A Comparative Study of Single Dose versus Multiple Dose Prophylactic Ceftriaxone in Laparoscopic Cholecystectomy

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ABSTRACT:

BACKGROUND:

Although laparoscopic cholecystectomy became the gold standard for the treatment of gallstone disease, there is some risk of surgical site infection that required prophylactic antibiotic. Prophylaxis for low risk patients is still controversial as well as whether single or multiple doses is needed.

AIM OF STUDY:

Compare between single vs. multiple dose of antibiotic prophylaxis in laparoscopic cholecystectomy in terms of post-operative infection and cost.

METHODS:

A prospective study conducted at Baghdad Teaching Hospital, from January 2017 to March 2018. 200 patients admitted for elective laparoscopic cholecystectomy randomly divided in two equal groups: single dose (SD) group was given ceftriaxone (2gm) intravenously at induction of anesthesia, and multiple doses (MD) group was given ceftriaxone (2gm) intravenously at induction of anesthesia followed by ceftriaxone (1gm) intravenously twice a day for two days postoperatively. Surgical site infection and treatment cost in two groups compared and analyzed.

RESULTS:

Postoperative infection rate was 1% in both groups; the difference was not significant (p=1). The cost was higher in MD group.

CONCLUSION:

Single dose prophylactic antibiotic administered at induction of anesthesia, is equally effective as multiple doses to prevent post-operative infection in low risk patients undergoing laparoscopic cholecystectomy and is cost effective.

KEYWORDS: Laparoscopic cholecystectomy, antibiotic prophylaxis, ceftriaxone.

INTRODUCTION:

Gallstone Overview

Gallstone disease is one of the most common and costly of all digestive diseases [1]. Gallstone disease is the presence of gallstones in the gallbladder and/or common bile duct and/or the associated complications that gallstones cause. The term cholelithiasis may refer to the presence of stones in the gallbladder or to the diseases caused by gallstones [2]. Gallstones constitute a significant health problem in developed societies, affecting 10% to 15% of the adult population, meaning 20 to 25 million Americans have (or will have) gallstones [3,4].

Treatment

There is uncertainty about the best way of treating gallstone disease. There is a range of endoscopic, surgical and medical treatments available, but it is unclear which treatments are the most appropriate for which patients [1,2]. However, there are three general options for people with gallstones; the best option depends upon the patient′s individual situation

Expectant management: Do nothing, wait and watch [1,2].♦

Non-surgical therapy: Eliminate the stones while preserving the gallbladder ♦

Surgical therapy: Remove the gallbladder and stones [1,2]. ♦

Surgical treatment

Cholecystectomy: It is one of the most commonly performed surgeries in the United States [1], [2]. Surgery may be done as an open or laparoscopic cholecystectomy [1]

Open cholecystectomy (OC): has been the mainstay of treatment for cholelithiasis and was first performed in 1882 by a German surgeon Carl August Langenbuch [5]

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Laparoscopic cholecystectomy (L.C): It was first introduced in the late 1980s, and now became the standard treatment for symptomatic gallbladder stones, and mild and moderate acute cholecystitis, based on superior outcomes compared with open cholecystectomy [2,4,5,6]. Laparoscopic cholecystectomy is easy to perform, less time-consuming procedure, with less pain and low complication rates as compared to open cholecystectomy. It also confers an advantage of a shorter hospital stay and early return to work as compared to the open procedure [4,5,6].

Main complications of LC are major bleeding, wound infection, and biliary leakage or injury which is mostly seen in developing countries. Surgeons' experience and patient selection are important determinants for complications [7].

Wound Infections: Surgical Site Infection (SSI) and Port Site Infection (PSI)

Surgical Site Infections is the most common and most serious complication in patients undergoing surgeries, leading to increased mortality and morbidity rates, hospital stay, as well as costs [8].

SSI: is defined as infections in the surgical site up to until one month after the operation in patients in whom no prosthesis has been used and up to one 90 days after the operation when prosthesis has been used [8,9].

PSI: is a type of SSI but limited to Laparoscopic surgery (LS). The same criteria for SSIs are applicable to PSIs, but the infections are limited to superficial and deep surgical sites only [9].

The incidence of SSI is higher after open versus laparoscopic cholecystectomy [8,9] with reported SSI rates after open cholecystectomy ranging from 1.1% to 8.4% versus 0.3% to 3.4% after laparoscopic cholecystectomy [8].

Antibiotic Prophylaxis in Laparoscopic Cholecystectomy

L.C. is classified as clean contaminated surgery according to CDC (Center for Disease Control and Prevention) criteria for SSI 2015 [9,10,11]. The use of prophylactic antibiotics (a brief course of an antimicrobial agent administered just before an operation) is mandatory to decrease the incidence of SSIs [10], and is an essential factor in improving the results of surgical procedures [12].

Administration of prophylactic antibiotics has been recommended by the CDC and widely used in clean-contaminated surgery such as cholecystectomy to reduce surgical site infections (SSI) [10]. However, the use of prophylactic antibiotics as a means of preventing SSIs is still controversial in elective LC, which has a low risk for infectious complications [12], [13]. Ideally, prophylactic antibiotics should prevent SSIs as well as SSI-related morbidity and mortality and reduce the duration and cost of health care [13], [14]. However, the incorrect use of prophylactic antibiotics can increase antibiotic resistance and the cost of health care. Unnecessary use of antibiotic adds to the cost and increases emergence of multidrug resistance [12,15]. Therefore, appropriate selection of prophylactic antibiotics has medical benefit and significance [14]. Single or multiple dosages of antibiotics are important to prevent surgical site infection [15]. In many trials worldwide it has been established that the single dose of prophylactic antibiotics is as effective as the multi-dose regimens. Single dose of antibiotics are more patient compliant, cost effective, less adverse effects, prevents emergence of antibiotic resistance and more rational than multiple dosages of antibiotics [15].

Selection of Ceftriaxone in prophylaxis of PSIs in LC

Worldwide, cephalosporins are being used frequently as prophylactic antibiotics. The reason being, they are safe, effective, nontoxic, having excellent antimicrobial activity and good tissue penetration [12]. Ceftriaxone is a parenteral third-generation cephalosporin with a long elimination half-life which permits once-daily administration [16]. It has good activity against Streptococcus pneumoniae, methicillin-susceptible staphylococci, Haemophilus influenzae, Moraxella catarrhalis and Neisseria spp. In the nosocomial setting, extensive data also confirm the efficacy of ceftriaxone with or without an aminoglycoside in serious Gram-negative infections, spontaneous bacterial peritonitis and for surgical prophylaxis. Ceftriaxone has a good tolerability profile [16].

Materials and Methods

A prospective controlled randomized open labeled study was begun from 1st. of January 2017 to beginning of March 2018 at Baghdad Teaching Hospital in Iraq. 200 patients were enrolled in this study (117 Female, 83 males) with cholelithiasis (proven by ultrasounds and MRI as well as physical examination). All the history taking, clinical examinations, and medication prescription in this study was done under supervision and consultations of surgeons.

Inclusion criteria

Adult patients with cholelithiasis with no other medical condition admitted for elective laparoscopic cholecystectomy.

Exclusion criteria

Adult patients with cholelithiasis associated with: acute cholecystitis, diabetes mellitus, hypertension, cardiac/renal/liver failure,ischemic heart disease, immunosuppression, conversion to open surgery, patients who had hypersensitivity reactions to cephalosporins,

patient with previous ERCP,and patients who lost to follow up.

Patients groups

The patients with cholelithiasis were admitted to the hospital one day before surgery and full investigations were done and after undergone inclusion and exclusion criteria, they were randomized into two groups in a 1:1 ratio (Single dose group and multiple dose group):

♦ Single dose group (SD Group):- 100 patients (60 female, 40 males) received single dose 2 g ceftriaxone IV (Triaxone® 1 g IV vial TABUK Pharmaceutical Mfg. Co., Saudi Arabia) at induction of anesthesia (administered in 100ml normal saline infusion) with no antibiotic post operatively.

♦ Multiple Dose group (MD Group):- 100 patients (57 female, 43 males) will receive 2 g ceftriaxone IV (Triaxone® 1 g IV vial TABUK Pharmaceutical Mfg. Co., Saudi Arabia) at the induction of anesthesia (administered in 100ml normal saline infusion) and 1 g ceftriaxone twice daily post operatively for two days. The second dose administered after 12 hr. from the first dose.

Data collection and patient's evaluation

The data were collected by using a pre-structured questionnaire filled by the researcher. The patients were diagnosed by a specialist. Laboratory investigations (includes CBC, RFT, LFT, serum electrolytes and virology test) as well as ECG and CXRs were done at the day of admission and the patients scheduled for L.C. The follow up was done in the 1st post-operative day, after one week, and after 3 weeks post operatively. The researcher communicated with the patients first in the hospital and by phone after discharge. All the cholecystectomies were done at the same surgical unit by the same surgical team and for the same duration of time

The patients were assessed for:

1. Hospital stay duration
2. Development of complications (Fever, port-site redness, wound discharge and wound abscess).

Mortality.3

Ethical approval

The study protocol was approved by the Research Ethics Committee of the Iraqi Board for Medical Specializations and an improvement to the study was obtained from the committee of scientific Council of Clinical Pharmacy and Scientific Council of Surgery. All patients that enrolled in the study signed their written consent forms before participating in the study.

Statistical Analysis

Data tabulation, input and coding was done by the use of IBM© SPSS© (Statistical Package for the Social Sciences) Statistics Version 22. For descriptive statistics, percentage was applied, and T-test to compare numerical variables and Fisher's exact test to categorical data. P-value less than 0.05 were considered significant throughout data analysis.

RESULTS:

The two groups matched with regard to age, gender, weight, and smoking history as well as laboratory investigations (hemoglobin level, RFTs, LFTs, and serum electrolytes). There was no significant difference between the two groups. The complications of L.C. in our study are represented by SSIs (which include fever, port-site redness, wound discharge and wound abscess). The rate of SSIs was (1%) for both groups, with statistically insignificant difference between the two groups (P value=1) as shown in table (1-1).

Both patients with SSI were treated conservatively (one patient in the SD group present with fever at the 2nd post-operative day that treated with antipyretic and after one week present with port site redness that treated with topical emollient cream, the other patient in the MD group present with fever at the 2nd post-operative day that treated with antipyretic) and at three weeks follow up all patients were asymptomatic.

Table 1-1: Relationship of postoperative infection between SD and MD groups.

Group		Single dose	Multi dose	Total	p-value
		No (%)	No (%)	No (%)	
Infection	Yes	1 (1.0%)	1 (1.0%)	2(2.0%)	1.000
	No	99(99.0%)	99(99.0%)	198(98.0%)	
Total		100(100.0%)	100(100.0%)	200 (100.0%)	
Fisher's exact test					

The individual characteristics of the patients with SSIs were shown in table (1-2), the case in single dose (SD) group was a 28 years old smoker male, weighed 90.0 kilograms, with a hemoglobin level of 15.65 g/dl, while the case in multiple dose (MD) group was a 43 years old non-smoker female, weighed 91.0 kilograms, with a hemoglobin level of 14.2 g/dl with a history of corticosteroids use (more than 5 years). All of obesity, smoking, and long term corticosteroids use are risk factors for infection.

Table 1-2: Characteristics of patients suffering postoperative infection.

Group	Age	Weight	Sex	Hb	Smoking
Single Dose	28	90.0	Male	15.7	Yes
Multi Dose	43	91.0	Female	14.2	No

There is significant difference in costs of antibiotics required for both group and multiple dose regimen is costly than single dose regimen. This clearly shows that mere economical burden on health care facility of unnecessary administration of antimicrobial in those patients who do not need it actually. The relationship of costs in both groups is shown in the following table:

Table 1-3: Relationship of cost between SD group and MD.

	Single Dose	Multiple Dose
Cost in iraqi dinnars	700000	1550000

DISCUSSION:

This study was conducted to compare the effect of single vs. multiple dose of antibiotic prophylaxis in L.C. in terms of post-operative infection and cost

Cholelithiasis is more common in females in their 4th decade of life [12]. In our study, 58.5% of the patients were females and the male: female ratio was 1:1.4 which coincides with the findings of Chaudhary Rajesh [10] and Sutariya PK et al [12].

In this study, both groups were similar at baseline. No significant differences existed between the two groups regarding age, gender, weight, smoking history as well as hemoglobin level, RFTs, LFTs, and serum electrolytes. All the procedures were performed at the same surgical unit and by the same surgical team.

The rate of post-operative wound infection in our study was 2/200 (1%). SSI was observed in 1% cases in single dose group (SD group) and 1% cases in multiple dose group (MD group), (P value=1 which is statistically non-significant).

Our findings are comparable with reported studies. In a randomized controlled trial by Thapa Sagun Bahadur et al, the overall infection rate was 2.2% [12], which is consistent with the results obtained in our study. In addition, our result is comparable with the result of Sutariya PK et al where they have the rate of SSI in SD group is 4.4% and that in MD group is 3.3%, and the rate of infection in both groups was found to be statistically insignificant ($p>0.05$) [11].

Similarly the results of Kumar Ashwani et al was low (0.41%) and there was no significant difference between wound infection in patients receiving prophylactic antibiotics and post-operative antibiotics [17].

All of these trials (that mentioned in the previous paragraph) as well as a prospective multicenter study by Spaziani Erasmo et al [18] and our study found that single dose of antibiotics is effective as multiple doses in preventing SSI in low risk patients undergoing elective L.C., and we also found that it is cost effective.

In contrary, Abro A et al [19] in their prospective randomized trial, concluded, that multiple doses of prophylactic antibiotic should be used instead of single dose in surgical prophylaxis in clean-contaminated and contaminated procedure.

However, till now there is no consensus on usage of prophylactic antibiotic in laparoscopic cholecystectomy for low risk patients [20]. In a reappraisal of previously reported meta-analyses by Matsui Yoichi et al[21], Nauman et al [22], and S. Sajid Muhammad et al[23] they recommend the use of prophylactic antibiotics for patients who are undergoing elective low-risk laparoscopic cholecystectomy in order to prevent postoperative infectious complications.

The main limitation of the study is the limited number of patients involved with a consequence low number of SSIs.

However, the prospective design and the absence of bias and lost-to-follow up patients are a significant strength.

CONCLUSION:

We conclude that single dose of prophylactic antibiotic administered at induction of anesthesia, is equally effective as multiple doses of antibiotics to prevent post-operative infection in low risk patients undergoing elective laparoscopic cholecystectomy and is cost effective.

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