



Cefazolin as a Prophylactic Antibiotic in Laparoscopic Cholecystectomy: A Systematic Review

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Abstract

Background: Cefazolin is a first-generation cephalosporin prophylactic antibiotic which recommended for open cholecystectomy. Laparoscopic cholecystectomy is a clean contaminated surgery that does not require prophylactic antibiotics. Some surgeons still have the habit of giving prophylactic antibiotics for laparoscopic cholecystectomy. This systematic review aimed to examine evidence from randomized controlled trials comparing the incidence of surgical wound infection with cefazoline use. **Methods:** We collected randomized controlled trials (RCTs) throughout the years 2010-2020 from the Cochrane Library and PubMed in English language, which examined the incidence of surgical wound infection between the cefazolin prophylactic antibiotic groups versus placebo on laparoscopic cholecystectomy. **Results:** Six RCTs were included in the final analysis for a qualitative assessment using the Jadad scale, with four articles in the high category and the other two in the good category. The incidence of surgical wound infection in the cefazolin group was 1.09-4.8% (mean 2.63%) and did not differ significantly from the placebo group. Old age (> 60 years), obesity, timing of antibiotics, as well as tissue trauma and billiard spill during laparoscopic cholecystectomy were not significant factors. **Conclusion:** The prophylactic antibiotic cefazolin was not significant in reducing the incidence of surgical wound infection in lapaoscopic cholecystectomy. It is necessary to review the guidelines for prophylactic antibiotics in each health service place.

Keywords: *Cefazolin, Prophylactic antibiotics, Laparoscopic cholecystectomy, Surgical wound infection.*

Introduction

Laparoscopic cholecystectomy is a medical procedure that is often performed in the field of digestive surgery. Laparoscopic cholecystectomy was first introduced in March 1987 by Philippe Mouret, a surgeon from Lyon, France, who performed laparoscopy, gynecological adhesiolysis, and cholecystectomy for a 50-year-old woman with complaints of unexplained abdominal pain. This achievement was followed by François Dubois from Paris who performed the first laparoscopic cholecystectomy in 1988; and Professor Jacques Perissat, who also started work in 1989 [1].

Laparoscopic cholecystectomy is the "gold standard" for cholestectomy surgery. Use of prophylactic antibiotics in low-risk clean category surgery, including laparoscopic cholecystectomy; deemed unnecessary. On the other hand, prolonged use of antibiotics

also carries a risk of increased antibiotic resistance and an increase in operating costs and length of stay. Several current guidelines for prophylactic antibiotics suggest a first-generation cephalosporin, cefazolin, should be used as prophylaxis in bile duct surgery if necessary [2]. Surgical site infection (SSI) accounts for 14-16% of all nosocomial infections and is the most frequent infection in surgical patients [3].

The SSI can lead to increased length of stay, use of antibiotics, risk of morbidity and mortality, and cost of care. The Centers for Disease Control (CDC) classifies the types of surgery into four categories. One category is clean contaminated surgical wounds, namely surgical wounds on the respiratory, digestive, genital, or urinary tract, under controlled conditions and without any unusual contamination [4].

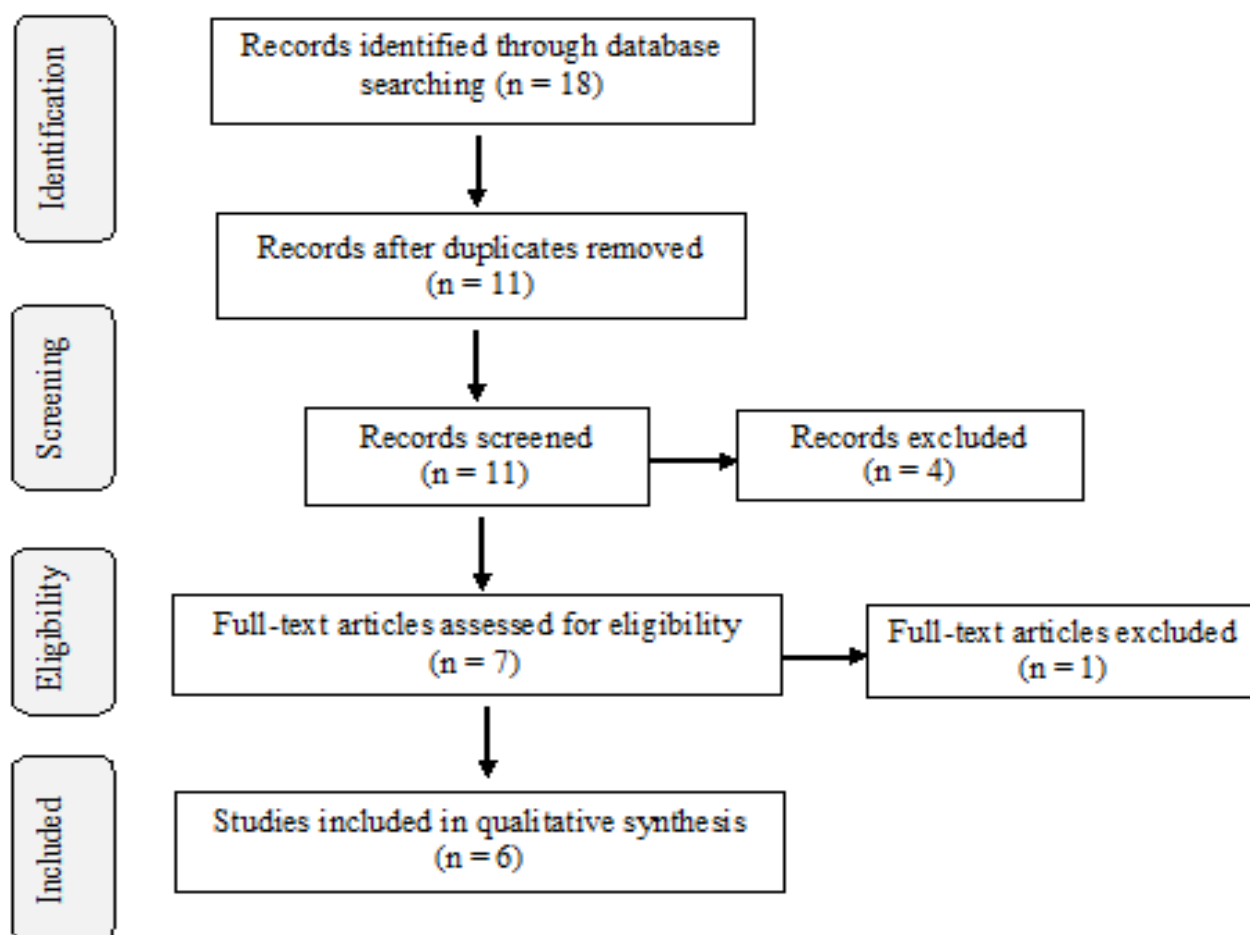
Bile duct surgery can be classified into the type of clean contaminated surgical wound. Antibiotic stewardship is carried out so that prophylactic antibiotics are carried out wisely, including an understanding of the plasma levels of prophylactic antibiotics that are effective during surgery to prevent surgical wound infection.

Prophylactic antibiotic administration after skin closure is not required, and the duration of administration of five days can lead to antimicrobial resistance and alter the local germ / antibiogram pattern [5]. Cefazolin is a prophylactic antibiotic recommended by the CDC for open cholecystectomy. The aim of this systematic review is to evaluate the need for the use of prophylactic antibiotics in elective laparoscopic cholecystectomy to

prevent surgical wound infection and antimicrobial resistance.

Method

Electronic literature searches were carried out through the Cochrane library and PubMed databases, with the keywords "Antibiotic Prophylaxis" AND "Cefazolin" AND "Cholecystectomy". The time filters used in this systematic review are publications that fall into the 10-year timeframe, namely 2010-2020. Inclusion criteria were randomized controlled trials (RCTs) that assessed the effect of cefazolin prophylactic antibiotics on surgical site infection (SSI) in laparoscopic cholecystectomy. Systematic reviews follow the rules or standards of Systematical Reviews, using the Jadad Score to test the quality of each RCT.



Process of identifying eligible studies for systematic review

Result

The first search resulted in 18 titles from the Cochrane Library and Pubmed screening databases. A total of 7 titles were duplicated so that after being removed there were 11

titles left. Four titles were included in the exclusion criteria because of differences in research methods, namely prophylactic antibiotic irrigation into the biliary tract, and articles could not be downloaded. A total of 7

titles met the inclusion criteria, namely the RCT (Randomize Controlled Trial) study, which then included one more title that was

included in the exclusion criteria because the control group used was not a placebo. The remaining six titles were designated as articles for systematic review.

Table 1: Characteristic data of research articles

Study Characteristics	Shah, J.N. <i>et al</i> , 2012 [6]	Turk E. <i>et al</i> , 2013 [7]	Ruangsin, S. <i>et al</i> , 2015 [8]	Passos MAT. <i>et al</i> , 2016 [9]	Sarkut, P. <i>et al</i> , 2017 [10]	Guler, Y. <i>et al</i> , 2019 [11]
Type of Study	RCT	RCT	RCT	RCT	RCT	RCT
Randomization	1	1	1	1	1	1
Randomization appropriate?	1	1	1	1	1	1
Blinding	1	1	1	1	1	1
Blinding appropriate?	0	1	1	1	1	0
Drop Out	0	1	0	0	0	0
Jadad Scale	3 (good)	5 (high)	4 (high)	4 (high)	4 (high)	3 (good)
Age (Mean)	13-76 (40,3) vs 10-76 (41,6)	51,9 (±13,1) vs 47,8 (±13,4)	54,19 (±14,86)	48 (±13,63)	51 (17-84) vs 53 (25-82) vs 54 (22-89)	49,8 (±13,8) vs 49,7 (±14,7)
Location	Nepal	Turki	Thailand	Brazil	Turki	Turki
Time	01 Oktober 2009 - 31 September 2010	Oktober 2009 sampai Juni 2012	1 Agustus 2009 - 30 April 2012	-	1 April 2007 - 31 Maret 2010	September 2017 - Mei 2018
Duration of Surgery (minute)	No data	66,45±18	118,8±41,0	77±28,70	60-120	32±15
Length of stay (day)	1,29	1,42	Few days	No data	No data	No data
Patients	310	547	299	100	570	206
Intervention	154 patients received cefazolin 1 gram IV	278 patients received cefazolin 1 gram IV	150 patients received cefazolin 1 gram IV	50 patients received cefazolin 2 gram IV	191 patients received cefazolin 1 gram IV; 186 patients received cefuroxim 750 mg IV	111 patients received cefazolin 1 gram IV
Control	156 patients did not receive antibiotics	269 patients received NaCl 0,9% 10 ml IV	149 patients received NaCl 0,9% 10 ml	50 patients did not receive antibiotics	193 patients received NaCl 0,9%	95 patients did not receive antibiotics
Follow Up	7 days post surgery	7-10 days, continued for up to 30 days	30 days post surgery	7 and 30 days post surgery	3rd and 4th weeks postoperatively	7 days and 30 days after surgery
SWI	4,8% (15/310)	1,09% (6/547)	2,3% (7/299)	2% (2/100)	1,2% (7/100)	4,4% (9/206)
Note	Intervention 3,9% (6/154); Control 5,8% (9/156)	Intervention 1,4% (4/278); Control 0,7% (2/269)	Intervention 1,3% (2/150); Control 3,4% (5/149)	Intervention 2% (1/50); Control 2% (1/50)	Intervention I 1,04% (2/191); Intervention II 1,07% (1), Control 1,5% (3/193)	Intervention 4,5% (5/111); Control 4,2% (4/95)
Statistical Test	p = 0,442	p = 0,44	p = 0,512	p = 0,05	p = 1,00	p = > 0,05
SWI = Surgical Wound Infection						

Discussion

The systematic review of the six studies above was carried out qualitatively using the Jadad scale [12], which divides the assessment into three things, namely randomization, blinding, and dropping out.

Four studies, each made by Turk E. et al, Ruangsinsin, S. et al, Passos MAT. Et al, and Sarkut P. et al, have a high qualitative assessment, because all four of them mention and describe randomization, which is a double-blind study accompanied by an explanation of how to do blinding; however, only Turk E. et al. described dropout. Two other studies, Shah, J.N. et al and Guler, Y. et al, did not explain the method of blindness and drop out, so it has a qualitative value of good based on Jadad.

The six studies contained clear information on inclusion and exclusion criteria. Prophylactic antibiotics in the clean contaminated category of surgery, namely laparoscopic cholecystectomy, there is no similarity in attitude. Some guidelines suggest that prophylactic antibiotics are not necessary, but several articles stated that there was a decrease in the incidence of surgical wound infection (SWI) although this did not differ significantly from the group that did not receive prophylactic antibiotics. The SWI is divided into three, namely the superficial, the inner, and the organ / cavity [4].

Research Shah, J.N. et al had results consistent with the other five studies, namely that there was no significant difference between the prophylactic antibiotic group and the control group. Sarkut, P. et al divided the groups into 3 [10], where the two treatment groups were the group that received cefazolin 1 gram and cefurozime 750 mg intravenously, which also gave the results of the SWI incidence did not differ significantly compared to the placebo group.

The incidence of the SWI from the five studies was 1.09-4.8% (2.63%). Thailand as a developing country in the tropics is said to have a higher incidence of infection, but the incidence of the SWI is 2.3%. These results are consistent with several other studies which stated that the incidence of SWI in laparoscopic cholecystectomy was 0.1-7.9% [8].

Administration of cefazolin was carried out according to the pharmacology of the drug with guidance that is 30-60 minutes before the surgical incision [2], but only Ruangsinsin, S. et al. Displayed the time of administration explicitly. Cefazolin is a first generation cephalosporin which is hydrophilic and has the ability to penetrate the bile ducts [13]. Cefazolin can be given to obese patients based on their adjusted body weight.

The cefazolin dose is 20-30 mg / kg, however, 2 gram IV administration of cefazolin is considered in obese patients [14]. Ruangsinsin S. et al presented data on obese patients with a BMI > 30 kg / m² of 16 of 299 patients (5.35%) and morbid obesity with a BMI > 40 kg / m² of 6 of 299 patients (2.00%), however BMI was not a risk factor for ILO in this study (p = 0.201).

Repetition of cefazolin prophylactic antibiotics is carried out with due regard to the half-life because this antibiotic is time dependent so that in prolonged surgery, it can be repeated within 2-5 hours after incision [14]; however, most laparoscopic cholecystectomies do not require repeat cefazolin because the duration of surgery is less than 2 hours (Table 1).

This is confirmed by the research of Loozen, C.S. et al, who obtained a single standard dose of cefazolin did not increase the SWI risk of laparoscopic cholecystectomy in patients with mild acute cholecystitis, compared to cefuroxime and metronidazole for 3 days after surgery [15]. Age more than 60 years is a factor in the consideration of prophylactic antibiotics.

Matsui Y., et al stated that age more than 65 years is one of the predisposing factors for postoperative infection [16]. In the study of Ruangsinsin S. et al, there were 4 out of 7 patients (57%) over 60 years of age who experienced infection after surgery, but it did not significantly influence (p = 0.109) in terms of prophylactic antibiotics. Bile duct perforation at surgery occurs in 11-35% of laparoscopic cholecystectomies [11].

Although tissue trauma is said to be one of the SWI risk factors, in this article's review, bile duct tearing was not shown to increase the incidence of SWI. In the research of Shah, J.N. et al, bile spillage in the antibiotic group occurred in 3 of 310 patients (3.55%); Turk et

al reported 97 of 547 patients (17.2%) whereas Guler et al reported 32 of 206 patients (15.5%).

The length of stay after laparoscopic cholecystectomy is generally not more than 3 days, however there are two studies that did not explicitly state length of stay (table 1). Administration of a single dose of prophylactic antibiotic cefazoline during laparoscopic cholecystectomy provides the advantage of lower length of stay, with the advantage of avoiding overuse of antibiotics that can induce antimicrobial resistance (AMR) and the possibility of other nosocomial infections.

Loozen Research, C.S. et al supported the administration of single-dose prophylactic antibiotics, because the administration of prophylactic antibiotics for one-time laparoscopic cholecystectomy was not inferior to three days postoperatively [15]. The results of the six articles above (table 1) are not the same as the results of the study by Matsui, Y. et al, with a length of stay in the hospital of 3-5 days [16].

This is related to the procedure for prophylactic antibiotics that are not in accordance with the guidelines, where antibiotics are given three times, namely before surgery, followed by the first 12 hours and 24 hours after surgery, regardless of the length of laparoscopic cholecystectomy.

Conclusion

We conclude that the prophylactic antibiotic cefazolin should not be administered to patients with low-risk laparoscopic cholecystectomy. Adjustments to the guidelines for administering antibiotics at local health facilities must always be carried out based on the latest guidelines and antibiogram. Further research is needed on the administration of prophylactic antibiotics in patients with acute cholecystitis who are prepared to undergo biliary tract surgery.

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