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Review article

Antibacterial prophylaxis for gram-positive and gram-negative infections in cranial surgery: A meta-analysis

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ABSTRACT

Background: Perioperative antibiotic prophylaxis against gram positive and gram negative infections is considered standard of care in the perioperative management of patients undergoing cranial surgery. The antibiotic regimen which best reduces the risk of surgical site infections (SSIs) remains controversial.
Objectives: A systematic literature review and meta-analysis were conducted to examine the effect of various prophylactic antibiotics on infection incidence among patients undergoing cranial surgeries.
Methods: A comprehensive search was conducted on Pubmed, EMBASE and Cochrane databases through October 2014 for studies that evaluated the efficacy of antibiotic prophylaxis among patients undergoing cranial surgeries. Pooled effect estimates using both fixed- and random-effect models were calculated.
Results: Eight articles were included in the meta-analysis, with a combined total of 1655 cranial procedures. Among these, 74 cases of SSIs were reported after patients received a single antibiotic or a combination of 2 or more antibiotics (pooled incidence of SSIs = 6.00%; 95% CI = 4.80%, 7.50%; fixed-effects model; I^2 = 73.7%; P-heterogeneity < 0.01). Incidence of SSI was 1.00% (95% CI = 0.40%, 2.60%) for non-MRSA gram-positive bacterial infections; 2.70% (95% CI = 0.90%, 8.00%) for gram-negative bacterial infections; 6.00% (95% CI = 4.50%, 7.80%) for gram negative, and non-MRSA gram-positive bacterial infections; and 11.3% (95% CI = 7.20%, 17.4%) for gram negative and MRSA gram-positive bacterial infections. Subgroup analysis revealed an effect modification by drug class (P = 0.05) and infection type (P-interaction = 0.01). More specifically, lincosamides (2.70%; n = 1 group), glycopeptides (2.80%; n = 1), third generation cephalosporins (5.30%; n = 2), antibiotics combination (4.90%; n = 4), and penicillin-family antibiotics (5.90%, n = 1) offered better coverage against infections than first generation cephalosporins (22.0%; n = 2). A meta-regression analysis on study length was not significant (P = 0.13). Random-effect models were not materially different form fixed-effects. No evidence of publication bias was found.
Conclusion: Lincosamides, glycopeptides, third generation cephalosporins, other combinations of prophylactic antibiotics, or penicillin-family antibiotics alone offer better coverage against SSIs than first generation cephalosporin among cranial surgery patients.

1. Introduction

Post-operative central nervous system infection (PCNSI) represents a rare, but potentially catastrophic complication following a variety of neurosurgical procedures [1]. Meningitis, epidural abscess, subdural empyema, and/or brain abscesses can result in prolonged hospital stays, long term intravenous antibacterial therapy, and in some cases, reoperation [1]. The most common culprits in PCNSIs are gram-positive cocci such as *S. aureus* and *S. epidermidis* [2]. Numerous studies have demonstrated that the risk of developing PCNSIs decreases significantly after administration of prophylactic antibiotics [3]. Without prophylactic antibiotics, the range of infection in "clean" neurosurgical procedures in randomized controlled trials ranges from 4.0 to 12.0%; however, with the

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administration of prophylactic antibiotics, this decreases to 0.3–3% [2,4]. Despite widespread evidence that antibiotic prophylaxis decreases the rate of post-operative infections, there is little consensus regarding the optimal antibiotic regimen. Given the potential consequences of PCNSIs, it is imperative to determine the optimal perioperative antibiotic regimen for neurosurgical patients.

In this study, an extensive literature search was conducted and a meta-analysis of the available studies was subsequently performed to identify the antibiotic prophylaxis that offered the best protection from post-operative infection following a cranial procedure.

2. Methods

2.1. Literature search

Relevant articles were searched in PubMed, EMBASE, and Cochrane databases from their establishment date through October 2014 for all relevant studies that evaluated the efficacy of prophylaxis use of antibiotics for infections, specifically gram-positive and gram-negative infections, in patients undergoing cranial procedures. The search strategy included medical subject heading (MeSH) terms, text words [tw], and Emtree terms for craniotomy surgery, prophylaxis antibiotics type and gram-positive and gram-negative infections (Appendix A). Additional articles were also identified from the reference list of relevant studies and reviews.

2.2. Study selection

Studies were included in the meta-analysis if (1) they reported antibiotic prophylaxis for adult patients (≥18 years old) after undergoing cranial procedures on neurosurgical craniotomy patients; (2) they reported surgical site infections (SSI), primary & secondary wound infections, or MRSA colonization after all craniotomy procedures; (3) the sample size was ≥20); and (4) the study was in English. Titles and abstracts were screened and potentially relevant articles were selected for full-text evaluation, which was performed independently by three investigators (PA, NL & MA). Discrepancies were resolved by consultation with neurosurgery specialists (HZ, TRS).

2.3. Data extraction

For each identified article, the following information was extracted: study characteristics (authors, publication year, country of origin, number of craniotomies), antibiotic administered, dose and time of antibiotic administered, length of study, years of follow up, age range of study population, number of infections after the cranial procedure, adverse events, type of bacteria found at the site of infection, number of surgeons participating in the surgery, study center, and the impact factor of the journal. Data was extracted independently by three authors (PA, NL & MA) and cross-verified.

2.4. Quality assessments

Study quality was evaluated using the Jadad score for RCTs [5], which assesses randomization, double blinding, and withdrawals/dropouts. Due to the non-comparative nature of the available studies (case series), the Newcastle-Ottawa Scale[19] was modified, by removing the comparability criteria, to assess the quality of included studies.

2.5. Data analysis

The fixed-effects model was used to calculate the overall incidence and 95% confidence intervals to assess the efficacy of antibiotic in preventing infections after neurosurgery. The DerSimonian and Laird random-effects model [6], which accounts for study heterogeneity, was used for comparison. Heterogeneity among the studies was evaluated using the Cochran's Q test ($p < 0.10$) as well as I^2 to measure the proportion of total variation due to that heterogeneity. An I^2 value of >50% was considered to be high [7]. To identify potential sources of heterogeneity, sub-group analyses were conducted by categorical covariates such as drug class (first generation cephalosporin; third generation cephalosporin; antibiotics combination; glycopeptides; lincosamides; and penicillin-family antibiotics); surgery type (craniotomy; craniectomy and cranioplasty; intra cranial pressure monitor placement); infection type as provided in the included studies (1-gram negative; 2-gram negative and non MRSA gram positive; 3-gram negative, non-MRSA gram positive, and MRSA gram positive; 4-non MRSA gram positive infection); country (USA; Turkey); drug administration timing (pre/post-operative); journal impact factor (<median; ≥median); and study quality (<median; ≥median). A univariate meta-regression was conducted on the continuous covariate (study length) to explore the heterogeneity source. Dose was not tested for effect modification because of the diversity of the interventions used in these studies. Safety analysis was not conducted because most of the studies did not report any adverse events after administering the antibiotics. Publication bias was assessed by using funnel plots, Egger's line regression test, and Begg's correlation test with a p-value of <0.05 being considered the level of significance. The analysis was done using Comprehensive Meta-Analysis (CMA) version 3 (Biostat, Inc., Englewood, NJ).

3. Results

A total of 538 articles were identified from 3 databases (Pubmed, Embase, and Cochrane) after removal of duplicates. After reviewing titles and abstracts, 58 articles were selected for full text review. Ultimately, 7 articles met this study's inclusion and exclusion criteria (Fig. 1) with a combined total of 1655 cranial procedures.

Study characteristics are shown in Table 1. Six studies were case series (9 groups total) while one was a randomized clinical trial (2 groups total). The number of participants ranged between 21 and 415 across all studies. Patients were assigned to receive either a particular antibiotic or a combination of 2 or more antibiotics. Six studies were conducted in the USA and one in Turkey. Six studies had a follow-up ranging between 1 and 4 years; one had a length of 7 years [8]. The administered antibiotics varied across studies: Ampicillin (class: penicillin) was administered in 1 study group post-operatively at a dose of 500 mg [9]. All the other studies administered the drug pre- or peri-operatively when indicated. A combination of at least 2 antibiotics was administered in three studies [10–12]. In Kourbeti et al. (2007) [10], a combination of first-generation cephalosporin, another cephalosporin, vancomycin (glycopeptides), penicillinase-resistant penicillin, and penicillin G was administered to patients; these drugs are mostly known to cover against gram positive infections (MRSA and non MRSA). In May et al. (2006) [11], a combination of ceftriaxone (third generation cephalosporin) with ciprofloxacin (fluoroquinolones) was administered to one group of patients and a combination of cefazolin (first generation cephalosporin) with vancomycin (glycopeptides) was administered to another group. In Pons et al. (1993) [12], a combination of vancomycin (glycopeptides) and gentamicin (aminoglycosides) was administered to one