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ORIGINAL ARTICLE

Diverticular Peritonitis: What Did Dilala Teach us? Methodological Analysis of its Design, Application and Results

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ABSTRACT

Background: *DILALA compared laparoscopic lavage (LL) with Hartmann's procedure (HP) in Hinchey 3. It was one of the few randomized trials carried out to date, therefore a thorough methodological review is necessary to validate or challenge its conclusions.*

Objective: *To analyze the methodology used in the design, application, analysis of results and conclusions of its publications. Secondly, collaborate in the improvement of the investigation of diverticular peritonitis and facilitate the analysis of the subject by the readers.*

Methods: *The main parts of all research were analyzed, from the research question, hypothesis elaboration, operationalization of variables and trial design, statistical analysis of results and conclusions. We looked for errors, biases and weaknesses that could object to the findings of the study.*

Results: *DILALA was designed as a 2-arm open, randomized, controlled trial with a 1: 1 distribution. This was a superiority study and its data were analyzed both by intention to treat and by protocol. In it, possible selection biases, weaknesses and methodological errors were found. According to its authors, DILALA demonstrated that LL is safe and feasible, with shorter operative time, shorter stay and fewer reoperations (both in proportion of patients and in number of reoperations per patient) than HP.*

Conclusions: *The validity of the main variable (reoperations) was compromised by including ostomy closure and excluding percutaneous drainage without anesthesia. In addition, 3 possible sample selection biases were found. The safety and feasibility inference was wrong since the sample is too small to show differences in morbidity and mortality. DILALA demonstrated the obvious, that HP entails the need for an ostomy and eventually surgery for its closure.*

Keywords: *Diverticular peritonitis; Perforated diverticulitis; Methodology; Investigation; DILALA study*

INTRODUCTION

DILALA was an international multicenter randomized study (Sweden and Denmark) that was carried out from February 2010 to February 2014. Nine surgical departments with different levels of specialization participated and it had the external monitoring of an independent committee. Its protocol and results were published in 2011, 2016 and 2018.[1-5] Together with LADIES, SCANDIV, and DIVERTI, it is one of the few randomized trials that compared surgical treatments for diverticular peritonitis, a topic that to date continues to be debated. Our aim is to analyze its design, application and results from a methodological perspective, with the primary objective of validating or putting under suspicion its conclusions. And as a secondary objective, to favor the improvement of the methodology used in the investigation of the topic and its analysis by the readers.

MATERIAL AND METHODS

The core parts of every research study were analyzed:

- Research question and hypothesis.
- Study design.
- Operationalization of variables.
- Statistical analysis and results.
- Conclusions.

In each of them, errors, biases and weaknesses that affect the logical sequence of the research process were looked for.

RESULTS

Research question and hypothesis

While DILALA does not explicitly mention the research question, we can infer it based on the design and alternative hypothesis.

Is laparoscopic lavage (LL) in Hinchey 3 superior to Hartmann's procedure (HP) (open) in terms of reoperations (primary outcome variable), morbidity and mortality, permanent ostomy, hospital stay, quality of life and health costs (secondary variables) during the follow-up period? Ha: LL reoperations < HP reoperations in Hinchey 3.

Cost analyzes will not be addressed due to the great differences between the participating countries and the local setting.

Study design

It was a randomized, open 2-arm study with a 1:1 dis-

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tribution, which compared the performance of LL versus HP (open) in Hinchey 3 peritonitis. The randomization was in blocks of 10. The selection criteria are detailed in Table 1.

No maneuvers to rule out colonic perforation were performed during laparoscopy or imaging studies. According to protocol, the primary outcome variable to be compared was the number of reoperations (12-month follow-up). However, the sample calculation was made based on the percentage of patients with reoperations. Thus, in order to detect a reduction in the percentage of reoperations from 40 to 10%, according to the chi-square analysis (X2), based on a power of 80% and $\alpha = 0.05$ for a 2-tailed study, 32 patients are required per branch. Taking into account possible losses to follow-up, the number used was 40 patients per arm.

Although it is not explicitly mentioned, it was a superiority study and its data were analyzed both by intention to treat and by protocol (for the latter, patients with a diagnosis of colorectal cancer and those who withdrew their consent were excluded).

All eligible patients were entered into a screening registry. Of 267 eligible patients, 139 were enrolled and underwent diagnostic laparoscopy. Of these, only 83 patients were Hinchey 3, who were randomized for intention-to-treat analysis, 43 for the LL group and 40 for the HP group. The per-protocol analysis was performed with 38 patients in the LL group and 36 in the HP group.

Variables operationalization

The primary outcome variable chosen was reoperations, it was defined as a categorical or nominal variable expressed in percentages according to the formula:

$$\frac{\text{Pts with one or more reoperations within the follow-up period}}{\text{Pts treated}}$$

It is worth mentioning that, according to the authors, the term "reoperations" includes the closure of the ostomies and excludes percutaneous drains without anesthesia, which were listed as adverse effects / morbidity. An indicator is considered valid when it measures what it intends to measure, in this sense the decision made by the authors could render the main variable of the study invalid.

Secondary outcome variables were mortality (categorical), adverse effects (categorical), hospital stay (quantitative), quality of life (quantitative), number of reoperations (quantitative, discrete), and number of admissions (quantitative, discreet). During the second year of follow-up, the secondary variables were added: percentage of patients with an ostomy at 24 months (categorical) and the number of operations (quantitative) possibly related to diverticulitis (intestinal resection, incisional hernias, intestinal obstruction, creation and closure of ostomy) from 12 to 24 months.

TABLE 1: SELECTION CRITERIA

Inclusion criteria	Exclusion criteria
Pain in left lower quadrant	Findings in diagnostic laparoscopy - Absence of free liquid - Hinchey 4 - Peritonitis from other causes
Fever	Patients not suitable for surgery*
Elevated C-reactive protein and leukocytosis	Lack of informed consent
Radiographic findings with fluid or air in the cavity	

** No mention is made of the definition used for this concept.*

Statistical analysis and results

Regarding the statistical analysis, the authors mention having used:

- Non-parametric tests: frequently used for variables with a non-normal distribution.
  - Mann-Whitney U.
- X2 and Fisher's exact test: both tests are used to analyze categorical variables, Fisher is used in case of event frequencies less than 5 because in such circumstances X2 loses reliability.
- Generalized linear model (GLM): they are a family of tests that do not require a normal distribution of the dependent variable since it is linearly related to the factors and covariates through a specific link function.
  - Linear log model (semi-logarithmic): belongs to MLG.
- Poisson distribution: used to count events in a certain period of time.
- Negative binomial distribution: while the binomial distribution counts successes in a fixed number of trials, the negative binomial counts failures up to a fixed number of successes (success is understood when the expected event occurs).
- Bonferroni correction: it is used to avoid the inflation of the alpha error (family wise error rate) which is the probability of rejecting the H0 when it is true in a series of tests (Type I error). It has been criticized, among other reasons, for causing loss of the power of the study.

The baseline characteristics of both populations did not show significant differences. The results of the procedures and the postoperative period with statistical significance are shown in Table 2. Regarding operative time, use of a suprapubic catheter, hospital stay and time of abdominal drainage, these variables can be understood as dependent on the type of procedure used, but in the case of colonic perforation, this difference can be interpreted in two ways. Either its frequency was truly low in the LL group and should be understood as a sample bias (and therefore independent of treatment) or its frequency was low because it was under diagnosed during LL. It was mentioned that there were no significant differences in mortality at 30 or 90 days (3/39 vs. 0/36; 3/39 vs. 4/36), nor in reoperations or early morbidity.

Table 3 shows the results corresponding to the main variable: reoperations after 12 and 24 months of follow-up. These results were consistent with the analysis performed adjusted for sex and age, as per protocol.

No statistically significant differences were found in adverse effects (morbidity and mortality) or in quality of life in the 12-month follow-up. Regarding the stay within 12 months, it was lower for LL than for HP (mean, 14 vs. 18 days, respectively), with a RR of 35% (RR 0.65 [CI 0.45 to 0.94]; p = 0.047). While at 24 months no statistically significant differences were found in hospital stay, admissions, or percentage of patients with ostomies.

TABLE 2: RESULTS OF THE PROCEDURE AND THE POSTOPERATIVE PERIOD WITH STATISTICAL SIGNIFICANCE

Variable	Group LL n=39 (%)	Group HP n=36 (%)	P
Operative time (hh: mm)	1:08	2:34	<0.01
Suprapubic urinary catheter	0/39	5/36 (14)	0.016
Visible colonic perforation	2/38 (5)	18/36 (50)	<0.01
Hospital stay (days)	6	9	<0.01
Abdominal drainage time (days)	3	2	<0.05

LL: Laparoscopic lavage group. HP: Hartmann's procedure group.

Conclusions DILALA

Synthesizing all the publications, the authors concluded that:

- LL is feasible and safe since there were no differences in morbidity or mortality when compared with HP. This statement cannot be supported on the basis of the design and application of the study since it was not part of the initial question and hypothesis and therefore the sample size could not be that required to detect the existing differences in the population.
- Operative time and hospital stay favored LL.
- After a 24-month follow-up LL had a lower proportion of patients with reoperations and a lower average number of reoperations per patient. The validity of the reoperation indicator is compromised, which makes the correct analysis difficult. As an example, an imaginary scenario could be given with patients in HP without adverse effects / morbidity with 100% reoperations (reconstructed) vs. 50% of reoperations in LL with 100% of patients requiring percutaneous drainage without anesthesia and the statement would remain the same.
- The authors mentioned that the lower number of colonic perforations found in LL vs. HP could be attributed to the fact that his search was not protocolized in LL and to the manipulation of the colon in HP. This finding may suggest the existence of bias in the sample and therefore invalidate all the conclusions that are inferred from the trial.
- They considered the use of the screening log to detect selection biases and the fact that the tests were performed as planned without post hoc subgroups were considered a strength. As limitations, the large number of eligible patients who were not enrolled was mentioned. Both statements refer to the possibility of biases in the chosen sample.

DISCUSSION

This study represents the results of a European population with purulent peritonitis, treated in centers of different levels of specialization.

His hypothesis raised the superiority of LL vs. HP, as it has a lower percentage of reoperations, however, the validity of this variable / indicator was compromised by the inclusions and exclusions mentioned above.

Regarding its design, possible biases were found such as the number of non-enrolled patients, the absence of definition of the aptitude of the patients for surgery and the greater presence of colonic perforations in the HP group.

The results presented were analyzed with consistent statistical techniques, and the differences found in the calculation of relative risks with the usual methods could not be clarified.

The sample was small to be able to show differences in morbidity and mortality, but the authors showed this lack of power of the study as feasibility and safety of LL. As an example, Table 4 shows the sample size required by virtue of the expected mortality of 2 procedures, the-

TABLE 3: RESULTS OF REOPERATIONS AT 12 AND 24 MONTHS

Variable	LL n=43	OH n=40	RR IDT*	RR PP†
Patients with reoperations 12m	12 (27.9)	25 (62.5)	0.41 (0.23-0.72)	0.28 (0.15–0.55)
n (%)	18 (41.9)	27 (67.5)	0.55 (0.36-0.84)	NR
Patients with reoperations 24m	0.35 (0.61)	0.80 (0.91)	0.40 (0.22–0.76)	0.28 (0.13–0.59)
n (%)	0.63(0.90)	1.08(1.16)	0.51 (0.31-0.87)	NR
Average reoperations per patient 12m	6	5		

LL: Laparoscopic lavage group. HP: Hartmann's procedure group.
RR IT: Relative risk or risk ratio according to intention to treat. RR PP: Relative risk according to analysis by protocol. NR: Not reported.
The values are lower than the expected results with the usual calculations; the publication does not mention what type of correction was used.

refore, it is not accurate to say that there were no differences between LL and HP, but rather that they could not be demonstrated. Similarly, it could not demonstrate differences in quality of life.

CONCLUSIONS

This study managed to demonstrate the obvious, that HP entails the need for an ostomy and eventually a new surgery for its closure.

In the words of David Kent and Rodney Hayward, "determining the best treatment for a particular patient is fundamentally different from determining which treatment is best for the average patient… reporting an isolated number gives the misleading impression that the treatment-effect relationship it is a property related to the drug (treatment) instead of being related to the interaction between the drug (treatment) and the complex risk-benefit profile of a certain group of patients".[6]

The correct approach to the problem does not seem to be based on demonstrating which surgery achieves better results in Hinchey 3 or 4, but rather detecting subpopulations that best benefit from each of the surgical options.

In this sense, the detection through maneuvers of the existence of colonic perforation, the measurement of the impact of the noxa and the need for mechanical cleaning of the rectum are lines of research that could be useful. Besides, should not be forgotten that the external validity or feasibility of the proposed treatments will depend on the context of the specialization of the treating centers and professionals.

TABLE 4: SAMPLE SIZE ACCORDING TO X2 BASED ON A POWER OF 80%, ALPHA = 0.05, TWO-TAILED STUDY

Procedure A mortality (%)	Procedure B mortality (%)	Patients needed per branch*
15	10	686
10	5	435
15	5	141

** It is usual to add 10% of patients to compensate for losses in follow-up or withdrawal of consent.*

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