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Research Article
Effect of Cefazolin Prophylaxis on Postoperative Infections for Implants Removal Surgery of Ankle

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Abstract

Background and Objective: There is not sufficient proof for the potential advantageous effect of antibiotic prophylaxis on the surgical site infection rates during removal of orthopedic implants but a high rate of the surgical site infection rates are reported for implant removal surgeries than internal fixation and/or open reduction of fractures. The objective of the study was to evaluate the effect of cefazolin prophylaxis on the surgical site infection. **Materials and Methods:** Total 298 patients with implants removal surgeries had subjected to randomize into two groups of 149 each. Patients had received bolus 1 g of cefazolin (CN group) or normal saline (NS group) before surgeries. The incidences of deep and superficial surgical site infection, health-related quality of life, functional outcome, visual analog scale, clinical and bacteriological assessments within 1 month after surgery were evaluated. Mann-Whitney test following Turkey *post hoc* tests were used for the surgical site infection at 95% of confidence level. **Results:** CN and NS groups had reported 19 (13%) and 21 (14%) superficial surgical site infection and 2 (1%) and 8 (5%) deep surgical site infection within 1 month, respectively. Both groups did not show a significant improvement in health-related quality of life, functional outcome and pain during 1 month. There were 12 (67%) microorganisms' species found sensitive and 6 (33%) found not sensitive to cefazolin in bacteriological assessments. **Conclusion:** Single dose of 1 g of cefazolin prophylaxis reduced numbers of patients with the surgical site infection.

Key words: Ankle, bacteriological assessments, cefazolin, implants removal surgery, surgical site infection

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Metal implants are preferred for internal fixation and open reduction of fractures. Implant removal after fracture fixation is controversial. There are no clear guidelines on implant removal. Some hospitals routinely remove implants electively after the fracture has healed if major complications arise, while others are not recommended implant removal and decided to keep the implants *in situ* because routine removal of implants is not justified[1]. However, if implant(s) is present in the ankle, weight-bearing activities may cause pain in the ankle. Therefore, implants removal surgery is recommended if it is in an ankle[2]. However, the surgical site infection (SI) is a most common complication for implant removal surgeries[3]. The SI rate in implant removal surgeries could be reduced by using antibiotic prophylaxis[4] but pre-operative prophylaxis using antibiotic is not recommended by current guidelines[5]. Moreover, previous studies have been revealed that intravenous antibiotic prophylaxis for surgeries of removal of orthopedic implants used for the treatment of fractures below the knee does not reduce the risk of SI rate[4, 6-8].

Postoperative infections for implants removal surgery could happen with methicillin-sensitive and/or methicillin-resistant *Staphylococcus epidermidis*[9] and the other *Staphylococcus* species[10]. These are susceptible to cefuroxime or cefazolin type of cephalosporins antibiotics[11]. Generally, first generation or the second generation cephalosporins are used for prophylaxis[12]. Moreover, there is not sufficient proof for the potential advantageous effect of antibiotic prophylaxis on SI rates during removal of orthopedic implants but a high rate of SI is reported for implant removal surgeries than internal fixation and/or open reduction of fractures. Therefore, antibiotic prophylaxis could be effective prior to implant removal surgeries to reduce SI.

The objective of the study was to evaluate the effect of single dose of 1 g of cefazolin prophylaxis on incidence of SI following implants removal surgery of ankle.

MATERIALS AND METHODS

Drugs: Cefazolin 1 g (reflin) was purchased from Ranbaxy (Guangzhou China) Limited. Normal saline was purchased from Baxter, USA.

Inclusion criteria: Patients aged 18 years and above who had admitted to the Department of Orthopedics of Dalian Municipal Central Hospital Affiliated with Dalian Medical University, Dalian and Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, Liaoning, China for removal of the implant following treatments of fractures of the ankle during 16 January, 2017-1 November, 2017 included into the trial. The characteristics of enrolled patients were reported in Table 1.

Exclusion criteria: Patients who had refused to the signed informed consent form and not follow study protocols were excluded from the final enrollment. Patients taking antibiotics treatment at the time of surgery were excluded from the study. Patients had allergic to cephalosporins, renal diseases, pregnancy and on immune suppressant treatments were also excluded from the study.

Design of the study: Maximum 3-4% of SI were reported with cefazolin prophylaxis[13], therefore, the incidence of SI was chosen to be 80% power for both groups and at a confidence level of 95%. Total, 298 patients were subjected to simple randomization. The sample size was calculated by OpenEpi 3.01-English (Open Source Epidemiologic Statistics for Public Health, USA) and was found to be 149 for each group. Randomization was performed in 1:1 ratio in both groups[4]. The CONSORT flow diagram of the study is represented in Fig. 1.

Interventions: Patients had received bolus 1 g of cefazolin[14] (CN group) or intravenous normal saline (NS group) in operation theater 44.52±8.12 min before surgery. Blinding was possible in operation theater because both group patients had received NS. Only CN group patients were received bolus antibiotic before surgery.

Primary outcome measures: The primary outcome was the incidence of SI within 1 month after implants removal surgery. SI was discriminated as deep or superficial. The superficial SI was defined as involvement of subcutaneous tissues or skin and considered incident event if purulent drainage from the incision without or with pathology confirmation, symptoms or signs of infection, heat, tenderness, pain, redness or localized swelling[4]. The deep SI was defined as involvement of deep tissues and considered incident event if a high amount of drainage from the incision, high localized pain, a temperature higher than 38°C for incision, an abscess, or infection[11]. The incidence of SI was evaluated by a physician who was blinded regarding the prophylaxis during 1 month after surgery. In superficial SI, debridement[4] had been performed with oral levofloxacin and in deep SI, debridement had been performed with oral moxifloxacin[15].

Table 1: Characteristics of enrolled patients

	CN group	NS group	Comparisons of groups	
Characteristics	n = 149	n = 149	p-value	q-value
Age (years)	44.42±7.2	44.74±7.41	0.3938	N/A
Nicotine use	8(5)	7(5)	0.32	N/A
Alcohol consumption	27(18)	25(17)	0.158	N/A
Reason for removal of ankle implant				
Pain	98(66)	93(62)	0.0077	0.836
Functional problems	42(28)	45(30)		
Implant failure	9(6)	11(8)		
Time of removal of implants (days)	330.30±9.32	331.40±9.56	0.195	N/A
Time of surgery (min)	41.44±5.5	41.56±5.2	0.82	N/A
BMI (kg m^{-2})	26.52±2.88	26.46±2.84	0.853	N/A
Type of implants				
Plates screws	65(43)	60(40)	0.826	N/A
Screws only	84(57)	89(60)		
Health-related quality of life*				
Min	0.6	0.6	0.135	N/A
Max	0.7	0.8		
Mean±SD	0.69±0.11	0.67±0.12		
Lower extremity functional scale scores¶				
Min	70	72	0.062	N/A
Max	77	77		
Mean±SD	73.3±3.26	74.2±2.29		
VAS score for pain#				
Min	5	5	0.073	N/A
Max	6	6		
Mean±SD	5.12±0.15	5.29±0.24		

BMI: Body Mass Index. Constant data were reported as number (percentage) and continuous data were reported as Mean±SD. Two-tailed paired t-test following Turkey *post hoc* tests were used for constant data and Chi-squared test following Turkey *post hoc* test were used for continuous data for statistical analysis. A $p<0.01$ and $q>4.154$ were used as significant. N/A: Not applicable. *1: Best health-related quality of life, 0: Worst health-related quality of life. ¶0: Possible worst, 100: Excellent. #0: Absent pain, 10: Possible worst pain

Secondary outcome measures: Secondary outcomes were measured at baseline (pre-operatively) and after 1 month of surgery.

Health-related quality of life: It was measured by questionnaires in the range of 0-1. A 1 was indicated as the best health-related quality of life and 0 was indicated as the worst health-related quality of life[16].

Functional outcome: The lower extremity functional scale was used to access the functional outcomes. Here questionnaires were made regarding patients daily living activities. Each item was made the score between 0 and 5, where, 0: The possible worst, 1: Poor, 2: Fair, 3: Moderate, 4: Good and 5: Excellent[17].

Visual analog scale (VAS): VAS was measured for each patient at baseline and the end of 1 month. VAS was characterized as 0: Absent pain and 10: Possibly the worst pain[18].

All questionnaires were asked in the hospital if patients were available physically. In absence of patients, the questionnaires were sent electronically. All patients were getting reminders until they did not reply (all were received maximum five reminders).

Data collection: Age, BMI (Body Mass Index) and habits (nicotine use, alcohol consumption) of patients, reasons for removal of implants, time of removal of implants, time of surgeries, conditions of SI were collected from DICOM file of the hospitals. Missing data for the lower extremity functional scale questionnaire was handled as per the guidelines of the developers of them, up to 3 items ($\leq$1 within 1 domain) within 1 questionnaire can be corrected by predefined rules[19]. In case of high numbers of missing values, multiple imputations (8 sets of data) was used (using predictive mean matching), data were subsequently prepared by the Rubin rule[20].

Clinical and bacteriological assessments: When the operation was performed the specimen taken for culture routinely. Acute wound fluid was collected from patients who had reported surficial and deep SI drainage within the first

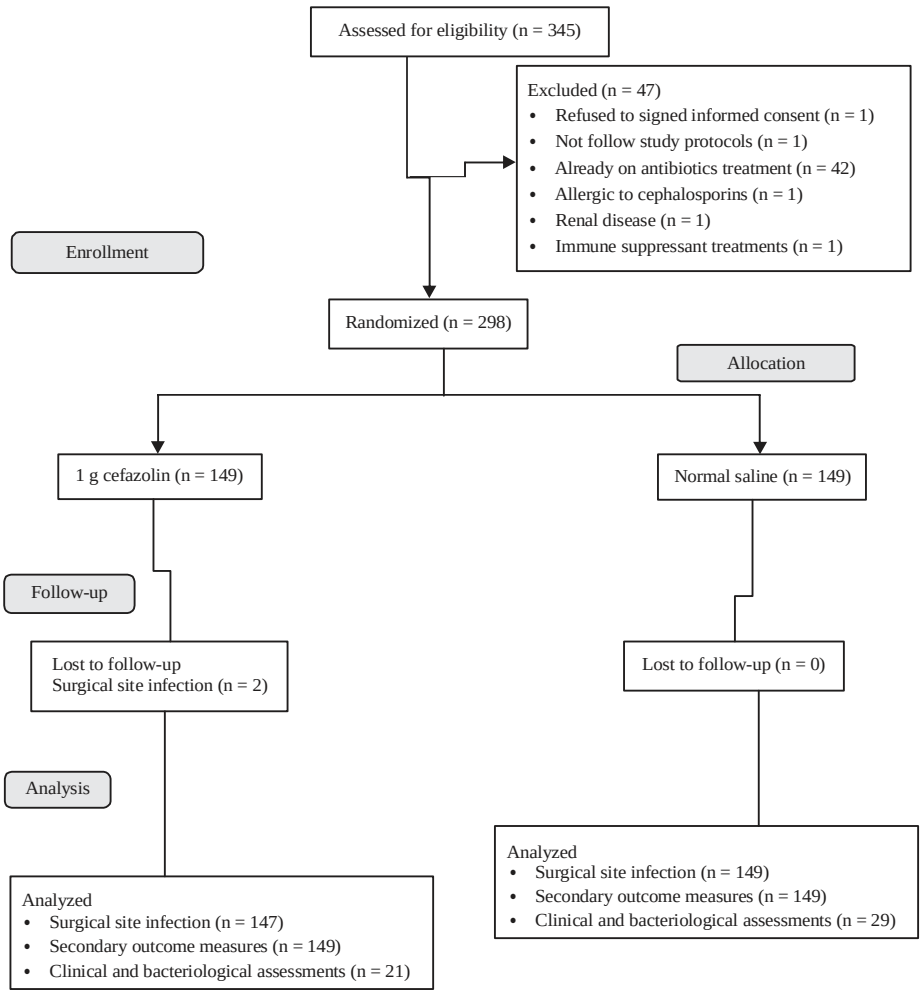

Fig. 1: CONSORT flow diagram of a randomized trial
80% power, confidence level 95%

4 h after surgery, centrifuged at 4100 rpm and 9.5°C for 16 min, filtered, the causative organisms, isolated, differentiated and tested for sensitivity to cefazolin using the agar diffusion test and Minimum Inhibitory Concentrations (MIC) was also evaluated if sensitive to cefazolin[21].

Statistical analysis: SPSS Statistic software version 24.0 (IBM, USA), was used for statistical analysis. Constant data were reported as number (percentage) and continuous data were reported as Mean±SD of all of them. Per Protocol method for analysis was used[6]. A two-tailed paired t-test or Mann-Whitney U tests following Turkey *post hoc* test was used for constant data[4]. Chi-squared test or Fisher exact tests following Turkey *post hoc* test was used for continuous data[22]. The data were considered significant at 95% of confidence level.

RESULTS

Data of two patients from CN group regarding SI had been lost. Total 50 patients reported SI within 1 month and were subjected to *in vitro* clinical and bacteriological assessments. Among them total 18 types of microorganisms were identified. There were 12 (67%) microorganisms' species found sensitive and 6 (33%) found not sensitive to cefazolin. These results showed that the double-blind clinical trial for implants removal surgery of ankle had compared a single dose of cefazolin prophylaxis with normal saline did not reduce the incidence of SI within 1 month (Table 2).

The minimum and maximum values of the lower extremity functional scale scores for SI and non-SI patients were 73 and 82 and 71 and 80, respectively at 1 month after surgery. The lower extremity functional scale scores between SI and non-SI patients was the same ($p = 0.052$, Fig. 2).

Table 2: Development of the surgical site infection in patients within 1 month

	CN group	NS group	Comparisons of groups	
Interventions	n = 147	n = 149	p-value	q-value
Superficial SI	19(13)	21(14)	0.8570	N/A
Deep SI	2(1)	8(5)	0.5270	N/A
Total SI	21(14)	29(19)	0.0043	2.059
Bacterial categories				
Sensitive to cefazolin	12(67)	12(67)	N/A	N/A
Not sensitive to cefazolin	6(33)	6(33)		

SI: Surgical site infection. Data were represented as a number (percentage). Mann-Whitney test following Turkey *post hoc* test was used for statistical analysis. A $p<0.05$ and $q>3$. 32 were used as significant. N/A: Not applicable

Table 3: Secondary outcome measures at 1 month after surgery

	CN group	NS group	SA
Parameters	n = 147	n = 149	(p-value)
Health-related quality of life*			
Min	0.6	0.6	0.075
Max	1.0	1.0	
Mean±SD	0.81±0.14	0.78±0.15	
Lower extremity functional scale scores¶			
Min	71	72	0.829
Max	80	80	
Mean±SD	76.1±4.11	76.2±3.89	
VAS score for pain#			
Min	4	4	0.389
Max	5	5	
Mean±SD	4.89±0.19	4.87±0.21	

SA: Statistical analysis between CN group and NS group. Fisher exact test was used for statistical analysis. A $p<0.05$ was considered as statistical significant. *1: Best health-related quality of life, 0: Worst health-related quality of life. ¶0: Possible worst, 100: Excellent. #0: Absent pain, 10: Possible worst pain

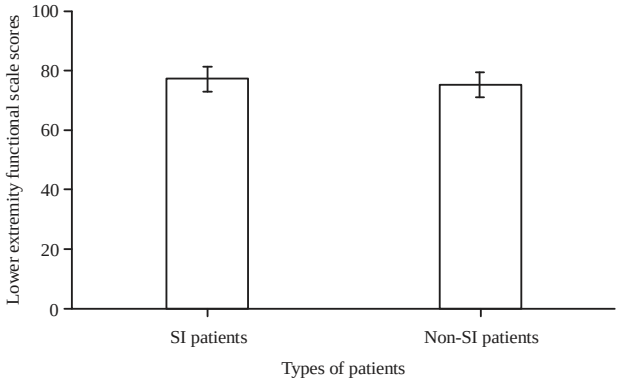

Fig. 2: Lower extremity functional scale scores and incidences of the surgical site infection (SI). 0: The possible worst, 100: Excellent. The lower extremity functional scale scores between SI and non-SI patients was the same ($p = 0.052$). The sample size for SI and non-SI patients were 50 and 246

Fisher exact test was used for statistical analysis. A $p<0.05$ was used as significant

Both groups did not show a significant improvement in health-related quality of life, functional outcome and pain during 1 month (Table 3).

DISCUSSION

The trial revealed that implant(s) removal surgery of ankle is not an easy procedure. The surgeries have a high rate of SI. Patients needed to counsel regarding that. Although a single dose of cefazolin was administered 44.52±8.12 min before surgeries in the operation theater itself, the trial reported a high rate of SI and no beneficial effect of cefazolin prophylaxis on the mean health-related quality of life score, the lower extremity functional scale score. Numbers of incidences of deep SI in CN group were lower than that of NS group. Cefazolin has good and rapid muscle, soft tissue and bone concentrations, effective as a prophylaxis treatment in orthopedic surgeries and widely used[23]. However, high numbers (16.8%) of SI was reported than expected and more than available reported trials[1,3,4,24,25]. High rates of SI were because of inadequate and common underreporting[26] methods and VAS score.

In vitro bacteriological assessments had found 67% microorganisms' species sensitive to cefazolin. It is confirmed by several studies that the most of pathogens in SI are sensitive to cefazolin[27]. In respect to the results of clinical assessments, the study was justified a use of cefazolin prophylaxis to overcome incidences of SI.

The timing for the administration of prophylaxis antibiotic has been debatable. It should be given 30-60 min before incision[23]. In respect to failure in the prevention of SI, patients may suffer from health and financial crisis.

The trial was performed power calculation for sample size and overcome type I and II errors. The available study has used power calculations but the sample size of both groups is different! (If randomization is performed at 80% power the sample population splits into two groups of equal sample size!) also not provided justification for 80% of power calculations for randomization. In an available clinical trial (a trial that is published in JAMA), the overall type I error rate is maintained but type II error is not overcome. Data were

represented as mean, not as Mean±SD. Overall satisfaction of patients is reported as a measure of VAS, however, several reasons for removal of the orthopedic implant are reported. Does only decrease in pain satisfy the patient? That is not justified. MIC value for cefazolin regarding clinical and bacteriological assessment is not performed. Selection of cefazolin is not justified[4,6-8]. In respect to the selection of sample size and way of presentation, the study contributes significantly to the existing literature.

In limitations of the study, for example, the study was failed in reporting of statistically significant difference regarding secondary outcome measures because of underreporting. In the other limitations of the study, for example, the study was not administered a single dose of 2 g cefazolin prophylaxis. Effect of BMI, systolic and diastolic pressures, history of serious diseases and their durations on the success rate of the cefazolin prophylaxis was not evaluated. Deficiencies in trial conduct, inadequate primary outcome, inappropriate treatment regimen and inappropriate population were also the drawbacks of the study. The effect of the surgical site infection following the index (fracture) procedure was not evaluated.

CONCLUSION

A double-blind, placebo-controlled trial for implants removal surgery of ankle concluded that numbers of the patients with surgical site infections were lower if a single dose of 1 g of cefazolin prophylaxis used.

SIGNIFICANCE STATEMENT

The study on cefazolin prophylaxis for implants removal surgeries of ankle concluded that a single intravenous pre-operative 1 g cefazolin reduced numbers of incidences of the surgical site infection. The finding will help the orthopedic surgeons to uncover the critical areas of the surgical site infections and preoperative cefazolin prophylaxis that a Dutch trial on cefazolin prophylaxis is not able to explore.

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