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Review Article

Clinical Efficacy and Safety of Ceftriaxone in Surgical Prophylaxis: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Adequate antimicrobial monitoring helps identify the changing pattern of infection prevention postoperatively. The review aims at assessing the efficacy and safety of prophylactic ceftriaxone in surgical site infection. **Materials and Methods:** The review followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. A systematic search was conducted in PubMed, EMBASE, and CINAHL databases. Randomized control trials, published till December 2022 in English, studying only preoperative ceftriaxone, and focusing on general surgical procedures were included. Meta-analysis was done using review manager software. **Results:** Of the 2961 articles, nine were included in the review. Elevated gram-positive (33%) and gram-negative (67%) isolates were observed from the surgical site post-prophylaxis. Surgical site infection was developed in 53 (3.41%) patients in the ceftriaxone group and 108 (6.9%) patients in the comparator groups [OR 0.47 (95% CI: 0.33-0.65), $p<0.0001$]. Adverse events were assessed in six studies, from which 111 (21.4%) and 163 (31.2%) patients in the intervention and comparator groups developed the same [RR: 0.56 (95% CI: 0.31-1.01), $p=0.06$]. An overall estimate of [MD: -1.12 (95%CI: -1.36 to -0.89), $p<0.00001$)] was obtained on assessing hospital stays in the included articles. **Conclusion:** The evidence generated identified various microbial isolates from the infected sites. The drug assured its efficacy profile in surgical prophylaxis. More studies in general surgery can give a better conclusion about ceftriaxone prophylaxis.

Keywords: Ceftriaxone, Prophylaxis, Surgical Site Infection.

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INTRODUCTION

The worldwide use of antibiotics needs to change urgently. Antibiotic resistance will pose a serious concern if the same practice continues, though new medications have been developed.[1] This can give a clear picture of each antibiotic towards their indications, thus reducing the irrationality in prescribing and usage.[2] A surgical site is where various microorganisms colonise.[3-5] Antibiotic administration in less than an hour prior can reduce the incidence of complications after surgery.[6] The utility of antimicrobials as prophylaxis in surgical complications is well recognised.[7,8] Healthcare providers' experience and infection prevention training make the practice of rationality in antimicrobial use effective.[9] The choice of antimicrobial prophylaxis should ensure its appropriateness considering suitable drug selection, type of surgery, and microbial isolates prone to cause infection. The antibiotics must be preferred based on their existing evidence on effectiveness, pharmacokinetics/pharmacodynamics, easiness of dosing, and Adverse Events (AE). Surgical Site Infections (SSI) occur due to the absence of preoperative administration of antibiotics in 2%-4% of patients before surgeries.[10,11] Antimicrobial therapy reduces hospital stay days compared to treatments without antimicrobial use, especially preoperatively.[12] Being a nosocomial infection, SSI causes a greater incidence of morbidity and mortality.[13,14]

The unrestricted use of cephalosporins, the broad-spectrum antibiotics, has given way to bacterial resistance due to the emergence of extended-spectrum β-lactamases.[15] Potz *et al.* in 2006 detailed the most frequent mechanism of ceftriaxone resistance in hospital and community settings as CTX-M type extended-spectrum beta-lactamase.[16] Ceftriaxone, a third-generation cephalosporin, is a prophylactic agent attributed to its broad antimicrobial spectrum and bioavailability, with the 2 g twice daily dosing strategy. Its primary utility lines around 55.1% as a therapeutic and a prophylactic drug. Ceftriaxone is used commonly in surgical prophylaxis, accounting for 33.3% as

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monotherapy and 45.4% with other antibiotics.[17,18] It is known to be sensitive towards most isolates, mainly gram-negative organisms, thus effectively administered in surgical prophylaxis.[4] Ceftriaxone is a long-acting drug rapidly absorbed through the intravenous route.[19] On comparing the pharmacokinetics and pharmacodynamics of various ceftriaxone regimens, the estimated 24 hr. serum concentration was 9.1-169.3 mg/L, below the Minimal Inhibitory Concentration (MIC) for the majority of microbial isolates derived from the infected site.[20]

Ceftriaxone is used alone for clean-contaminated surgeries and with metronidazole for contaminated surgeries.[21] Although cephalosporin uses even in known penicillin-allergic patients is well recognised, ceftriaxone has safety consensus related to its chances of causing eosinophilia, nephropathy-associated death, anaphylaxis, and Clostridium difficile infection within 90 days of administration.[22] Thus, it is necessary to study prophylaxis with antibiotics, especially those used extensively and have higher chances of developing microbial resistance. The current systematic review aimed to assess the efficacy and safety of the prophylactic use of ceftriaxone in general surgery.

MATERIALS AND METHODS

Search strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline (http://www.prisma-statement.org/) was followed for the review. Electronic databases like PubMed, EMBASE, and CINHAL using keywords such as, "ceftriaxone", "preoperative", "perioperative", "prophylaxis", "chemoprophylaxis", "preventive treatment", "surgical site infection", "surgical wound infection", "postoperative wound infection" was used for the systematic search. Boolean operators such as "AND", "OR", "NOT" were used to combine the keywords.

Inclusion and exclusion criteria

All open, single, or double-blinded randomised control trials, published till December 2022 in the English language, were included. The studies assessing preoperative or perioperative ceftriaxone prescribed as the only antibiotic were considered. Articles with the pediatric population were excluded. Studies in which additional antibiotics were given preoperatively with ceftriaxone, postoperative ceftriaxone therapy either started postoperatively or continued from the preoperative till the postoperative periods were excluded.

Data extraction

The process was carried out independently using a pre-designed Excel sheet. A third reviewer settled the discrepancies raised. The SSI and AE that occurred, including infections at other body parts after the procedures and hospital stay, were our primary outcome of interest. The microbial culture report analysis was our secondary outcome of interest. Risk factor analysis, including common surgeries carried out with the duration of surgeries in each intervention arm, is the secondary outcome of interest. The demography of the study participants from the individual studies was also considered. The included studies were assessed for the risk of bias by Cochrane risk of bias tool.[23] It involved assessing the overall risk of bias for each of the included studies and the given information based on the five domains: selection bias, reporting bias, performance bias, attrition bias, and detection bias. The judgments were classified as high, low, or unclear risk. The assessment was carried out independently by two reviewers. A third reviewer was consulted in case of any variations in the decisions.

Statistical Analysis

The frequencies of microbial isolates from the infected surgical sites were tabulated in an Excel sheet separately for ceftriaxone and comparator groups. A doughnut chart was plotted, and an account of microbial isolate trends was provided comparatively.

Common surgeries carried out at each study arm were descriptively defined. The average duration of surgeries and analysis of total hospital stay days were statistically computed. The frequency of the SSI and AEs were compared, and the differences were stated as Odds Ratio (OR) or Relative Risk (RR), based on the Mantel Haenszel test with a 95% confidence interval (CI). OR>1 and RR>1 indicated that the chances of the condition were more likely to be achieved in the intervention group. A narrow range of 95% CI, not passing through the line of no effect, showed the intervention to be statistically significant. The I^2 test was used to test for heterogeneity across the studies. The fixed-effect model was considered as I^2 was less than 50%, and the study was more towards homogeneity. The overall effect was considered significant if $p < 0.05$.[24] Review manager was used for the meta-analysis. [RevMan Computer program version 5.4. The Cochrane Collaboration, 2020].

RESULTS

The database search yielded 2961 articles, following which the duplicates were removed to obtain 2893 articles. The first pass screening based the title and abstracts, where some articles were excluded due to study design, disease conditions, and irrelevant exclusion criteria. The articles included after the pre-screening were subjected to full-text screening, where articles were excluded based on intervention and outcomes. Only nine articles fulfilling the inclusion criteria were retrieved.[25-33] The article retrieval process based on PRISMA is presented in Figure 1.

Study characteristics

The included articles had 3081 patients, with 1537 patients ranging from 49.3 to 57.5 years and 1544 patients from 50.2 to 60.3 years in the intervention and the comparator group, respectively. The

studies were conducted globally, including in Germany, Libya, Italy, New Zealand, England, and Iran. Among the nine included studies, one was a multicentre, open-labelled study, three were single-centred, double-blinded trials, and one was a brief report explaining a randomised open-labelled single-centred study. The sites of surgeries were the abdominal regions of the body, particularly the colon, rectum, and gallbladder, as well as the breast. All the studies included chose an intravenous administration route except for one with topical povidone-iodine in the comparator arm.[29] A single dose of ceftriaxone therapy was provided to all the patients in the intervention group. One study did not receive a prophylactic antibiotic in the control group.[32] Two studies compared ceftriaxone therapy against 10 mL intravenous sodium chloride and placebo, respectively.[25,31] The remaining five studies compared ceftriaxone therapy to IV cefoxitin, IV ceftazidime, IV clavulanic acid /amoxicillin, IV ciprofloxacin and IV cefepime.[27-30,32] Ceftriaxone was given in 1 g and 2 g doses in three[26,28,31] and six studies[25-28,32,33] each SSI, risk factor analysis of SSI and AEs occurring after the procedures were the primary outcomes of interest. The data extraction criteria for SSIs were diagnosis of infection, sub-hepatic fluid wound discharge, or clinical failure. AEs were analysed in six of the included studies.[26-29,33] The microbial culture and the hospital stay days were analysed in four studies.[28,29,31,32]

The surgical procedures like mastectomy (intervention group: 57.4%, control group: 57.2%), gastrectomy (0.52%, 0.71%), gastroenterology (0.06%, 0.19%), whipple procedure (0.07%, 0%), vagotomy (0.7%, 0.19%), biliary tract surgery (39%, 39%)

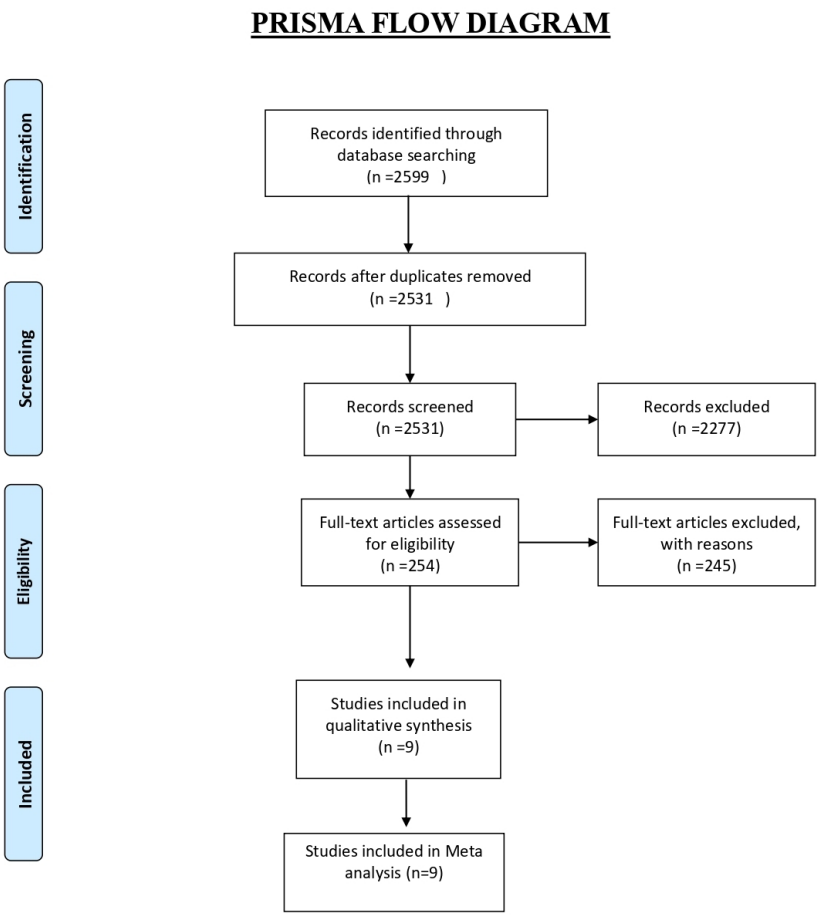

Figure 1: PRISMA flow chart.

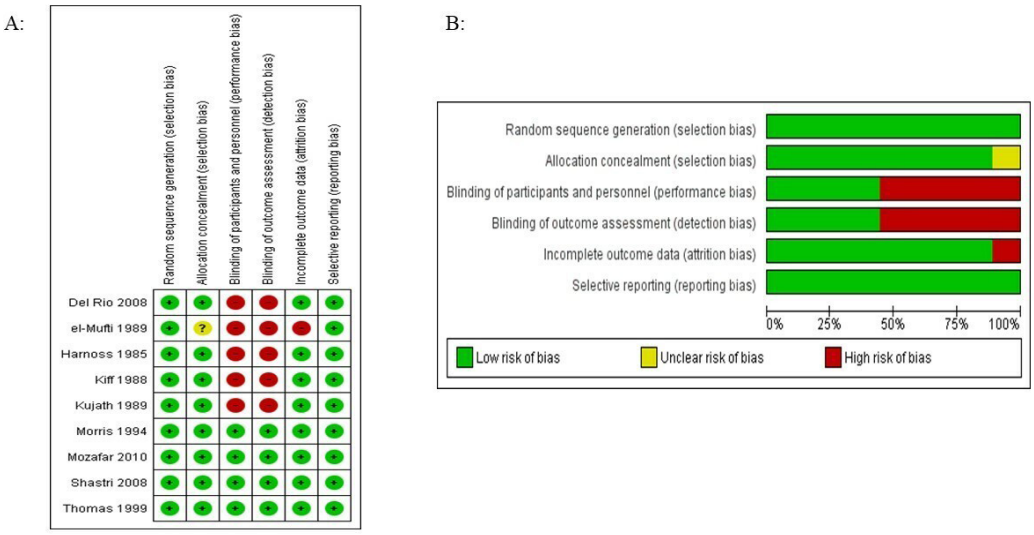

Figure 2: A: Risk of bias summary; B: Risk of bias graph.

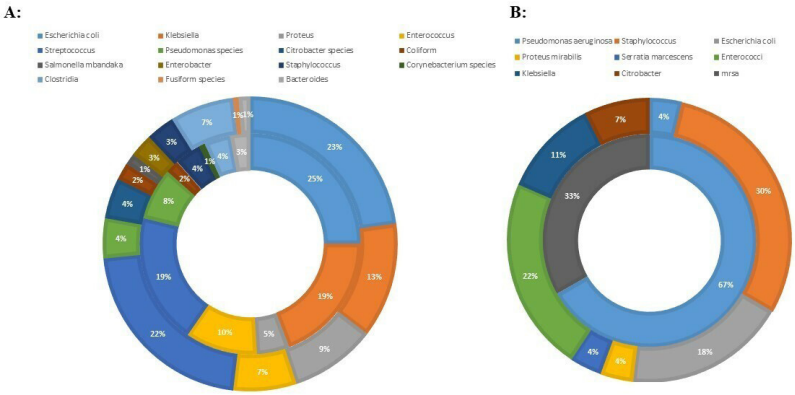

Figure 3: Assessment of microbial culture A: Bacterial population (preoperative); B: Bacterial population (Infected state postoperatively).

and gastropexy (3.2%, 3.1%) were carried out in the included studies. The average surgery duration was estimated to be 83.39 min in the intervention group and 86.57 min in the comparator group. A detailed description of the included studies is given as a supplementary file.

Risk of Bias

On an overall judgment of the nine included studies, using the Cochrane risk of bias tool, five were judged to have a high risk of bias[26,27,29,30,33] and four were considered to have a low risk of bias.[28,31-33] Assessment of studies under various domains showed that all the included studies were under allocation concealment and selective reporting. Many studies under allocation concealment and incomplete outcome data showed a low risk of bias. An unclear risk was judged in the case of allocation concealment in one of the studies.[29] High risk was only assessed under blinding of participants and personnel, blinding of outcome assessment and incomplete outcome data among the included studies.[26,27,29,30,33] Figure 2 shows the risk of bias and quality assessment of individual studies.

Assessment of microbial culture

The pattern of microbial isolates from the included studies is shown in Figure 3. The graphs represented the microbial isolates from the operation site before surgery[26,27,29] and after the diagnosis of SSI[28,31-33] for both groups.

In the preoperative microbial population analysis, gram-negative isolates (63%) consisted of *Escherichia coli, Klebsiella, Proteus, Pseudomonas* species, *Citrobacter* species, *Coliform* species, *Salmonella mbandaka, Enterobacter* and *Bacteroides*; gram-positive (38%) included *Enterococcus, Streptococcus, Staphylococcus, Corynebacterium* species, *clostridia*, and *Fusiform* species. The predominant isolates were *Escherichia coli, Klebsiella,* and *Streptococcus* from the ceftriaxone-treated and comparator groups.

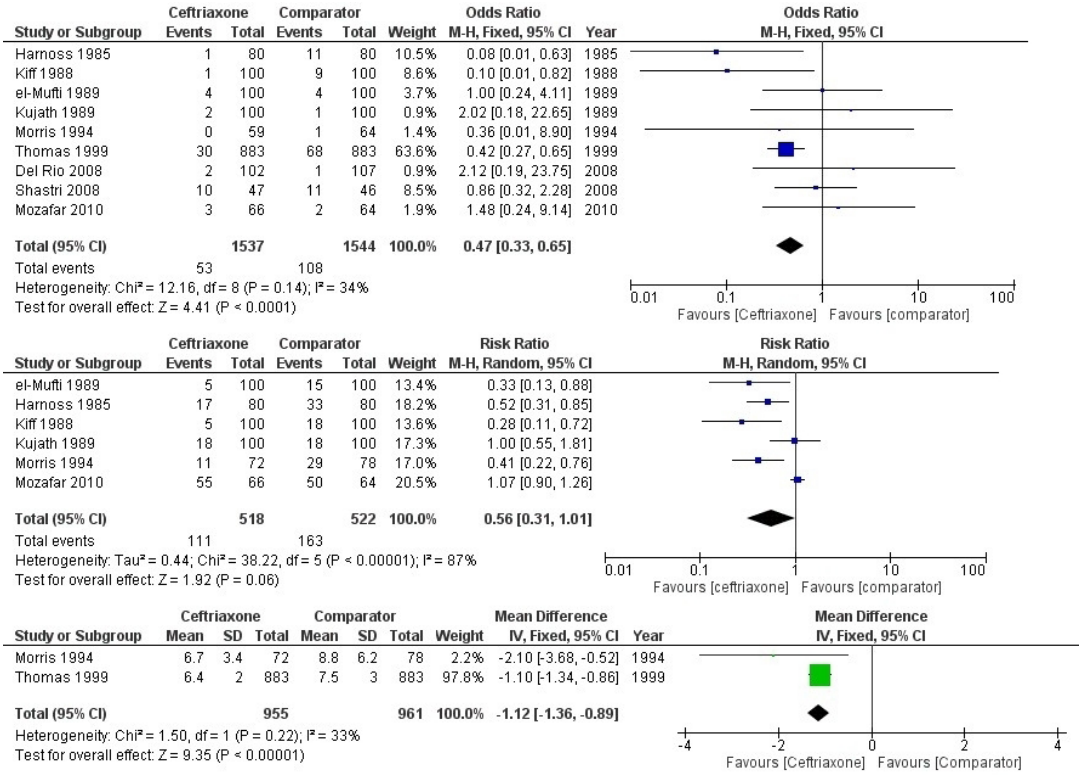

Figure 4: A: Surgical site infection; B: Adverse event; C: Hospital stays.

Both gram-positive and gram-negative isolates were observed on microbial isolate analysis from the infected sites. These consisted of 67% gram-negative isolates, i.e., *Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Serratia marcescens, Klebsiella*, and *Citrobacter* and 33% gram-negative isolates, i.e., *Enterococci* and *Staphylococcus* species including Multi-drug Resistant *Staphylococcus aureus* (MRSA).

Assessment of SSI

All nine studies assessed SSI postoperatively. Among these, 53 (3.41%) in the ceftriaxone group and 108 (6.9%) patients in the comparator group developed SSI. The summary estimates [OR 0.47 (95% CI: 0.33-0.65), $p<0.0001$] showed that it was less likely for SSI to occur in the ceftriaxone prophylaxis group compared to the standard of care. The range of 95% CI, passing through the line of no effect and the p-value, indicated that the overall impact was significant. As $I^2=34\%$, the fixed effect model was selected. The results are presented as a forest plot in Figure 4 A.

Adverse events

Fever and chest infections were diagnosed in 1.04% and 3.17% of patients in the intervention group and 3.18% and 3.10% in the control group. Other AEs reported were intra-abdominal sepsis, urinary tract infection, septicaemia, intra-abdominal collection, infected bile, intraoperative rupture of the gallbladder, and spillage of bile/gallstone.

AEs were reported in 111 (21.4%) and 163 (31.2%) patients in the ceftriaxone and comparator, respectively. The summary estimates were [RR: 0.56 (95% CI: 0.31-1.01), $p=0.06$], showing that the AEs occurred in the comparator group more than in the ceftriaxone group. The test of heterogeneity showed that the intervention was significant. As $I^2=87\%$, the random effect model was selected for the analysis. The forest plot for AE is presented in Figure 4B.

Hospital stay

Hospital stay was reported for both groups in four studies. Still, due to insufficient data to calculate standard deviation, only two studies were considered for analysing the length of hospital stay difference between the intervention and the comparator groups. Intervention and control groups included 955 patients and 961 patients, respectively. The summary estimate was [MD: -1.12 (95% CI: -1.36 to -0.89), $p<0.00001$)], showing that the length of hospital stay was longer in the control group than in the ceftriaxone group. The test of heterogeneity claimed the significance of the outcome. As the $I^2=34\%$, the fixed effect model was selected for the analysis. The forest plot for the hospital stay is presented in Figure 4C.

DISCUSSION

Antibiotic prophylaxis preoperatively, is administering antibiotics before surgery to decrease the risk of postoperative infections. The timing of antibiotic administration may vary, but the goal

is to attain the highest concentration in the tissues at the start and during the surgery.[34-37] Antimicrobial agents have a positive effect, regardless of the procedure.[38] In surgery departments, the non-identifiable reason for the antibiotic administration, increased hospital stays, and days of cumulative antibiotic therapy leading to the antibiotic prescription being in non-accordance with local policy guidelines.[39] Ayele *et al.* 2018 assessed the preoperative antibiotic utilisation patterns in East Ethiopia, where all surgical procedures use ceftriaxone or metronidazole alone or in combination.[40] A comparative study of ceftriaxone alone and in combination with sulbactam studied the postoperative infections, morbidity, mortality and cost of therapy arising due to surgery. The study concluded no differences between the groups.[41] According to Rahman *et al.*, 2016 a single dose of ceftriaxone given preoperatively was found to be as effective as the same, followed by an injection of ceftriaxone for two days followed by oral cefixime for five days in wound infections.[42] Our meta-analysis showed no statistically significant efficacy and safety in ceftriaxone therapy compared to the preoperative comparators.

Ceftriaxone, having the best gram-negative microbial coverage, also shows a resistance trend towards them. This was confirmed in a cross-sectional study of 248 bacterial isolates resistant to ceftriaxone 140 (56.5%), including 33% *Escherichia coli*, 8% *Citrobacter freundii*, 9% *Klebsiella pneumonia*, 8% *Staphylococcus aureus* and *Enterobacteriaceae*. The study showed the drug was resistant to 47% of the gram-negative bacteria isolates from the wound swab.[4] A hospital-based cross-section study showed *Escherichia coli* (19.2%), *Acinetobacter* spp. (17.3%), *Klebsiella pneumoniae* (9.6%), *Klebsiella ozaenae* (2.8%), *Pseudomonas aeruginosa* (4.8%), *Pseudomonas vulgaris* (0.9%) were resistant towards ceftriaxone (Esposito *et al.*, 2004).[43] In a prospective cohort study, ceftriaxone resisted *Escherichia coli* (100%) and *Klebsiella species* (11.1%). At the same time, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were the organisms that were sensitive to the drug. The drug was resistant to 3 (19%) of gram-negative bacteria isolates tested in the study.[3] The current review showed a trend of isolates like *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Proteus mirabilis, Serratia marcescens, Klebsiella, Citrobacter, Staphylococcus, Enterococci* and MRSA from patients treated with ceftriaxone, preoperatively. The study showed a trend of increased gram-negative bacteria isolates of 67% from the infected sites.

Ceftriaxone was known to have efficacy towards elective and emergency surgical procedures with a p-value<0.05. This was studied in other meta-analyses by taking the entire surgery specialities. A study taking 43 open or blinded randomised studies, published between 1986 and 1996, with 13,482 patients, was conducted to show that ceftriaxone was efficacious to other cephalosporins in postoperative SSI prevention [RR: 0.70 (95% CI: 0.55-0.89); p=0.0002].[43] Esposito *et al.*, 2004 conducted a meta-analysis taking 48 open, single, or double-blinded randomised controlled trials in elective surgeries. The articles were published from 1984 to 2003, with a total of 17,565 patients showing ceftriaxone superiority to other anti-bacterial drugs in SSI prevention, postoperatively [log OR: -0.30 (95% CI: -0.50 - -0.13); p<0.0001].[42] A meta-analysis of 64 randomised clinical trials published between 1983 and 2005 with a total of 22,888 patients showed the efficacy of ceftriaxone over the other prophylactic antibiotics [OR: 0.68; (95% CI: 0.53- 0.7), p<0.001].[44]

A subgroup analysis showed that in abdominal surgeries such as upper gastrointestinal surgery, biliary surgery, and colorectal surgery, the ceftriaxone effect in SSI prevention was significant [OR: 0.68; (95% CI: 0.51-0.84); p<0.001].[44] The published meta-analysis showed that ceftriaxone is effective towards SSI prevention. The current meta-analysis included general surgical procedures like mastectomy, gastrectomy, gastroenterostomy, whipple's procedure, vagotomy, biliary tract surgery and gastropexy, in which the efficacy of ceftriaxone was assessed and found to be effective in SSI prevention.

Allergic events, toxicities, end-organ damage, and *Clostridium difficile* infections were the most common AEs caused due to the unrestricted use of antibiotics.[45] Ceftriaxone caused 33.8% of cases of isolated eosinophilia and 50.8% of nephropathy-associated death, as the patients were given the drug within 30 days of the incident. 29.4% of cases have shown parenteral use of the drug before surgeries to be effective, and it can also lead to a higher incidence of *Clostridium difficile* infection.[46] It was stated in a meta-analysis that, in both ceftriaxone and the comparator, AEs were observed in an almost similar pattern, representing 0.35% and 0.23%, respectively, which included anaphylactoid reactions (n=1), *Candida* spp. infection (n=1), *Clostridium difficile* (n=3), diarrhoea (n=3), temporary itching (n=1), rash (n=3), phlebitis (n=3), pseudomembranous colitis (n=1), urticaria (n=1), temporary cutaneous rash (n=1), and transaminase minimal elevation (n=13).[44] The present meta-analysis for safety parameters on ceftriaxone showed many reported AEs like fever, chest infections, Intra-abdominal sepsis, urinary tract infection, septicemia, intra-abdominal collection, Infected bile, Intraoperative rupture of the gallbladder and Spillage of bile/ gallstone due to the ceftriaxone. These were more in the control group than the ceftriaxone group and were found to be statistically significant.

Preoperative antimicrobial therapy has given an opportunity to increase patient care by reducing the length of hospital stay. In a systematic review comparing the cost-effectiveness of antimicrobial treatment preoperatively, Allen *et al.* in 2018 showed a reduction in the length of hospital stay in the antimicrobial pretreated patient group compared to the control group.[47] In a study to identify the usage pattern and predictor determination for ceftriaxone at a hospital in Kilimanjaro, Tanzania, 195 (61.9%) Patients in the ceftriaxone group had less than seven days of

hospital admission. The frequency of patients decreased with increased hospital stay days in the ceftriaxone group.[48] Our study also showed efficacy for the ceftriaxone therapy in reducing the hospital length of stay with an overall estimated mean difference of [MD: -1.12 (95% CI: -1.36 - -0.89), p<0.00001)].

According to the Cochrane risk of bias tool, most selected studies were considered high risk. The missing data could influence the studies and the results obtained. The study didn't assess the variations in ceftriaxone therapy within the intervention group, considering the different doses of the drug, as drug selection and dose selection are essential in surgical prophylaxis. Further research should focus on subgroup analysis taking incisional and organ/space SSI, which could give detailed knowledge on antibiotic efficacy in patients. Assessing the risk factors of SSI, such as patient demographics, and studying settings in which the surgery is carried out could be an exciting area to be explored.

CONCLUSION

The study showed an elevated trend in microbial isolates from the infected surgical sites from the ceftriaxone prophylaxis group. It was more effective and safer when used in SSI prevention. Setting up local guidelines on prophylactic antimicrobial use in surgery, yearly checks, and renewal of these guidelines helps in choosing the prophylactic antibiotics rationally. The inclusion criteria allowed only the least number of articles in the review. Further, real-world studies should be conducted in various healthcare settings to give a definitive conclusion about ceftriaxone prophylaxis in SSI.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AE: Adverse Events; **SSI:** Surgical Site Infections; **MIC:** Minimal Inhibitory Concentration; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analysis; **OR:** Odds Ratio; **RR:** Risk Ratio; **MD:** Mean Difference; **CI:** Confidence interval; **Vs:** Versus.

SUMMARY

Ceftriaxone is used in general surgical departments widely. The rationality in antibiotic use is essential to check the resistance emergence. Studies in the cephalosporins, which are the main prophylaxis therapies in surgeries, can restrict the spread of multidrug-resistant microorganisms.

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supplementary

Table 1: Characteristics table.

Sl. No.	Comparisons of interest				No. randomized patients analyzed		
	Test drug Vs Comparator	Study Reference	Characteristic of prophylactic therapy	Study type, Surgery	Test drug	Comparator	Outcomes Measured
1	2 g IV ceftriaxone Vs Clavulanate potentiated-amoxycillin (1200 mg, to be repeated for 2 more doses).	el-Mufti 1989	Single intravenous dose 2 hr before surgery.	Prospective randomized study, Biliary surgery	Ceftriaxone	Clavulanate potentiated-amoxycillin.	Superficial wound infection. Adverse Event Microbial culture
2	1 g IV ceftriaxone Vs topical povidone iodine.	Kiff 1988	a bolus over 5 min at the time of anaesthetic induction	Prospective randomized study, Biliary surgery	Ceftriaxone	Povidone iodine	Wound infection Adverse Event Microbial Culture
3	1 g ceftriaxone Vs 10 mL isotonic saline as placebo.	Mozafar 2010	During induction of anesthesia.	Double blind randomized control trial, Biliary surgery	Ceftriaxone	Saline (placebo)	Incisional site infection+ Subhepatic fluid. Microbial culture
4	1 g of intravenous ceftriaxone at induction of anesthesia Vs 1 g of intravenous cefoxitin at induction and two subsequent l g doses at 8 hr intervals.	Morris 1994	At induction of anesthesia.	Open labelled Randomised control trial, Upper abdominal Surgeries.	Ceftriaxone	IV cefoxicin	Wound infection Adverse event Microbial Culture Hospital stay
5	Single IV infusion of 2 g ceftriaxone Vs 2 g Cefepime.	Rio 2008	1 hr before surgery	Multicentric comparative trial, Biliary surgery	Ceftriaxone	Cefepime	Clinical failure Adverse events
6	2 g ceftriaxone injection Vs Placebo.	Shastri 2008	30 min before the procedure.	Multicenter prospective randomized double blind placebo controlled study, Gastropexy	Ceftriaxone	Placebo	Surgical Wound infection Microbial culture

Sl. No.	Comparisons of interest				No. randomized patients analyzed		
	Test drug Vs Comparator	Study Reference	Characteristic of prophylactic therapy	Study type, Surgery	Test drug	Comparator	Outcomes Measured
7	2 g IV ceftriaxone Vs 2 g IV ceftazidime	Thomas 1999	At induction of anesthesia.	Double-Blind Randomized control trial, Breast surgery	Ceftriaxone	Ceftazidime	Wound infection Microbial culture Hospital stay
8	2 g ceftriaxone dissolved in 50 mL of intravenous fluid Vs 200 mg ciprofloxacin dissolved in 50 mL of intravenous fluid	Kujath 1989	Infusion over 15 to 20 min. The administration was completed before the surgical incision was made.	Randomized study (Brief report), Biliary surgery	Ceftriaxone	Ciprofloxacin	Wound infection Adverse Events Microbial culture
9	2 g IV of ceftriaxone Vs No antibiotic	Harnoss 1985	At induction of anesthesia.	Prospective randomized study, Biliary surgery	Ceftriaxone	No antibiotic	Wound healing disorders(hematoma,seroma,abscess) Adverse Events

Table 2: Effect of test drug versus comparator on Primary outcome (SSI).

		No. patients with SSI/Total no. of patients				
Outcome measure	Studies included	Ceftriaxone	comparator	Estimate	Effect [95% CI]	I^2 % (*p* value)
SSI	Harnoss 1985 Kiff 1988 El-Mufti 1989 Kujath 1989 Morris 1994 Thomas 1999 Del Rio 2008 Shastri 2008 Mozafar 2010.	53/1537	108/1544	OR	0.47 [0.33,0.65]	I^2=34%, p<0.00001

Table 3: Effect of test drug versus comparator on Secondary outcome (AE).

		No. patients with SSI/Total no. of patients				
Outcome measure	**Studies included**	**Ceftriaxone**	**Comparator**	**Estimate**	**Effect [95% CI]**	**I^2 % (*p* value)**
AE	El-mufti 1989 Harnoss 1985 Kiff 1988 Kujath 1989 Morris 1994 Mozafar 2010.	111/518	163/522	RR	0.56 [0.31,1.01]	I^2=87%, p=0.06

Table 4: Effect of test drug versus comparator on Secondary outcome (Hospital stay).

		No. patients with SSI/Total no. of patients				
Outcome measure	**Studies included**	**Ceftriaxone**	**Comparator**	**Estimate**	**Effect [95% CI]**	**I^2 % (*p* value)**
Hospital stay	Morris 1994 Thomas 1999	955	961	MD	-1.12[-1.36, -0.89]	I^2=33% p<0.00001