University Hospital of Pisa
University Operative Emergency Surgery unit
Director: Prof. M. Chiarugi

PROJECT EXPERIMENTAL NON-PROFIT CLINICAL STUDY

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Principal Investigator Prof. Massimo Chiarugi

Co-Investigator Dr. Dario Tartaglia

Clinical Study Title

Laparoscopic peritoneal lavage versus laparoscopic sigmoidectomy in perforated Acute diverticulitis: A multicentric, prospective and observational study

NCT number :03008707

Summary of the clinical study project

The aim of the study is to evaluate which surgical strategy between laparoscopic peritoneal lavage (LPL) and laparoscopic sigmoidectomy (SL) can give better results in patients with acute perforated diverticulitis (APD), identifying the pre-operative characteristics of patients undergone LPL and SL and investigating data obtained during the surgical interventions, the hospitalization and the follow-up.

Rationale of clinical Study

LPL has been recently emerging as an effective alternative to SL in patients with APD[1], (GRADE II and III of the Hinchey's[2] scale). In the literature, there is no consensus regarding the role of laparoscopic lavage in the management of patients with complicated acute diverticulitis[3]. Several studies have reported a high success rate of LPL (even higher than 95%) with a mortality of less than 5%[4], although other studies have shown an important morbidity value (more than 30%) and a high rate of re-intervention[5]. In addition, it has been reported that LPL can significantly improve the clinical course of the patient and reduce hospitalization costs[6].

Although there are several international guidelines that confirm that LPL represents a safe approach in acute diverticulitis[7,8], many surgeons continue to prefer the standard approach, represented by laparoscopic sigmoidectomy

Objectives, materials and methods of the clinical study

This project consists of a clinical, prospective, observational experimental study on patients undergoing surgical treatment for APD (Hinchey II-III stage) at hospital general surgery units involved in the study, during the period between December 2015 and Dicember 2018. During this period, two groups will be identified: Group A, which includes patients undergoing LPL and group B who consider those who will undergo SL. All clinical, laboratory, radiological and surgical parameters will be systematically recorded, patient-by-patient, within a Database (Microsoft Excel, Microsoft Corporation, Redmond, Washington, US), which was created specifically for this study.

Both techniques are routinely used in the treatment of complicated acute diverticulitis. These surgical procedures, the choice of which depends mainly on the patient's clinical conditions, are performed by experienced surgeons, or under their supervision, in accordance with national and international Guidelines on treatment of acute diverticulitis.

The inclusion criteria include: acute abdominal pain, signs of diffuse peritonitis in the presence of a radiologically suspected condition of acute perforated diverticulitis and signature of a consent form by the patient.

Each patient with acute abdominal pain will undergo routine bloods examinations (cell blood count, urea, creatinine, electrolytes, liver function exams, coagulative profile, C-reactive protein and Procalcitonin), radiological examinations such as X-Ray of the abdomen, chest X Ray, ultrasound of the abdomen, abdominal CT scan. Radiological criteria needed to define a condition of acute diverticulitis perforate are: intraperitoneal free air, diffuse peritoneal collection, pelvic abscess in the presence of diffuse colonic diverticulosis.

Every single patient considered for this study, as is the case in routine clinical practice, will undergo a rigorous pre-operative evaluation of the anaestheological risk.

Criteria for exclusion and/or exit from the study are: previous surgical interventions, septic shock, important comorbidities, immunodepression, elevated levels of C reactive protein (> 10 mg/L), Grade IV according to Hinchey's classification (diffuse fecal peritonitis), Mannheim Peritonitis Index > 22 and age groups under 18 years and higher than 85 years, withdrawal of consent.

With regard to the surgical techniques described in this study, these will follow the principles outlined in the guidelines of the most important international surgery companies, including those of the Society of Gastrointestinal and endoscopic surgeons American (SAGES). LPL is performed by induction of pneumoperitoneum, subsequent irrigation of all the quadrants of the abdominal cavity with at least 6 liters of saline and then positioning of a drainage in silastic through one of the positioned trocars. SL is performed according to the traditional technique adopted at the operative Unites involved and the eventual protective ileostomy is decided at the discretion of the operator surgeon.

The primary variables considered are: Average operative time, morbidity and mortality, clinical and laboratory control of sepsis. Secondary variables: Average duration of post-operative hospitalization, incisional hernia rate, re-intervention rate; Recurrence rate of acute diverticulitis in patients undergoing LPL over a follow-up of about 6 months,including eventual remissions and re-interventions. All these data will be collected in a database, analyzed and compared according to the appropriate statistical surveys.

Description of surgical techniques considered, risk/benefit of SL and LPL

Both of these patient groups will receive the same type of treatment in the post-operative course with regard to the infusion of liquids, the type of antibiotics used, the passive and active mobilization, blood exams, in order to reduce the possible presence of bias in the evaluation of short-term clinical outcomes. The patients operated will be assessed daily by the medical staff and will undergo blood examinations every day. Any radiological investigations, such as abdominal X-Ray, US, and CT scan with contrast, will be performed in relation to the general clinical conditions of the patients. After the hospital discharge, each patient will be visited at a distance of about 6 months, at the operative units of the hospitals involved in the study.

Laparoscopic peritoneal lavage started with the induction of pneumoperitoneum by using a Verress needle at the umbilicus or Hasson's open technique and CO2 with an intraperitoneal pressure of 14 mmHg. Three trocars were used: a 5-mm trocar in the supra-umbilical area for the advance of the laparoscope (30-degree, 10 mm), another 5-mm trocar in the right flank and a further 5-mm one in the right iliac fossa. Exploration of the peritoneal cavity was accurate and included a gentle blunt dissection of the inflamed sigmoid colon. Gross fecal finding in the cavity and /or the identification of a bowel perforation were considered valid reasons to change strategy. Once the presence of the purulent collection in the peritoneal cavity was identified, a sample for bacteriological examination was taken and, consequently, a complete evacuation was performed. Hence, irrigation and suction with 3 to 6 L of warm saline were carried out until clear fluid was returned. In case of dubious integrity of the colonic wall, an air test was performed to confirm the absence of leakage. The operation ended with an accurate revision of the hemostasis and the placement of two large silastic drains in the pelvis, respectively along the medial and lateral sides of the sigma.

Pneumoperitoneum was obtained as previously described. After placing a 12-mm trocar at the umbilicus, a 30°-10mm laparoscope was introduced. Subsequently, other three trocars were positioned under vision: two 5 mm respectively in the left and the right flank and one 12 mm in the right iliac fossa. A careful exploration of the abdominal cavity was performed. If present, peritoneal adhesions were lysed. The inferior mesenteric vein (IMV) was dissected free below the inferior pancreatic margin, ligated with Hem-o'-lok® clips (Teleflex, Morrisville, NC, USA) and divided. A cautious mobilization from the left colonic flexure to the sigma, along with the Toldt' s avascular plane, was then carried out with the help of radiofrequency or ultrasound devices. After the identification and preservation of the left ureter, the inferior mesenteric artery (IMS) was clipped with Hem-o'-Lok ® clips and then divided distally. In case of intense phlogosis, the clipping of the artery could be performed distally from the origin of the left colic artery. The proximal rectum was then stapled and divided by using a laparoscopic articulated stapler. Resection was completed and the specimen delivered through a supra-pubic wound-protected mini-laparotomy. At this point, the decision to perform the anastomosis or not (Hartmann's procedure), was established by the surgeon according to patient's previous co-morbidities (i.e.: diabetes, immunosuppression, malnutrition, severe cardiac disease), patient's hemodynamical status (septic shock requiring vasopressors) and the grade of perfusion of the two intestinal stumps. In case of anastomosis, a colorectal end-to-end or side-to-end mechanical anastomosis was done. A hydropneumatic

test or a test with trans-anal irrigation with blue of methylene stained saline solution was performed to rule out the presence of a leak of the suture line. Before wound closure, the pelvis was drained, and the creation of a protective ileostomy was decided case by case at the discretion of the surgeon.
The benefits of LPL are associated with minor post-operative pain, early mobilization and early resumption of intestinal function. Laparoscopic sigmoidectomy offers, instead, a radical solution to complications related to acute diverticulitis, reducing the risks of recurrence in the short and long term.
The execution of one of these two surgical procedures exposes the following risks:
-In the case of laparoscopic peritoneal lavage: general-order complications (pneumonia, deep venous thrombosis, pulmonary embolies, acute cardiac and/or cerebral events, etc), wound infections, abdominal abscesses, visceral perforations, bleeding, acute diverticulitis recurrence, incisional hernia.
-In the case of laparoscopic sigmoidectomy with/without protective ileostomy: general-order complications (pneumonia, deep venous thrombosis, pulmonary emboli, acute cardiac and/or cerebral events, etc), wound infections, abdominal abscesses, anastomosis dehiscence, anastomotic stenosis, bleeding, incisional hernias and psychological discomfort due to the presence of a stoma.

Statistical analysis

We expect to consider about 25-30 patients per group in the time period considered on the basis of the case studies of the General surgery units of the hospitals involved in the study. For statistical analysis, the T Test or the Mann-Whitney U Test (if the data are not normally distributed) will be used for the determination of the parametric data. The Pearson's chi square test or the Fisher's exact test will be used for the analysis of categorical and dichotomic. The differences will be considered statistically significant in case of $p < 0.05$. The statistical analysis will be conducted using the software SPSS 20.0 software (IBM SPSS Inc., Chicago, IL, USA).

Data management

The data will be collected in an Excel database (Redmond, WA, USA).As regards the anonymity of patients, only the patient's code (patient's initials), sex, date of birth and age will be reported. The Principal Investigator, Prof Massimo Chiarugi, is responsible for the preservation of this data. The data will be stored for seven years.

Purpose of the study

The aim of this study is to collect and analyze the data of the two techniques taken into account, in relation to the following parameters: mean operating time, morbidity, mortality, clinical and laboratory control of sepsis, average postoperative hospital stay, incisional hernia rate, re-intervention rate, acute diverticulitis recurrence rate in patients undergoing LPL over a follow-up of about 6 months and total costs associated with hospitalization.

Flow-Chart of the study

	Time 0 - Hospitalization	Time 1- Follow up to 6 months
Average operating time	X	
Clinical and laboratoristic control of sepsis	X	
Morbidity	X	
Mortality	X	X
Re-intervention rate	X	
Average post-operative stay	X	
Incisional hernia rate		X
Acute diverticulitis recurrence rate		X

Ethical considerations

Before starting the study, the Protocol and the various attached documents will be subject to approval by the local Ethics Committee of the Coordinating Centre. Any amendments to the Protocol which substantially could alter the study will be subject to the evaluation of the local Ethics Committee coordinator before their implementation.

The principal investigator undertakes to ensure that this study is conducted in accordance with international law [Dir. EU 2001/20/EC] and national [DM 15/07/1997; D.L. 211/2003; D.L. 46/1997].

The experimental study will follow the principles drafted in the Helsinki Declaration, comply with the International Conference Guidelines for the Good Clinical Practice and guidelines for Standard Operating Procedures (SOPs).

Participation in the study of each patient will be established on the basis of the overexposed criteria. Of fundamental importance will be the signature of the informed consent of the candidate to the study, one whose signed copy will be provided to the same or to his legal representative. Each patient will be exhaustively informed about the treatment of their personal data, in accordance with the current privacy regulations [D. Lvo. 196/2003]. Any person carrying out an adverse event shall be examined by a physician as soon as possible; Any anomalies will be followed until complete healing or clinical stabilization. Each adverse event will be described in the Clinical Chart using standard medical terminology in order to study its severity and any actions to be undertaken.

Summary of the work plan of the clinical study

First, two groups undergo LPL and SL respectively for acute perforated diverticulitis (stage II-III according to Hinchey' s classification) at the hospital general surgery units involved in the study in the period December 2015- December 2018.

We will then create a database with the primary and secondary variables,

with appropriate systems of statistical investigation.
We expect to consider about 25-30 patients for each group. All patients included in this study will be evaluated at a distance of approximately 6 months after surgery.

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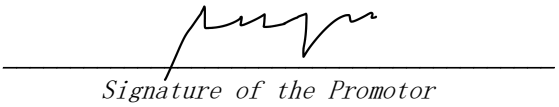
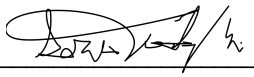
In Faith



Signature of the Promotor

In Faith



Signature of the Co-Investigator