

Laparoscopic peritoneal lavage or sigmoidectomy for perforated diverticulitis with purulent peritonitis: a multicentre, parallel-group, randomised, open-label trial



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Summary

Background Case series suggest that laparoscopic peritoneal lavage might be a promising alternative to sigmoidectomy in patients with perforated diverticulitis. We aimed to assess the superiority of laparoscopic lavage compared with sigmoidectomy in patients with purulent perforated diverticulitis, with respect to overall long-term morbidity and mortality.

Methods We did a multicentre, parallel-group, randomised, open-label trial in 34 teaching hospitals and eight academic hospitals in Belgium, Italy, and the Netherlands (the Ladies trial). The Ladies trial is split into two groups: the LOLA group comparing laparoscopic lavage with sigmoidectomy and the DIVA group comparing Hartmann's procedure with sigmoidectomy plus primary anastomosis. The DIVA section of this trial is still underway but here we report the results of the LOLA section. Patients with purulent perforated diverticulitis were enrolled for LOLA, excluding patients with faecal peritonitis, aged older than 85 years, with high-dose steroid use (≥ 20 mg daily), and haemodynamic instability. Patients were randomly assigned (2:1:1; stratified by age [< 60 years vs ≥ 60 years]) using secure online computer randomisation to laparoscopic lavage, Hartmann's procedure, or primary anastomosis in a parallel design after diagnostic laparoscopy. Patients were analysed according to a modified intention-to-treat principle and were followed up after the index operation at least once in the outpatient setting and after sigmoidoscopy and stoma reversal, according to local protocols. The primary endpoint was a composite endpoint of major morbidity and mortality within 12 months. This trial is registered with ClinicalTrials.gov, number NCT01317485.

Findings Between July 1, 2010, and Feb 22, 2013, 90 patients were randomly assigned in the LOLA section of the Ladies trial when the study was terminated by the data and safety monitoring board because of an increased event rate in the lavage group. Two patients were excluded for protocol violations. The primary endpoint occurred in 30 (67%) of 45 patients in the lavage group and 25 (60%) of 42 patients in the sigmoidectomy group (odds ratio 1.28, 95% CI 0.54–3.03, $p=0.58$). By 12 months, four patients had died after lavage and six patients had died after sigmoidectomy ($p=0.43$).

Interpretation Laparoscopic lavage is not superior to sigmoidectomy for the treatment of purulent perforated diverticulitis.

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Introduction

Diverticular disease is the fourth most costly gastrointestinal disorder in developed countries with an estimated annual hospital admission rate of 209 per 100 000 adults in Europe.^{1,2} The prevalence of this disorder increases with age and is estimated at 5% of people in their forties and can be as high as 80% in those aged older than 80 years.^{2,3} Of patients with acute diverticulitis, 8–35% presented with perforated disease with abscesses or peritonitis.^{2,4} Perforated diverticulitis is graded according to the Hinchey classification,⁵ with abscess formation scored as Hinchey I or II, purulent peritonitis as Hinchey III, and faecal peritonitis as Hinchey IV.

Laparoscopic peritoneal lavage has emerged as a promising alternative to sigmoidectomy in patients with

purulent peritonitis owing to perforated diverticulitis. This non-resectional strategy was first described in 1996.^{6,7} In 2008, Myers and colleagues⁸ reported a 95% success rate of laparoscopic peritoneal lavage in 92 patients. 2 years later a systematic review⁹ of case series showed a mortality rate of less than 5% and a colostomy was avoided in most patients. Since these publications, laparoscopic lavage for purulent perforated diverticulitis has gained popularity because of its great potential to improve outcomes and reduce costs. Despite the absence of robust evidence from randomised trials, laparoscopic lavage has been embraced by many surgeons. Even some national and international guidelines state that it is a safe approach in purulent perforated diverticulitis.^{10,11}

The laparoscopic lavage (LOLA) group of the Ladies trial¹² postulated that laparoscopic lavage compared with

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sigmoidectomy for purulent perforated diverticulitis would lead to a reduction in composite outcome of major morbidity and mortality in a randomised multicentre trial.

Methods

Study design and participants

The Ladies trial is a multicentre, parallel-group, randomised, open-label superiority trial done in 34 teaching hospitals and eight academic hospitals in Belgium, Italy, and the Netherlands. It was designed to compare laparoscopic lavage and sigmoidectomy for purulent perforated diverticulitis in the LOLA group and to compare Hartmann's procedure versus sigmoidectomy with primary anastomosis in both purulent and faecal perforated diverticulitis in the DIVA group. Patients with signs of general peritonitis and suspected perforated diverticulitis were eligible for inclusion. Radiological examination by radiography or a CT scan had to show diffuse-free intraperitoneal air or fluid for patients to be classified as having perforated diverticulitis. Exclusion criteria were dementia, previous sigmoidectomy, pelvic irradiation, chronic treatment with high-dose steroids (>20 mg daily), being aged younger than 18 years or older than 85 years, and having preoperative shock needing inotropic support. Patients with Hinchey I and II perforated diverticulitis were excluded from the study and patients with Hinchey IV peritonitis or overt perforation could only be included in the DIVA group. The study protocol¹² was approved by the ethical review board and written informed consent was obtained from all patients before randomisation. This study was investigator initiated and designed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Randomisation and masking

After preoperative informed consent was obtained by the surgeon or surgical resident, diagnostic laparoscopy was done to confirm the diagnosis of perforated diverticulitis and to distinguish between purulent and faecal peritonitis or overt perforation. Only patients with purulent perforated diverticulitis without overt perforation were randomly assigned within the LOLA group with secure online computer randomisation, either directly in the operating room or by the trial coordinator on the phone. Patients were randomly assigned (2:1:1) to receive either laparoscopic lavage, sigmoidectomy without primary anastomosis, or sigmoidectomy with primary anastomosis (with or without defunctioning ileostomy), allowing for a 1:1 comparison between lavage and sigmoidectomy in the LOLA group (figure, appendix). Patients with an overt perforation or faecal peritonitis were included in the DIVA group of the study and not analysed within the LOLA group. We used a random and concealed block size of 2, 4, or 6 for randomisation and stratified for age (younger or older than 60 years). Treatment allocation was not masked to patients, physicians, or researchers at any timepoint.

Procedures

The procedures for surgery, reintervention, and stoma reversal have previously been described.¹² To determine the presence of a sigmoid perforation, adherent tissues were carefully removed, but when firmly adherent, they were left in place. Laparoscopic lavage was done by irrigation with up to 6 L of warm saline throughout the abdominal cavity. A Douglas drain was inserted in the right lateral port site. Sigmoidectomy with primary anastomosis was done according to the guidelines of the American Society of Colon and Rectal Surgeons and the creation of a defunctioning ileostomy was at the discretion of the surgeon.¹³

4–6 weeks after laparoscopic lavage, sigmoidoscopy was done to exclude malignancy as the underlying cause of perforation. In the sigmoidectomy group, patients were offered stoma reversal if they were fit enough and willing to undergo surgery. Routine sigmoidectomy was not recommended for patients after laparoscopic lavage.

Patients were followed up after the index operation at least once in the outpatient setting and after sigmoidoscopy and stoma reversal, according to local protocols. If the patient was not in active follow-up by the surgeon at 12 months, the patient was contacted to verify the remaining follow-up.

Outcomes

The primary endpoint of the LOLA group was a composite endpoint including major morbidity and mortality within 12 months. Major morbidity was defined as the occurrence of the following events or conditions: surgical reintervention, abdominal wall dehiscence, abscesses needing percutaneous drainage during the full period and urosepsis, myocardial infarction, renal failure, and respiratory insufficiency within 30 days after operation or in hospital.¹² Elective stoma reversal surgery was not defined as morbidity or reintervention for either group, whereas elective sigmoidectomy after lavage was scored accordingly. Secondary outcomes were operating time, length of hospital stay, days alive and outside the hospital, short-term morbidity and mortality, incisional hernia, reinterventions within 12 months, and health-related quality of life (measured with Short Form-36 version 2 [SF-36v2], Gastrointestinal Quality of Life Index [GIQLI],¹⁴ and EuroQol 5D 3 level [EQ-5D-3L] questionnaires at 2, 4, 13, and 26 weeks). These timepoints were chosen to address both short-term and long-term postoperative recovery. Short-term morbidity and mortality were defined as within 30 days after operation or until discharge, if the patient was still admitted at that time.

We did a post-hoc analysis of the incidence of recurrent diverticulitis and the incidence of underlying perforated colorectal carcinoma diagnosed during follow-up. Failure of treatment was defined as persisting abdominal sepsis, resulting in surgical reintervention or death.¹⁵

See Online for appendix

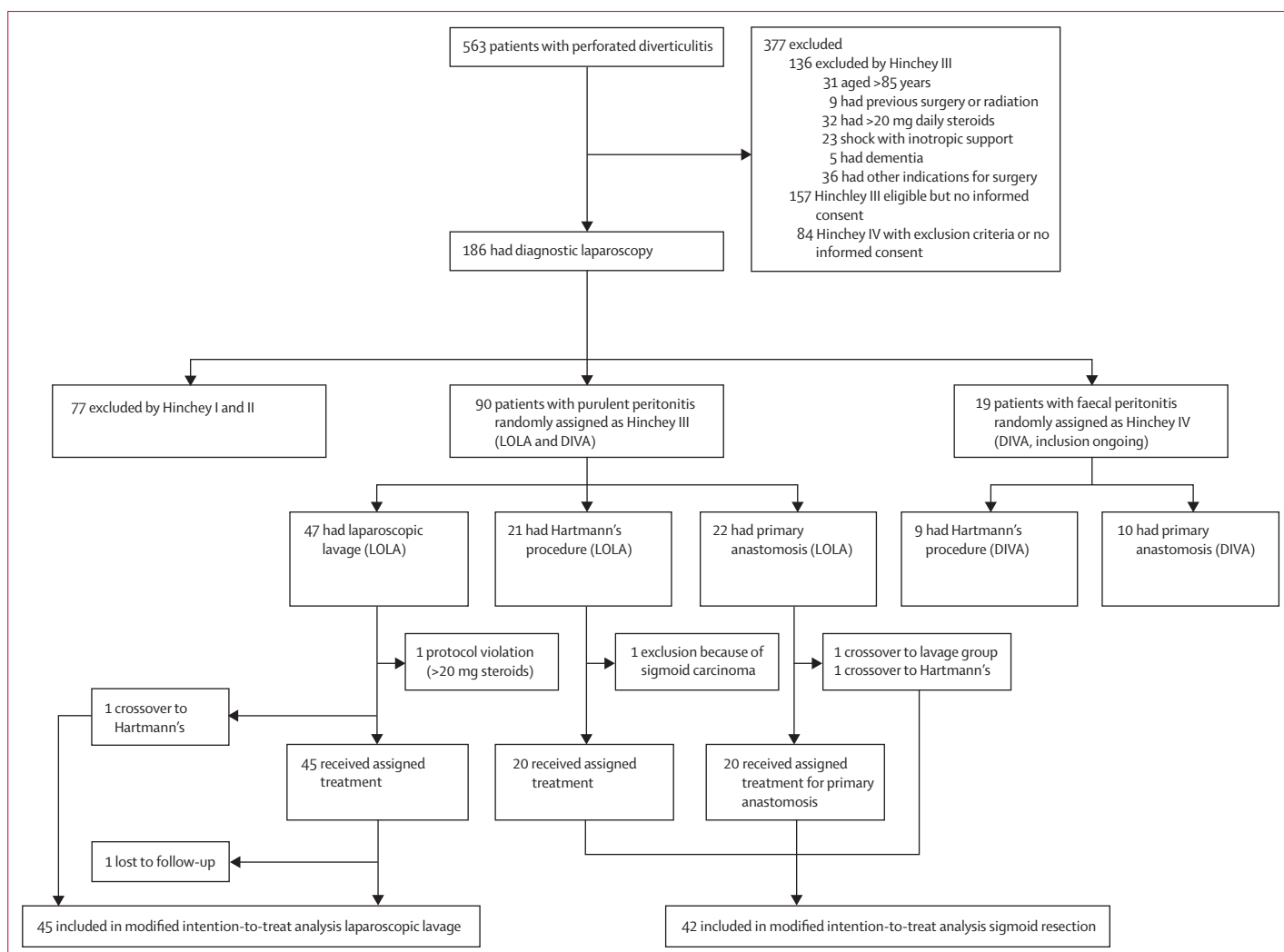


Figure: Trial profile

Statistical analysis

We calculated that a sample size of 264 patients for the LOLA group was needed to detect a 15% difference in the composite endpoint of major morbidity and mortality, with an expected rate of 25% in the sigmoidectomy group and 10% in the laparoscopic lavage group at 12 months. We used a two-sided likelihood ratio test and a power of 90%.¹² The assumption of 10% major morbidity and mortality is based on the reported morbidity and mortality by Toorenvliet and colleagues,⁹ whereas 25% major morbidity and mortality was based on adjusted data from the scientific literature because we only included patients with a Hinchey III score and excluded those with Hinchey IV or other risk factors for postoperative morbidity and mortality according to our set exclusion criteria.^{16,17}

We designed a monitoring plan for source data verification on the basis of the assumption that the trial was a moderate-risk study. The first three participating

patients in each centre, followed by a 50% sample control of the following included patients, were verified by an independent clinical research associate. The clinical research associate verified informed consent, inclusion criteria, adverse events, and adherence to Good Clinical Practice guidelines, with the resources available (eg, patient charts at the participating hospital).

In regular interim analyses, an independent data and safety monitoring board (DSMB) assessed the progress of the trial and examined safety variables after inclusion of every 25 patients. Although no stopping rules were defined in the protocol, a formal DSMB charter was developed and approved by the central ethical committee. This charter allowed the DSMB to stop the study for safety or early superiority without any prespecified definitions. According to this charter, the DSMB assessed the progress and analysed outcomes on the basis of the data supplied by the researchers—eg, for early morbidity (<30 days) and major morbidity as defined in the study

protocol. The DSMB was granted access to individual data for those patients with study-related severe morbidity and mortality.

We analysed patients according to a modified intention-to-treat principle. We tested the primary endpoint using binary logistic regression analysis with post-hoc correction for the planned stratified age groups (<60 years and ≥ 60 years) with a two-sided significance level of 5%. We tested secondary outcomes with linear and binary logistic regression analysis with post-hoc correction for the planned stratified age groups (<60 years and ≥ 60 years) to compare groups. For categorical data and binary data with no events in one of the groups, we calculated numbers and percentages and compared these between groups with unadjusted Fisher's exact test. We reported data with effect sizes, mean differences (MD), odds ratios (OR) and 95% CI, or with 1000 samples bias corrected and accelerated bootstrapped 95% CIs in the case of non-parametric data. We tested continuous variables for normality using the Shapiro-Wilk test and Q-Q plots. We summarised data as either means with SDs or medians (IQRs), depending on normality.

We did post-hoc subgroup analysis for the American Society Anesthesiologists physical status classification (ASA) grade because ASA grade differed significantly between the two treatment groups at baseline. Subgroup analyses have been done with logistic regression analysis.

We used a complete case analysis approach apart from the quality of life questionnaires (SF-36v2, GIQLI, and EQ5D), assuming random missing data. All questionnaires were scored according to the relevant manuals and presented as domains and summarised scores. In cases of missing items within domains of the SF-36 and GIQLI, missing items were substituted with the mean value if at least half of the items in the subscale were known. When questionnaires were not returned for any of the four timepoints, missing data were imputed by linear interpolation if the borderline timepoints (eg, 2 weeks and 6 months) were available. Missing observations in the first or last timepoint were imputed with the first observation carried backward and last observation carried forward method. At least one returned questionnaire was needed for imputation of the missing timepoints. Questionnaire outcome comparisons were corrected for multiple testing with the Benjamini-Hochberg method, although this correction was not prespecified in the protocol. The trial was registered with the trialregister.nl, number NTR2037 and ClinicalTrials.gov, number NCT01317485.

Role of the funding source

The funder of the study critically reviewed and adjusted the study design, but had no role in data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and had full responsibility for the decision to submit for publication.

Results

Between July 1, 2010, and the early termination of the trial on Feb 22, 2013, we randomly assigned 90 patients in the LOLA group; 47 patients were assigned to laparoscopic lavage and 43 to the sigmoidectomy. Patients were followed up for 12 months (figure). Two patients were excluded because of protocol violations of the inclusion criteria; one used high-dose steroids and the other was randomly assigned despite a known diagnosis of perforated rectal carcinoma at the time of surgery. One patient in the lavage group was lost to follow-up at 12 months because he could not be located after he moved house.

Patients in this trial were included from 30 hospitals (28 from the Netherlands, one Belgian, and one Italian). Because the registration of non-included patients seemed to be incomplete, a chart review was done in all participating hospitals in the Netherlands to verify the number of excluded and missed patients within the study period. In these hospitals, 563 patients with acute surgery for perforated diverticulitis were identified of whom 186 were eligible and underwent diagnostic laparoscopy, 77 were excluded with Hinchey I or II diverticulitis. Of 247 eligible patients with Hinchey III perforated diverticulitis, 84 were included in the LOLA group. Another six patients were included from foreign participating hospitals (appendix, table 1).

The baseline characteristic of patients included in this trial (table 1) did not differ from the eligible but not included patients (appendix). The mean age in the 88 analysed patients was 63 years (SD 12.5) and 51 (58%) were men. The proportion of patients with ASA grade III or IV was lower in the lavage group. The physiological score and operative severity score (POSSUM-OS) reported in the sigmoidectomy group was higher than that in the lavage group, but can be attributed to the two point higher procedure score for sigmoidectomy (appendix).

Within the sigmoidectomy group, 20 patients were allocated to sigmoidectomy with end colostomy and 22 to sigmoidectomy with primary anastomosis, of whom one was converted to a Hartmann's procedure and one crossed over to laparoscopic lavage (because this patient could not be placed in the stirrups, needed to use the circular stapler because of recent knee surgery). 14 patients were diverted with an ileostomy. One patient in the lavage group was converted to open Hartmann's because of faecal contamination of the pelvis identified during lavage. Seven sigmoidectomies were completed by laparoscopy, all others were converted to open surgery after randomisation.

The LOLA group of the Ladies trial was terminated early for safety reasons after the third planned interim analysis after 75 patients were enrolled, the data were reported to the DSMB on Nov 14, 2012. As the DSMB requested additional data, the final data on which the decision was taken included 46 lavage and 40 sigmoidectomy patients

from the LOLA group. During the first two analyses, the DSMB raised concerns about the safety of the patients in the lavage group because of the high short-term morbidity and reintervention rate, but the numbers were too small to form a conclusion. At the third analysis, the interim data for in-hospital major morbidity or mortality was 16 (35%) of 46 in the lavage group versus seven (18%) of 40 (complete data were not available for 2 patients) in the sigmoidectomy group ($p=0.12$), with 37 events in the lavage group and ten events in the sigmoidectomy group ($p=0.0005$). Surgical reinterventions accounted for most of these adverse events with 18 (lavage) versus two (sigmoidectomy) in-hospital reinterventions ($p=0.0011$) and 28 (lavage) versus 11 (sigmoidectomy) overall surgical reinterventions ($p=0.0219$). Therefore, the DSMB advised to us to end the LOLA group of the trial as the safety of the participants in the lavage group was at risk. As the safety concerns were limited to the laparoscopic lavage group, the DIVA group was continued as planned after the ethical committee approved the amended protocol. Therefore, data about the comparison between sigmoidectomy with and without primary anastomosis will not be presented until the remaining DIVA group is closed.

During the 12-month follow-up, no difference was reported in the incidence of the composite primary endpoint (30 patients in the lavage group vs 25 patients in the sigmoidectomy group; OR 1.28, 95% CI 0.54–3.03, $p=0.5804$). This rate includes four (9%) and six (14%) patients who had died either postoperatively or during the follow-up in the lavage and sigmoidectomy group (OR 0.53, 95% CI 0.13–2.15, $p=0.3772$). Five patients died during their primary hospital stay or shortly thereafter, whereas the remaining five late deaths (two in the lavage group, three in the sigmoidectomy group) were unrelated to the study procedures (appendix).

The mean operating time was shorter for the lavage group with 60 min compared with 120 min in the sigmoidectomy group (mean difference [MD] -54.53 , 95% BCa CI -68.04 to -40.26 , $p=0.0010$). The length of postoperative hospital stay did not differ between the two groups, 8 days (IQR 6–15) after lavage and 10 days (7–14) after sigmoidectomy (MD -0.62 , 95% BCa CI -8.34 to 6.38 , $p=0.8751$).

The combined major morbidity and mortality rate within 30 days after operation or in hospital was higher after laparoscopic lavage (18 [39%] patients in the laparoscopic lavage group compared with eight [19%] in the sigmoidectomy group [OR 2.74, 95% CI 1.03–7.27, $p=0.0427$]), most of which could be explained with the higher rate of reinterventions in the lavage group (16 and three patients, OR 6.93, 95% CI 1.85–26.00, $p=0.0041$). Short-term adverse events are summarised in table 2 and the appendix.

Sepsis was controlled successfully in the short term, defined as not needing surgical reoperation and being alive, in 35 (76%) of the patients in the lavage group and 38 (90%) of the patients in the sigmoidectomy group

(appendix). Persistent sepsis in the lavage group needed surgical reoperation in nine patients and was caused by faecal peritonitis or overt perforation in six patients. One patient was diagnosed with an underlying carcinoma during pathological assessment. Seven patients had a Hartmann's procedure, one a primary anastomosis with ileostomy, and one patient had four relaparotomies after laparoscopic lavage, followed by delayed elective sigmoidectomy. Two other patients died from multiorgan failure.

Three patients in the sigmoidectomy group needed reoperation because of an acute fascial dehiscence, an unconfirmed anastomotic leakage, and a negative second look laparotomy in a patient with an abdomen left open. One patient died because of massive arterial embolism and another two patients died shortly after extended hospital stay because of renal or respiratory failure. Routine pathological assessment revealed two patients with underlying carcinoma in the sigmoidectomy group, both treated with adjuvant chemotherapy.

Stoma reversal surgery was done in five of 11 patients (one ileostomy, four of ten colostomies) in the lavage group and 24 of 35 in the sigmoidectomy group

	Laparoscopic lavage (n=46)	Sigmoidectomy (n=42)
Age (years)	62.3 (12.7)	64.0 (12.3)
Sex		
Men	26 (57%)	25 (60%)
Women	20 (43%)	17 (40%)
Body-mass index (kg/m ²)*	27.6 (6.2)	27.0 (4.4)
ASA		
I	10 (22%)	8 (19%)
II	21 (46%)	13 (31%)
III	5 (11%)	13 (31%)
IV	3 (7%)	2 (5%)
Missing	7 (15%)	6 (14%)
Previous diverticulitis†	12 (32%)	10 (26%)
Previous laparotomy‡	4 (9%)	3 (7%)
Disease severity preoperative		
APACHE II	7.3 (4.2)	9.0 (4.8)
POSSUM PS	20.8 (6.2)	22.8 (6.2)
POSSUM OS	17.1 (0.5)	20.0 (2.2)
Interval from ER to surgery (h)	13 (8–32)	13 (6–42)
Number of patients operated on by a gastrointestinal surgeon	37 (80%)	36 (86%)

Data are mean (SD), n (%), or median (IQR). ASA=American Society of Anesthesiologists classification. APACHE II=acute physiology and chronic health evaluation II. POSSUM-PS=physiology and operative severity score for the enumeration of mortality and morbidity—physiology score. POSSUM-OS=POSSUM operative score. ER=moment of presentation at the emergency department. *n=40 in the laparoscopic lavage group; n=39 in the sigmoidectomy group. †n=38 in the laparoscopic lavage group; n=38 in the sigmoidectomy group. ‡n=45 in the laparoscopic lavage group; n=41 in the sigmoidectomy group.

Table 1: Baseline characteristics in randomly assigned patients with perforated diverticulitis

	Laparoscopic lavage (n=46)		Sigmoidectomy (n=42)		p value
	Patients	Events	Patients	Events	
Short-term serious adverse events	18 (39%)	39	8 (19%)	14	0.0427
Death	2 (4%)	2	1 (2%)	1	0.6237
Surgical reintervention	9 (20%)	15	3 (7%)	3	0.1230
Abscess with drainage	9 (20%)	12	0	0	0.0027
Fascial dehiscence	0	0	3 (7%)	3	0.1046
Myocardial infarction	0	0	1 (2%)	1	0.4773
Respiratory failure	6 (13%)	6	2 (5%)	2	0.1955
Renal failure	2 (4%)	2	2 (5%)	2	0.9207
Long-term serious adverse events	17 (37%)	30	17 (40%)	20	0.1156
Death	2 (4%)	2	5 (12%)	5	0.1875
Surgical reintervention	13 (28%)	16	5 (12%)	6	0.1156
Abscess with drainage	2 (4%)	4	2 (5%)	2	0.9207
Fascial dehiscence	5 (11%)	5	5 (12%)	5	0.4359
Sigmoid carcinoma	5 (11%)	5	2 (5%)	2	0.3047
Recurrent diverticulitis	9 (20%)	9	1 (2%)	1	0.0315
Composite primary outcome (major morbidity or mortality at 12 months)	30 (67%)	..	25 (60%)	..	0.5804

Data are n (%), unless otherwise stated. Short term is defined as within 30 days or in hospital, long term is defined as after 30 days or discharge and within 12 months.

Table 2: Serious adverse events, defined as major morbidity

(12 of 14 ileostomies, 12 of 21 colostomies). Morbidity occurred in one patient in the lavage group and six patients in the sigmoidectomy group after stoma reversal, including one patient (lavage) and three patients (sigmoidectomy) with a surgical reintervention, after Hartmann's reversal. No reversal-related mortality occurred (appendix).

Laparoscopic lavage was successful in 24 (52%) patients in the long term, defined as no acute or elective surgical reintervention or related mortality, and 31 (74%) of the 42 patients alive never had a stoma (appendix). Seven patients had elective laparoscopic sigmoidectomy, of whom two were converted to laparotomy. Four had open surgery for colorectal cancer, of whom three were diagnosed during follow-up colonoscopy. The other patient presented with a colovesical fistula after 8 months. Two of these four patients developed metastases. Two patients that had acute reoperation after laparoscopic lavage needed additional surgical reintervention, including one haematoma after Hartmann's reversal.

In the sigmoidectomy group, no further surgery was done in 13 (31%) patients, of whom 6 never had a stoma (appendix). During follow-up, two patients needed surgical reintervention; one for revision of the obstructed anastomosis before the ileostomy could be reversed and the other patient needed splenectomy and video-assisted thoracoscopic surgery for a splenic abscess and thoracic empyema. Three more patients had surgical reintervention after Hartmann's reversal, two postoperative haematomas, and one anastomotic leakage.

36 (78%) patients in the lavage group and 30 (71%) in the sigmoidectomy group were alive and stoma free after

12 months (OR 1.53, 95% CI 0.55–4.30, $p=0.4193$). In each group, another six patients were alive but not stoma free at 12 months.

Incisional hernia occurred in five patients each in both groups. Four of five hernias in the laparoscopic group occurred after conversion or relaparotomy, three had surgical repair. Of the five patients who had hernias in the sigmoidectomy group, only one parastomal hernia was corrected during colostomy reversal. Long-term adverse events are summarised in table 2 and the appendix. The number of days alive and outside the hospital during the 12-month period did not differ between both groups (appendix).

The response rate of the quality of life questionnaires varied between 56 (64%) of 88 at 2 weeks and 52 (59%) of 88 at 6 months. 69 (78%) patients completed at least one of the questionnaires. No differences were identified in the main scores of the SF-36, GIQLI, and EQ5D questionnaires, and no subscale remained significant after the p values were corrected post hoc for multiple testing (appendix).

In a post-hoc subgroup analysis for patients aged younger than 60 years or 60 years and above, the primary endpoint did not differ between the two treatment groups. Post-hoc stratified analysis for patients with a low ASA grade (I or II) or high ASA grade (III or IV) did not show a significant between-group difference in the primary outcome (OR 1.36, 95% CI 0.51–3.62, $p=0.5337$; appendix).

Discussion

In this study, which was terminated early, laparoscopic peritoneal lavage for purulent perforated diverticulitis did not result in a reduction in the composite endpoint of major morbidity and mortality compared with sigmoidectomy at 12 months. Although laparoscopic lavage did result in a higher acute reintervention rate, 76% of patients were discharged without further surgery. The higher morbidity rates did not result in excess mortality, suggesting that patients that fail lavage can be salvaged when reintervention is timely.

The 24% failure to control sepsis with lavage could be attributed to misdiagnosis of faecal peritonitis in most cases. As the phlegmon is often located at the pelvic entrance, occluding the view on Douglas pouch, the limited exploration as described in our study protocol might have resulted in these misdiagnoses. A third of the pathological specimens from the sigmoidectomy group showed a perforation, similar to the 37% perforations identified in the pathological specimens of a previous study. These rates suggest a similar rate of sealed or missed perforations in the lavage group.¹⁸ A CT scan with rectal contrast might be able to discriminate faecal from purulent peritonitis by showing contrast extravasation. However, the use of rectal contrast for acute abdominal CT scans is not routine practice and is barely discussed in guidelines.¹⁹

The use of rectal contrast might also help to diagnose underlying colorectal carcinoma. Seven (8%) patients were diagnosed with a sigmoid carcinoma, which is not unusual compared with the 3% and 7% reported in two previous trials on perforated diverticulitis.^{20,21} These carcinomas have been responsible for a third of the elective sigmoidectomies in the lavage group.

At the time we initiated the Ladies trial, the evidence for laparoscopic lavage consisted of limited and low quality evidence from case series. A success rate of 96% for laparoscopic lavage with low mortality (2%) and morbidity (10%) was reported in a systematic review including 231 patients from 13 papers.⁹ More recently published case series show higher failure rates of up to 34% and a morbidity rates up to 56% for laparoscopic lavage^{15,22} (panel and appendix). The favourable results of the largest series by Myers and colleagues⁸ and several other series might have a selection bias because the complete population from which these patients were selected was not described and a large proportion of patients without perforation (Hinchey II) were included. The excellent results of the early case series are unlikely to be reproduced in large randomised controlled trials because selection bias is usually stronger in the series and the patient's condition is a major predictor of postoperative outcomes.¹⁷

Although the results of laparoscopic lavage were not as good as expected, the 30-day mortality rate of 2% in the sigmoidectomy group of this study was low compared with previous studies. However, these previously reported rates of 10–22% include patients with faecal peritonitis, with a reported odds ratio for increased mortality of 3·9 in patients with faecal peritonitis.^{17,27,28}

While designing the study, we assumed that taking the short-term morbidity and mortality as the primary endpoint would underappreciate the benefits of lavage. We expected that in the sigmoidectomy group more late surgeries—eg, abdominal wall repairs, and morbidity associated with stoma closure—would occur. Stoma closure was part of the sigmoidectomy strategy and therefore not counted as an adverse event. Our power calculation was done on the basis of a 15% difference in the composite endpoint. Both the 10% and 25% for lavage and sigmoidectomy were conservative estimates, allowing for a clinically relevant difference and sufficient group size to avoid an underpowered study.

Traditionally, surgical studies focused on morbidity and mortality and used these as primary outcomes. Similar outcomes are used in the other trials on perforated diverticulitis.^{24–26} Other definitions of success can be used provided that no excess mortality exists in one of the study groups—eg, no further surgery, never having had a stoma, and enabling delayed laparoscopic surgery.

Because of the design of the study, it had insufficient power to conclude on non-inferiority. A non-inferiority trial with mortality as the primary endpoint would need a very large sample size, while patient accrual in emergency

Panel: Research in context

Systematic review

As an update of the systematic review by Toorenvliet and colleagues,⁹ we searched Medline and the Cochrane Library for studies on laparoscopic lavage in patients with perforated diverticulitis using the keywords “diverticulitis”, “periton*” and “laparoscop*” up to Nov 24, 2014. We screened the relevance of the studies by assessment of titles, abstracts, and full texts published in all languages and were able to identify 13 studies about laparoscopic lavage in addition to the 13 series in the previous review. Study quality assessment was done according to a modified checklist adapted from Downs and Black²³ (appendix).

No published randomised trials were identified; however, three other randomised trials are currently underway to compare laparoscopic lavage with sigmoidectomy for purulent perforated diverticulitis (DILALA,²⁴ LapLAND,²⁵ and SCANDIV²⁶ trials). The 26 identified studies were case series (22), comparative studies (three), or population-based cohorts (one). They included 898 patients in 20 original reports and six were about a previously reported or extended series. Of the included patients, 324 had Hinchey III perforated diverticulitis in addition to an unknown proportion of the 427 patients from the population study.

Interpretation

Our trial is the first randomised trial to report the long-term results of laparoscopic lavage and sigmoidectomy for purulent perforated diverticulitis. The trial was stopped early at 33% of the planned sample size as advised by the Data Safety Monitoring Board because of the high major morbidity and mortality rate in the lavage group. Despite the promising results of previous case series, our study could not show superiority of laparoscopic lavage with regard to major morbidity and mortality. Failure to properly distinguish Hinchey III from Hinchey IV perforated diverticulitis and underlying colorectal cancer accounted for most of the lavage failures. Improved preoperative diagnostics—eg, CT with rectal contrast might optimise the results of laparoscopic lavage.

trials has been shown to be difficult.²⁹ Two earlier randomised trials of perforated diverticulitis were terminated at less than half of the calculated sample size because of a declining accrual rate.^{20,21}

Because of the parallel randomisation in the DIVA group, the ostomy reversal rate in the sigmoidectomy group was affected by the allocation to Hartmann's or primary anastomosis. However, this was not expected to affect the 12-month morbidity and mortality rate in our study because no differences were shown in recent randomised trials.^{20,21}

Although no differences between groups could be identified in the quality of life questionnaires, we did not collect data for patients' satisfaction with the long-term result of the treatment. A higher satisfaction might be expected in those patients who never had a stoma and never needed additional surgery, even if an interventional drain had been necessary.

Strengths of this study include conduct according to Good Clinical Practice principles and source verification of the data by an independent monitor. Running investigator driven trials according the Good Clinical Practice principles is uncommon in surgery, but was demanded by the Dutch Inspectorate of Health Care after irregularities reported in the conduct of the Dutch PROPATRIA study.³⁰

Another important strength of the study is that we were able to account for the eligible but not included patients. In this way, we have been able to assess and rule out a patient selection bias despite the low accrual rate of 34%. The participation of a large number of hospitals strengthens the external validity and applicability of the study results. At the same time, the low number of included patients per hospital can be seen as a weakness because of heterogeneity.

We conclude that laparoscopic lavage is not superior to sigmoidectomy for the treatment of purulent perforated diverticulitis in terms of major morbidity and mortality at 12 months. Although the acute reintervention rate was higher after lavage, in more than three-quarters of these patients, the sepsis was controlled. No excess mortality was present in patients who failed lavage. Optimisation of preoperative imaging is warranted to identify those patients who are likely to fail lavage because of the presence of a persistent perforation or a perforated carcinoma. Pooling of the forthcoming data of the other perforated diverticulitis trials (DILALA, LapLAND, and SCANDIV)^{24–26} with our data might identify additional factors that contribute to an improved selection of patients that either need lavage or sigmoidectomy in the acute setting.

Contributors

SV, GDM, IMM, HAS, JV, JFL, and WAB contributed to the study design or coordination. SV, GDM, HAS, ECC, EHB, AAvG, MFG, MJG, WMvG, AGH, PMK, SWN, and WAB contributed to data acquisition. SV and SvD contributed to data analysis. SV, ECC, MAB, SvD, JFL, MAB, and WAB contributed to data interpretation. SV and WAB drafted the report. SV, GDM, IMM, HAS, ECC, EHB, AAvG, MFG, MJG, WMvG, AGH, PMK, SWN, MAB, JV, SvD, JFL, WAB critically revised the content and approved the final manuscript.

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Declaration of interests

We declare no competing interests.

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