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ORIGINAL ARTICLE

Efficacy and Safety of Ceftriaxone vs Cefuroxime in Preventing Surgical Site Infection in Patients Undergoing Laparoscopic Cholecystectomy: An Open label, Prospective, Randomized, Comparative Study

Saima Bashir, Vishal R. Tandon, Zahur Hussain*

Abstract

Background: antimicrobial prophylaxis plays an important role in reducing the rate of SSI, the issue still remains controversial and unanswered in many aspects. **Aim and Objective:** the current study was done to assess and compare the efficacy and safety of intravenous Ceftriaxone Vs Cefuroxime in patients undergoing Laparoscopic Cholecystectomy in preventing SSI's.Method: The present randomized, prospective, open-label, comparative study was done on the patients with USG documented gallstones scheduled for elective Laparoscopic Cholecystectomy. The subjects were divided into two groups. Groups I: I/V single dose ceftriaxone 1g, 30 minutes prior to the incision followed by BD 1g for 2 days post-operatively. Group 2: I/V single dose cefuroxime 1.5g, 30 minutes prior to the incision followed by 1g BD for 2 days post-operatively. To compare the overall incidence of SSI between two groups for first 0 hour, 24 hours, day 7 and week 4 of the surgery, CDC classification for Superficial, deep, organ/space incisional surgical site infection, ASA scale, WHO QOL Scale, Grade of fever, port-site redness/tenderness, wound gape, wound discharge, wound abscess, Hospital stay due to SSI were evaluated and compared between two arms.Result: The results of the current study thus clearly revealed comparable efficacy and safety of both the drugs and failing to prove any superiority over each other with regards to both primary and secondary endpoint.**Conclusion:** The current study revealed comparable efficacy and safety of single dose 30 minutes prior to the incision and followed by twice daily of inj. Ceftriaxone as well as inj. Cefuroxime after surgery for two days in preventing surgical site infection.

Key Words

Ceftriaxone, Cefuroxime, Surgical Site Infection, Laparoscopic Cholecystectomy

Introduction

Cholelithiasis has a prevalence of 10-15% in the developed countries and 10-22% in India. [1] SSIs are the most common hospital acquired infections, accounting 38% of all infections among postoperative patients. [2] Although antimicrobial prophylaxis plays an important role in reducing the rate of SSI, the issue still remains controversial and unanswered in many aspects i.e, prophylactic antibiotic is needed or not, single dose Vs multiple dose, choice of drugs like beta-lactum antibiotics or cephalosporins, narrow spectrum or wide spectrum, preventive and therapeutic treatment vs only preventive treatment is required in preventing SSIs etc.[3] In light of various unanswered questions stated above and scarcity

PG Deptt. of Pharmacology & Surgery*, Govt Medical College, Jammu (J&K), India

Correspondence to: Dr. Vishal R Tandon, Professor, Department of Pharmacology GMC, Jammu- J&K India

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of data from Indian and our setup, it was of great surgical practice interest to compare Ceftriaxone Vs Cefuroxime in preventing SSIs in patients undergoing Laparoscopic Cholecystectomy (LC). Further, the prevalence of cholelithiasis and the patients undergoing LC is relatively very high along with SSI's in this region. Hence, the current study was done to assess and compare the efficacy and safety of intravenous Ceftriaxone Vs Cefuroxime in patients undergoing Laparoscopic Cholecystectomy in preventing SSI's.

Material and Methods

The present randomized, prospective, open-label, comparative study was conducted in the Department of Pharmacology in collaboration with Department of Surgery, Government Medical College (GMC), Jammu for period of 1 year from November 2019 onwards. The study protocol was approved by the Institutional Ethics Committee, Government Medical College, Jammu, vide no. IEC/GMC/2021/402 dated 25-1-2021. A written, informed consent was obtained from all the participants who satisfied required inclusion and exclusion criteria before inclusion in the study. Patients were explained about procedure and purpose of the study in the vernacular language. Patients with USG documented gallstones scheduled for elective Laparoscopic Cholecystectomy were included in the study.

Inclusion Criteria: ASA Score, patients of either sex, age between 18 to 55 years, patients with USG, documented gallstones scheduled for elective Laparoscopic Cholecystectomy, patients with no ADR to any of the studied drug, patients undergoing clean elective surgery.

Exclusion Criteria: Patients 55years and who did not give Informed Consent, on retroviral drugs, with Cancer, using Cortisone or other Immuno-suppressants, H/O ADR to cephalosporin or beta-lactam antibiotics, with co-morbidity like (HT,DM ,Bronchial Asthma, Bleeding Disorder, etc), patients, who were on Antibiotics within 7 days preoperatively, ASA score>2, documented Fever 100°F within one week of planned surgery and Leukocytosis>15,000/mm^3, acute Cholecystitis, obstructive jaundice, cholangitis, previous biliary tract surgery, ongoing infection confirmed within 7 days prior to surgery. Treatment Allocation: The eligible patients were randomly allocated into one of the following two groups after randomization block permutation method i.e. pharmacologically equivalent dose range of the two following drugs as follows:

GROUP 1: I/V single dose ceftriaxone 1g, 30 minutes prior to the incision followed by BD 1g for 2 days post-operatively

GROUP 2: I/V single dose cefuroxime 1.5g, 30minutes prior to the incision followed by 1g BD for 2 days post-operatively

Prior to the intervention, a detailed clinical history, physical examination and baseline investigations was carried out. All the patients were given the respective single dose intravenous antibiotics 30 minutes prior to the incision. Follow up was done at day 0, 24hours, day 7 and at 4th week following the surgery.

Primary end points: To compare the overall incidence of surgical site infection between two groups for first 0 hour, 24 hours, day 7 and week 4 of the surgery. - CDC classification for Superficial, deep, organ/space incisional surgical site infection.-ASA scale -WHO QOL Scale o Grade of fever, port-site redness/tenderness, wound gape, wound discharge, wound abscess. o Hospital stay due to SSI

Secondary end points:

-Rescue treatment with antimicrobials therapeutically required, if patient develops any sign of surgical site infection.

-Any adverse drug reaction.

-Monitoring vitals like temperature, blood pressure, heart rate.

Efficacy assessment:

ASA score [4]

CDC classification [5]

WHOQOL-BREF scale [6]

Patients in both the groups were observed for the occurrence of adverse drug reaction at study period. ADRs will be recorded on the adverse drug reaction form provided by Pharmacovigilance Programme of India (PVPI) (Naranjo Scale). Results in both treatment arms were analysed and compared.

Further, to meet primary end points, the rate and type of surgical site infections were compared in (n%) between the two groups during the study period. To have an access of the same, the patients between the two groups were

Table 1. Rate of SSI as per CDC classification: Comparison between the Ceftriaxone (Group-I) and Cefuroxime(Group-II)

	Wound infection, n(%)	No wound infection, n(%)	p-valu
Ceftriaxone group	4(13.3%)	26(86.6%)	1.000
Cefuroxime group	4(13.3%)	26(86.6%)	(NS)

The data is shown as percentage (n%). Chi square was applied and values between the two groups on day 7 were compared and was found to be non-significant.

Table 2. Type of SSI as per CDC classification: Comparison between the Ceftriaxone and Cefuroxime Group

Group	Superficial SSI (n/%)	Deep SSI (n/%)
Ceftriaxone (Group-I)	3 (10%)	1 (3.3%)
Cefuroxime (Group-II)	4 (13.3%)	0%
	NS	NS

The data is shown as percentage (n%). Chi square was applied and values between the two groups on day 7 were compared and was found to be non-significant.

Table 3. Comparison of ASA scores between the two groups

	Ceftriaxone (group-I)	Cefuroxime (group-II)	P value	
ASA GRADING (n%) Score I-day 0	19(63.3%)	19(63.3%)	1.000	NS
Score I-week 4	19(63.3%)	19(63.3%)	1.000	NS
ASA GRADING (n%) Score II-day 0	11(36.6%)	11(36.6%)	1.000	NS
Score II-week 4	11(36.6%)	11(36.6%)	1.000	NS

The data is shown as percentage (n%).Chi square was applied and value on day 0 and week 4 between the two groups were compared and was found to be non significant.

Table 4. Comparison of mean 'overall QoL' score of Ceftriaxone Vs Cefuroxime group in WHOQOL-BREF scale

	CEFTRIAXONE (Group-I) (Mean ± SEM)	CEFUROXIME (Group-II) (Mean ± SEM)	P value
WHO QOL 0 Day	64.83 ± 1.564	64.07 ± 1.520	0.7265]
WHO QOL 4 Week	61.99 ± 1.896	61.09 ± 1.754	0.7287]

The data is shown as Mean±SD showing paired t test in comparison to respective 0 day p<0.05 NS(not significant). Comparison between the groups at 0 day and week 4 using unpaired students t test which were non significant throughout the study. P-value <0.05 non significant.

Table 5. Features of SSI on follow up

	Ceftriaxone n (%)			Cefuroxime n (%)			
	24 hour	Day 7	Week 4	24hours	Day 7	Week 4	
Fever	0%	4(13.3%)	0%	0%	4(13.3%)	0%	NS
Port-site redness/tenderness	0%	4(13.3%)	0%	0%	4(13.3%)	0%	NS
Wound discharge	0%	4(13.3%)	0%	0%	3(10%)	0%	NS
Wound gape	0%	1(3.3%)	0%	0%	0%	0%	NS
Wound abscess	0	1(3.3%)	0	0	0	0	NS

(n%).Chi square was NS

Table 6. Patients using Rescue Treatment In Ceftriaxone and Cefuroxime treatment groups

		N (%)	Rescue Treatment
Ceftriaxone (Group-I)	Superficial SSI	3 (10%)	IV Linezolid +cefepime
	Deep SSI	1 (3.3%)	IV Vancomycin + Amikacin
Cefuroxime (Group-II)	Superficial SSI	4 (13.3%)	IV Linezolid +cefepime
	Deep SSI 0		Not required

followed at 24 hours, 7 days and 4 weeks. However, for the convenience of the presentation of data, the rate and type of surgical site infections were compared between two groups and picked up at any point of time.

The ASA grading was done and was compared as (n %) at 0 day and 4 weeks and compared between the two arms.

WHOQOL scale was taken at 0 day and 4 week and was compared as total WHOQOL-BREF score as Mean ± SEM score between the two treatment arms. The Grade of Fever, Port-site Redness/Tenderness, wound discharge, wound gape and wound abscess incidence were also compared in (n %) between the two treatment arms as and when picked up during the study period. The Hospital stay in days was again computed for the patients requiring hospital developing deep surgical site infections between the two groups and same was compared between the two treatment arms.

To meet secondary end points, the rescue treatment decided by the team of surgeons as per the available hospital Antibiogram will be in the form of Inj. Linezolid + Inj Cefepime for superficial surgical site infection and Inj. Vancomycin + Inj. Amikacin for deep surgical site infection. The requirement rate (n %) of the rescue treatment was compared between the two treatment arms. Vitals in the form of blood pressure, temperature and heart rate of patient were assessed at day 0, 24 hours, 7th day and week 4 and were compared between the two treatment arms.

Statistical Analysis:

The analysis shall be done on an intention-to-treat basis. Data shall be recorded as n (%) or mean ± SD. Continuous variable (normal distribution) shall be compared within the group by paired t test and between groups by unpaired t test. Categorical variables shall be reported as percentage and statistical analysis shall be done by using chi-square test. P-value in accordance to Bonferroni correction shall be used to assess level of significance and p-value <0.05 shall be considered significant.

Results

Baseline demographic details of all patients in both the groups were comparable. In terms of the baseline investigations, there was no significant difference between the two groups, thereby proving null hypothesis. The baseline vitals were within normal limits and there was no significant intergroup variation.

As per CDC classification of wound infection, the rate of SSI within both the groups i.e, Ceftriaxone group (group-I) and Cefuroxime (Group-II) was not found to be varying from each other. It was also found that the type of SSI in both the groups did not show any statistical variation among each other thereby failing to prove superiority of any of the treatment group over each other. 7(11.6%) patients with superficial SSI in both the groups developed features like fever, port-site redness and tenderness and wound discharge and 1(1.6%) patient in cefuroxime group (Group-II) who developed deep SSI had additional features like wound gape and wound abscess. On 4th week, we noticed no change from the baseline status of day 0 ASA scores between both the groups.(*Table-1, 2*)

On the 4th week of follow-up, we re-evaluated the patients according to ASA. We noticed no change from the baseline status of day 0 ASA scores.(*Table-3*)

While comparing both the groups on various domains of WHOQOL-BREF.i.e, Physical health, Psychological health, Social well-being and environmental, both the drugs failed to prove statistical superiority over each other. Similarly, no statistically significant difference was assessed on overall QOL between the two groups with regard to WHOQOL-BREF. (*Table-4*)

Features of SSI: Additional features of SSI were noted in each patient at each follow up. Temperature was charted, local wound was examined for redness, local warmth, presence of discharge, gaping of surgical wound and presesnce of wound abcess. The following table demostrates the findings in each group.(*Table-5*)

Rescue Treatment: 1(1.6%) patients with deep surgical site infection was hospitalised for 5 days while other 7(11.6%) patients who developed superficial surgical site infection were managed conservatively at home. 7(11.6%) patients who developed superficial surgucal site infection were treated with Inj Linezolid+ Inj cefepime and 1(1.6%) patient who developed deep surgical site infection was treated with inj Vancomycin+ Inj Amikacin. No statistical significant difference was seen 8(13.3%) patients requiring rescue treatment in both the arms, failing to prove their superiority over each other on intergroup comparison.(*Table-6*)

Adverse Drug events in Ceftriaxone (Group-I) and Cefuroxime (Group-II) group:

In both the groups commonest adverse drug event reported was thrombophlebitis followed by nausea, vomiting and epigastic discomfort. While comparing Adverse drug events between the two groups (Group-I & Group-II), all the ADEs were mild and non-serious which did not warranted any hospitalisation or medication and were reported to ADRM centre PVPi. While excluding the casuality assessment of these ADEs, all were (possible) as per WHO casuality assessment scale. Vitals such as blood pressure, heart Rate and temperature showed no clinical as well as statistical variation, thereby establishing relative safety of both these groups comparatively.

Discussion

The results of the current study thus clearly revealed comparable efficacy and safety of both the drugs and failing to prove any superiority over each other. The results are in agreement with various studies [7-10] which suggested that a single dose of ceftriaxone given intravenously was as effective as 2 doses of cefuroxime for prophylaxis of wound infection in patients of high risk biliary surgery. These studies suggested only 0.9% and 1.9% rate of intra-abdominal abscess and septicaemia in both the groups respectively.

Contrary to the result of the current study, a meta-analysis by Woodfield JC *et al* [11] making various randomized controlled trials between 1993 to 2005 reported and confirmed that prophylactic ceftriaxone is more effective than second and third generation cephalosporins and penicillins in preventing surgical site infections in the abdominal, Gastrointestinal and pelvic surgical procedures. Further, result of the current study are also contrary to the result of Al-Qahani HH [12] wherein he proposed that there is no added advantage of adding antimicrobial prophylaxis in the form of cefuroxime over not at all giving any preventive antimicrobial prophylaxis.

The possible reasons for the contrary results might be due to variation in socio-demographic profile of participants and varied study design, variation and number of patients included in the study and particularly most of the studied origin from western world.

Similarly, few other studies [13-16] suggested unlike the results of our study that there is no significant benefit of addition of prophylactic antibiotic in preventing surgical site infections over giving any preventive anti-microbial drugs.

Their were few studies in which results proposed equal efficacy of single dose with multiple dose. [17-23]. Whereas, in the current study we evaluated multiple dose of ceftriaxone and cefuroxime.

The current study failed to establish superiority of ceftriaxone over cefuroxime in preventing surgical site infection thereby clearly suggesting that there is no added advantage of using third generation antimicrobials with regard to any of the parameters studied in the current study.

Further, in light of huge problem of antimicrobial resistance across the globe, the results of the current study thus also warrant and cautions the utility of higher generation antimicrobials particularly when there is a huge risk of antimicrobial resistance.

There were few limitations in the current study that number of subjects enrolled in the study were less amid covid-19 pandemic, the study period was extended for 3 months as per guidelines of NMC. Thus, study had a break period of nearly 2 months amid covid peak due to suspension of routine surgeries. Duration of study was shorter, the Antibiogram could not be framed in the current

study and the choice of the rescue treatment was not based on culture and sensitivity patterns.

Conclusion

The current study revealed comparable efficacy and safety of single dose 30 minutes prior to the incision and followed by twice daily of inj. Ceftriaxone as well as inj. Cefuroxime after surgery for two days in preventing surgical site infection in patients undergoing laparoscopic cholecystectomy. Thereby, failing to establish superiority of one over other. The results of current study thus cautions the use of third generation antimicrobials over second generation cephalosporins in preventing surgical site infection

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Conflicts of Interest

There are no conflicts of interest.

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