality rate of only 3% and

morbidity rate of 4% in this group. In a smaller study looking at the management of Hinchey 3 diverticulitis by comparing laparoscopic peritoneal lavage with primary anastomosis with defunctioning stoma, the authors did not find any differences in morbidity or mortality. However laparoscopic lavage reduced the length of hospital stay and avoided a stoma (12).
In the last years Hartmann`s operation has been the most common treatment for acute perforated diverticulitis in Scandinavia whereas primary anastomosis has been reserved for less severe cases and younger patients. We see now that some centers have adopted the new technique of laparoscopic lavage without any existing randomized data confirming its efficiency.
In 2004 Clavien, Dindo and colleagues proposed a modified classification of surgical complications based on Claviens original classification system which was published in 1992 (Table 3). This classification has been validated and has become a widely used tool in evaluation of the severity of postoperative complications (14,15,16,17). We are planning to use this classification system in the assessment of complications.

Main goals

The primary aim of this study is to evaluate whether there is a statistically significant difference in severe complications of acute diverticulitis if treated by primary sigmoid resection versus laparoscopic lavage. We will also evaluate whether there is a difference in recurrence of disease, long term morbidity and quality of life. For this reason each included patient will be followed up for at least one year.
Furthermore, in follow-up studies we wish to explore the cost-effectiveness of both treatments. Long-term follow-up will determine whether the patients undergoing laparoscopic lavage ultimately will require an operation to remove the diseased bowel segment.

Methods

Study design

Prospective multicenter randomized controlled trial including many centres in Scandinavia. The study will be administrated from Akershus University Hospital.
All patients admitted with clinical findings indicating acute perforated diverticulitis will be referred to an abdominal CT scan. Patients meeting the criteria listed in table 2 are offered participation in the trial. Further information and consent papers are given to the patients who must be thoroughly informed by the surgeon. Regardless of randomization, all included patients are immediately put on antibiotics preoperatively. The choice of antibiotic will depend on local guidelines used in each hospital. Preoperative supportive treatment is optimized independent of which group the patient has been randomized to. The following blood tests are registered at time of admission, discharge and follow up: Hemoglobin, WBC (white blood cell count) and CRP.

Table 2.

Inclusion criteria:

1. Age over 18
2. Clinical suspicion of perforated diverticulitis with indication for urgent surgery
3. CT scan with free air and findings suggesting diverticulitis.
4. Patient tolerates general anaesthesia
5. Patients written consent

Exclusion criteria:

1. Pregnancy
2. Bowel obstruction

Randomization

Patients are stratified according to participating centres. Dependent on the hospital capacity, each hospital will be likely to include between 3 and 10 patients per year. Randomization will be done online based. All participating hospitals will get access to the website for randomisation (https://webcrf.medisin.ntnu.no/client/index.php) with their site specific password and username. The randomization will be based on a block randomization with blocks of different size. This is to secure an even distribution of procedures at the different hospitals. Akershus University Hospital will keep a register of the randomization.

Randomization takes place as soon as the criteria above are met. The patient will be informed about the chosen operation method postoperatively. Subjects not wishing to participate in the study will be given treatment according to local hospital protocol. It is crucial that all operations for perforated diverticulitis irrespective of patients being included or not are registered in every participating hospital during the whole study period.

Surgical procedure

All patients are stoma marked preoperatively. All patients with Hinchey grade 4 proven peroperatively will be operated with Hartman`s procedure irrespective of preoperative randomization. Primary analysis will be on intention to treat. In case of a clearly visible hole in the bowel patients should be classified as Hinchey grade 4.

Primary sigmoid resection

The surgeon decides whether to perform the procedure open or laparoscopic. Determination of Hinchey grade and evacuation of contamination should always be done. It is up to the surgeon and local guidelines whether primary anastomosis or Hartmann`s procedure should be conducted.

In Hartmann`s procedure, the diseased colon segment should be resected down to the rectum with or without mobilization of left colon flexure. The rectum (defined as the part of the bowel where there is no taenia) is closed with staples and marked with a non-absorbable suture. A blind rectal pouch is left. A temporary sigmoid stoma is made at the preoperatively marked area.

In all cases the abdominal cavity is rinsed with at least 4 litres of saline until the drainage is clear. A drain is placed in the pelvis. The resected specimen should be referred to the pathologist for examination.

Laparoscopic lavage

Pneumoperitoneum is preferably obtained by open technique with an umbilical incision and placement of 12 mm port. Gas insufflation, followed by placement of at least two 5 mm ports for example in the left hypochondrium and in the lower right quadrant. The peritoneal cavity is inspected thoroughly and Hinchey classification is determined. Patients with Hinchey grade III or lower will undergo lavage with at least 4 litres of saline. All quadrants are rinsed until drainage is clear. Adhesions to the sigmoid should not be dissected. Two non-suction drains are inserted preferably through port openings with one to the left side of the pelvis and one to the right side of the pelvis. Patients graded to Hinchey IV (including those with a visible hole in the bowel) are converted to Hartmann's procedure.

Postoperative treatment and follow-up

Intravenous antibiotic treatment is continued for a minimum of 3 days. Depending on clinical findings, oral antibiotic treatment can be continued. Antibiotic treatment is given for a total of 10 days. It is recommended that patients start enteral nutrition as early as possible. Early mobilization and discharge is favoured. At discharge blood tests are registered, including haemoglobin, C-reactive protein and WBC, and complications are registered as listed below.

Endpoints

The primary endpoint of this study is severe complications within 90-days. Other than that we will look at secondary endpoints as listed below. (Table 3) In order to classify complications as severe we are planning to use the Clavien-Dindo Classification of Surgical Complications scoring system. All scores over grade IIIa will be considered as severe complications. (Table 4)

Table 3. Endpoints

Primary endpoint:
90 days severe complications (Clavien-Dindo IIIb, IV or V)

Secondary endpoints:
1. Duration of operation
2. Length of hospital stay
3. Complications individually
a. Reoperation
b. Wound infection
c. Bleeding
d. Secondary peritonitis
e. Heart and lung complications
f. Stoma complications
g. Urinary tract infection
h. Deep vein thrombosis/thromboembolism
i. Cerebrovascular event
j. Others
4. Stoma one year postoperatively
5. Quality of life after operation according to "Cleveland Global Quality of Life" (18)
6. Cost effectiveness

Table 4. Clavien-Dindo Classification of Surgical Complications (15)

Grade	Definition
Grade I	Any deviation from the normal course without the need for pharmacological treatment or surgical, endoscopic and radiologic interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
III a	Intervention not under general anesthesia
III b	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
IV a	Single organ dysfunction (including dialysis)
IV b	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

**Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.*
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Outpatient follow-up

I **3-4months:** Registration of 90 days morbidity and complications.

II **1 year:** Registration of morbidity and stoma reversal. If stoma reversal was not conducted, the reason for this is registered.

Patients in the laparoscopic group should be examined with colonoscopy 2-3 months after the operation. Patients in the Hartmann group should have a colonoscopy before reversing the stoma.

Statistics

Primary analysis is based on "intention to treat".

Power calculation:

Nil hypothesis (H_0) is that there is no difference in 90-days severe complications. The alternative hypothesis (H_1) is that the frequency of severe complications within 90-days differs. We have no sufficient data to estimate those frequencies. Earlier trials have reported quite high morbidity rates for primary resection (30-50%) whereas the morbidity rate for laparoscopic peritoneal lavage seems to be much lower (ca 10 %). It is assumed that the real rates for 90-days severe complications are 0,3 and 0,1. Significance is put to the 5% (0,05) level and power to 80% (which means that presuming H1 and the assumed mortality rates are right there is an 80% probability of finding significance at the 5% level). This makes it necessary to include 130 patients, 65 in each group. Given the uncertainty in our estimates we wish to include 150 patients (75 in each group) in order to avoid an underpowered study.

Interim analysis:

Providing the rate of severe complications is much lower for one of the treatments it would be unethical to continue the study as soon as the collected material confirms this difference with high probability.

One single interim analysis by an independent observer is therefore planned when 75 patients have been included. This analysis is made with a significance level at 1% (0, 01). This requires that the significance level at the end of the study is put to 0,045 in order to achieve a total significance level of 0,05 (cancelling out the effect of the interim analysis).

Realisation

Up to 20 patients are treated annually for acute perforated diverticulitis at Akershus University Hospital with a catchment area of 320.000 persons. We are aiming to yearly include 10-15 patients at our hospital. A catchment area of around 3 million will be needed in order to include the estimated number of patient within a period of 2 years. We are inviting all hospitals in Scandinavia to join this project.

- *1st quarter 2010 – 4th quarter 2011*: Patient inclusion
- *1st quarter 2010 – 4th quarter 2012*: Data collection
- *1st quarter 2011 – 2nd quarter 2011*: Interim analysis
- *2nd quarter 2012 – 2nd quarter 2013*: Data analysis
- *2nd quarter 2012 – 2nd quarter 2013*: Subgroup analysis
- *1st quarter 2013 – 4th quarter 2015*: Registration of 1 year follow up

The project is approved by a Norwegian ethical committee and we are now applying for the approval by a Swedish ethical committee. The protocol has been subject for a broad discussion with colleagues at many other hospitals in Norway and Sweden. We have made a couple of adjustments after this and it seems now realistic to include the first patients in the beginning of 2010.

Scientific significance

Hartmann's procedure still is the preferred treatment for perforated diverticulitis despite the relatively high mortality rate and low rate of stoma reversal. Recent studies have suggested a significantly lower mortality related to laparoscopic lavage (10,11,12,13). However, there are currently no randomized controlled trials supporting this theory. In preliminary reports the laparoscopic operation seems to require less hospital resources and has a potential for less morbidity. We therefore consider our study as scientifically highly significant.

Publication

A writing committee will be appointed. Those participating in this committee will have their names on the publication. The intention is also that all hospitals randomizing at least 10 patients will have one co-author on the publication. All participating surgeons will in any case be mentioned under the heading "the diverticulitis study group" The results will be submitted to an internationally renowned peer reviewed scientific magazine. The schedule for publication should be realistic if we manage to include enough patients within 2 years.

Spin off

By registering all operations for acute diverticulitis in the aforementioned hospitals a prospective database will be established. This will allow for studies on long term outcomes, quality of life, health economics etc. A collaborative network will hopefully be established for future cooperative research.

Research forum

The study is headed and supervised by Professor Tom Øresland MD, PhD at the Dep of Surgical Gastroenterology, Akershus University Hospital. Johannes Schultz MD, and Sheraz Yaqub MD, PhD currently residents at Surgical Unit, Akershus University Hospital will be administrating the study. The following hospitals have decided to participate or declared a definite interest in this trial, and several others have shown interest to join as well (Table 5).

Table 5.

Hospital	Responsible surgeons
Diakonhjemmet sykehus	*Anders Husby*
Innlandet sykehus, Hamar	*Arnulf Kjos*
Karolinska sjukhuset, Stockholm	*Monika Egenvald, Per-Olof Nystrøm, Karin Strigard,*
Levanger Sykehus	*Aras Talabani*
Linköpings universitetssjukhus	*Conny Wallon*
Malmø Akademiska sjukhus	*Ingvar Syk*
Molde sykehus	*Inge Holm Nygaard*
Oslo universitetssykehus, Ullevål	*Gro Wiedswang*
Stavanger Universitetssykehus	*Hartwig Kørner*
Sykehuset Østfold Fredrikstad	*Ljiljana Blecic*
Universitetssykehus i Nord-Norge Tromsø	*Stig Norderval*
Uppsala Akademiska sjukhus	*Joakim Folkesson, Lars Påhlmann,*
Västerås Lasarett	*Abbas Chabok*
Vestere Viken HF	*Ronny Helander; Johan Bondi*
Akershus Universitetssykehus	*Johannes Kurt Schultz, Tom Øresland,*
Helsingborg Lasarett	*Pamela Buchwald*
Mälarsjukhuset	*George Dafnis*
Hudiksvalls Sjukhus	*Dan Gustafson*
Vrinnevisjukhuset Norköping	*Gunnar Arbman*
Haukeland Universitetssykehus Bergen	*Håvard Forsmo*

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Protocol Amendment 16th October 2015 (Long term follow-up)

The primary results from this study were published in JAMA (October 6, 2015; Vol 314, No 13) and show that laparoscopic lavage is not superior to primary resection in treatment of acute perforated diverticulitis. In contrast, there were more complications in the laparoscopic lavage group than in the resection group. This is the largest study done on this condition. We have already planned a one-year follow-up on these patients, and most of the data is collected. However as patient inclusion took longer time than originally planned it is now possible to do another long term follow-up with a median follow up time of approximately 3 years. This would add a lot of information. We know that patients can have a relapse of diverticulitis during the next years and patients treated with resection and stoma (Hartmann's operation) may have the stoma reversed later than one year from primary operation. Moreover, there may be complications related to the new surgery as well as problems with bowel function. We have applied the Regional Ethical Committee to extend follow-up of the patients included in the SCANDIV trial to 10 years. This will make it possibility to assess the results once more after 10 years which will add final information to how many of the patients in the lavage group did have their bowel removed in the end, and how many patients had a stoma after so many years.

For the long-term follow-up we will register similar data as for the one-year follow-up, in addition we will ask for complications due to all reoperations related to diverticulitis including reversal of stoma.

The timetable for further project plan is:

- *1st quarter 2016 – 2nd quarter 2016*: Registration of long term results (long-term follow-up)
- *2nd quarter 2016 – 3rd quarter 2016*: Data analysis and publication of long-term results. (1-year and median 3-years)
- *Approximately 2020 – 2024, 10 year follow up*