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Abstract

This systematic review and meta-analysis investigates current evidence on the therapeutic role of laparoscopic lavage in the management of diverticular peritonitis. A systematic review of the literature was performed on PubMed until June 2016, according to preferred reporting items for systematic reviews and meta-analyses guidelines. All randomised controlled trials comparing laparoscopic lavage with surgical resection, irrespective of anastomosis or stoma formation, were analysed. After assessment of titles and full text, 3 randomised trials fulfilled the inclusion criteria. Overall the quality of evidence was low because of serious concerns regarding the risk of bias and imprecision. In the laparoscopic lavage group, there was a statistically significant higher rate of postoperative intra-abdominal abscess (RR 2.54, 95% CI 1.34–4.83), a lower rate of postoperative wound infection (RR 0.10, 95% CI 0.02–0.51), and a shorter length of postoperative hospital stay during index admission (WMD = −2.03, 95% CI −2.59 to −1.47). There were no statistically significant differences in terms of postoperative mortality at index admission or within 30 days from intervention in all Hinchey stages and in Hinchey stage III, postoperative mortality at 12 months, surgical reintervention at index admission or within 30–90 days from index intervention, stoma rate at 12 months, or adverse events within 90 days of any Clavien–Dindo grade. The surgical reintervention rate at 12 months from index intervention was significantly lower in the laparoscopic lavage group (RR 0.57, 95% CI 0.38–0.86), but these data included emergency reintervention and planned intervention (stoma reversal). This systematic review and meta-analysis did not demonstrate any significant difference between laparoscopic peritoneal lavage and traditional surgical resection in patients with peritonitis from perforated diverticular disease, in terms of postoperative mortality and early reoperation rate. Laparoscopic lavage was associated with a lower rate of stoma formation. However, the finding of a significantly higher rate of postoperative intra-abdominal abscess in patients who underwent laparoscopic lavage compared to those who underwent surgical resection is of concern. Since the aim of surgery in patients with peritonitis is to treat the sepsis, if one technique is associated with more postoperative abscesses, then the technique is ineffective. Even so, laparoscopic lavage does not appear fundamentally inferior to traditional surgical resection and this technique may achieve reasonable outcomes with minimal invasiveness.

Keywords

Acute diverticulitisPeritonitisHinchey classificationAbdominal sepsisIntra-abdominal infectionsLaparoscopyLaparoscopic lavageSigmoid resectionColostomyHartmann resection

Electronic supplementary material

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Introduction

The management of patients with peritonitis from perforated colonic diverticular disease is a challenging clinical problem. During the past decades, an increased incidence of acute diverticulitis has been reported [1]. In these potentially critically ill patients, a rapid and accurate diagnosis may facilitate the selection of an appropriate surgical strategy [2, 3].

In the last century, a range of surgical treatments were used to treat perforated diverticular disease. In 1910, Lockhart-Mummery [4] described peritoneal lavage, drainage and colonic suturing, while the classical three-stage operation was being developed at the Mayo Clinic [5]. In the early 1920s, the Hartmann procedure (HP) was described; the original paper by Henri Hartmann focused on the treatment of sigmoid cancers and consisted of a sigmoid resection, burying the rectal stump and performing a terminal colostomy for the treatment of rectal cancer, as an alternative to abdomino-perineal resection. Subsequently, HP started to gain in popularity as a treatment for complicated diverticulitis [6]. Recently, single-stage procedures, including colonic anastomoses in the acute inflammatory setting and non-mandatory use of ostomies, have been used. A resurgence in less aggressive and non-operative strategies has been observed [7].

Laparoscopy, though challenging in the setting of acute inflammation, offers both diagnostic and therapeutic utility, allowing peritoneal lavage, drainage of abscesses, and bowel resection [8]. This approach offers enhanced patient recovery and reduced morbidity [9].

Contemporary advances in surgical treatments provide the surgeon with a range of options, including entirely non-operative approaches, diagnostic and therapeutic laparoscopic interventions, and open surgical resections, with or without ostomy formation: a patient-tailored surgical therapy appears appropriate [10]. This systematic review and meta-analysis aims to assess the current evidence about the therapeutic role of laparoscopic lavage in the management of peritonitis due to perforated diverticular disease.

The objective of this study was to compare laparoscopic abdominal lavage with surgical resection, with or without synchronous anastomosis, for the management of generalised peritonitis due to perforated sigmoid diverticulitis.

Materials and methods

Types of studies

Randomised controlled trials (RCTs) were identified through a systematic review of published literature (full article, thesis, or abstract). All languages were reviewed.

Types of participants

The patients had generalised purulent or faecal (Hinchey grade III or IV) peritonitis due to acute perforated diverticular disease.

Types of interventions

The types of interventions were laparoscopic peritoneal lavage compared with resection (Hartmann-type procedures, or primary anastomoses with or without stoma formation).

Types of outcome measures

Primary outcomes

- Postoperative mortality at index admission or within 30 days from index intervention.
- Postoperative mortality at 12 months.
- Surgical reintervention at index admission or within 30 days from index intervention.
- Postoperative intra-abdominal abscess at index admission or within 30 days from index intervention.
- Postoperative intra-abdominal abscess at 90 days.
- Presence of stoma at 12 months.

Secondary outcomes

- Operating time.
- Postoperative persistent peritonitis.
- Postoperative secondary peritonitis.
- Postoperative wound infections at 90 days.
- Length of postoperative hospital stay during index admission.
- Length of hospital stay during index admission.
- Adverse events within 90 days according to the Clavien–Dindo classification.
- Surgical reintervention within 90 days.
- Postoperative mortality at 90 days.
- Surgical reintervention within 12 months.
- Total length of hospital stays within 12 months.
- Postoperative quality of life.

A systematic literature search, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards [11], was conducted using the PubMed search engine up until 19 June 2016 employing the terms: “abdominal lavage” and/or “laparoscopy” and/or “peritonitis” and “diverticulitis”. Articles were initially reviewed by title and abstract, facilitating full-text screening of relevant publications by two authors independently. When multiple articles were published from a single-study group and where overlapping study periods were reported, only the most recent article was considered so as to avoid duplication of data. The PubMed function “related articles” was used to broaden each search, and the reference list of all potentially eligible studies was also reviewed. To minimise retrieval bias, a manual search of the Science Citation Index Expanded, Scopus and Google Scholar databases was also performed. The final decision regarding eligibility was reached by consensus between the two screening authors. Data were extracted independently by two review authors; any disagreement was resolved through discussion or consulting a third review author. A protocol for this meta-analysis has been registered on PROSPERO (http://www.crd.york.ac.uk/prospero), registration number CRD42016045202.

Assessment of methodological quality

Two authors independently read the included studies and assessed their methodological quality (risk of bias) using the instructions and the items given in the Cochrane Handbook for Systematic

Reviews of Interventions [12]. The items of the risk of bias included: sequence generation and allocation concealment [13] for selection bias, blinding of participants or personnel for performance bias [13], blinding of outcome assessors for detection bias [13], incomplete outcome data for attrition bias [14], and selective reporting bias [15]. Because there were fewer than 10 studies in any outcome, we did not examine funnel plots for asymmetry.
We assessed the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues such as risk of bias, inconsistency, imprecision, indirectness, and publication bias.

Statistical analysis

Meta-analysis was performed using the Review Manager version 5.0 software package (Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2011). Quantitative statistical analysis for dichotomous variables was carried out using the Manthel–Haenszel method, assessing the risk ratios (RR) as the summary statistic. Weighted mean differences (WMD) were used as summary statistic for quantitative analysis of continuous variables. Both the RR and WMD values were reported with 95% confidence intervals (CI). For those studies using continuous data, the mean and standard deviation (SD), when not directly reported, were calculated using the methods described by Hozo et al. [16]. Because substantial heterogeneity between trials was expected, we used only the random-effects model. Clinical heterogeneity was tested by means of the I^2 value where a value exceeding 50% was indicative of heterogeneity. This assumes that the effects estimated in different studies are not identical so that the centre of the distribution describes the average effects and the width, the degree of heterogeneity.

Results

Results of the literature search

The PRISMA flow diagram for systematic reviews is presented in Fig. 1.

Fig. 1
Preferred reporting items for systematic reviews and meta-analyses flow chart of literature search
We identified 142 publications using the literature search strategy described. After excluding 37 by title and abstracts, 95 manuscripts were eligible for full-text evaluation. We identified 4 publications with 2 published protocols that fulfilled the inclusion criteria [17–22], 2 of which [20, 21] reported different outcomes from the same RCT (the DILALA trial). We identified one ongoing trial (LapLAND) following a search of the metaRegister ClinicalTrials.gov [23].

Characteristics of included studies

We report the characteristics of the 3 included studies in "Characteristics of included studies" section (Tables 1, 2). Two publications reported short- and long-term results of the same trial (DILALA trial). Therefore, we included only 3 studies in our meta-analyses: the DILALA, the LADIES, and the SCANDIV trial.
Table 1

Characteristics of included studies

Table 2
Characteristics of treatment in included studies

Country

All trials were conducted in Europe. The DILALA trial was conducted in Sweden and Denmark; the SCANDIV trial was conducted in Norway and Sweden; and the LADIES trial recruited participants in the Netherlands, Belgium, and Italy.

Participants

Overall, 334 participants were included in the meta-analysis: 75 in the DILALA trial, 87 in the LADIES trial, and 172 in the SCANDIV trial. The inclusion criteria and the definition for diverticulitis among the studies differed considerably.

- The SCANDIV trial considered eligible patients those with a preoperative diagnosis of suspected perforated diverticulitis, a clinical indication for emergency surgery, and free air on an abdominal computed tomography scan. In this trial, the protocol was that randomisation was done preoperatively and patients were randomly assigned to undergo either laparoscopic lavage or colon resection. If Hinchey grade III (purulent peritonitis) from perforated diverticulitis was observed intra-operatively, patients received their per protocol allocated intervention. Irrespective of preoperative randomisation, the HP was performed on all patients with feculent peritonitis (Hinchey grade IV), including patients with a visible defect in the colon wall. In the resection group, the choices of laparoscopic versus open resection and also of HP versus primary resection and anastomosis (PRA) were determined by surgeon preference and local practices. In May 2013, the SCANDIV Study Group agreed to slightly increase the sample size because of the unexpectedly high number of included patients with incorrect preoperative diagnoses. Inclusion was to be continued until at least 65 patients with Hinchey grades I, II, or III had undergone treatment per protocol in each study group.
- The LADIES trial included two arms: the LaparOscopic LAvage and drainage (LOLA) arm and the perforated DIVerticulitis: sigmoid resection with or without Anastomosis (DIVA) arm. The LOLA arm of the LADIES trial included only participants with purulent perforated diverticulitis without overt perforation or intra-abdominal faecal contamination with randomisation 2:1:1 to either laparoscopic lavage or HP or sigmoidectomy and primary anastomosis, whereas the intra-operative finding at diagnostic laparoscopy of an Hinchey IV peritonitis would direct the case into the DIVA arm with 1:1 randomisation to HP or sigmoidectomy and primary anastomosis.
- The DILALA trial included only patients with purulent perforated diverticulitis (Hinchey III defined as purulent peritonitis and inflamed sigmoid) confirmed at laparoscopy after radiological diagnosis of perforated diverticulitis and then randomised to either laparoscopic lavage or HP. The severity of general preoperative condition was evaluated using a heterogeneous mix of scoring systems.

The American Society of Anaesthesiologists (ASA) physical status classification system was used in the SCANDIV and DILALA trials, the Charlson comorbidity index score was used in the SCANDIV trial, the Acute Physiology and Chronic Health Evaluation II (APACHE II) was used in

the LADIES trial, the Physiology and Operative Severity Score for the enumeration of mortality and morbidity—Physiology Score (POSSUM-PS) was used in the LADIES trial, and the Physiology and Operative Severity Score for the Enumeration of Mortality and Morbidity—Operative Score (POSSUM-OS) was used in the LADIES trial. In the analysis of all included trials, the percentage of ASA I and ASA IV patients was nearly the same in each arm, but there was a greater percentage of ASA II patients in the laparoscopic lavage group (57%) compared to the resection group (37%) and a greater percentage of ASA III patients in the colonic resection (33%) compared to the laparoscopic lavage group (17%) (Supplemental digital content (SDC) 1).
The three trials used a variety of methods to evaluate the time to surgery. The SCANDIV trial reported the symptom onset to surgery time in Hinchey I–III and admission to surgery time in Hinchey I–III; however, the DILALA trial reported the time from decision until surgery, and the LADIES trial reported the elapsed time between presentation to the emergency department and theatre. In both trials, the time before surgery was nearly the same in the laparoscopic lavage arm and the colonic resection arms (SDC 2).

Intervention

All trials compared laparoscopic lavage to laparoscopic or open surgical resection with synchronous anastomosis or without synchronous anastomosis (HP) for the management of generalised peritonitis caused by perforated sigmoid diverticulitis.

Experimental group

Details of the laparoscopic and open surgical procedures are given in Table 2.
The SCANDIV trial was the only study to report that all surgeons had basic laparoscopic skills.
In the LADIES trial, the patients with overt sigmoid perforation demonstrated through laparoscopy were excluded. In the other two trials, this intra-operative finding was not reported.
The three trials treated adhesions differently: in the SCANDIV trial the "adhesions to the sigmoid were not to be dissected"; in the LADIES trial, investigators were instructed in case of peritonitis due to a perforated diverticulum to attempt "gently to locate the site of perforation". "Careful removal of adherent omentum or bowel" is recommended and "if clearly adherent, it should be left in place". The DILALA trial did not address this issue.
In the peritoneal lavage group, the abdominal cavity was irrigated with different amounts of normal saline solution: 6 L in the LADIES trial, 4 L in the SCANDIV trial, and 3 L in the DILALA trial.

Control group

In the LADIES and DILALA trials, HP or sigmoidectomy and anastomosis were performed through open access. In the SCANDIV trial, the procedures were attempted laparoscopically.

Assessment of methodological quality

For details on the risk of bias in the included studies, see "*Characteristics of Included Studies*" section. SDC 3–4 show results from the study quality assessment.
All the studies were at low risk of selection bias. In the DILALA trial, the randomisation sequence was computer based, handled by an independent statistician. The LADIES trial used an online computer randomisation, either directly in the operating room or by the trial coordinator on the phone. The SCANDIV trial used a centralised web-based randomisation to allocate participants to treatment. Given the nature of the intervention all the trials were at low risk of performance bias, hence we focused our attention on the blinded assessment to the outcome of interest when it was subjective. Two trials (LADIES and SCANDIV) provided sufficient information of the independent

assessment of outcomes. No clear statement concerning the blinding of the outcome assessment was provided in the DILALA trial. In terms of incomplete outcome data, the DILALA trial reported that 5 (11%) participants in the laparoscopic group and 5 (12%) in the HP group were excluded because of several reasons including cancer, infection, and withdrawal. In the DILALA trial Agenete used the modified intention to treat for the report of results, differently Thornell used the intentention to treat. The percentage of exclusions is balanced between the two groups; however, it was not clear how this might affect the estimation of the results. In the remaining two studies, no concern of attrition bias was reported. All the studies reported the outcomes that were considered relevant for our assessment and were considered at low risk of bias. In terms of other bias, the LADIES trial was judged to be at high risk of bias because it was stopped early, at 33% of the planned sample size, due to higher major morbidity and mortality rates in the lavage group.
Overall the quality of evidence was low because of serious concern regarding the risk of bias and imprecision (Tables 3, 4).
Table 3
Summary of findings

Table 4
GRADE working group grades of evidence

					□□□□
Patients with stoma at 12 months	213 per 1000	107 per 1000 (183–159)	RR 0.50 (0.14–1.75)	167 (2 studies)	Very low[c,d]

GRADE working group grades of evidence. High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate
CI confidence interval, *RR* risk ratio
* The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)
[a]One trial with possible attrition bias (the DILALA trial): 5 (11%) participants in the laparoscopic group and 5 (12%) in the Hartman group excluded because of several reasons including cancer, infection, and withdrawal. Serious concern of bias with one early stopped trial (LADIES trial): higher major morbidity and mortality rate in the lavage group (at 33% of the planned sample size)
[b]Wide confidence interval
[c]Serious concern of bias: higher major morbidity and mortality rate in the lavage group (at 33% of the planned sample size)

[d]Small sample size; very wide confidence interval

Findings

Primary outcomes

Postoperative mortality at index admission or within 30 days from index intervention

All the included trials reported this outcome. In the LOLA arm of the LADIES trial, 88 Hinchey III patients were assessed with 3 deaths during the patients' primary hospital stay or shortly after (2 in the lavage group and 1 in the sigmoidectomy group). In the SCANDIV trial, patients in all Hinchey stages were included; the modified intention to treat analysis included 144 patients with Hinchey stages I–III: 2 in the lavage group and 3 in resection group died. In the short-term data on the DILALA trial reported in 2015 by Agenete et al. [20], 75 patients were classified as Hinchey III stage. The modified intention to treat analysis reported that 3 patients in the lavage group died whereas none in the operative resection group died. In our analysis, the mortality was lower in the resection group (4/148, 2.7%) than in the lavage group (7/159, 4.4%), but there was no statistically significant difference between the two groups of interventions in terms of postoperative mortality at index admission (studies = 3; participants = 307; RR 1.33, 95% CI 0.37–4.74; I^2 = 0%) (low quality evidence) (Fig. 2a). We performed a subgroup analysis for patients in the Hinchey III stage. In the SCANDIV trial, it was impossible to differentiate patients in Hinchey stage III from those in Hinchey stages I and II, so we excluded this trial from our subgroup analysis. In our subgroup analysis, the mortality was lower in the resection group (1/78, 1.3%) than in the lavage group (5/85, 5.8%). Again, there was no statistically significant difference between the two groups of interventions in terms of postoperative mortality at index admission (studies = 2; participants = 163; RR 3.01, 95% CI 0.48–18.93; I^2 = 0%) (low quality evidence) (Fig. 2b).

Fig. 2
a Postoperative mortality at index admission or within 30 days from index intervention in all Hinchey stages. **b** Postoperative mortality at index admission in Hinchey III patients

Postoperative mortality at 12 months

Two trials (LADIES and DILALA) reported this outcome. In the LOLA arm of the LADIES trial, 88 patients were in the Hinchey III stage: 4 patients died after lavage and 5 patients died after sigmoidectomy. In the long-term data from the DILALA trial reported in 2016 by Thornell et al. [21], 86 patients were in the Hinchey III stage: 6 patients in each study arm died. In our analysis, the mortality rate was lower in the lavage group (10/89, 11.2%) than in the resection group (11/82, 13.4%), but there was no statistically significant difference between the two groups of interventions in terms of postoperative mortality at 12 months (studies = 2; participants = 171; RR 0.84, 95% CI 0.38–1.88; I^2 = 0%) (very low quality evidence) (Fig. 3).

Fig. 3
Postoperative mortality at 12 months

Surgical reintervention at index admission or within 30 days from index intervention

All the included trials reported this outcome, and we considered surgical reintervention at index admission or within 30 days from index intervention as an unplanned procedure. In the DILALA trial, the reoperation rate (modified intention to treat) at 30 days was 5/38 (13.2%) in the

laparoscopic lavage group and 6/35 (17.1%) in HP group. In the LADIES trial, the reoperation rate at 30 days was 9/46 (20%) in the laparoscopic lavage group and 3/42 (7%) in the sigmoidectomy group ($p = 0.12$). In the SCANDIV trial, a higher reoperation rate was observed in the lavage group: 12/74 (16%) versus 3/70 (4%) ($p = 0.03$). In our analysis, there was no statistically significant difference between the two groups of interventions in terms of surgical reinterventions (studies = 3; participants = 305; RR 1.93, 95% CI 0.71–5.22; $I^2 = 53\%$) (low quality evidence) (Fig. 4). The subgroup analysis of only patients in Hinchey stage III included in the LOLA arm of the LADIES trial, and DILALA trial did not show statistically significant differences between the two groups of interventions (studies = 2; participants = 161; RR 1.40, 95% CI 0.71–4.90; $I^2 = 57\%$).

Fig. 4
Surgical reintervention at index admission or within 30 days from index intervention

Postoperative intra-abdominal abscess at index admission or within 30 days from index intervention

Two trials (LADIES and DILALA) reported this outcome, but the LADIES trial reported only the abscesses needing percutaneous drainage, whereas the DILALA trial reported only abscesses necessitating surgical reintervention. For these reasons, it was not possible to perform a meta-analysis of this outcome.

Postoperative intra-abdominal abscess at 90 days

Two trials (SCANDIV and DILALA) reported this outcome. At 90 days, the SCANDIV trial reported a higher incidence of intra-abdominal abscess in patients who underwent laparoscopic lavage (21.6%) than in those who underwent surgical resection (10%): 16/74 versus 7/70 ($p = 0.07$). Nine patients in the laparoscopic lavage group and 3 patients in the surgical resection group underwent percutaneous drainage of intra-abdominal abscesses. Only a small number of patients underwent surgical reintervention (3 in laparoscopic lavage group and none in surgical resection group) or antibiotic treatment alone (4 in the laparoscopic lavage group and 4 in the surgical resection group). In the DILALA trial, there was also a significantly higher rate of intra-abdominal abscesses in the patients undergoing laparoscopic lavage. Reoperations for the management of abdominal abscess were required in 2 patients initially managed with laparoscopic lavage and in 1 patient initially managed with resection. The authors of the DILALA trial did not consider percutaneous drainage of an abscess to be a surgical reintervention. In the LOLA arm of LADIES trial, the authors reported on abscesses needing percutaneous drainage and did not report abscess rates in patients undergoing surgical reintervention. The rate of abscesses needing percutaneous drainage was higher in those patients who underwent laparoscopic lavage compared to those who underwent resection: 9 (20%) in the short term and 2 (4%) in the long term after laparoscopic lavage versus none in the short-term period and 2 (5%) in the long term after resection. In our meta-analysis, there was a significantly higher rate of postoperative intra-abdominal abscess in the patients who underwent laparoscopic lavage (30/117, 25.6%) than in patients who underwent surgical resection (11/110, 10%) (participants = 227; studies = 2; RR 2.54, 95% CI 1.34–4.83; $I^2 = 0\%$) (moderate quality evidence) (Fig. 5).

Fig. 5
Postoperative intra-abdominal abscess at 90 days

Patients with stoma at 12 months

Two trials (LADIES and DILALA) reported this outcome. In the DILALA trial, 3 patients (3/43, 6.97%) in the lavage group had a stoma at 12 months, compared with 11 in the resection group (11/40, 27.5%). In the LADIES trial, 6 patients in each group (6/46, 13%, in the lavage group and 6/42, 14.2%, in the sigmoidectomy group) were alive and had a stoma at 12 months. The stoma formation rate at 12 months was lower in the lavage group compared with the resection group, but there was no statistically significant difference between the two groups in terms of surgical reinterventions (studies = 2; participants = 167; RR 0.50, 95% CI 0.14–1.75; I^2 = 0%) (very low quality evidence) (Fig. 6). This outcome was underpowered because these data were not available from the SCANDIV trial.

Fig. 6
Patients with stoma at 12 months

Secondary outcomes

Operating time

This outcome was reported in the SCANDIV trial although a definition of operating time was not provided. In the DILALA trial, the duration of surgery and time between end of surgery and the end of anaesthesia were reported. In the LADIES trial, the results of a comparative analysis were provided in the absence of the primary data. Because of the incongruous reports of operating time, we did not perform a meta-analysis on this outcome. In all trials, the operating time was significantly shorter in the laparoscopic lavage arm with the exception of Hinchey IV patients in the SCANDIV trial (p = 0.13) (Table 5).

Table 5
Operating time

Trial	Evaluation of the operating time	Laparoscopic lavage (min)	Colonic resection (min)	*p*
LADIES [17, 18]	Operating time, mean	60	120	0.001
DILALA [19–21]	Operating time, median (range)	68 (28–194)	154 (58–266)	<0.0001
	Time between end of surgery and end of anaesthesia	19 (5–42)	29 (0–97)	<0.0001
SCANDIV [22]	Operating time, mean (SD), in Hinchey I–III	72 (26)	149 (54)	<0.001
	Operating time, mean (SD), in Hinchey IV	157 (44)	133 (45)	0.13

Postoperative persistent peritonitis

Only the DILALA trial analysed this outcome as persistent peritonitis: no patient in the lavage group (0/38) and only 1 patient in the resection group (1/35, 2.8%).

Postoperative secondary peritonitis

Only the SCANDIV trial analysed this outcome of persistent peritonitis: 9 patients (9/74, 12%) in the laparoscopic lavage group and none in the resection group (0/70). Six of these patients with postoperative secondary peritonitis had a subsequent reoperation.

Postoperative wound infections at 90 days

Two trials (SCANDIV and DILALA) reported this outcome. At 90 days, the SCANDIV trial reported a lower incidence of superficial wound infection in patients who underwent laparoscopic lavage (1.3%) than in those who underwent surgical resection (12.8%): 1/74 versus 9/70 ($p = 0.08$). The DILALA trial reported wound infections in only 5 patients who underwent resection. In this meta-analysis, the wound infections rate was significantly lower in the laparoscopic lavage group than in the resection group (studies = 2; participants = 227; RR 0.10, 95% CI 0.02–0.51; $I^2 = 0\%$) (Fig. 7).

Fig. 7
Postoperative wound infection at 90 days

Length of postoperative hospital stay during index admission

Two trials (LADIES and DILALA) reported this outcome. In the LADIES trial, the length of postoperative hospital stay did not differ between the two groups: 8 days (6–15) after lavage and 10 days (7–14) after sigmoidectomy ($p = 0.8751$). In the DILALA trial, laparoscopic lavage resulted in a shorter hospital stay (median 6 days) compared with the resection group (median 9 days; $p = 0.037$). In this meta-analysis, the outcome length of postoperative hospital stay during index admission was significantly lower in the laparoscopic lavage group than in the resection group (studies = 3; participants = 163; WMD = −2.03, 95% CI −2.59 to −1.47; $I^2 = 0\%$) (SDC 5).

Length of hospital stay during index admission

Only the DILALA trial reported this outcome. Laparoscopic lavage resulted in a shorter hospital stay (median 6 days) compared with HP (median 9 days; $p < 0.05$).

Adverse events within 90 days by Clavien–Dindo grade

Two trials (SCANDIV and DILALA) reported this outcome.

Clavien–Dindo grade I–II

Only the DILALA trial reported this outcome: 25 patients (58.1%) in the laparoscopic lavage group had adverse outcomes within 90 days, compared with 16 patients (40%) in the resection group. The complication rate in the resection group was lower than in the laparoscopic lavage group, but there was no statistically significant difference between the two groups of interventions.

Clavien–Dindo grade IIIa

Only the DILALA trial reported this outcome: 4 patients (9.3%) in the laparoscopic lavage group had adverse outcomes within 90 days, compared with one patient (2.5%) in the resection group. The

adverse out come rate in the resection group was lower in the laparoscopic lavage group, but there was no statistically significant difference between the two groups of interventions ($p = 0.090$).

Clavien–Dindo grade IIIb

In the SCANDIV trial, this outcome was reported merging all Hinchey grades:13 patients in the laparoscopic lavage group had adverse events within 90 days compared with 5 patients in the resection group. In the DILALA trial, 6 patients in the laparoscopic lavage group had adverse outcomes within 90 days, compared with 7 in the resection group. In this meta-analysis, there was no statistically significant difference between the two groups of interventions (participants = 255; studies = 2; RR 1.40, 95% CI 0.47–4.17; $I^2 = 59\%$) (SDC 6).

Clavien–Dindo grade IVa

In the SCANDIV trial, this outcome is reported in patients with all Hinchey grades: 2 patients in the laparoscopic lavage group had adverse events within 90 days, compared with 4 in the resection group. In the DILALA trial, 3 patients in laparoscopic lavage group had adverse outcomes within 90 days, compared with 4 in the resection group. In this meta-analysis, there was no statistically significant difference between the two groups of interventions (participants = 255; studies = 2; RR 0.59, 95% CI 0.20–1.75; $I^2 = 0\%$) (SDC 7).

Clavien–Dindo grade IVb

In the SCANDIV trial, this outcome was reported in patients with all Hinchey grades (1 patient in the laparoscopic lavage group had adverse outcomes within 90 days, compared with 2 in the resection group). In the DILALA trial, 1 patient in laparoscopic lavage group had adverse outcomes within 90 days, compared with 1 in the resection group. In this meta-analysis, there was no statistically significant difference between the two groups of interventions (participants = 280; studies = 2; RR 0.62, 95% CI 0.10–3.75; $I^2 = 0\%$) (SDC 8).

Surgical reintervention at 90 days

Only one trial (SCANDIV) reported this outcome. The SCANDIV trial made a clear distinction between planned and unplanned reoperations. The unplanned reoperation rate was significantly higher in the laparoscopic lavage group (15 of 74 patients, 20.3%), than in the resection group (4 of 70 patients, 5.7%; WMD = 14.6%, 95% CI 3.5–25.6%; $p = .01$) for patients who did not have faecal peritonitis.

Postoperative mortality at 90 days

Two trials (SCANDIV and DILALA) reported this outcome. In the SCANDIV trial, mortality did not differ significantly between the laparoscopic lavage group (12 patients) and the resection group (7 patients). In the DILALA trial, mortality within 90 days was not significantly different between the study groups (3/39 vs. 4/36). In the present meta-analysis, there was no statistically significant difference between the two groups of intervention in terms of postoperative mortality at 90 days (studies = 2; participants = 247; RR 1.27, 95% CI 0.60–2.69; $I^2 = 0\%$) (SDC 9).

Surgical reintervention at 12 months

Two trials (DILALA and LADIES) reported this outcome. In the DILALA trial, 12 (27.9%) patients in the laparoscopic group had one or more reoperations, compared with 25 (62.5%) in the

HP group; there was a risk reduction of 59% (RR 0.41, 95% CI 0.23–0.72). In the LOLA arm of the LADIES trial, the reoperation rate was higher in the laparoscopic lavage group [20/46 (43.48%) vs. 27/42 (64.28%)]. In this meta-analysis, there was a statistically significant difference between the two groups with regard to the surgical reintervention rate at 12 months; the surgical reintervention rate was significantly lower in the laparoscopic lavage group (studies = 2; participants = 171; RR 0.57, 95% CI 0.38–0.86; I^2 = 34%) (Fig. 8). We posited two reasons for this heterogeneity. In the reoperation group, the DILALA trial included stoma reversal but did not include percutaneous drainage of abscess as a surgical reintervention. In the LOLA arm of the LADIES trial, stoma reversal was not included in the surgical reintervention group, but percutaneous drainage of abscesses was also included. The DILALA trial considered Hartmann's stoma reversal as a reoperation, merging planned and unplanned surgery after the index procedure; this perspective may be misleading as the perception of reoperation is commonly negative due to complications or treatment failure (unplanned reoperation), whereas Hartmann's reversal is a standard part of the procedure (planned reoperation). Moreover, the LADIES trial made a clear distinction between planned and unplanned reoperations with significantly higher rates of unplanned reoperation after laparoscopic lavage. We used the overall reoperation rate of LADIES to reduce the heterogeneous inclusion of patients.

Fig. 8
Surgical reintervention at 12 months

Total length of hospital stay within 12 months

Only the DILALA trial reported this outcome. The total length of hospital stay was shorter in the laparoscopic group (mean 14 days) than in the resection group (mean, 18 days), with a relative risk reduction of 35% (RR 0.65, 95% CI 0.45–0.94; p = 0.047) in the laparoscopic group compared with the HP group.

Quality of life

All the included trials reported this outcome, but the data of quality of life questionnaires were not comparable. Therefore, we did not perform an analysis of the included trials. The results of all trials reported no differences between the laparoscopic lavage and resection groups.

Discussion

Laparoscopic peritoneal lavage was introduced into the management options for perforated sigmoid diverticulitis, in an attempt to use minimally invasive techniques in treating this challenging disease [24, 25]. Results from the first case series reported good control of peritonitis, even in physiologically and physically frail patients, raising expectations regarding this operative strategy among surgeons [26–29]. In these first series, the authors reported that they had a 95% success rate in controlling sepsis and that none of their patients was readmitted for subsequent episodes of diverticulitis. Probably these results were affected by a strong selection bias, which would explain why the subsequent RCTs did not report such outstanding results. The idea of a relatively quick, technically feasible, minimally invasive surgical option was particularly attractive given the alternative: standard open sigmoidectomy and stoma formation.
This systematic review has identified 3 published RCTs, as well as one ongoing trial, which aimed to assess the role of laparoscopic peritoneal lavage in the management of peritonitis caused by perforated sigmoid diverticular disease, compared to surgical resection. In none of the 3 published trials is laparoscopic peritoneal lavage superior to resection. The aim of our meta-analysis is to

resolve this dilemma. The present meta-analysis of these data suggests several benefits of laparoscopic peritoneal lavage compared to laparoscopic or open surgical resection with or without synchronous anastomosis. These benefits include a reduced operating time, a shortened overall and postoperative index hospital stay, a lower surgical re-intervention rate at 12 months and a reduced total length of hospital stay within 12 months. Although the stoma rate, postoperative mortality at 12 months, and Clavien–Dindo grade IV adverse events were also improved in the laparoscopic lavage groups, these improvements did not reach statistical significance. On the contrary, the postoperative mortality rate at the index operation and at 90 days, the surgical reintervention rate during the index hospitalisation and at 90 days, as well as the Clavien–Dindo grade I–III adverse events rate were all in favour of emergency resection, but also in this case the difference did not reach statistical significance. The only statistically significant finding which provides evidence against laparoscopic lavage was significantly increased postoperative intra-abdominal abscess formation within 90 days from the presentation, which perhaps explains the observed trend towards higher unplanned reintervention in the laparoscopic lavage group.

The time to treatment is important in terms of both potential clinical impact and its effect on the degree of peritonitis and pathological evolution of the disease. Early treatment may prevent physiological deterioration. Delayed treatment may select patients with more favourable pathological conditions, amenable to less aggressive or different surgical treatment. In two of the randomised controlled trials, the interval between onset of symptoms and surgical treatment was similar in the laparoscopic lavage and the resection groups. Future studies should focus on further clarification of this potentially important variable.

Postoperative mortality is an important outcome measure for patients with peritonitis. The inability to demonstrate a significant difference is highly relevant: the fact that the mortality rate is similar to the “less aggressive” laparoscopic lavage approach challenges the need for highly invasive and more traumatic surgery. The same argument applies to the lack of a significant difference in surgical morbidity and the need for further surgery.

Each randomised controlled trial demonstrated improvements in the quality of life of patients in the laparoscopic lavage study groups. While meta-analysis was precluded given the varying quality measures, the message is clear. This observation was consistent with the reduced stoma formation rate among patients who underwent laparoscopic lavage. Significant rates of permanent stoma formation, particularly in the elderly, following emergency HP, have been reported [30–32]. All this provides strong clinical grounds for a more conservative approach with laparoscopic lavage.

The laparoscopic lavage approach appears to minimise costs. The operative time is shorter and the hospital stay reduced, both at the index operation and cumulatively within the year. These benefits are even more significant in the light of evidence that there is no higher risk of early reoperation. As mentioned above, laparoscopic lavage is not inferior to resection: a potentially less invasive procedure is yielding the same effect. All these effects have to be balanced with the higher number of total late procedures in the laparoscopic lavage treatment groups, most likely related to the fact that some patients experienced ongoing sepsis, mainly due to intra-peritoneal abscesses, and the associated treatment. Patients undergoing these unplanned procedures may experience significant morbidity, though robust data to support this concern are outstanding.

There are considerable variations among the trials included in this meta-analysis, with heterogeneity in the precise inclusion criteria, clinical timing of intervention and almost certainly in the clinical care provided. Among reported variables, there are clear variations in the disease stage treated (Hinchey grade), and measures used to assess the physiological well-being and comorbidities of the patients (Charlson index, APACHE II, and POSSUM-PS). Regrettably, no study considered the Mannheim Peritonitis Index.

Surgical technique varied significantly among studies, almost certainly with bias relating to this heterogeneity. Even though the individual trials attempted to describe the technique in detail, subtle technical variations, unique to the individual operating surgeon, are difficult to quantify, and hard to account for. The trial protocol methodologies do leave room for clinical interpretation: for example,

in the LADIES trial the definition of "weak" and "firm" adhesions. The variable quantity of fluid used in peritoneal lavage (3–6 l) adds a further point of technical heterogeneity. In any case, we believe that the quantity of fluid is most likely less important than the quality of the fluid aspirated and drained. Detailed criteria for patient inclusion and a well-defined, standard surgical technique are two mainstays of an eventual further study on this issue.

Perhaps the outcomes of laparoscopic lavage may be influenced by inter-hospital and inter-operator variability; moreover, the results and outcomes can be also affected by the specific level of experience and skills of the operating surgeons, depending on their level of experience in the subspecialty of colorectal surgery and laparoscopic surgery [33].

Three other systematic reviews and a meta-analysis have been recently published by Ceresoli et al. [34], Angenete et al. [35] and Marshall et al. [36] on this same topic. These three meta-analyses have limitations since they only reviewed purulent peritonitis (Hinchey III), while the present systematic review includes a meta-analysis of all types of diverticular peritonitis of any Hinchey grade (Hinchey I–IV) and includes a subgroup analysis of purulent peritonitis (Hinchey III). The results of the current meta-analysis are significantly different from those published in the previous analyses in various ways:

In the analysis of postoperative mortality at index admission or within 30 days from index intervention in patients with purulent peritonitis, Marshall included all 3 trials and Ceresoli et al. reported only the data of 2 trials (LADIES and SCANDIV) and did not include the results of the DILALA trial. But the SCANDIV trial excluded patients with faecal peritonitis (Hinchey IV), but included patients with Hinchey I and II diverticulitis. In our meta-analysis, we performed the analysis for all Hinchey stages, including all 3 trials (Fig. 2a), and a subgroup analysis for Hinchey III, including the DILALA and LADIES trials (Fig. 2b). In our analysis, the results are in favour of resection, but do not reach statistical significance (all Hinchey stages: RR 1.33, 95% CI 0.37–4.74; I^2 = 0%. Hinchey III stage: RR 3.01, 95% CI 0.48–18.93; I^2 = 0%). The same results were reported by Ceresoli (OR 0.93; 95% CI 0.23–3.82; p = 0.92) and Marshall (RR 1.34, 95% CI 0.37–4.79).

Regarding postoperative mortality at 3 months from the index intervention in patients with purulent peritonitis (Hinchey III) in their analysis Ceresoli and co-authors included the SCANDIV and LADIES trials, but excluded the DILALA trial. On the other hand, Marshall et al. and Angenete et al. included all 3 trials (DILALA, LADIES, and SCANDIV) and mixed the mortality at 90 days of the DILALA and SCANDIV trials with the postoperative mortality at index admission or within 30 days from index intervention reported in the LADIES trial. As previously reported, the SCANDIV trial excluded patients with faecal peritonitis (Hinchey IV), but included patients with Hinchey stages I–III. In our meta-analysis, we performed the analysis for all Hinchey stages, including only the DILALA and SCANDIV trials (SDC 9), and we did not perform a subgroup analysis for the Hinchey III patients. In our review, the results were not statically significant although in favour of resection (RR 1.27, 95% CI 0.60–2.69; I^2 = 0%). The same results were reported by Ceresoli et al. (OR 0.83; 95% CI 0.32–2.11; p = 0.69), Agenete et al. (RR 0.86, 95% CI 0.40–1.83) and Marshall et al. (RR 0.86; 95% CI 0.40–1.84).

Concerning the surgical reintervention rate at index admission or within 30 days from index intervention, Marshall and colleagues performed an analysis of all 3 trials, while Ceresoli et al. performed an analysis of data reported in the LADIES and SCANDIV trials, excluding the DILALA trial that reported the data about this outcome. As previously reported, the SCANDIV trial excluded the patients with faecal peritonitis (Hinchey IV), but included the Hinchey I and II patients. In our meta-analysis, we performed the analysis for all Hinchey stages, including all 3 trials (Fig. 4), and a subgroup analysis for the Hinchey III patients, including only the LADIES and DILALA trials, as in the meta-analysis performed by Agenete et al. In the analysis carried out by Ceresoli et al., the results favoured the resection group, reaching statistical significance (OR 3.75, p = 0.006); similar results were reported in the Marshall analysis (RR = 3.03, 95% CI 1.16 to 7.89; I^2 = 60%). In our analysis in all Hinchey stages (RR 1.93, 95% CI 0.71–5.22; I^2 = 53%) and in Hinchey III (RR 1.40, 95% CI 0.71–4.90; I^2 = 57%), the results were in favour of the resection

group but without reaching statistical significance. Agenete et al. reported results similar to our review, including the LADIES and DILALA trials (RR 1.34, 95% CI 0.59–3.04). Regarding surgical reintervention at 12 months, Ceresoli et al. reported a statistically significant results in favour of the laparoscopic lavage group (OR 0.32, $p = 0.0004$), similar to the meta-analysis performed by Agenete et al. (RR 0.54, 95% CI 0.38–0.76). Our analysis (RR 0.57, 95% CI 0.38–0.86; $I^2 = 34\%$) agrees with the previous results reported by Ceresoli and Agenete (Fig. 8).
We did not perform any analysis of intra-abdominal abscesses at index admission or within 30 days from index intervention because the LADIES trial reported only the data regarding abscess treated with percutaneous drainage and the DILALA trial reported only data regarding abscess treated by surgical reoperation. Ceresoli and colleagues performed an analysis with statistically significant results in favour of resection (OR 3.50; 95% CI 1.79–6.86; $p = 0.0003$). The DILALA and SCANDIV trials reported the data about intra-abdominal abscess at 90 days. We evaluated only postoperative intra-abdominal abscess at 90 days and the results were in favour of the resection (RR = 2.54, 95% CI 1.34–4.83; $I^2 = 0\%$) (Fig. 5). Regarding postoperative wound infections, Ceresoli et al. included all 3 trials, although in the LADIES trial this outcome was reported at 30 days and in the Scandiv and DILALA was reported at 90 days, the result was statistically significant (OR 0.14; 95% CI 0.04–0.45; $p = 0.0009$). In our analysis, we included only the SCANDIV an LADIES trials and obtained statistically significant results at 90 days in favour of lavage (RR 0.10, 95% CI 0.02–0.51; $I^2 = 0\%$) (Fig. 7).
Finally, we were unable to analyse the difference in quality of life between the 3 studies since the questionnaires were all different: the relevance of this parameter is quite evident if only considering the different rates of stoma formation.
Many questions regarding the optimal treatment of peritonitis from perforated diverticular disease remain unanswered. Patient characteristics favouring specific treatments have not been adequately researched and remain ill-defined. Studies that address and better define the optimal surgical strategy are needed. As stated in article by Marshall and co-workers, the results of 2 ongoing studies are eagerly awaited: one prospective randomised trial, LapLAND, and one multicentre retrospective study on patients treated with laparoscopic lavage, the LLOStudy [37]. Similarly, factors relating to hospital practices and resources are unclear. The role of damage control surgery validated in selected patients is not well defined. All these factors highlight the crucial role of clinical judgement in the application of the available data in the daily clinical setting.
In a recent letter, Slim [38] analysed the role of meta-analysis in peritoneal lavage for sigmoid perforation peritonitis surgery ("What do the meta-analyses tell us?"): "Reading these two papers, one becomes immediately aware of a serious discrepancy: the two meta-analyses that had included exactly the same trials came to opposite conclusions. One concluded that there is no difference in terms of mortality and higher rate of reoperation and intra-abdominal abscess formation with or without laparoscopic lavage. The other reported a similar result for mortality but a lesser risk for reoperation (at 12 months) after laparoscopic lavage. How can this discordance be explained?"
This systematic review and meta-analysis has not demonstrated any significant difference between laparoscopic peritoneal lavage and traditional surgical resection in patients with peritonitis from perforated diverticular disease, as regards postoperative mortality and surgical reintervention rate, although laparoscopic lavage is associated with a lower rate of stoma formation. Overall the quality of evidence was low because of serious concern regarding the risk of bias and imprecision. The finding of a significantly higher rate of postoperative intra-abdominal abscess in patients undergoing laparoscopic lavage compared to those undergoing surgical resection is of concern. Even so, laparoscopic lavage does not appear fundamentally inferior to the traditional surgical resection and manages to achieve reasonable outcomes in a minimally invasive fashion, and using reduced hospital resources. The fundamental flaw of this technique is the lack of a robust diagnosis. The present systematic review and previous systematic reviews on this topic, as reported in a recent letter by Ceresoli [39], were unanimous in finding no difference in morbidity and mortality at 3 and 12 months between laparoscopic lavage and sigmoid resection and also showed an increased rate of

reoperations in the resection group, primarily due to planned stoma closure. However, laparoscopic lavage was associated with a significantly higher incidence rate of intra-abdominal abscesses and higher reoperation rate during the index admission.
The long-term results of the ongoing randomised trials (LapLAND) are eagerly awaited and will hopefully shed more light on this difficult area of clinical decision making [40].
In conclusion, we found no difference between laparoscopic peritoneal lavage and surgical resection in any parameters other than intra-abdominal abscess formation and higher same admission re-operation rate for patients with peritonitis caused by perforated diverticular disease.

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