Surgery ■■ (2018) ■■–■■

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/ymsy

Extended antibiotic therapy versus placebo after laparoscopic cholecystectomy for mild and moderate acute calculous cholecystitis: A randomized double-blind clinical trial

Martín de Santibañes [a,*], Juan Glinka [a], Pablo Pelegrini [a], Fernando A. Alvarez [a], Cristina Elizondo [b], Diego Giunta [b], Laura Barcan [c], Lionel Simoncini [d], Nora Cáceres Dominguez [d], Victoria Ardiles [a], Oscar Mazza [a], Rodrigo Sanchez Claria [a], Eduardo de Santibañes [a], and Juan Pekolj [a]

[a] Department of General Surgery, Hospital Italiano de Buenos Aires, Buenos,Aires, Argentina
[b] Department of Internal Medicine and Statistics, Hospital Italiano de Buenos, Aires, Buenos Aires, Argentina
[c] Department of Internal Medicine and Infectology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
[d] Department of Pharmacy & Pharmacology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

ARTICLE INFO

Article history:
Accepted 22 January 2018

ABSTRACT

Background. Acute calculous cholecystitis (ACC) is the most common complication of cholelithiasis. Laparoscopic cholecystectomy (LC) is the gold standard treatment in mild and moderate forms. Currently there is consensus for the use of antibiotics in the preoperative phase of ACC. However, the need for antibiotic therapy after surgery remains undefined with a low level of scientific evidence.

Methods. The CHART (Cholecystectomy Antibiotic Randomised Trial) study is a single-center, prospective, double blind, and randomized trial. Patients with mild to moderate ACC operated by LC were randomly assigned to receive antibiotic (amoxicillin/clavulanic acid) or placebo treatment for 5 consecutive days. The primary endpoint was postoperative infectious complications. Secondary endpoints were as follows: (1) duration of hospital stay, (2) readmissions, (3) reintervention, and (4) overall mortality.

Results. In the per-protocol analysis, 6 of 104 patients (5.8%) in the placebo arm and 6 of 91 patients (6.6%) in the antibiotic arm developed postoperative infectious complications (absolute difference 0.82 (95% confidence interval, –5.96 to 7.61, P = .81). The median hospital stay was 3 days. There was no mortality. There were no differences regarding readmissions and reoperations between the 2 groups.

Conclusion. Although this trial failed to show noninferiority of postoperative placebo compared to antibiotic treatment after LC for mild and moderate ACC within a noninferiority margin of 5%, the use of antibiotics in the postoperative period does not seem justified, because it was not associated with a decrease in the incidence of infectious and other types of morbidity in the present study.

The incidence of cholelithiasis in the adult population is 10%, and acute calculous cholecystitis (ACC) is the most common complication.[1,2] Acute cholecystitis affects >20 million Americans annually, with costs in excess of $6.3 billon, constituting a major health burden that has increased >20% in the past 3 decades.[3,4] The diagnostic criteria and severity assessment of ACC were well established in the Tokyo guidelines 2007[5] and updated in 2013.[6] According to this expert consensus, ACC is classified into 3 grades: mild, moderate, and severe. Laparoscopic cholecystectomy (LC) is the gold

Author Statement: The concept of the study was derived from MDS. This study was designed by PP, JG, FA, DG, CE, VA, LB, LS, NC, EDS, JP, RSC, OM AND MDS. The article was written by PP, JG, FA, VA, DG, CE AND MDS. DG, VA, CE, and MDS performed the sample size calculation and planned the statistical analyses. PP, JG, FA, DG, CE, VA, LB, LS, NC, EDS, JP, RSC, OM AND MDS were involved in trial implementation and critically revised the manuscript. PP, JG, FA, DG, CE, VA, LB, LS, NC, EDS, JP, RSC, OM AND MDS, give final approval of the version to be published.

* Corresponding author. Department of Surgery, Division of HPB Surgery, Liver, Transplant Unit, Hospital Italiano de Buenos Aires, Juan D. Perón 4190. C1181ACH., Buenos Aires, Argentina.
E-mail address: martin.desantibanes@hospitalitaliano.org.ar (M. de Santibañes).

https://doi.org/10.1016/j.surg.2018.01.014
0039-6060/

standard treatment in mild and moderate forms.[7] Currently there is consensus for the use of antibiotics in the preoperative phase of ACC, with controversies about its usefulness after the surgical treatment has been completed. Recent guidelines suggest that antibiotics should be administered only up to 24 hours after surgery for mild ACC and 4 to 7 days for moderate or severe forms.[8] It has been suggested that a scheme with β-lactam/inhibitor of β-lactamase combinations would be adequate in patients with mild and moderate ACC, according to most frequently isolated germs.[2,8,9] Despite this, the need for antibiotic therapy after surgery remains ill defined with a lack of high-quality evidence.[10,11] Hence, we conducted a randomized controlled trial in patients undergoing LC for mild and moderate ACC, randomizing patients to receive antibiotics or placebo after surgery. The primary objective of the present trial was to assess whether antibiotic treatment after LC in mild or moderate ACC reduces the incidence of postoperative infectious complications. The hypothesis was that postoperative antibiotic treatment has no positive impact on the patient's outcome and therefore should not be indicated in this subset of patients.

Methods

Study design and ethics

The Cholecystectomy Antibiotic Randomised Trial (CHART) is single-center, randomized, controlled trial with blinded patients and investigators. It compares antibiotic treatment after LC due to mild and moderate ACC versus no antibiotic treatment. The study design has been reported in detail previously.[12] This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Regulations ICH E6, and applicable regulatory requirements. Written informed consent was obtained from all patients, and the Hospital Italiano de Buenos Aires (HIBA) Institutional Review Board gave ethical approval to perform this study (N° 2111). The CHART has been registered at Clinicaltrial.gov database (ClinicalTrials.gov, identifier: NCT02057679).

Study aims

Primary endpoint

Postoperative infectious complications, defined as any infection occurring within the first 30 postoperative days, classified according to the Clavien-Dindo Classification.[13] Any of the following infectious complications were considered: intra-abdominal collections (abscesses, biloma, subphrenic collection or fluid collection from another location within the abdomen), hepatic abscesses, surgical wound infections presence of erythema and/or phlogosis, turbid or purulent drainage and extra-abdominal infectious complications such as pneumonia or urinary tract infections.

Secondary endpoints

Secondary endpoints included the following: (1) duration of hospital stay: number of days from admission to hospital discharge; (2) readmission: need of readmission due to postoperative complications that require hospital care (hydration, intravenous antibiotics, percutaneous drainage or surgical treatment); (3) reintervention: need of surgical treatment under general anesthesia or percutaneous procedure in complicated patients; and (4) overall mortality: deaths occurring during the first postoperative month.

Study population and study treatment

All consecutive patients from February 2014 with a new diagnosis of mild or moderate ACC according to the Revised Tokyo Guidelines[6] admitted to the HIBA were screened for eligibility to be enrolled in the CHART. Patients received parenteral hydration; gastric protection with proton pump inhibitors; and analgesics and treatment with ampicillin/sulbactam intravenously every 6 hours until surgery, which was carried out within 5 days after admission. Patients were approached for randomized inclusion if they met each of the following inclusion criteria: diagnosis of mild or moderate ACC[6]; willingness to participate in the study; ability to understand the nature of the study and what was required of them; men and nonpregnant, nonlactating women between 18 and 85 years of age who undergo early LC. The main exclusion criteria were as follows: rejection of participation in the trial or the process of informed consent; hypersensitivity to amoxicillin/clavulanic acid (AMC) or lactose (used in placebo); severe ACC; moderate ACC associated with liver and/or gallbladder abscesses, cholangitis, or bile peritonitis; intraoperative findings such as liver cancer, liver metastases, common bile duct stones, or gallbladder carcinoma; conversion to laparotomy; previous treatment with antibiotics for >5 days; active oncologic diseases; AIDS; transplanted patients. If there were no intraoperative criteria for exclusion, patients were randomly assigned to either group of intervention:

1. Experimental group: antibiotic treatment after surgery (AG): received 1,000 mg of AMC orally every 8 hours for 5 days, immediately after surgery.
2. Control group: placebo treatment after surgery (PG): received 1,000 mg of placebo orally every 8 hours for 5 days, immediately after surgery.

Simple randomization was used, and patients were assigned using a randomizer provided by the HIBA statistical department.

The HIBA pharmacy was the only nonblind participant in the study and was in charge of preparing, storing, and distributing the medication, also ensuring that medication was used exclusively for the purposes of the study. Each treatment pack (TP) had a code that was used to identify which group of treatment modalities the patient was assigned. Each TP contained capsules for 5 days of treatment. The antibiotic and placebo capsules were packaged and labeled identically.

Surgical procedure

The American technique for LC was used, as described previously.[14] Intraoperative cholangiography was used as a routine in all patients after having achieved the "critical view of safety."[15]

Safety, tolerability, and follow-up

Any adverse events detected during ambulatory monitoring were recorded and classified according to their severity as mild, moderate, or severe and by relationship to study treatment according to the decision of the blinded investigator. Treatment relationship was determined with a reasonable probability that the event might have been caused by treatment. Each patient received written instructions to mark the intake of each medication as stipulated. Patients were clinically monitored at an outpatient clinic 7 and 30 days after surgery. They received the telephone number of the investigators for any concerns or for the need to report any event. Postoperative adverse events were evaluated according to the Clavien-Dindo classification.[13]

Statistical analysis

Sample size calculation was based on an expected postoperative infection rate of 3% in the antibiotic group,[16-19] following the hypothesis that the absence of postoperative antibiotic treatment would not be inferior to the use of antibiotic treatment after LC for

Please cite this article in press as: Martín de Santibañes, et al., Extended antibiotic therapy versus placebo after laparoscopic cholecystectomy for mild and moderate acute calculous cholecystitis: A randomized double-blind clinical trial, Surgery (2018), doi: 10.1016/j.surg.2018.01.014