Trials

STUDY PROTOCOL

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A single-centre randomised controlled trial comparing the standard method and target-controlled infusion as a method of administering cefoxitin, which is used to prevent surgical site infections in colorectal surgical patients: study protocol

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Abstract

Background Prophylactic parenteral administration of antibiotics is strongly recommended to prevent surgical site infection (SSI). Cefoxitin is mainly administered intravenously in colorectal surgery. The current standard method for administering prophylactic antibiotics in adults is to administer a fixed dose quickly before skin incision. The percentage of time that the unbound concentration is maintained above the minimum inhibitory concentration ($fT > MIC$) during surgery is used as a surrogate measure for the effectiveness of prophylactic antibiotics. Target-controlled infusion (TCI) is a method of administration that changes the infusion rate to maintain a constant target concentration set by the user in consideration of the patient's physical characteristics. When cefoxitin is administered using the TCI method, it is possible that $fT > MIC$ can be well maintained while reflecting the patient's physical characteristics compared to the standard method.

Methods This prospective, single-centre, parallel-arm, single-blinded, randomised controlled trial with a 1:1 allocation was designed to compare the effectiveness of the TCI method with that of the standard cefoxitin administration method. We shall enrol 2494 patients scheduled to undergo colon or rectal surgery. Prior to the procedure, we shall randomise each patient to the control group (standard administration method) or study group (TCI method). In the control group, 2 g of cefoxitin was dissolved in 100 ml of normal saline and administered for approximately 10 min. Redosing was performed every 2 h from the start of the first dose of cefoxitin. In the study group, 2 g of cefoxitin was dissolved in 50 ml of normal saline and administered using a commercialised TCI syringe pump until the end of surgery. It was administered at a target concentration of 80 μg/ml using the total concentration pharmacokinetic model of cefoxitin. In all groups, 2 g of cefoxitin was administered using the standard administration method 12 h after the end of surgery. The primary outcome will be the incidence of SSI. The secondary outcome will be the administered dose of cefoxitin. Preoperative, intraoperative, and postoperative data were collected.

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Discussion This study will provide evidence for the effectiveness of administering cefoxitin using the TCI method compared to the standard method.

Trial registration ClinicalTrials.gov, NCT05253339, Registered on February 23, 2022 {2a, 2b}.

Keywords Cefoxitin, Infection, Infusion, Pharmacokinetic, Prevention

Introduction

Background and rationale {6a}

Surgical site infection (SSI) is defined as an infection of the incision site, organ, or space that occurs within 30 days after surgery [1]. Prophylactic parenteral administration of antibiotics is strongly recommended to prevent SSI [1, 2]. Cephalosporin is widely used as a prophylactic antibiotic [2], and cefoxitin, a second-generation cephalosporin, is mainly administered intravenously in colorectal surgery [3], where the incidence of SSI is relatively high [2]. To maintain the appropriate concentration during surgery, it is recommended in the Surgical Infection Society guidelines to readminister cefoxitin every 2 h during surgery [2].

The current standard administration method for prophylactic antibiotics in adults is to administer a fixed dose of 2 g quickly before skin incision [2]. The fixed dose is a dose that does not take into account the patient's physical characteristics (e.g. weight, kidney function) and is known to be determined empirically [4]. This dose was also determined empirically rather than based on scientific evidence [4], and there was a strong tendency to prioritise user convenience. When antibiotics are administered quickly, they reach a concentration that is excessively higher than the minimum inhibitory concentration (MIC) known to inhibit the occurrence of pathogens that cause SSI [5], and this may not have a positive effect on patient safety.

The percentage of time that the unbound concentration is maintained above the MIC ($fT > MIC$) during surgery is used as a surrogate measure for the effectiveness of prophylactic antibiotics [6]. There is still no clear consensus on how to maintain $fT > MIC$ during surgery, but there are studies that aim to maintain $fT > MIC$ for 90–100% of the dosing interval [7]. If cefoxitin can be administered to maintain $fT > MIC$ of 90% or more during surgery while taking into account the patient's physical characteristics, it can be a personalised administration method that maximises the effect of prophylactic antibiotics. In the field of anaesthesiology, hypnotic agents have been administered via targeted controlled infusion (TCI) for more than 25 years [8]. The TCI is a method of administration that changes the infusion rate to maintain a constant target concentration set by the user in consideration of the patient's physical characteristics [9]. It may be expected that administering cefoxitin using the TCI method will improve the limitations of the current standard administration method.

Objective {7}

The purpose of this study is to compare the effectiveness of the TCI method with that of the standard administration method, cefoxitin, which is intravenously administered to prevent SSI in patients undergoing colorectal surgery.

Trial design {8}

This is a prospective, single-centre, parallel-arm, single-blinded, superiority randomised controlled trial with a 1:1 allocation.

Methods

Study setting {9}

This single-centre trial is currently being conducted at the Asan Medical Center, a tertiary hospital in Seoul, Republic of Korea. This study protocol was written in compliance with the 2013 SPIRIT reporting guidelines [10].

Eligibility criteria {10}

The inclusion criteria are as follows:

- Over 20 years old
- Patients who are scheduled to undergo colon or rectal surgery
- Patients scheduled to receive cefoxitin as a prophylactic antibiotic

The exclusion criteria are as follows:

- Known allergies, hypersensitivity, or intolerance to cefoxitin
- Patients with a history of receiving cefoxitin within 3 days of the scheduled surgery
- Patients receiving therapeutic antibiotics
- Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2

Who will take informed consent? {26a}

Five doctors registered as researchers in this clinical trial will obtain written informed consent from patients the

day before elective surgery. The screening will be conducted after consent will be obtained.

Intervention

Anaesthesia induction and maintenance will be performed according to the standard operating procedure of the Asan Medical Center [11]. Cefoxitin will be administered before the skin incision.

Explanation for the choice of comparators {6b}

We shall randomly allocate patients to the study group (administration of cefoxitin via TCI method) and the control group (administration of cefoxitin using standard method). We chose standard administration method as the comparator because it is the administration method currently used around the world.

Control group (standard administration method) {11a}

Two grams of cefoxitin will be dissolved in 100 ml of normal saline and administered for approximately 10 min. Redosing will be performed every 2 h from the start of the first dose of cefoxitin. The maximum intraoperative dose will be limited to 8 g per day. An additional 2 g of cefoxitin will be administered in the general ward 12 h after the first cefoxitin dose.

Study group (target-controlled infusion method) {11a}

Two grams of cefoxitin will be dissolved in 50 ml of normal saline and administered using a commercialised TCI syringe pump until the end of surgery. It will be administered at a target concentration of 80 μg/ml using the total concentration pharmacokinetic model of cefoxitin constructed and validated in previous studies [5, 12]. The TCI syringe pump (PION TCI®; Bionet Co. Ltd., Seoul, Korea) will be connected to a personal computer (PC) by an RS232c cable and controlled by a TCI software (Asan pump, version 2.1.5; Bionet Co. Ltd., Seoul, Korea, https://www.ksap.co.kr/html/, last accessed: December 15, 2023) installed on said PC. Figure 1 shows the operation of the Asan pump program, which is used to administer cefoxitin to a hypothetical patient using the TCI method. Plasma concentration, dose infused, and infusion rate data will be recorded at 10-s intervals and stored in 'CSV' format. Twelve hours after starting cefoxitin administration in the operating room, 2 g of cefoxitin will be administered in the general ward using the standard administration method.



Fig. 1 Operation screenshot of the Asan Pump program. Cefoxitin is administered to a hypothetical patient at a target total concentration of 80 μg/ml

Criteria for discontinuing allocated interventions {11b}
If the study protocol is violated, intraoperative bleeding exceeds 1.5 L, or the patients withdraw their informed consent, the participants will be dropped from the study.

Strategies to improve adherence to interventions {11c}
Not applicable. The designated intervention will be applied only to one method of administration allocated.

Relevant concomitant care permitted or prohibited during the trial {11d}
Not applicable. No relevant concomitant care will be permitted or prohibited.

Provisions for post-trial care {30}
The principal investigator (BM Choi) has clinical trial liability insurance. This insurance provides coverage for any damage to the research participants through injury or death caused by the study. Insurance applies to damages that became apparent during the study or within 5 days after the end of the study.

Outcomes and follow-up {12}
The primary outcome will be the incidence of SSI. The secondary outcome will be the administered dose of cefoxitin. The trial endpoint will be established 1 month after the discharge of the last included patient. Each patient will visit the colorectal surgery outpatient clinic 1 month after discharge, and the surgeon in charge will evaluate the patient for the occurrence of surgical site infection.

Participant timeline {13}
The participant timeline is shown in Fig. 2.

Sample size {14}
The primary endpoint of this study is to compare the incidence of SSI between the two groups. Since cefoxitin will be dosed every 2 h during surgery in the standard administration group, the time for which the unbound concentration was maintained above the MIC to inhibit pathogens did not differ from that in the TCI group during surgery. This was confirmed in a stochastic simulation using the pharmacokinetic model of a previous study [5, 12]. Given that there is no difference in the incidence of SSI between the two groups, the sample size in which the TCI group would show a dose reduction of approximately 30% compared to the standard dose administration group was calculated. Using Bonferroni correction, an alpha of 0.025 and a beta of 0.1 were applied. The sample size that

	Study period						
	Hospitalization						Follow-up
Time point	Admission	Recruitment	Allocation	Operation	POD	Discharge	1 month
Recruitment:							
Eligibility screen		O					
Informed consent		O					
Allocation			O				
Interventions:							
Standard administration method				O			
Target-controlled infusion method				O			
Assessment:							
Baseline characteristics & comorbidities	O						
Surgical site infection				O	O	O	O
Cefoxitin dose administered intraoperatively					O	O	
Acute kidney injury				O			
Operation duration				O			
Estimated blood loss				O			
Adverse events				O	O	O	O

Fig. 2 Participant timeline. POD, postoperative day. Patients will be admitted at least 1 day before surgery. After the surgery schedule will be confirmed, informed consent will be obtained from the patients in the general ward the day before surgery. Group allocation will be performed on the morning of surgery after confirming whether cefoxitin will be used as a prophylactic antibiotic. In general, patients who underwent laparoscopic surgery will be discharged on the 5th day after surgery, and patients who underwent open surgery will be discharged on the 7th day after surgery. Approximately 1 month after discharge, the patients will visit the outpatient clinic

satisfied the first condition that $fT > MIC$ would not differ between the two groups was 270 patients per group, and the sample size that satisfied the second condition that the dose in the TCI group would be reduced by approximately 30% was 1187 patients per group. To satisfy both assumptions, a larger sample size must be selected, and considering a dropout rate of 5%, the sample size was determined to be 1247 patients per group.

Recruitment {15}

Patients will be admitted at least 1 day before surgery. After the surgery schedule was confirmed, written informed consent form will be obtained from the patients in the general ward the day before surgery.

Assignment of interventions: allocation

Sequence generation {16a}

A computer-generated random allocation sequence will be generated by simple randomisation with an allocation ratio of 1:1. Patient randomisation will be performed by a doctor who was not involved in this study.

Concealment mechanism {16b}

A doctor who is not participating in the study will keep the randomisation table. Randomisation was computer-generated, with allocation concealment ensured by opaque sequentially numbered sealed envelopes. The allocation will be concealed until the last participant's study protocol ends.

Implementation {16c}

After the participants will be enrolled, a doctor who was not involved in the study checked the inclusion/exclusion criteria. After confirming final enrolment, randomisation will be performed, and the results will be delivered to the nurse working in the operating room, where the patient would undergo surgery on the morning of the surgery.

Assignment of interventions: blinding {17a, 17b}

When the patient is hospitalised, the occurrence of SSI will be initially assessed by nurses assigned to the infection control unit. The surgeon who operated on the patient will make the final assessment of whether an SSI occurred. These nurses and surgeons are entirely unaware of the randomisation. In Korea, it is stipulated by national policy to investigate whether surgical site infections occur after colorectal surgery. The data analysts will be blinded to the group allocation. The anaesthesiologists who directly administered cefoxitin were not blinded.

If a severe adverse reaction occurs due to antibiotic administration, the administration will be stopped immediately, and unblinding will be allowed. Patients for whom blinding cannot be maintained will be treated as dropouts.

Data collection {18a}

The occurrence of SSI will be assessed by dividing it into superficial, deep, and organ/space SSIs according to the standards presented in the guidelines (Table 1) [4, 13]. The cefoxitin dose in the TCI group will be examined through records saved in the Asan pump program after the completion of surgery. To evaluate whether acute kidney injury (AKI) occurs, serum creatinine and urine output will be checked and evaluated according to KDIGO guidelines [14]. Patients are assigned numerical codes instead of their hospital ID to ensure the confidentiality of personal information. Preoperative, intraoperative, and postoperative data will be collected. Preoperative data includes demographic data (age, sex, height, weight, American Society of Anesthesiologists (ASA) physical status), comorbidities, and laboratory test results before surgery. Intraoperative data includes total cefoxitin dose, operation duration, anaesthesia duration, estimated blood loss, fluid administration volume, urine output, and temperature. Postoperative data includes cefoxitin total dose, operation name, postoperative laboratory tests, daily input and output, adverse events, and 1-month follow-up outcomes.

Plans to promote participant retention and complete follow-up {18b}

The study timeline will be completed on the day of discharge. One-month follow-up is required after discharge. The patient will visit the colorectal surgery outpatient clinic one month after discharge, and the surgeon in charge will make a final evaluation for the occurrence of SSI.

Data management {19}

The principal investigator (BM Choi at Asan Medical Center) is responsible for recruiting patients and conducting the study. On-site investigators (HJ Kim and KM Kim at Asan Medical Center) are recording data on the worksheet (paper-based case report form). The records will be entered into the electronic case report form (http://210.122.4.138:8080/OpenClinica). Data entry and verification will be double-checked by two on-site investigators (HJ Kim and KM Kim).

Statistical methods {20a}

The data will be expressed as the mean ± standard deviations for normally distributed continuous variables, medians (25–75%) for non-normally distributed continuous variables, or counts. Statistical analysis will be conducted using the SigmaStat software version 3.5 for

Table 1 Criteria for defining a surgical site infection (SSI)

Superficial incisional SSI
Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician

Do not report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration)
2. Infection of an episiotomy or newborn circumcision site
3. Infected burn wound
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI)

Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds

Deep incisional SSI
Infection occurs within 30 days after the operation if no implant[a] is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (e.g. fascial and muscle layers) of the incision and at least one of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (> 38 °C), localized pain, or tenderness, unless site is culture-negative
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician

Notes:

1. Report infection that involves both superficial and deep incision sites as deep incisional SSI
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI

Organ/space SSI
Infection occurs within 30 days after the operation if no implant[a] is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g. organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

1. Purulent drainage from a drain that is placed through a stab wound[b] into the organ/space
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of an organ/space SSI by a surgeon or attending physician

[a] National Nosocomial Infection Surveillance definition: a nonhuman-derived implantable foreign body (e.g. prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery

[b] If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth

Windows (Systat Software, Inc., Chicago, IL, USA) or R software (version 4.3.2; R Foundation for Statistical Computing, Austria). The intention-to-treat principle will be applied for outcomes analysis. The incidences of SSI and AKI between the two groups will be compared using the χ^2 test. The intraoperative dose of cefoxitin will be evaluated using the two-sample *t*-test or Mann–Whitney rank sum test. Differences in other variables, including demographics, between the two groups will be compared using two-sample *t*-tests, Mann–Whitney rank sum tests, or χ^2 tests, as appropriate. *P* values less than 0.05 will be considered to indicate statistical significance.

Interim analysis and method for additional analyses {20b, 21b}

No interim analysis will be conducted during this study period. No additional analysis, such as subgroup analysis, is intended for this study.

Methods of analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

The intention-to-treat (ITT) principle will be prioritised in the analysis. In the case of protocol nonadherence, a per-protocol analysis is also planned. Multiple imputations will be used to handle missing data.

Plans to give access to the complete protocol, participant-level data, and statistical code {31c}

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Confidentiality {27}

The written informed consent forms and worksheets will be stored in a locked document storage box, and only investigators registered with the IRB will have access. After 3 years of storage after the completion of the research, the documents will be destroyed.

Monitoring

Composition of the coordinating centre and trial steering committee {5d}

The coordinating centre is the Department of Anesthesiology and Pain Medicine of Asan Medical Center, Seoul, Korea. The trial steering committee consists of the principal investigator (BM Choi) and other investigators (HJ Kim and KM KIM), who are responsible for recruiting patients, conducting the study, and data entry.

Composition of the data monitoring committee and its role and reporting structure {21a}

Data monitoring will be conducted by the clinical research coordinator. An internal inspection will be conducted at the Clinical Research Protection Center at Asan Medical Center in Seoul. Patient safety and the data adequacy will be monitored every 6 months under the supervision of the principal investigator.

Adverse event reporting and harms {22}

The principal investigator will report any serious adverse events to the institutional review board within 14 days of notice. The report included the causality, onset time and resolution time, severity, provided management, and relevance to the present clinical trial.

Frequency and plans for auditing trial conduct {23}

Self-auditing will be performed by the site management organisation every 6 months. This trial may be audited at any time by the Ministry of Food and Drug Safety of Korea or the institution's quality assurance team.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants and ethical committees) {25}

Any amendment to the protocol will be reviewed by the Institutional Review Board of Asan Medical Center. After approval, the changes will be reported and reviewed by the Ministry of Food and Drug Safety of Korea. These changes will be reflected in the public registry site (https://clinicaltrials.gov/study/NCT05253339).

Dissemination plans {31a}

The results will be disseminated via publication in a peer-reviewed journal, available at the registry site (https://clinicaltrials.gov/study/NCT05253339) and presented at scientific meetings.

Discussion

Target-controlled infusion is a scientific administration method in which a drug is administered to maintain the target concentration in the plasma or effect site set by the user. To administer a drug through the TCI method, a dedicated syringe pump equipped with a pharmacokinetic model of the drug is needed. Dosing is tailored to each patient according to covariates such as weight and age included in the pharmacokinetic parameters of the model obtained using population analysis [8]. In other words, even if administered at the same target concentration and for the same period of time, the dosage varies depending on the covariates, and this may be considered personalised medication. The TCI method is a common method for administering hypnotics, including propofol, and analgesics, including remifentanil, during surgery. It is used in most countries except the United States, and its safety has been sufficiently confirmed [15]. However, since antibiotics have never been administered via the TCI method, various studies are needed to confirm the effectiveness of the TCI method in the antibiotic field. This study also began from this perspective. When antibiotics are used for preventive purposes, the concentration-related index, such as $fT > MIC$, acts as a significant surrogate measure for effectiveness, so administering antibiotics using the TCI method is expected to have an advantage over the standard administration method.

To effectively prevent the occurrence of SSI, it is essential to maintain an unbound concentration above the MIC during the surgical period, so it is necessary to set an appropriate target concentration. However, in previous studies, the performance of maintaining a constant target concentration was better for the total concentration than for the unbound concentration [12, 16]. Therefore, the target concentration should be administered based on the total concentration, and the unbound fraction in the plasma (fu) should be considered to maintain the unbound concentration above the concentration that suppresses the occurrence of pathogens that cause SSI. An unbound concentration of 16 μg/ml or more was needed [17], and the target concentration was determined considering the presence of cefoxitin obtained in a previous study [12]. A more detailed explanation of

setting the target concentration to 80 μg/ml has already been described in previous research [12].

This study has several limitations. First, because the actual concentration was not measured in the TCI group, it was not confirmed whether the unbound concentration was greater than 16 μg/ml. Of course, it may be necessary to measure the concentration even once or twice during surgery to adjust the target concentration, but in the case of antibiotics, it is more meaningful to maintain the concentration above the MIC. In a prior study, pharmacokinetic models for administering cefoxitin using the TCI method were constructed [5], and the predictive performance of these models was evaluated in another population that did not participate in model construction [12]. In this external validation study, it was confirmed that the unbound concentration remained higher than 16 μg/ml during surgery in all patients [12]. Therefore, although we were unable to measure the unbound concentration, we cautiously expect that the unbound concentration in most patients would have been maintained above 16 μg/ml during the operation. Second, 2 g of cefoxitin was additionally administered in the ward 12 h after the end of the surgery, and at this time, the standard administration method was used for the TCI group. It is recommended that additional prophylactic antibiotics be administered within 24 h after surgery [18]. Because manufacturers do not allow individual users to freely load pharmacokinetic models built by commercial TCI pumps, a PC equipped with software (i.e. Asan pump) that can control the TCI pump is needed. Therefore, because it was difficult to use the relevant equipment in the hospital room and administer cefoxitin at night, the TCI group was also administered cefoxitin using the standard administration method. In addition, if cefoxitin was administered using the TCI method in the ward, it was also considered that there was a possibility that patients and medical staff would be aware of the group assignment. Although this may affect the assessment of the effectiveness of the TCI method, it is unlikely to further exaggerate the efficacy of the TCI.

In summary, through this study, we would like to evaluate whether cefoxitin, which is administered to patients undergoing colorectal surgery to prevent surgical site infection, is more valuable than the standard administration method when administered via the target-controlled infusion method.

Trial status {3}

The final protocol version is 2.2 (February 15, 2024), and the first patient was recruited on April 4, 2022. Recruitment is expected to be complete by April 2025. For the final analysis, the database will be cleaned and checked for completeness before being locked, and statistical analysis will be carried out.

Final protocol version: v2.2 (date: February 15, 2024)

Recruitment of the first patient: April 4, 2022

Number of patients recruited: 1044 (date: March 14, 2024)

Expected date for recruitment completion: April 30, 2025

Abbreviations

AKI	Acute kidney injury
ASA	American Society of Anesthesiologists
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
*f*T > MIC	Percentage of time that the unbound concentration is maintained above the MIC
KDIGO	Kidney Disease: Improving Global Outcomes
MFDS	Ministry of Food and Drug Safety
MIC	Minimum inhibitory concentration
SSI	Surgical site infection
TCI	Target-controlled infusion

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08716-x.

Supplementary Material 1.

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Authors' contributions {5a, 31b}

BM Choi is the principal investigator; he conceived the study and led the proposal and protocol development. HJ Kim contributed to the study design and development of the proposal. All authors have read and approved the final protocol.

Funding {4, 5b, 5c}

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Data availability {29}

The datasets generated by the current study protocol are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate {24}

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Asan Medical Center (approval number: 2022–0180, approval date: February 12, 2022). This study was registered on an international clinical trials registry platform (https://clinicaltrials.gov/study/NCT05253339, principal investigator: Byung-Moon Choi, registration date: February 23, 2022). With this study protocol, the Ministry of Food and Drug Safety of Korea approved the clinical trial (approval number: 101076, protocol number: 202200837). Written informed consent was obtained from one of the parents of each participant.

Consent for publication {32}
Not applicable. No identifying images or other personal or clinical details of the participants are presented here or will be presented in reports of the trial results. Informed consent materials are available from the corresponding author upon request.

Competing interests {28}
The authors declare that they have no competing interests.

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References

1. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg. 2017;152:784–91.
2. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt). 2013;14:73–156.
3. Poeran J, Wasserman I, Zubizarreta N, Mazumdar M. Characteristics of antibiotic prophylaxis and risk of surgical site infections in open colectomies. Dis Colon Rectum. 2016;59:733–42.
4. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control. 1999;27:97–132 quiz 133-134; discussion 196.
5. Kim KM, Kim SH, Yun HY, et al. Development of a new pharmacokinetic model for target-concentration controlled infusion of cefoxitin as a prophylactic antibiotic in colorectal surgical patients. Br J Clin Pharmacol. 2021;87:4648–57.
6. de Velde F, Mouton JW, de Winter BCM, van Gelder T, Koch BCP. Clinical applications of population pharmacokinetic models of antibiotics: challenges and perspectives. Pharmacol Res. 2018;134:280–8.
7. Naik BI, Roger C, Ikeda K, et al. Comparative total and unbound pharmacokinetics of cefazolin administered by bolus versus continuous infusion in patients undergoing major surgery: a randomized controlled trial. Br J Anaesth. 2017;118:876–82.
8. Absalom AR, Glen JI, Zwart GJ, Schnider TW, Struys MM. Target-controlled infusion: a mature technology. Anesth Analg. 2016;122:70–8.
9. Struys MM, De Smet T, Glen JI, Vereecke HE, Absalom AR, Schnider TW. The history of target-controlled infusion. Anesth Analg. 2016;122:56–69.
10. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
11. Choi BM, Park C, Lee YH, et al. Development of a new analgesic index using nasal photoplethysmography. Anaesthesia. 2018;73:1123–30.
12. Kang HU, Kim KM, Choi JM, et al. Predictive performance of pharmacokinetic models for target concentration-controlled infusion of cefoxitin as a prophylactic antibiotic in patients with colorectal surgery. Clin Exp Pharmacol Physiol. 2022;49:1126–35.
13. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol. 1992;13:606–8.
14. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120:c179-184.
15. Schnider TW, Minto CF, Struys MM, Absalom AR. The safety of target-controlled infusions. Anesth Analg. 2016;122:79–85.
16. Lee SH, Yoon H, Park J, et al. External validation of a pharmacokinetic model for target-controlled infusion of cefazolin as a prophylactic antibiotic. Br J Clin Pharmacol. 2024;90:582–7.
17. Boisson M, Torres BGS, Yani S, et al. Reassessing the dosing of cefoxitin prophylaxis during major abdominal surgery: insights from microdialysis and population pharmacokinetic modelling. J Antimicrob Chemother. 2019;74:1975–83.
18. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013;70:195–283.

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