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REVIEW ARTICLE

Antibiotic administration after cholecystectomy for acute mild-moderate cholecystitis: a PRISMA-compliant meta-analysis

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Abstract

Introduction Acute cholecystitis is a common disease and a frequent cause of emergency admission to surgical wards. Evidence regarding antibiotic administration in urgent procedures is limited and remains a contentious issue. According to the Tokyo guidelines, the antibiotic administration should be guided by the severity of cholecystitis, but internationally accepted guidelines are lacking. In particular, the need to perform antibiotic therapy after laparoscopic cholecystectomy is controversial for mild and moderate acute calculous cholecystitis (Tokio I and II).

Materials and methods We performed a comprehensive computer literature search of PubMed and MEDLINE databases in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. We selected patients treated with cholecystectomy for mild or moderate acute calculous cholecystitis (Tokio I or II), only randomized controlled trials, (post-operative antibiotic administration versus placebo or untreated), data about local or systemic infection rate in the next 30 days after surgery.

Results Three hundred and fifty-nine articles were identified, and three articles were considered eligible for the meta-analysis, including 676 patients. Overall surgical site infections were documented in 18 (5.49%) of 328 patients treated with post-operative antibiotics versus 25 (7.18%) of 348 patients treated without post-operative antibiotics. Overall results and the subgroup analysis (superficial and deep incisional infection and organ/space infection) showed no statistically significant reduction of surgical site infections rate under antibiotic therapy.

Conclusions Our meta-analysis shows no significant benefit of extended antibiotic therapy in reducing SSI after cholecystectomy for mild and moderate acute cholecystitis (Tokio I and II). Further RCTs with adequate statistical power and involving a higher number of patients with subgroups are needed to better evaluate the benefit of post-operative antibiotic treatment in reducing the rate of organ/space surgical site infections.

Keywords Cholecystectomy · Calculous · Cholecystitis · Antibiotics · Gallstones · Post-operative

Gallstone disease is endemic in developed countries and affects 10–15% of the adult population in the Western world. A study of the natural history of cholelithiasis demonstrates that approximately 35% of patients initially diagnosed with gallstones, but not treated for, later developed complications or recurrent symptoms leading to cholecystectomy [1]. Laparoscopic cholecystectomy is today one of the most common surgical operations in the West countries and, despite being usually a low-risk procedure, the incidence of post-operative infectious complications represents a serious clinical problem [2]. The incidence of surgical site infection (SSI) was found to be 2.4–3.2% in a large meta-analysis of studies on peri-operative antibiotics in patients undergoing laparoscopic cholecystectomy [3]. Several randomized trials

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evaluated the benefits of antibiotic prophylaxis in planned cholecystectomy but none of them showed any benefit in low-risk patients and in elective procedures [4]. Acute cholecystitis is seen in 6–11% of patients with symptomatic gallstones over a median follow-up of 7–11 years and represents a frequent cause of emergency admission to surgical wards [5]. Evidence regarding antibiotic administration in urgent procedures is limited. The choice and duration of antibiotics remain a contentious issue in this situation [6]. Updated Tokyo Guidelines [7] classified the patients with acute cholecystitis into three broad groups on the basis of severity of infection (Table 1).

According to the Tokyo guidelines and the guidelines published by the Surgical Infection Society and the Infectious Diseases Society of America, the selection and duration of the Antibiotic Prophylaxis (AP) should be guided by the severity of cholecystitis and whether or not the source of infection is well controlled. Antibiotic treatment for 4–7 days is recommended if perforation, surgical emphysema or gallbladder necrosis is encountered during surgery [8]. The lack of internationally accepted guidelines concerning AP in cholecystectomy has led to divergent routines regarding the use of AP in surgery for acute cholecystitis [9]. In particular, the need to perform antibiotic therapy after laparoscopic cholecystectomy for acute calculous cholecystitis is controversial [10]. In current practice, many patients with acute cholecystitis receive peri-operative antibiotic prophylaxis, often continued for several post-operative days to reduce infectious complications [8].

The use of post-operative antibiotics has several negative aspects. It is well known that continuation of antibiotic treatment promotes the selection of multiresistant bacteria [6]. In addition, extended intravenous antibiotic prophylaxis leads to prolongation of hospital stay and increase of costs [11]. The aim of our meta-analysis is to evaluate the role and the effectiveness of post-operative antibiotic administration for mild and moderate acute cholecystitis (Tokio I and II) after cholecystectomy.

Methods

The meta-analysis was based on previous published studies, no ethical approval and patient consent were required.

Search strategy and selection criteria

A comprehensive computer literature search of PubMed and MEDLINE databases was carried out independently by two researchers, to find relevant published articles (last search was updated on September 30 2017) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The terms used to search were "cholecystectomy" AND "antibiotics" AND "post-operative". Finally, we searched for additional eligible trials in reference lists of retrieved publications and relevant meta-analyses. No language restrictions were set.

Data collection and quality assessment

Studies or subsets in studies investigating the role of the post-operative antibiotic administration after cholecystectomy for acute cholecystitis were eligible for inclusion. Case reports, small case series, review articles, letters, editorials, and conference proceedings were excluded.

The following inclusion criteria were applied to select studies for this meta-analysis: patients treated with cholecystectomy for mild or moderate acute calculous cholecystitis (Tokio I or II), only randomized controlled trials, (post-operative antibiotic administration versus placebo or untreated),

Table 1 Tokio severity grades for acute cholecystitis

Grade	Criteria
Grade I	
Mild	Acute cholecystitis that does not meet the criteria of grade II or III
Grade II	
Moderate	Acute cholecystitis associated with anyone of the following conditons • WBC > 18,000/mm^3 • Palpable tender mass in right upper quadrant • Duration > 72 h • Marked local inflammation
Grade III	
Severe	Acute cholecystitis associated with one of the following conditions • Cardiovascular dysfunction • Neurological dysfunction • Respiratory dysfunction • Renal dysfunction • Hepatic dysfunction • Hematological dysfunction

data about local or systemic infection rate in the next 30 days after surgery.

Exclusion criteria were: acute severe cholecystitis (Tokyo III), pancreatitis or jaundice, pregnancy, concurrent antibiotic therapy, immunosuppression, studies published with insufficient information.

We extracted study characteristics (author name, publication year, country, sample size, age, study design, inclusion and exclusion criteria, antibiotics, method of randomization, blinding), primary outcomes (30-day infection rate), secondary outcome (Clavien-Dindo [12] and length of hospital stay) and risk of bias. Any disagreements between reviewers were resolved by discussion. Only studies providing such complete information were finally included in the meta-analysis. To evaluate the quality assessment of the studies, we applied the Jadad [13] composite scale, which is a 5-point quality scale in which high quality studies scoring ≥ 3. Quality assessment was independently performed by two authors (Table 2).

Three researchers independently reviewed titles and abstracts of the retrieved articles, applying the above-mentioned selection criteria. Articles were rejected if they were clearly ineligible. The same three researchers then independently evaluated the full-text version of the included articles to determine their eligibility for inclusion.

The 2011 Oxford Center for Evidence-Based Medicine checklist for diagnostic studies was used for quality assessment of the included studies. This checklist has five major parts as follows: representative spectrum of the patients, consecutive patient recruitment, ascertainment of the gold standard regardless of the index test results, independent blind comparison between the gold standard and index test results, and enough explanation of the test to permit replication [14].

Statistical methods

A statistical expertise was available to the authors and conducted the analysis. The power analysis was estimated using 1-sided 2-sample proportion and assuming 5% type I error rate. With a sample size of 328 and 348 for patients treated with or without antibiotics groups respectively, we achieved > 50% power interval.

Table 2 Jadad composite scale for the quality assessment of a clinical trial

Study	Randomized method	Double binding	Withdrawals dropouts	Total
Regimbeau et al. [18]	2	0	1	3
Kim et al. [20]	2	1	1	4
Loozen et al. [19]	2	0	1	3

As effect estimate we computed for each study the Risk Difference (RD) i.e., the difference between the proportional frequencies of each outcome in treated (p1) and controls (p0) and its 95% confidence interval (95% CI), using the RD standard error as measure of within-study variability i.e.

$$\sqrt{\frac{p1 \times (1-p1)}{n1} + \frac{p0 \times (1-p0)}{n0}}$$

where n1 and n0 are the number of treated and controls, respectively. The overall measure of the effect was estimated by applying to RDs the random effects model as suggested by DerSimonian and Laird [15]. This model allowed to assess the amount of the variability between studies and accordingly provided suitable estimates of the standard errors of the model coefficients. As p1 and p0 were both zero to estimate RD standard error, the proportion of positive outcomes computed on all studies was used. The Higgins' I2 index was computed to achieve a quantitative measure of the degree of inconsistency in the results of the studies included [16]. STATA software was used for all statistical analyses and the generation of forest plot [17].

Results

Literature search

The comprehensive computer literature search from PubMed and MEDLINE databases revealed 359 articles. Results have been matched and all the studies found in Medline were present in Pubmed. Reviewing titles and abstracts, 341 records were excluded as reviews, editorials or letters, case reports or did not match the main topic. 15 articles were excluded since are not prospective randomized controlled trial. Finally, three articles including 676 patients were selected and were eligible for the meta-analysis (Fig. 1); no additional studies were found screening the references of these articles.

Study characteristics

All eligible trials [18–20] were multicenter studies (17 hospitals/388 patients in France, six hospitals/150 patients in the Netherlands, five hospitals/188 patients in Korea) and published from 2013 to 2017. One study was placebo controlled and 2 studies were untreated controlled. The mean age of the patients was 53 years (range 18–94). The follow-up was 30 days for all the studies. Different antibiotics and duration of post-operative treatment were evaluated in the selected trials. The characteristics of the included studies are presented in Table 3.

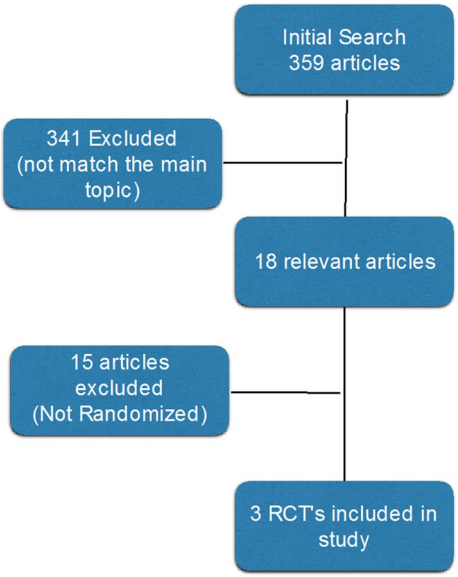

Fig. 1 The flow-chart with studies selection for analysis

In all the studies the definition of surgical site infection was similar. Post-operative infections were defined as superficial or deep incisional infections or organ-space infections, in accordance with Centers for Disease Control and Prevention's (CDC's) guidelines on the prevention of SSI [21] (Table 4).

Statistical results

Overall surgical site infections were documented in 18 (5.5%) of 328 patients treated with post-operative antibiotics versus 25 (7.2%) of 348 patients treated without post-operative antibiotics. Pooled analysis revealed an overall risk difference of −0.32 (95% confidence limits, −3.39 to 2.75) indicating no statistically significant reduction of overall Surgical Site Infections under extended antibiotic therapy.

Superficial and deep incisional infections were documented in 16 (4.9%) of 328 patients treated with post-operative antibiotics versus 14 (4.0%) of 348 patients treated without post-operative antibiotics. Pooled analysis revealed an overall risk difference of 1.01 (95% confidence limits, −1.84 to 3.86) indicating no statistically significant reduction of superficial and deep incisional SSI under extended antibiotic therapy.

Organ/space infections were documented in 2 (0.6%) of 328 patients treated with post-operative antibiotics versus 11 (3.2%) of 348 patients treated without post-operative antibiotics. Pooled analysis revealed an overall risk difference of −1.81 (95% confidence limits, −3.88 to 0.26) indicating no statistically significant reduction of organ or space infections under extended antibiotic therapy (Figure 2).

In all the investigated outcomes, the reduced I^2 values (max 21%; $p = 0.28$) suggest a seemly agreement between the studies.

Table 3 Studies characteristics

	Regimbeau et al. [18]	Loozen et al. [19]	Kim et al. [20]
Per-protocol patients	Total: 338 pts Antibiotic: 158 pts Non treatment: 180 pts	Total: 150 pts Antibiotic: 77 pts Non treatment: 73 pts	Total: 188 pts Antibiotic: 93 pts Non treatment: 95 pts
Study	Randomized Antibiotic versus Non treatment	Randomized Antibiotic versus Non treatment	Randomized Antibiotic versus placebo Double blind
Inclusion criteria	Cholecystitis Tokio 1 or 2 90% laparoscopic 10% laparotomy	Cholecystitis Tokio 1 or 2 97% laparoscopic 3% laparotomy	Cholecystitis Tokio 1 or 2 100% laparoscopic
Primary end point	Rate of infectious complications within 30 days after operation SSI was classified as incisional (superficial or deep) or organ-occupying	Rate of infectious complications within 30 days after operation SSI was classified as incisional (superficial or deep) or organ-occupying	Rate of infectious complications within 30 days after operation SSI was classified as incisional (superficial or deep) or organ-occupying
Antibiotics	Pre-operative: Amoxicillin + ac. Clavulanic 1,2 g single shot Post-operative Gr1: Amoxicillin + ac. Clavulanic three time a day for 5 days Gr2: no treatment	Pre-operative: Cefazolin 2 g single shot Post-operative Gr1: Cefuroxime 750 mg + Metronidazole 500 mg three times a day for 3 days	Pre-operative and intra-operative: Cefoxitin 1 g Post-operative Gr1: Cefoxitim 1 gr, three times a day for about 7 days Gr2: NaCl and then Vitamin C for about 7 days

Table 4 Definition of surgical site infection [21]

Surgical site infection	Definition
Superficial incisional	Affecting the skin and subcutaneous tissue
Deep incisional	Affecting the fascial and muscle layers
Organ or space	Involves any part of the anatomy other than the incision that is opened or manipulated during the surgical procedure

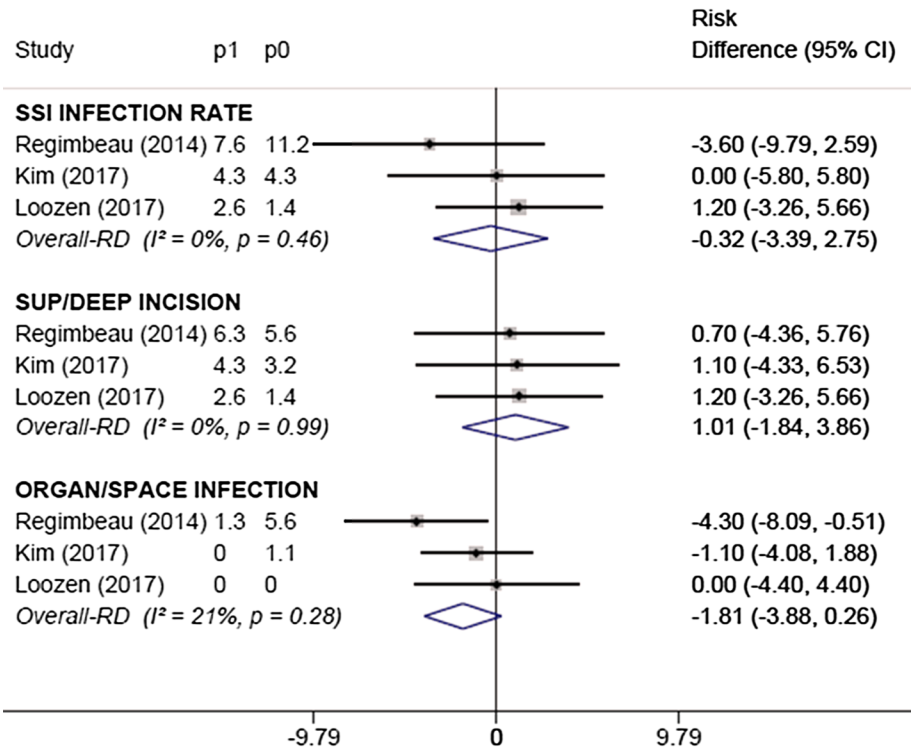

Fig. 2 Forest plot of the statistical analyses. p1, p0 represent the percentage of positive outcome in treated patients and controls, respectively. *RD* risk difference

Discussion

In our meta-analysis, antibiotic therapy after laparoscopic cholecystectomy for mild and moderate acute cholecystitis (Tokio I and II) resulted in no statistically significant benefit for SSI.

At present, there are no standardized guidelines for antibiotic treatment after cholecystectomy for acute calculous cholecystitis. Actual recommendations are based on low-quality evidence and the use of antibiotics often depends on the surgeon's preference. In 2014, the World Health Organization reported on the escalating global incidence of multidrug resistance caused by antibiotic overuse, which has become a significant threat to public health worldwide [22]. Just one organism, methicillin resistant Staphylococcus aureus (MRSA), kills every year more Americans than emphysema, AIDS, Parkinson's disease and homicide combined [22].

Use of antibiotics is a risk factor for Clostridium difficile infection. In addition, prolonged antibiotic treatment after surgery can cause nausea, allergic reactions and digestive complaints. Extended intravenous antibiotic prophylaxis leads to prolongation of hospital stay and increase of costs. There is currently a tendency to minimize the use of post-operative antibiotics for uncomplicated appendicitis and anorectal abscess [22].

A recent systematic review from van Dijk et al. [23] demonstrated little evidence even on the conservative management of acute cholecystitis, finding only a one small study that compared antibiotic treatment with a conservative strategy without antibiotics. This study shows that antibiotics did not improve the outcome of acute calculous cholecystitis.

Considering that cholecystectomy for acute calculous cholecystitis is a very common surgical procedure, post-operative

antibiotic treatment should be avoided when possible and its routine use should be based on evidence-based principles.

We used for this meta-analysis only randomized controlled multicenter trials including varying populations (Europe, Asia). This study has several limitations including variability in interval between admission and operation and heterogeneity of the antibiotic regimens used in the trials, although only beta-lactam antibiotics with a fairly similar spectrum of activity were used (Amoxicillin in Regimbeau et al. [18], Cefuroxime in Loozen et al. [19], Cefoxitin in Kim et al. [20]). In addition, 10% of patients in the study by Regimbeau et al. and 3% of patients in the study by Loozen et al. were treated with open cholecystectomy.

Our pooled analysis revealed an overall risk difference of −0.32 (95% confidence limits, −3.39 to 2.75) indicating no statistically significant reduction of overall SSI under extended antibiotic therapy after cholecystectomy for acute cholecystitis Tokio I and II.

The analysis shows no statistically significant reduction of superficial and deep incisional SSI under extended antibiotic therapy as the overall risk difference was 1.01 (95% confidence limits, −1.84 to 3.86). Similar results were achieved analyzing the data concerning the organ/space SSI rate as the overall risk difference was −1.81 (95% confidence limits, −3.88 to 0.26). Nevertheless, the analysis of the organ/space SSI rate requires further considerations. Although the pooled analysis indicates no statistically significant reduction of organ or space infections under extended antibiotic therapy, we believe the outcome should be evaluated with caution. In fact, in the largest study of the meta-analysis, Regimbeau et al. found in the subgroup organ/space SSI a significant infection rate difference of 5.6% (10/180 patients) in the non-treatment group versus 1.3% (2/158 patients) in the antibiotic group [Risk difference (95% CI) −4.3% (−8.09, −0.51)]. Therefore, it was not shown to be statistically significant in our meta-analysis, in part due to a relatively low power analysis (achieving > 50% interval), and may be assumed to be clinically relevant, yet not currently demonstrable. Based on these considerations and being only three studies included in the meta-analysis, further RCTs with adequate statistical power and involving a higher number of patients with subgroups are required to evaluate the benefit of post-operative antibiotic treatment in reducing the rate of organ/space SSI after cholecystectomy for acute calculous cholecystitis Tokio I and II. Particularly, it would be interesting to analyze subgroups with risk factors for SSI such as ASA score, diabetes, operative duration and blood loss.

Conclusions

Our meta-analysis shows no significant benefit of extended antibiotic therapy in reducing SSI after cholecystectomy for mild and moderate acute cholecystitis (Tokio I and II). Further RCTs with adequate statistical power and involving a higher number of patients with subgroups are needed to better evaluate the benefit of post-operative antibiotic treatment in reducing the rate of organ/space SSI.

Compliance with ethical standards

Disclosures Drs. Davide La Regina, Matteo Di Giuseppe, Stefano Cafarotti, Andrea Saporito, Marcello Ceppi, Francesco Mongelli, Florian Bihl, Ruben Carlo Balzarotti Canger and Antonjacopo Ferrario di Tor Vajana have no conflicts of interest or financial ties to disclose.

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