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Role of Prophylactic Antibiotics on Surgical Site Infection in Elective Laparoscopic Cholecystectomy: A Randomized Control Trial

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ABSTRACT

Background: Although laparoscopic cholecystectomy is a common and widely accepted technique, the use of prophylactic antibiotics in elective laparoscopic cholecystectomy remains controversial. This study aimed to find out the efficacy of antibiotic prophylaxis in preventing postoperative infective complications in low-risk elective laparoscopic cholecystectomy patients.

Objective: The objective of this study was to compare the frequency of postoperative SSI in patients receiving prophylactic antibiotics and those not receiving prophylactic antibiotics, with the aim of evaluating the effectiveness of antibiotic administration in reducing the incidence of surgical site infections (SSIs) following various surgical procedures.

Material and methods: We conducted a randomized controlled trial over six months involving 218 patients undergoing laparoscopic cholecystectomy (LC) in the surgical unit-1 of the Holy Family Hospital in Rawalpindi, Pakistan. The patients were randomly placed into two categories: Group A and Group B. Group A was given prophylactic antibiotic 1 gram of ceftriaxone and Group B was given 0.9% normal saline 5 ml (placebo) thirty minutes before surgery. Postoperative surgical site infections were recorded as per operational definition on the day 7, 14, and 28 days follow-up after surgery.

Results: The frequency and percentage of post-operative surgical site infection in patients receiving prophylactic antibiotics and without prophylactic antibiotics after elective laparoscopic cholecystectomy was 9 (8.3%) and 2 (1.8%) respectively, which is statistically significant (p-value 0.030).

Conclusion: The study concludes that prophylactic antibiotics are not necessarily preventive in low-risk patients and should be avoided.

Keywords: Cholelithiasis, Surgical Site Infection, Prophylactic Antibiotics, Laparoscopic Cholecystectomy.

Abbreviations: Surgical Site Infections (SSI); Laparoscopic cholecystectomy (LC); Blood sugar random (BSR); Body mass index (BMI).

INTRODUCTION

Surgical Site Infection (SSI) stands as a prevalent healthcare concern, constituting one of the most common postoperative complications. With an estimated incidence rate ranging between 3-4%, SSIs pose a substantial risk to patient well-being, leading to heightened morbidity and mortality[1]. Traditionally, the management of SSIs involves the routine administration of prophylactic antibiotics, despite emerging evidence suggesting their superfluous use in low-risk patients. A promising alternative approach revolves around preoperative skin preparation, specifically employing chlorhexidine gluconate scrub, which may serve as a viable substitute for prophylactic antibiotics in preventing infection-related complications, particularly in elective laparoscopic cholecystectomy procedures[2].

This study delves into the intricate relationship between prophylactic antibiotics and SSIs in the context of elective laparoscopic cholecystectomy. Despite the widespread acceptance of laparoscopic cholecystectomy as a standard technique, the application of prophylactic antibiotics in this elective procedure remains a subject of considerable debate. Notably, unnecessary exposure to antibiotics has been linked to the emergence of drug-resistant pathogens, emphasizing the need for a judicious approach to antibiotic administration[3]. Therefore, the primary objective of this research is to assess the efficacy of antibiotic prophylaxis in averting postoperative infective complications among low-risk patients undergoing elective laparoscopic cholecystectomy.

METHODOLOGY

Study design

This is a randomized controlled trial that was conducted for six months from 1st May 2022 to 1st November 2022.

Ethical approval

Ethical approval was taken from the Institutional Research Ethics Forum Rawalpindi Medical University (RMU) and permission from the associated department.

Sampling technique

A consecutive non-probability sampling technique was used to recruit 218 patients undergoing laparoscopic cholecystectomy (LC) in the surgical unit-1 of the Holy Family Hospital in Rawalpindi, Pakistan.

Sample size

The sample size was determined using the World Health Organization (WHO) calculator, with the level of significance set at 5% and the power of the test at 80%.

Operational definitions

Acute cholecystitis is defined as an inflammation of the gall bladder. The patient may present with positive Murphy's sign, nausea, vomiting, or fever of over 100 degrees Fahrenheit. Following the confirmation of diagnosis with necessary investigations.

Postoperative infection is characterized as any infection arising within 30 days following surgery, potentially stemming from the surgical procedure or the subsequent postoperative period. It encompasses symptoms such as purulent discharge, pain or tenderness, localized swelling, redness, and the identification of organisms through aseptically obtained cultures from fluid or tissue at the surgical site. A stitch abscess (Minimal inflammation and discharge confined solely to the points of suture penetration) is not classified as a surgical site infection[4].

Inclusion criteria

Male and female patients aged 18-65 years undergoing Lap cholecystectomy were included in the study.

Exclusion criteria

Patients with acute cholecystitis, a body mass index of ≥ 30, patients with diabetes mellitus; Blood Sugar Random >200mg/dl, and those who have used antibiotics within one week of the planned LC were excluded from the study.

Randomization

The participants were randomly placed into two categories: Group A and Group B. Group A was given prophylactic antibiotic 1 gm ceftriaxone 30 minutes before the surgery and Group B was given 5 ml of 0.9% normal saline 30 minutes before surgery as a placebo. Postoperative surgical site infections were recorded as per the operational definition on the 7th, 14th, and 28th day after surgery upon scheduled follow-up.

Analysis

All the data was entered and analyzed using SPSS Version 27. Qualitative variables like wound infection, gender, and previous history of acute cholecystitis were measured as frequency and percentage. Quantitative variables like age and BMI were presented as mean ± SD. Surgical site infection in the two study groups was analyzed using the chi-square test. A P-value of <0.05 was considered statistically significant. For effect modifiers like age, gender, and previous history of acute cholecystitis, BMI stratification was done and the post-stratification chi-square test was applied at a 5 % level of significance.

RESULTS

Data was entered and analyzed in SPSS version 27.0. A total of 218 patients were included according to the inclusion criteria of the study. Descriptive statistics of the age (years) of the patients were also calculated in terms of mean and standard deviation. The mean age (years) in the study was 45.62+12.66. There were 128 (58.1) male and 90 (41.3) female patients who were included in the study according to the inclusion criteria. Descriptive statistics of the body mass index (BMI) of patients were also calculated in terms of mean and standard deviation. The mean body mass index in the study was 28.36+5.35. The frequency and percentage of previous history of acute Cholecystitis were assessed in the study. 30 (27.5%) patients presented with a history of acute Cholecystitis (Table 1).

Table 1: Socio-demographic data and history of acute cholecystitis of patients

		Two groups		
Construct	**Categories**	**Group A (antibiotics)**	**Group B (Placebo)**	**Total**
Gender	Male	70 (64.2%)	58 (53.2%)	128 (58.7%)
	Female	39 (35.8%)	51 (46.8%)	90 (41.3%)
Age	Mean	46.36	44.88	45.62
	Standard deviation	13.10	12.22	12.66
Body Mass Index (BMI)	Mean	28.66	28.06	28.36
	Standard deviation	5.67	5.02	5.35
Previous History of Cholecystitis	*Yes*	30 (27.5%)	1 (0.9%)	31 (14.2%)
	No	79 (72.5%)	108 (99.1%)	187 (85.8%)

The frequency and percentage of post-operative SSI in patients receiving prophylactic antibiotics after elective LC was 9 (8.3%), while that of those who did not receive prophylactic antibiotics was 2 (1.8 %), which was statistically significant (p-value 0.030). Among patients aged 18-40 years, the frequency and percentage of post-operative SSI in patients receiving prophylactic antibiotics and those who did not receive prophylactic antibiotics after elective LC was 5 (13.2%) and 1 (2.7%) respectively, which was statistically insignificant (p-value 0.095). In comparison, in patients aged 41-65 years, the frequency and percentage of post-operative SSI in patients receiving prophylactic antibiotics and those who did not receive prophylactic antibiotics after elective LC was 4 (5.6%) and 1 (1.4%) respectively, which was statistically insignificant (p-value 0.167).

Effect modifiers like gender stratification were done and compared with the frequency of postoperative SSI in patients receiving prophylactic antibiotics and without prophylactic antibiotics after elective LC. Among male patients, frequency and percentage of post-operative SSI in patients receiving prophylactic antibiotics and without prophylactic antibiotics after elective LC was 4 (5.7%) and 1 (1.7%) respectively, which was statistically insignificant (p-value 0.246); whereas among female patients, frequency and percentage of post-operative SSI in

patients receiving prophylactic antibiotics and without prophylactic antibiotics after elective LC was 5 (12.8%) and 1 (2.0%) respectively, which was statistically insignificant (p-value 0.041).

Effect modifiers like body mass index stratification were compared with the frequency of postoperative SSI in patients receiving prophylactic antibiotics and without prophylactic antibiotics after elective LC. Among patients with BMI < 23, the frequency and percentage of post-operative SSI in patients receiving prophylactic antibiotics and without prophylactic antibiotics after elective LC was 2 (7.1%) and 0 (0.0%) respectively, which was statistically insignificant (p-value 0.165); whereas among patients with BMI > 23, frequency and percentage of post-operative SSI in patients receiving prophylactic antibiotics and without prophylactic antibiotics after elective LC was 7 (8.6%) and 2 (2.4%) respectively, which was statistically insignificant (p-value 0.080).

Effect modifier like previous history of acute cholecystitis stratification was done and compared with the frequency of postoperative SSI in patients receiving prophylactic antibiotics and without prophylactic antibiotics after elective LC. Among patients presenting with a previous history of acute cholecystitis, frequency, and percentage of post-operative SSI in patients receiving prophylactic antibiotics and without prophylactic antibiotics after elective LC was 8 (26.7%) and 0 (0.0%) respectively, which was statistically insignificant (p-value 0.549) (Table 2).

Table 2: Effect of Various Modifiers on SSI

			Groups		Total	P-value
			Group A (antibiotics)	Group B (Placebo)		
Surgical site infection (Postoperatively at day 28)		Yes	9 (8.3%)	2 (1.8%)	11 (5.0%)	0.030
		No	100 (91.7%)	107 (98.2%)	207 (95.0%)	
Surgical site infection (Postoperatively at day 28)	**Age group 18-40 years**	Yes	5 (13.2%)	1 (2.7%)	6 (8.0%)	0.095
		No	33 (86.8%)	36 (97.3%)	69 (92.0%)	
	Age group 41-65 years	Yes	4 (5.6%)	1 (1.4%)	69 (92.0%)	0.167
		No	67 (94.4%)	71 (98.6%)	138 (96.5%)	
	Male	Yes	4 (5.7%)	1 (1.7%)	5 (3.9%)	0.246
		No	66 (94.3%)	57 (98.3%)	123 (96.1%)	
	Female	Yes	5 (12.8%)	1 (2.0%)	6 (6.7%)	0.041
		No	34 (87.2%)	50 (98.0%)	84 (93.3%)	
	Body mass Index ≤ 23	Yes	2 (7.1%)	0 (0.0%)	2 (3.7%)	0.165
		No	26 (92.9%)	26 (100%)	52 (96.3%)	
	Body mass Index > 23	Yes	7 (8.6%)	2 (2.4%)	9 (5.5%)	0.080
		No	74 (91.4%)	81 (97.6%)	155 (94.5%)	

	Previous history of acute Cholecystitis	Yes	8 (26.7%)	0 (0.0%)	8 (25.8%)	0.549
		No	22 (73.3%)	1 (100.0%)	23 (74.2%)	
	No previous history of acute Cholecystitis	Yes	1 (1.3%)	2 (1.9%)	3 (1.6%)	0.753
		No	78 (98.7%)	106 (98.1%)	184 (98.4%)	

DISCUSSION

Surgical Site Infections (SSIs) are a notable complication following surgery and they can result in significant patient morbidity and mortality. The reported incidence of SSIs in laparoscopic cholecystectomy (LC) varies in the literature, ranging from 0.4% to 6.3%[5]. The prevention of postoperative infections is crucial for optimizing surgical outcomes, and prophylactic antibiotics have been a cornerstone in this regard. Recognized for their efficacy in reducing bacterial contamination during clean-contaminated operations, such as cholecystectomy, and contaminated operations, preoperative antibiotics have become a standard practice[6].

Currently, LC stands as the primary treatment for symptomatic cholelithiasis, because it offers a significantly lower incidence of infectious complications compared to open cholecystectomy[7]. However, the debate surrounding the use of prophylactic antibiotics in elective LC, particularly in cases with low infectious risk, remains controversial. Many previously conducted randomized control trials have shown that antibiotic prophylaxis may not be necessary in low-risk patients undergoing elective LC[5,8,9-11]. Although, a study suggests that even low-risk patients in poor nutritional state with low albumin levels should be considered for prophylactic antibiotics[9]. On the contrary, many other surgeons still use and recommend the administration of prophylactic antibiotics as some studies suggest perioperative administration of prophylactic antibiotics should be recommended in laparoscopic cholecystectomy to prevent postoperative infectious complications and to reduce medical costs[12,13]. Another study conducted by Sikandar et al suggests single antibiotic prophylaxis for elective cholecystectomy is recommended provided strict aseptic measures are taken during the surgery along with good surgical technique[14].

Studies consistently indicate a lower rate of surgical site infections (SSIs) for laparoscopic cholecystectomy (LC) compared to open cholecystectomy[15]. The incidence of SSIs in LC ranges from 0.4% to 1.13%, significantly lower than the 3% to 47% range observed in open cholecystectomy[16]. This disparity is attributed to factors such as smaller incisions and the use of trocars, resulting in minimal to no wound contamination in LC compared to open procedures. Despite established guidelines recommending antibiotic prophylaxis in open cholecystectomy to reduce postoperative infectious complications, its necessity in LC remains debated. Lippert and Gastinger conducted a prospective, population-based, multi-center study suggesting that both laparoscopic and open cholecystectomy should include perioperative antimicrobial prophylaxis, as patients receiving prophylaxis experienced significantly fewer postoperative infections, complications, reoperations, and mortality rates compared to those without prophylaxis[17]. Similar findings have been echoed in several other studies, highlighting

the substantial reduction in infectious complications with prophylactic antibiotics[18,19]. Conversely, other prospective studies suggest that antibiotic prophylaxis may be unnecessary in elective LC due to its already low infection rate, positing that it may not effectively decrease SSIs or other postoperative complications[5,8-10].

Goldfaden and Birkmeyer, in a review of 98 randomized studies on antibiotic prophylaxis since 1990, suggested that routine antibiotic use in LC may be unnecessary for low-risk patients. They called for a multi-center prospective randomized controlled clinical trial to provide a definitive answer to this question due to the absence of sufficient randomized trials with a large sample size needed to avoid type II errors. The theoretical number of patients necessary for such a trial was estimated to include more than 3500 patients[20].

The positive bile culture rate among patients with gallbladder stones has been documented to range from 10% to 42.5% in prior research[21,22]. Perforation during gallbladder surgery, attributed to traction, grasping, dissection, and gallbladder removal, occurs in 11% to 35% of laparoscopic cholecystectomies (LCs)[20,21-23]. The impact of positive bacterial culture in bile or stone spillage due to perioperative gallbladder perforation on the incidence of surgical site infections (SSIs) remains contentious. Bactibilia emerges as a significant predictor of wound infection in low-risk patients undergoing elective LC, warranting the use of prophylactic antibiotics to mitigate the risk of wound infection, as routine investigation may not reliably identify patients with bactibilia. Preoperative prophylaxis with 0.5g sulbactam and 0.5g cefoperazone has been shown to significantly reduce positive bile cultures, thereby decreasing postoperative infection-related complications[24]. However, both positive bile culture and intraoperative gallbladder rupture have been strongly linked to SSI development, with the pathogens identified in intraoperative cultures mirroring those causing SSIs. Nevertheless, some studies, including ours, have found that the overall rate of SSIs does not necessarily correlate with the presence of bacteria in bile or gallbladder rupture. Additionally, it has been reported that umbilical flora and bile are not implicated as sources of SSIs after laparoscopic surgery[25]. Mechanical isolation of the gallbladder from the umbilical wound with routine endobag use during gallbladder extraction from the abdomen and local peritoneal irrigation in cases of gallbladder perforation have proven effective in preventing contamination with potentially infected bile. The use of an endo bag made from talc-free gloves is a simple and cost-effective method that can be adopted routinely. Several other studies have similarly suggested that SSIs are not directly linked to bile culture, gallbladder rupture, or spillage of gallbladder stones or bile[21,22,26].

The findings of this RCT show that the mean age (years) in the study was 45.62 $\pm$12.66 whereas there were 128 (58.1%) male and 90 (41.3%) female patients who were included in the study according to the inclusion criteria. The average body mass index in the study was 28.36 $\pm$5.35. Frequency and percentage of postoperative surgical site infection in patients receiving prophylactic antibiotics and without prophylactic antibiotics after elective laparoscopic cholecystectomy were 9 (8.3%) and 2 (1.8%) respectively which was statistically significant (p-value 0.030) whereas the study conducted by Chong Ju showed that average age of patients in his study were 44.6 $\pm$23.4 with gender distribution 15% and 85% respectively, the study showed that surgical site infection among both the groups was 4.41% and 2.63% respectively showing that use of prophylactic antibiotics does not decrease the rate of postoperative infection complications and surgical-site infections and is not necessary in low-risk patients undergoing laparoscopic cholecystectomy.

The possible limitation of this randomized control trial could be the lesser number of participants that fulfilled the inclusion criteria and eventually became a part of the study. Such better and large-scale studies need to be conducted on this topic to find a definitive answer and make it a standardized practice as the careful use of antibiotics is essential to prevent the increasing rates of antimicrobial resistance.

CONCLUSION

The study concluded that there is a difference in the frequency of surgical site infection in patients receiving prophylactic antibiotics and those without antibiotics, undergoing laparoscopic cholecystectomy. This is likely to happen because of the overuse and misuse of antibiotics which are the key factors contributing to antibiotic resistance. Hence, it would be advisable that patients should be prevented from unnecessary exposure to antibiotics which will be cost-effective as well. Thus, the general public and doctors should play a role in avoiding unnecessary exposure of antibiotics to the low risk patients as in such cases antibiotics are not proven to play any significant role in preventing surgical site infection.

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Author's Contributions:

1. **Sidra Ahmad:** Conception of work, Interpretation of data and analysis, and critical reviewing.
2. **Sumaira Nawaz:** Conception of work and interpretation of data. Composition of a part of the manuscript.
3. **Maryam Iftikhar:** Data collection, Drafting, and Data Analysis.
4. **Sadia Iram:** Composition of the manuscript and added references. Helped in Data collection.
5. **Syed Abdullah Haider**: Data collection and composition of the manuscript.
6. **Aden Ghani:** Data collection, arrangement, and manuscript composition.

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