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Review

Third-generation cephalosporins as antibiotic prophylaxis in neurosurgery: What's the evidence?

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ABSTRACT

To analyze the role of third-generation cephalosporins as prophylactic antibiotics in neurosurgery. We reviewed the literature for data from randomized controlled trials (RCTs) on third-generation cephalosporins compared to other antibiotic regimen in neurosurgery. End point of the RCTs was the occurrence of surgical site infections (SSIs) – data were pooled in a fixed-effects meta-analysis.

Five randomized controlled trials enrolling a total of 2209 patients were identified. The pooled odds ratio for SSIs (overall) with third-generation cephalosporins prophylaxis in the five RCTs was 0.94 (95% CI, 0.59–1.52; $P = 0.81$). No significant difference between third-generation cephalosporins and alternative regimen was identified. When analyzing organ SSIs (osteomyelitis, meningitis, and others intracranial infections) in data derived from four RCTs (1596 patients), third-generation cephalosporins failed to show superiority (pooled odds ratio 0.88; 95% CI 0.45–1.74; $P = 0.72$).

Third-generation cephalosporin antibiotic prophylaxis fails to show superiority over conventional regimens regarding both incisional and organ related SSIs in neurosurgery.

Contents

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1. Introduction

Although surgical site infections (SSIs) are not common in neurosurgery, 1–5% of craniotomies [1] and 3% of spinal procedures [2] are complicated either by infections at the incision site (incisional infections) or even involve the central nervous system and its surrounding structures (organ infections). For cerebrospinal fluid (CSF) shunt insertions infection rates range between 1.5% and 38% [3]. While all SSIs increase morbidity, mortality, length of hospital stay, and cost [4], postoperative infections in neurosurgery are associated with a particular high burden of disease [5].

Therefore, antibiotic prophylaxis is widely considered as an option to reduce SSIs in neurosurgical procedures. Since clinical trials determined the effectiveness of antibiotic prophylaxis given shortly before the start of the operation, most guidelines recommend the perioperative administration of antibiotics [6–8]. Cefazolin, a first-generation cephalosporin, has been originally advocated for its adequate coverage for clean and clean-contaminated operations [9]. It has a good safety profile, acceptable pharmacokinetics, and reasonable cost per dose [10]. Since a change in the spectrum toward more Gram-negative bacteria with broader antibiotic resistance has been observed, experts suggested to use extended spectrum beta-lactam antibiotics [11]. Third-generation cephalosporins have been put forward for their better Gram-negative coverage and favorable pharmacokinetic and pharmacodynamic properties. Thus, third-generation cephalosporins achieve CSF concentrations that are expected to be well above the minimum inhibitory concentrations of the most frequent pathogens. Studies on the use of third-generation cephalosporins for antibiotic prophylaxis in neurosurgery showed good results, suggesting effective SSIs prevention with acceptable side effects [12–14]. This article will focus on randomized controlled trials comparing third-generation cephalosporins to conventional antibiotic prophylaxis regimens which had already shown efficiency in previous RCTs.

2. Materials and methods

2.1. Inclusion criteria

We identified RCTs comparing third-generation cephalosporins to conventional antibiotic regimens in neurosurgery. Neurosurgical procedures included craniotomies, spinal procedures, ventriculoperitoneal (VP) shunts, external ventricular drains (EVDs), biopsies and stereotactic surgery. For the purpose of analyzing which antibiotic regimens are likely to be more effective and safe, we excluded placebo controlled studies as well as trials comparing just dosing or timing of a single antibiotic regimen.

2.2. Types of interventions

Studies were included that compared the effectiveness of third-generation cephalosporins with conventional antibiotics. We considered third-generation cephalosporins most frequently used in clinical routine such as cefdinir, cefixime, ceftibuten, ceftriaxone, cefotaxime, ceftizoxime, or cefoperazone.

The conventional regimen was regarded as perioperative administration of a single or a combination of antibiotic compounds that had already shown efficiency in previous RCTs, including broad-spectrum penicillins (ampicillin), first- or second-generation cephalosporins (*i.e.* cefazolin and cefuroxim), aminoglycosides (gentamicin), and glycopeptides (vancomycin).

2.3. Types of outcome measures

We considered surgical site infections (SSIs) including superficial incisional surgical site infections, deep incisional surgical site infection and organ infection as the primary endpoint. We defined SSIs based on clinical evidence of infection and according to the CDC/NHSN surveillance definition of health care-associated infection criteria [15] as follows:

Superficial incisional primary (SIP) SSI or superficial incisional secondary (SIS) SSI: involves only skin and subcutaneous tissue of the incision within 30 days after surgery.
Deep incisional primary (DIP) or deep incisional secondary (DIS) SSI: involves deep soft tissues (*e.g.* fascial and muscle layers) of the incision within 30 days after surgery (1 year if implant is in place).
Organ/space surgical site infections involve organs and organ cavities beyond the fascia and muscular layers that were opened or manipulated during the operative procedure. Infections are regarded as SSIs if occurring within 30 days after surgery or 1 year if implant is in place. In neurosurgical procedures the specific sites of organ/space SSIs include:
BONE: osteomyelitis
MEN: meningitis
IC: intracranial infection, including brain abscess, subdural or epidural infection and encephalitis
DISC: disk space

We also evaluated adverse drug effects reported, including nausea, vomiting, diarrhea, allergic reactions, and others which might have led to premature discontinuation of prophylaxis and to other adverse effects in relation to the antibiotics used.

2.4. Search strategy

We searched the CENTRAL (Cochrane Central Register of Controlled Trials, 2012, Issue 6), MEDLINE, EMBASE, LILACS (Latin American and Caribbean Center on Health Sciences Information) and CMB (Chinese Biomedical Database). The cut-off time of the retrieved documents was the end of November 2012. We used the search strategy described in detail in Table 1 to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version [16]. We adapted the search strategy for EMBASE, LILACS and CMB.

2.5. Data collection and analysis

Three authors (WL, HZ, MN) independently selected trials for inclusion. Outcomes were cross-checked – ambiguities or misinterpretations were resolved through discussion and consensus finding.

Two authors (WL, HZ) independently assessed potential biases of the selected trials according to the Cochrane Handbook for Systematic Reviews of Interventions [16] based on six domains, (i) random sequence generation, (ii) allocation concealment, (iii) blinding, (iv) incomplete outcome data, (v) selective reporting, and