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CEFUROXIME PROPHYLAXIS IS EFFECTIVE IN NONINSTRUMENTED SPINE SURGERY

THESE

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Rapport de synthèse

Plusieurs investigateurs ont démontré que l'utilisation d'une antibiothérapie prophylactique lors d'interventions neurochirurgicales en terrain non infecté (chirurgie propre) réduisait le taux d'infection. Toutefois, ces taux d'infections sont très variables en fonction des types de chirurgie et de la durée des interventions. Les craniotomies, la mise en place ou le remplacement de shunt ventriculo-cardiaque, l'extirpation de méningiomes intracrâniens et les interventions d'une durée de plus de quatre heures sont grevées d'un taux d'infections post-opératoires plus élevé. Si une prophylaxie antibiotique est maintenant reconnue et utilisée dans ce type de chirurgie, il n'a jamais été démontré que cette pratique amène un bénéfice dans les cas de chirurgie pour hernie discale. Des études ont montré que de nombreux organismes potentiellement pathogènes pouvaient être collectés et cultivés à proximité voire dans le champ opératoire. Malgré ces observations, le taux d'infections post-opératoires reste peu important (entre 1-4% selon les centres). Il n'est actuellement pas possible de distinguer le rôle respectif d'une antibiothérapie prophylactique et des pratiques d'asepsie habituelles (y compris l'usage de solutions de rinçage antiseptiques) dans la faible incidence des infections post-opératoires en ce qui concerne la chirurgie des hernies discales. Lorsque des opérations de chirurgie dite « propre » sont grevées d'un taux de complications aussi bas, une prophylaxie antibiotique n'est généralement pas recommandée, en raison d'un rapport coût-bénéfice défavorable.

Le but de cette étude est d'évaluer la nécessité d'une antibiothérapie prophylactique par une céphalosporine de seconde génération (cefuroxime 1,5 g intraveineuse) dans la prévention des infections post-opératoires au cours d'une chirurgie pour hernie discale. Il s'agit d'un essai clinique prospectif, contrôlé contre placebo en insu réciproque, à répartition aléatoire.

L'étude a été conduite dans les services de neurochirurgie de l'Hôpital Universitaire de Genève et du Centre Hospitalier Universitaire Vaudois de Lausanne. L'ensemble des patients admis dans ces deux services pour une opération de hernie discale et ayant donné leur consentement ont été inclus dans l'étude qui s'est déroulé sur une période de 6 ans.

Mille trois cent soixante-neuf patients opérés pour une hernie discale ont été inclus dans cet essai et 132 patients ont été exclus de l'analyse pour diverses raisons. Au total 1'237 patients ont été analysés, respectivement 613 et 624 patients dans le groupe cefuroxime et le groupe placebo. Les patients des deux groupes présentaient des caractéristiques identiques. Nous n'avons objectivé aucun effet secondaire indésirable attribuable à la cefuroxime ou au placebo. Huit (1.3%) patients du groupe cefuroxime et 18 patients (2.8%) du groupe placebo ont développé une infection du site opératoire (P=0.073). Neuf des patients infectés dans le groupe placebo présentaient une infection profonde du site opératoire (spondylodiscite, abcès épidural) et aucun dans le groupe cefuroxime (P<0.01). Tous les patients avec infection profonde du site opératoire ont été traités par antibiothérapie par voie intraveineuse pour au moins 4 semaines et il a été procédé à une reprise chirurgicale chez deux patients.
Ces résultats montrent qu'il faut traiter 69 patients avec une antibiothérapie prophylactique de cefuroxime pour prévenir une infection du site opératoire.

En conclusion, l'administration d'une dose de cefuroxime 1.5 g intraveineuse comme prophylaxie lors d'opération de hernie discale, permet de réduire significativement le risque d'infection profonde du site opératoire.

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Cefuroxime Prophylaxis Is Effective in Noninstrumented Spine Surgery

A Double-Blind, Placebo-Controlled Study

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Study Design. Double-blind, placebo-controlled randomized clinical trial.

Objective. To assess the efficacy of 1 preoperative 1.5 g dose of cefuroxime in preventing surgical site infection after surgery for herniated disc.

Summary of Background Data. Antibiotic prophylaxis was only tested in nonconclusive trials in this setting.

Methods. The study was conducted in 2 university hospitals in Switzerland. Patients were assessed for occurrence of surgical site infection (defined by the criteria of the Centers for Diseases Control and Prevention), other infections, or adverse events up to 6 months after surgery. Outcome measures were compared in a univariate, per-protocol analysis.

Results. Baseline characteristics were similar in patients allocated to cefuroxime (n = 613) or placebo (n = 624). Eight (1.3%) patients in the cefuroxime group and 18 patients (2.8%) in the placebo group developed a surgical site infection ($P = 0.073$). A diagnosis of spondylodiscitis or epidural abscess was made in 9 patients in the placebo group, but none in the cefuroxime group ($P < 0.01$), which corresponded to a number necessary to treat of 69 patients to prevent one of these infections. There were no significant adverse events attributed to either cefuroxime or placebo.

Conclusion. A single, preoperative dose of cefuroxime significantly reduces the risk of organ-space infection, most notably spondylodiscitis, after surgery for herniated disc.

Key words: antibiotic prophylaxis, bacterial infections/prevention and control, surgical wound infection/prevention and control, neurosurgery, postoperative complications/prevention and control, clinical trial [publication type]. **Spine 2008;33:1919–1924**

Several clinical trials have shown that antibiotic prophylaxis is effective in reducing surgical site infections after neurosurgical procedures, such as craniotomies,[1] shunt replacement procedures,[2,3] extirpation of cerebral meningiomas, and operations lasting for more than 4 hours.[4,5] Antibiotic prophylaxis is now generally recommended for these procedures.[6–9] Many surgeons also administer prophylactic antibiotics in spinal surgery, although the benefit of this practice has never been demonstrated in a double-blind randomized trial. Others argue that antibiotic use may unnecessarily expose patients to adverse drug reactions, encourage the emergence of resistant bacteria, and increase costs. This opinion is based on the fact that clean surgical procedures like spinal surgery carry a low risk of infection, which implies that the expected number of patients who should receive prophylaxis to avoid one infection would necessarily be high.

A recent meta-analysis of 6 open, prospective, nonrandomized trials or subgroup analyses[1] enrolling 843 patients suggested that prophylactic antibiotics were beneficial for spinal surgery, even if infection rates in the absence of antimicrobial prophylaxis were as low as 5.9%. The odds ratio was 0.37 (95% confidence interval, 0.17–0.78) favoring antibiotic prophylaxis. However, meta-analyses are not exempt from bias. In a number of areas of clinical controversy in which nonrandomized trials were unable to yield a clinical consensus, randomized clinical trials produced clear results while exposing far fewer patients to ineffective therapy.[2,10] Moreover, the above-mentioned meta-analysis did not distinguish superficial and deep surgical site infections, particularly spondylodiscitis, the burden of which is substantially different.

The purpose of the present double-blind, randomized trial was to assess the efficacy of antibiotic prophylaxis in preventing infections after spinal surgery. Cefuroxime was chosen since current guidelines commonly recommend first- or second-generation cephalosporins when prophylaxis is indicated for clean surgery.[11]

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Materials and Methods

Patients and Setting

This randomized, placebo-controlled, double-blind trial was performed in one neurosurgery department that included 2 services, 1 at the Centre Hospitalier Universitaire Vaudois, Lausanne, and the other at the University of Geneva Hospitals, Geneva (Switzerland). The study protocol was approved by the ethical review committees of the 2 institutions.

Patients older than 18 years requiring spinal surgery for herniated disc (hemilaminectomy, laminectomy, flavectomy, spondylosyndesis) were recruited from April 1994 through March 2000. Exclusion criteria were: known or suspected hypersensitivity to cephalosporins or type I hypersensitivity to betalactams; severe renal function impairment; acquired immune deficiency syndrome or other conditions of severe immuno-suppression; antibiotic therapy for concomitant infection at the time of surgery; refusal to participate; or pregnancy.

Study Design and Intervention

Once informed consent was obtained, eligible patients were allocated to receive one numbered vial of either 1.5 g of intravenous cefuroxime (Zinacef, GlaxoSmithKline AG Münchenbuchsee, Switzerland) or a placebo of identical appearance. Randomization was performed by the hospital pharmacist according to a computer-generated random scheme. The allocation was blinded to the surgeon, the patient, and the study investigator. Both placebo and cefuroxime were prepared and numbered by the hospital pharmacies, and were administered intravenously by the anesthesiologist at the time of induction. The timing of administration was not supervised but was documented on the anesthesiology sheet. The surgeon was asked about the occurrence of a break in asepsis during operation.

Patients were observed prospectively during hospitalization by a study nurse (and an investigator in case of any abnormal findings), and the following information was recorded: temperature, symptoms or signs of infection, diagnostic tests performed, and prescription of antibiotics, analgesics or anti-inflammatory drugs. All patients were seen by the surgeon-in-charge 6 weeks after the operation. During this follow-up visit, a standardized questionnaire recorded information about difficulties in wound healing, evidence of any infection during follow-up, unscheduled visits to a physician and prescription of antibiotics.[12] All patients were also seen or contacted by phone at 3 and 6 months after the operation to collect standardized follow-up data.

Outcome Measures

Surgical site infection was the primary outcome, defined according to the criteria of the Centers for Disease Control and Prevention.[13] In brief, a superficial infection of the incision site was diagnosed in the presence of clinical signs of infection that involved the skin, subcutaneous tissue, or muscle located above the fascial layer and accompanied by at least one of the following criteria: purulent drainage located above the fascial layer and/or isolation of a microorganism from a wound culture showing signs of inflammation. A deep incisional infection was diagnosed when infection was found to involve tissue below the fascia on opening and exploration by the surgeon. An organ-space infection was diagnosed when clinical and imaging (CT-scan or magnetic resonance imaging) signs were suggestive of an infection of a disc, a vertebra, or a paravertebral structure, associated or not with a positive culture of blood or of material obtained by needle aspiration of the vertebral space, needle biopsy of the bone, or open bone biopsy. Postoperative infections other than surgical site infections were diagnosed according to CDC criteria,[8] which included a diagnosis of infection by the surgeon.

All included patients were monitored for signs of drug toxicity and serious adverse events, such as *Clostridium difficile*-associated colitis, allergic reaction or anaphylactic shock.

Statistical Analysis

We evaluated clinical outcomes in a per-protocol analysis that included all randomized patients who had received the study drug and completed follow-up at 6 weeks. Patients who did not complete the protocol until the follow-up visit at 6 weeks were excluded from this analysis.

Assuming an infection rate of 3% in the placebo group and 0.75% in the antibiotic group,[1,11] 656 patients per group were required to detect the difference with a power of 0.8 at a significance level of 0.05 (2-sided tests). Baseline characteristics and outcomes were compared in univariate analyses, using χ^2 test (or Fisher exact test when appropriate) for categorical variables and the Wilcoxon rank sum test for continuous variables.

The code of the study was broken after all analyses had been performed.

Role of the Funding Source

The study sponsor had no role in designing the study, the management and the analysis of data, the writing and the submission of this article.

Results

Of the 1369 patients who initially fulfilled inclusion criteria, 132 (9.6%) were excluded from the analysis for the following reasons: 107 patients (59 in the cefuroxime group and 48 in the placebo group) because they did not receive the study medication; 5 patients (2 in the cefuroxime group and 3 in the placebo group) because of lack of follow-up at 6 weeks; and 20 patients for other reasons (11 in the cefuroxime group and 9 in the placebo group). (Figure 1). Among the 1237 patients analyzed, 613 received cefuroxime and 624 received the placebo. Follow-up was possible in 1232 patients at 3 months and in 1222 at 6 months. Patients in both groups were similar with respect to baseline characteristics (Table 1).

Infections

A total of 71 infections were recorded in 70 patients, of which 30 occurred during hospitalization. The overall rate of infection was 5.2% (32/613) in the cefuroxime group and 6.3% (39/624) in the placebo group (P = 0.44).

Surgical Site Infections

Eight patients who received cefuroxime (8/613, 1.30%) and 18 patients who received placebo (18/624, 2.9%) developed a surgical site infection (relative risk with cefuroxime: 0.45, 95% confidence interval 0.20–1.03, P = 0.07), which corresponded to a number necessary to treat of 63 patients to avoid one surgical site infection. The characteristics of the patients with surgical site infections are detailed in Tables 2 and 3.

There were 6 incisional wound infections in the cefuroxime group and 7 in the placebo group, and 2 deep

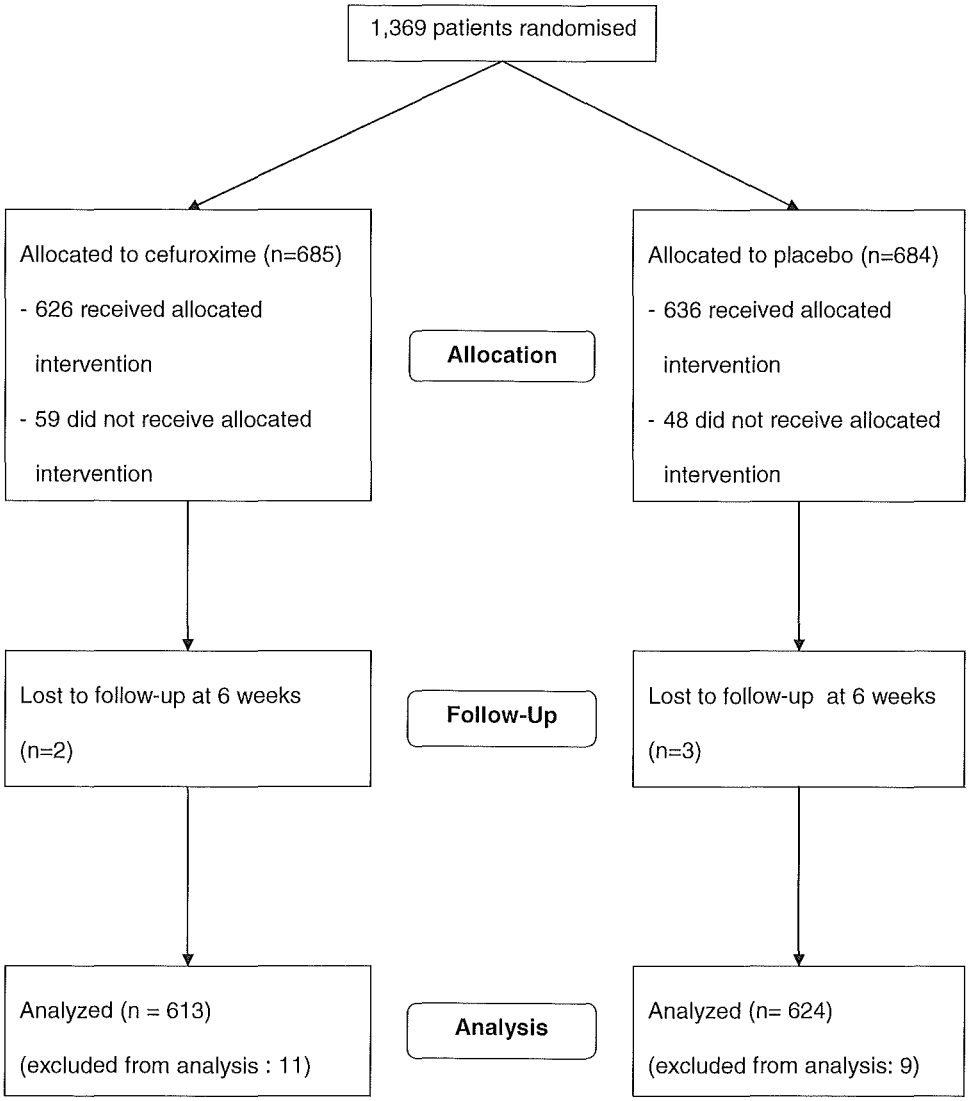

Figure 1. Randomization, follow-up, and data analysis for study participants.

wound infections in each group. Nine patients in the placebo group presented an organ-space infection (documented microbiologically in all but one), most notably spondylodiscitis, compared to none in the cefuroxime group ($P < 0.01$), which corresponded to a number necessary to treat of 69 patients to avoid one infection. All these patients were treated with systemic antibiotics for 4 weeks or more, and 5 of 9 required reintervention (Table 3).

Table 1. Baseline Characteristics of the Patients in the Two Study Groups*

	Cefuroxime n = 613	Placebo n = 624
Male (%)	380 (62)	382 (61)
Median age in years (range)	46 (18–86)	45 (19–85)
Elective operation (%)	596 (97)	606 (97)
Laminectomy (%)	110 (18)	87 (14)
Hemilaminectomy (%)	252 (41)	261 (42)
Discectomy (%)	242 (39)	267 (43)
Combined operation (%)	9 (1)	9 (1)
Bone graft (%)	10 (2)	15 (2)
Surgery on one intervertebral space (%)	531 (87)	563 (90)
Lumbar operation (%)	542 (88)	539 (86)
Broken asepsis during operation	10 (1)	10 (1)
Comorbidities (%)	19 (3)	13 (2)
Median length of operation in minutes (range)	77 (23–270)	73 (15–355)

*There was no significant difference between the groups.

Five of the 18 surgical site infections in the placebo group (2 spondylodiscitis and 3 wound infections), but none of the 8 infections in the cefuroxime group were diagnosed during hospital stay. The microorganisms recovered from wound infections were *Staphylococcus aureus*, *S.* epidermidis, *S. lugdunensis*, *Klebsiella pneumoniae*, and *Propionibaterium acnes*. All were susceptible to second-generation cephalosporins (even the *S. epidermidis* strains).

Other Infections

Sixteen nonsurgical site infections occurred in each of the study group. Nine of the 16 urinary tract infections were documented microbiologically: 4 in the placebo group (all caused by *Escherichia coli* susceptible to cefuroxime) and 5 in the cefuroxime group (caused by *K. pneumoniae*, *Morganella morganii*, *Citrobacter braakii*, *En-*

Table 2. Characteristics of Incisional and Deep Wound Infections

Case Number	Type of Surgery	CDC Criteria for Diagnosis	Microbiology	Local Treatment	Systemic Antibiotics	Interval Since Operation (d)
Incisional wound infections						
Cefuroxime group						
1	H	Physician's diagnosis*	Not obtained	Local care	Yes	12
2	H	Physician's diagnosis*	Not obtained	Local care	No	5
3	H	Physician's diagnosis*	Not obtained	Local care	Yes	9
4	D	Physician's diagnosis*	Not obtained	Local care	No	5
5	D	Purulent discharge	Not obtained	Local care	No	28
6	H	Abscess	Negative	Incision and slitting up	Yes	9
Placebo group						
7	H	Physician's diagnosis*	Not obtained	Slitting up	No	16
8	H	Physician's diagnosis*	*Staphylococcus epidermidis*	Slitting up	Yes	6
9	L	Physician's diagnosis*	Not obtained	No	Yes	18
10	D	Physician's diagnosis*	Not obtained	No	No	30
11	H	Purulent discharge	Not obtained	No	No	19
12	H	Abscess	Not obtained	Incision and slitting up	No	15
13	H	Purulent discharge	Not obtained	Slitting up	No	9
Deep wound infection						
Cefuroxime group						
14	D	Purulent discharge	Not obtained	No	Yes	9
15	D	Scar dehiscence, inflammation and discharge	*Staphylococcus aureus*	Slitting up	Yes	17
Placebo group						
16	L	Scar dehiscence, inflammation and discharge	*Staphylococcus aureus*	Slitting up	Yes	6
17	C	Scar dehiscence, inflammation and discharge	*Klebsiella pneumoniae*	Slitting up	Yes	18

*According to predefined criteria.
CDC indicates Centers for Disease Control and Prevention, Atlanta (Ge); L, laminectomy; H, hemilaminectomy; D, discectomy; C, combined operation.

terococcus spp, *E. coli*, and *Pseudomonas aeruginosa*, all resistant to second generation cephalosporins).

Side Effects

There was no significant side effect attributable to either cefuroxime or placebo.

Discussion

The present double-blind, placebo-controlled study showed the substantial effect of one single dose of prophylactic cefuroxime in preventing the most severe surgical site infections in patients undergoing spinal surgery.

Table 3. Characteristics of Space Infections and Spondylodiscitis (All in the Placebo Group)

Case Number	Type of Surgery	Description	Surgical Treatment	Microbiology		Interval Since Operation (d)
				Local Specimen*	Blood	
1	H	Discitis and muscular abscess	Slitting up	*Staphylococcus epidermidis*	Sterile	28
2	D	Discitis, cervical and mediastinal abscesses	Slitting up, vertebral repair	*Staphylococcus epidermidis, Propionibacterium acnes*	*Propionibacterium acnes*	16
3	H	Epidural abscess	Slitting up	*Staphylococcus aureus*	*Staphylococcus aureus*	4
4	H	Discitis and paravertebral abscesses	Slitting up	Sterile	Sterile	35
5	H	Discitis	None	*Staphylococcus epidermidis*	Sterile	174
6	D	Epidural abscess	Slitting up	*Staphylococcus epidermidis*	Sterile	17
7	D	Spondylodiscitis	None	Not done	*Propionibacterium acnes*	86
8	D	Spondylodiscitis	None	Not done	*Staphylococcus lugdunensis*	60
9	D	Spondylodiscitis	None	*Propionibacterium acnes*	Sterile	72

*Surgical specimen or CT-scan guided needle aspiration.
H indicates hemilaminectomy; D, discectomy.

To our knowledge, this study is the first to clearly demonstrate such an effect in this setting that carries a low risk of infection. Recently, a meta-analysis of 6 selected, open, randomized trials or trial subgroups also concluded that antibiotic prophylaxis was beneficial for spinal surgery.[1] The rate of surgical site infection was 5.9% in this meta-analysis for patients without antibiotics. Of particular interest is the fact that this rate was 2 times lower in the control group of the present study (2.9%). For such a low level of risk, some experts advise against antibiotic prophylaxis for most spinal procedures because of possible drug reactions, emergence of antibiotic resistant bacteria, and additional costs.[14–18] Others argue that prophylaxis should only be used for selected interventions such as internal fixation or fusion of the spine, as these procedures are associated with a higher risk of infection than simple discectomies.[15,19] In contrast, the present study showed a significant prevention of the most severe of these infections, *i.e.*, spondylodiscitis and other organ-space infections (0/613 *vs.* 9/624).

The reason why the prophylactic effect was only observed against deep-seated wound infections remains unclear. An observer bias is unlikely given the double-blind design of the study. This finding may reflect the fact that in an era where high standards of asepsis are enforced during surgical interventions, some of the superficial infections are acquired after surgery. Different from deep infections, these late-onset infections could not be prevented through antibiotic prophylaxis. Similarly, there was no difference in rates of infections other than surgical site infections in the present study. However, data are scarce in the literature regarding postoperative determinants of surgical site infections.[20]

Classic microorganisms were recovered from wound infections.[5,17,21,22] All of them were susceptible to second-generation cephalosporins including the *S. epidermidis* strains. The external validity of the study may be limited for settings with increased resistance of *S. epidermidis* to β-lactam antibiotics, or hyper-endemic occurrence of methicillin-resistant *S. aureus*.

There was no adverse event reported in relation with use of prophylaxis. However, among the microbiologically-documented urinary tract infections, there was a clear shift towards causative microorganisms resistant to second-generation cephalosporins in patients who had received cefuroxime. Thus, there may be some association between cefuroxime use and urinary tract infection caused by resistant microorganisms.[17,23] This underscores the possible risk related to prolonged use of prophylaxis.[24]

The study suffers from several limitations. No information was available on the number of patients assessed for eligibility. In addition, we did not perform an intent-to-treat analysis because few patients crossed-over to the other assignment arm. Thus, the difference between an intent-to-treat analysis and the per-protocol analysis is only minimal and would not change the main results. Another limitation comes from the fact that the diagnosis of surgical site infection largely relied on the physician in charge. However, the impact of these possible bias or confounders is probably very limited thanks to the double-blind design of the study. Finally, the present study does not prove that cefuroxime was better than other antibiotics frequently used for prophylaxis such as first-generation cephalosporins.

This double-blind randomized trial demonstrates that the administration of a single dose of prophylactic cefuroxime before spinal surgery reduces the risk of organ-space infection and presumably saves costs, although it had no impact on other types of surgical site infection or on infections at other body sites. Based on these results, a formal recommendation for using such a prophylaxis should be considered in this setting.

■ Key Points

- This double-blind, placebo-controlled trial demonstrates that the administration of a single dose of prophylactic cefuroxime before spinal surgery reduces the risk of organ-space infection.
- According to the results, the prophylactic antibiotic should be given to 69 patients to prevent one of these infections.
- To our knowledge, this study is the first to clearly demonstrate such an effect in this setting that carries a low risk of infection.

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