Birjand University of Medical Sciences

Journal of Surgery and Trauma

Original Article

Evaluating the efficacy of antibiotic prophylaxis during laparoscopic cholecystectomy on surgical site infection: a randomized clinical study

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Abstract

Introduction: Given the alterations in definitions and the varied, at times entirely contradictory results, the need for new studies regarding the factors influencing the occurrence of Surgical Site Infections (SSIs) is increasingly felt. This study aims to investigate the role of prophylactic antibiotics in reducing surgical site infections (SSIs) following Laparoscopic Cholecystectomy (LC) in low-risk patients.

Methods: In this clinical trial, 120 patients underwent laparoscopic cholecystectomy as per the inclusion criteria. Between September 2021 and May 2022, within the Department of Surgery at Birjand Medical University, candidates slated for elective laparoscopic cholecystectomy were systematically allocated into two distinct groups: one receiving prophylactic antibiotics and the other not. The principal outcome measured was the incidence of postoperative infectious complications. Data were analyzed in SPSS (Version. 23) software using Mann-Whitney, t-test, Fisher's Exact, and Chi-square tests. The level of significance was set to $P < 0.05$.

Results: A total of 120 patients underwent laparoscopic cholecystectomy, divided into two groups: 59 received preoperative prophylactic antibiotics (Antibiotic Group, AG) and 61 did not (No Antibiotic Group, NAG), with no significant differences in clinical characteristics like gender, age, body mass index (BMI) and operation times. Surgical site infection (SSI) occurred in two patients (3.4%) in the AG and four patients (6.7%) in the NAG, with no significant overall difference in SSI incidence between the groups (P=0.679). The study found no significant differences in preoperative WBC, hemoglobin, or creatinine levels between patients with and without SSI, indicating similar preoperative conditions across both groups.

Conclusion: The outcomes of our study revealed no substantial disparities between patients administered prophylactic antibiotics and those not during laparoscopic cholecystectomy (LCC). Consequently, the utilization of prophylactic antibiotics in elective LCC is not requisite for low-risk patients.

Key words: Cholecystectomy, Laparoscopic, Antibiotics, Infections

Citation: Nadjafi-Semnani A , Behroozifar A , Sarmadi M ,Ghasemian Moghadam M. Evaluating the efficacy of antibiotic prophylaxis during laparoscopic cholecystectomy on surgical site infection: a randomized clinical study. J Surg Trauma.2023;11(4): 132-140.

Received: January 24, 2024 ***Revised: April 8, 2024*** ***Accepted: April 23, 2024***

[DOI: 10.61186/jsurgtrauma.11.4.132]

Introduction

According to the latest CDC (Centers for Disease Control and prevention) guidelines, surgical site infections are the most common type of healthcare-associated infection (HAI), accounting for over 31% of these types of infections (1). For years, scientific literature and surgical guidelines have recommended the use of prophylactic antibiotics to reduce postoperative complications, particularly surgical site infections, across different types of surgeries (Clean, Clean-contaminated, Contaminated, Dirty). across different types of surgeries (Clean, Clean-contaminated, Contaminated, Dirty).

For years, Laparoscopic Cholecystectomy (LC) has been recognized by surgeons as the gold standard treatment for symptomatic gallstones (2). This surgical procedure is among the most common surgeries performed by general surgeons. Some of the benefits of this surgical method include less post-operative pain, shorter hospital stays, reduced morbidity and mortality, and a decrease in the financial burden of the disease on society. A lower risk of Surgical Site Infection (SSI) is one of these advantages, with an average prevalence ranging from 0.4 to 1.1 percent, primarily associated with the umbilical port (3).

This low incidence of infection in such a large population has led surgeons to question whether there's a place for prophylactic antibiotics in laparoscopic cholecystectomies. Extensive research has been undertaken to elucidate the efficacy of prophylactic antibiotics in mitigating surgical site infections, yielding a spectrum of outcomes. Recent years have seen a proliferation of randomized clinical trials focused on this domain. The consensus emerging from these studies indicates that the administration of prophylactic antibiotics does not substantially influence the reduction of postoperative complications following Laparoscopic Cholecystectomy (LC) in patients classified as low-risk (4-9).

However, there have been criticisms directed at these studies. One significant concern is the underreporting of surgical site infections (10, 11). Based on this issue, Matsui et al. designed a study, demonstrating that the use of prophylaxis significantly reduced SSI (10). After serious criticisms were raised regarding the definition and assessment of SSI, researchers sought to provide a more precise definition. The CDC, in its latest guidelines related to wound infections, has introduced a newer and more accurate definition for it (1).

Patients characterized as low risk are those devoid of associated risk determinants. These determinants encompass an age exceeding 60 years, active tobacco use, and any antecedent conditions that compromise immune function, notably diabetes. Additionally, a History of Endoscopic Retrograde Cholangiopancreatography (ERCP), perforation of the gallbladder during surgery, and acute clinical presentations like acute cholecystitis or acute biliary pancreatitis are also considered critical risk factors absent in this patient group (12).

According to the CDC guidelines, surgical site infections (SSI) are categorized into three groups: Superficial Incisional SSI, Deep Incisional SSI, and Organ/Space SSI. The definitions for each type of infection are referred to in Table 1. In summary, the onset of infection symptoms within thirty days post-surgery, such as discharge from the wound, positive culture results, or local signs including erythema, tenderness, or swelling around the wound, coupled with systemic symptoms like a fever above 38 degrees and leukocytosis, indicates the occurrence of an SSI. Its classification is based on its location (13). Given the alterations in definitions and the varied, at times entirely contradictory results, the need for new studies regarding the factors influencing the occurrence of Surgical Site Infections (SSIs) is increasingly felt.

This study aims to investigate the role of prophylactic antibiotics in reducing SSIs following low-risk cholecystectomy surgeries. It is hoped that the findings of this study will assess the role of prophylaxis in diminishing postoperative complications.

Materials and Methods

This research was carried out at Emam Reza Hospital, affiliated with Birjand University of Medical Sciences, and was structured as a double-blind clinical trial in the year 2021. The protocol

[DOI: 10.61186/jsurgtrauma.11.4.132]

was approved by The Institutional Review Board for Clinical Research of Birjand Medical University (approval No. IR.BUMS.REC.1401.436) and it was registered with the Iranian Registry of Clinical Trials (IRCT), registry ID: IRCT20221230056987N1 before enrollment of participants had begun, and written informed consent was obtained from all participating patients. The authors confirm that all ongoing and related trials for this intervention are registered.The inclusion criteria encompass all patients over 18 years old who were candidates for cholecystectomy due to symptomatic gallbladder stones, gallbladder polyps, chronic cholecystitis, or a history of biliary pancreatitis ("Low-risk cholecystectomy").

Patients who exhibited evidence of acute cholecystitis (tenderness in the right upper quadrant, increased thickness of the gallbladder wall) during hospitalization or those with a history of antibiotic use within five days prior to surgery were excluded from the study. Similarly, individuals with a documented history of immunocompromised conditions, such as diabetes or a history of corticosteroid use, were not included in the research study. Preoperative tests included Complete Blood Count (CBC), Creatinine level, Liver function profile, and other tests requested during preoperative anesthesia consultation. Participants were assigned to one of two groups through a randomized process managed by computer-generated numbers at the beginning of the study. An independent individual conveyed the group assignments to the surgical team via telephone. In the Antibiotics arm, patients were administered a single dose of 1-gram cefazolin sodium intravenously.

An additional dose was administered during procedures exceeding 3 hours in duration. Conversely, individuals in the No Antibiotics cohort did not receive any prophylactic antibiotics. The treatment allocation was concealed from the surgeons performing the procedures. All patients underwent classic four-port laparoscopic cholecystectomy at Imam Reza Hospital by experienced attending surgeons with surgeons in training. Site preparation for the procedure was carried out following the Imam Reza Hospital operating room guidelines using a 10% iodine solution. Standard dissections of Calot's triangle were performed.

Both the cystic duct and artery were secured with double clips on the proximal side. Following the resection of the cystic duct and artery, hemostasis was ensured, and saline irrigation was carried out if deemed necessary. The gallbladder was removed directly without the use of an Endo-bag through the xiphoid port site. Patients experiencing intraoperative gallbladder rupture with consequent bile or stone leakage into the peritoneal cavity were excluded from the study, in which case postoperative antibiotics were administered.

The duration of the surgery and any gallbladder perforation or bleeding were recorded for each patient. Postoperatively, patients were discharged upon pain relief and tolerance of diet, provided they were afebrile and the wound was clean, at the attending physician's discretion.

Examination for SSI was made daily while hospitalized. Patient follow-up was conducted in the form of an office visit 5 to 7 days post-operation, followed by a telephone check-in or (if deemed necessary) another visits one-month post-operation. The doctor in charge of the outpatient follow-up was unaware of the randomization and treatment group. The CDC definition of a Surgical Site Infection (SSI) was utilized for the wound assessment (14). Patients presenting with symptoms of abdominal pain, erythema, discharge, or spontaneous opening of sutures were evaluated that was according to the surgeon's discretion and will include relevant tests such as Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), and cultures from discharges, as well as abdominal, pelvic, and incisional area ultrasonography. Patient information was recorded using a questionnaire designed by the project's principal investigator. Data processing utilized IBM SPSS Statistics software, version 20.

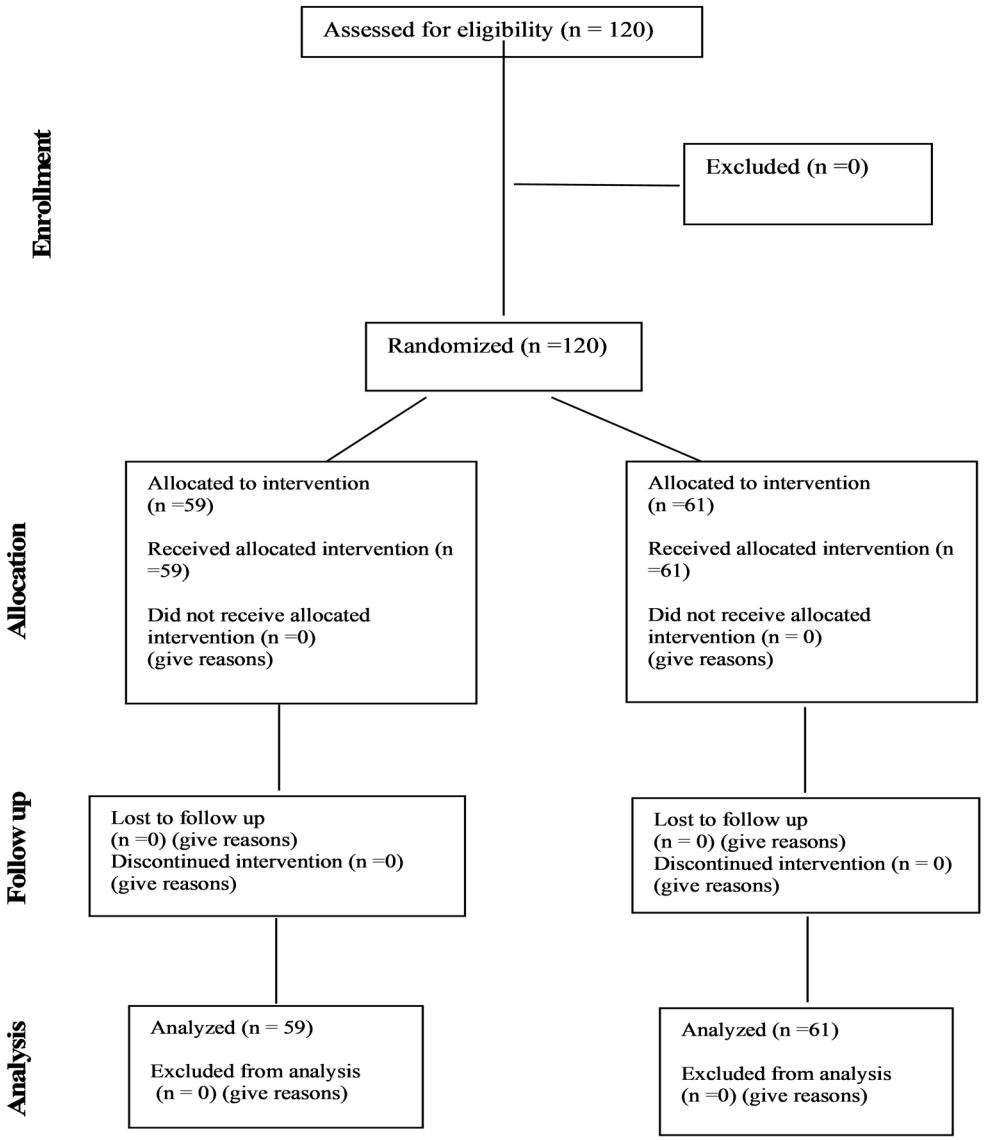
Continuous variables were expressed as mean± standard deviation (SD) or median [Q1-Q3] and categorical variables were expressed as frequency (%). Differences in categorical variables were

[DOI: 10.61186/jsurgtrauma.11.4.132]

compared between groups using the Chi-square test and/or Fisher's Exact test as needed. Unpaired samples were compared using Student's t-test or Mann-Whitney U test as needed.

For determining the distribution pattern of continuous variables, the Shapiro-Wilk test was applied. Variables incorporated as predictors included antibiotic administration, patient age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification, white blood cell count, hemoglobin level, Alkaline Phosphatase (ALP) and Creatinine level. The occurrence of SSI was the outcome of interest. A p-value threshold of less than 0.05 was established as the criterion for statistical significance.

This research encompassed 120 sequential patients undergoing laparoscopic cholecystectomy at our facility. Patients were divided into two groups: those who received preoperative prophylactic antibiotics (Antibiotic Group, AG; N=59) and those who did not (No Antibiotic Group, NAG; N=61) (flow diagram 1).



Consort flow diagram 1. The consort flow diagram of the study

[DOI: 10.61186/jsurgtrauma.11.4.132]

Results

This research encompassed 120 sequential patients undergoing laparoscopic cholecystectomy at our facility. Patients were divided into two groups: those who received preoperative prophylactic antibiotics (Antibiotic Group, AG; N=59) and those who did not (No Antibiotic Group, NAG; N=61) (flow diagram 1). Clinical characteristics such as gender, age, ASA classification and BMI were comparable between the groups, as detailed in Table 1. Additionally, no significant differences were noted in operation parameters, including operation times. Patients were selected for surgery based on criteria including symptomatic gallbladder stones, gallbladder polyps, chronic cholecystitis, or a history of biliary pancreatitis. Gallbladder stones were significantly more prevalent in the patients of the group without antibiotics (n=0.032). The frequencies of these conditions are reported in Table 1.

Table 1. Clinical Characteristics of Patients

Patient	Antibiatic Group (N=59)	No Antibiatic Group (N=61)	P- Value
Gender (Male%)	18(30.51%)	10 (16.40%)	0.085
Age (Year)	45.46(13.07)	46.57(14.08)	0.654
BMI (KG/M2)	36.30 (4.33)	25.77 (4.70)	0.526
ASA class			0.096
I (%)	46 (77.97%)	40 (65.57%)	
II (%)	13 (22.03%)	21 (34.43%)	
operation times(min)	73.98 (27.13)	69.67 (15.38)	0.284
GB stones	52 (88.1%)	59 (98.3%)	0.032
GB polyp	7 (11.9%)	5 (8.3%)	0.558
Chronic Cholecystitis	16 (27.1%)	10 (16.7%)	0.189
History of pancreatitis	8 (13.6%)	8 (13.3%)	0.999

[DOI: 10.61186/jsurgtrauma.11.4.132]

Preoperative results, presented in Table 2, WBC was significantly higher in the antibiotic group patients than the non-antibiotic group patients (P=0.046), but it still showed a normal range in the antibiotic patients group. This finding indicates similar conditions before surgery in both groups. Similarly, creatinine levels were higher in patients in the antibiotic group than those in the group without antibiotics (P=0.018). Other laboratory results before surgery did not show significant differences in the two groups. In the context of our study's primary endpoint, surgical site infection (SSI), there were two instances (3.4%) in the Antibiotic Group. The first case, patient number 21, initially showed no signs of SSI during her postoperative clinic visit. However, she reported serous discharge from her umbilical port site during a follow-up call on day 14. Subsequent examination confirmed a superficial SSI. No additional laboratory or imaging diagnostics were utilized. Oral antibiotics were prescribed, and at the one-month follow-up, her condition had resolved. In the second case of SSI, patient 24, presented at the clinic with purulent discharge and erythema at his umbilical port site. The wound sutures were opened, and the site was cleansed daily for a week, accompanied by an oral antibiotic regimen. Further evaluations, including routine laboratory tests and sonography, indicated no signs of systemic infection. The wound was sutured at 30 days post-op. Neither of these patients reported fever during their hospitalization. In the NAG, four cases (6.7%) of SSI occurred. Patient 52 reported a fever during hospitalization. No deep SSI or intra-abdominal pathology was found in any of the patients. The overall incidence of SSI did not significantly differ between groups (6.7% in NAG vs. 3.4% in AG, p=0.679). Detailed results of each SSI subgroup are presented in Table 3. Additionally, there were no significant differences in preoperative WBC counts, hemoglobin, or creatinine levels between patients with SSI and those without (p=0.677, 0.115, and 0.421, respectively).

Table 2. Preoperative Results

laboratory parameter	**Antibiatic Group (N=59)**	**No Antibiotic Group (N=61)**	P-Value
WBC	8054 (2747)	7191 (1808)	0.046
HB	13.54 (1.53)	13.87 (1.21)	0.202
Creatinine	0.93 (0.15)	0.86 (0.16)	0.018
Alkaline Phosphatase	207.67 (61.02)	210.7 (98.52)	0.840
Data presented as frequency (percent), WBC: White Blood Cell count, HB: Hemoglobin			

[DOI: 10.61186/jsurgtrauma.11.4.132]

Table 3. Comparative Analysis of SSI prevalence in Patients Receiving Antibiotics Versus Those Not Receiving Antibiotic

SSI subgroup	Antibiatic Group (N=59)	No Antibiotic Group (N=61)	P-Value
Superficial SSI	2	4	0.679
Deep SSI	0	0	1.000
Organ/Space SSI	0	0	1.000
Data presented as frequency (percent), SSI: Surgical Site Infection			

Discussion

Our study found a total postoperative complication rate of 4.9% which aligns with previously reported rates of surgical site infections (SSIs) and other complications, which range from 1.4% to 7.9% (3, 14, 15). Previous studies and their collective meta-analyses have shown Contradictory results regarding antibiotic prophylaxis; whether it is necessary or not for laparoscopic cholecystectomy (9, 10, 13, 16-19). These contrary results could be explained by four main categories. First is the difference of power between these studies. A lower power might miss a rather significant difference, due to a lower sample size. Second is the difference between the intervention protocol. A variety of anti-biotic protocols were used in the aforementioned studies, ranging from a single dose of prophylaxis to as many as 3 doses of anti-biotics post-op. Matsui et al, recommended three doses of antibiotics, prophylaxis, and 2 post-op doses, as they claimed it would prevent postoperative infections (10). Third is the methodology for follow-up. The primary outcome of interest in this study, surgical site infection (SSI), generally manifests within about a week post-surgery. However, as most patients are discharged a few days following their operation, there is a risk of missing infection-related complications unless there is diligent follow-up. To mitigate this issue and ensure comprehensive detection of such complications, it is imperative to implement rigorous follow-up procedures. In this study, a thorough follow-up of all enrolled patients was conducted, with a follow-up rate of 88%. Fourth, the application of surgical drains and the choice of incision techniques, such as the transumbilical approach, play a crucial role in influencing infection rates. While the insertion of drains is beneficial for addressing complications like bile leakage from gallbladder perforation and hemorrhaging, it also carries a risk of inducing infection. In our research, we specifically excluded cases of gallbladder perforation, effectively negating the heightened infection risk associated with subsequent drain placement.

In the current study focusing on patients undergoing laparoscopic cholecystectomy (LCC), the incidence of postoperative complications, including surgical site infections (SSIs), was found to be infrequent. Furthermore, this study indicates that the routine administration of prophylactic antibiotics does not substantially diminish these complication rates.

Drawing from both recent research and the findings of this study, our institution has revised its protocol, choosing not to administer

[DOI: 10.61186/jsurgtrauma.11.4.132]

prophylactic antibiotics to patients undergoing elective LCC. This decision is supported by data from this study involving 109 patients at low risk for complications, where the use of prophylactic antibiotics did not significantly impact the rate of postoperative infections. However, to solidify these findings, further verification through future multicenter trials with higher sample size and power is recommended.

The limitations of this study include its single-center design, which may limit the generalizability of the findings to other settings.

Additionally, the somehow small sample size could affect the statistical power of the analysis, potentially overlooking subtle differences in outcomes. Finally, the exclusion criteria, such as the exclusion of patients with acute cholecystitis, may restrict the applicability of the results to a broader patient population undergoing laparoscopic cholecystectomy.

Conclusion

In conclusion, this study investigated the efficacy of prophylactic antibiotics in reducing surgical site infections (SSIs) following laparoscopic cholecystectomy (LC) in low-risk patients.

The findings revealed no substantial disparities in SSI incidence between patients administered prophylactic antibiotics and those who were not. Consequently, the utilization of prophylactic antibiotics in elective LC is not deemed requisite for low-risk patients.

These results prompt a reconsideration of antibiotic prophylaxis protocols in LC procedures, aligning with recent research suggesting minimal impact on postoperative infection rates. However, further verification through future multicenter trials with higher sample sizes and power is recommended to solidify these findings and guide clinical practice effectively.

Acknowledgments

None.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interests

All authors declare that they have no conflicts of interest.

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[DOI: 10.61186/jsurgtrauma.11.4.132]

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[DOI: 10.61186/jsurgtrauma.11.4.132]