Single- versus multiple-dose antimicrobial prophylaxis for major surgery: a systematic review

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Authors' objectives
To determine the overall efficacy of single- versus multiple-dose antimicrobial prophylaxis for major surgery and across surgical disciplines.

Searching
MEDLINE was searched from 1966 to 1997 using the following keywords: 'antibiotic prophylaxis'; 'antimicrobial prophylaxis' plus 'surgical prophylaxis'; and 'single-dose', 'multiple-dose'. Current Contents was also searched and the references from other publications, especially reviews, were back-searched for additional material.

Study selection
Study designs of evaluations included in the review
Prospective randomised controlled trials (RCTs) of antimicrobial surgical prophylaxis, with comparable treatment arms that involved major surgery, were included if they compared single and multiple pre-operative doses of the same antimicrobial agent(s), and if comparative data of the SSI could be extracted for analysis. Pharmacokinetic studies and trials comparing at least two different antimicrobials, placebo-controlled trials, and placebo arms of multiple-dose studies, were excluded.

Specific interventions included in the review
Single-dose pre-operative and multi-dose antimicrobial therapy. Single-dose therapy was defined as allowing the administration of a second dose of antimicrobial during surgery if the procedure was unduly long, and the plasma half-life of the drug was short. The definition does not allow for any antimicrobial agent to be given at the end of the procedure, in the recovery room, or at a later time. The drugs used included beta-lactam drugs (penicillins and cephalosporins) amongst others.

Participants included in the review
Participants having major pulmonary, gynaecological, obstetric, urological, pelvic, or abdominal surgery were included.

Outcomes assessed in the review
The outcome assessed was that of surgical site infection (SSI), defined according to the guidelines of the Centres for Diseases Control (see Other Publications of Related Interest no.1). The guidelines included the presence of pus, wound dehiscence, post-operative re-opening of the wound for drainage, antimicrobials given for the wound, and the clinician's diagnosis of an SSI. Infections at sites other than the surgical sites were excluded.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The validity criteria included evidence of adequate randomisation and appropriate data for extraction. No further details were given. The studies were quality checked by two authors acting independently.

Data extraction
The following data were extracted by two people independently: type of surgical procedure; adequacy of methods of randomisation; blinding and who was blinded; antimicrobial agent; length of multiple-dose regimes (less than 24 hours.
versus greater than 24 hours); antimicrobial complications; analysis on an intention to treat basis; length of post-operative follow-up; final SSI rates for each group converted, if required, to odds ratios (OR) and 95% confidence intervals (CIs). Any discrepancies were resolved by group discussion.

Methods of synthesis
How were the studies combined?
The ORs with 95% CIs were combined across studies using a fixed-effect model, and the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Heterogeneity of the ORs across studies was assessed using Zelen’s exact test for multiple 2x2 tables (see Other Publications of Related Interest no.3). Heterogeneity was investigated by considering the following subgroups: beta-lactam and non-beta-lactam; obstetric or gynaecological and the remainder; post-operative wound assessment blinded and the remainder; multiple dose regimes of greater than 24 hours and less than 24 hours; and the overall infection rate in each study with the rate considered as a continuous covariate.

Results of the review
Twenty-eight RCTs (N=9,478) were included.

It was not possible to analyse the combined data relating to post-operative fever, pneumonia and septicaemia, due to inconsistent information. In addition, there was a lack of clear differentiation between sepsis and fever due to other causes.

Single versus multiple-dose prophylaxis: the OR was 1.06 (95% CI: 0.89, 1.25) when using the fixed-effect model, and 1.04 (95% CI: 0.86, 1.27) when using the random-effects model. Zelen’s test for homogeneity (P) was 0.091, indicating some evidence of heterogeneity.

The following results were all obtained using a random-effects model in a post-hoc analysis.

Beta-lactam (21 RCTs): the OR was 1.10 (95% CI: 0.90, 1.33).

Non-beta-lactam (7 RCTs): the OR was 0.65 (95% CI: 0.34, 1.23; P=0.13).

Obstetric or gynaecological (10 RCTs, N=1,480: the OR was 1.14 (95% CI: 0.62, 2.09).

Non obstetric or gynaecological (19 RCTs): the OR was 1.03 (95% CI: 0.82, 1.28; P=0.75).

Post-operative wound assessment blinded (15 RCTs): the OR was 1.24 (95% CI: 0.95, 1.63).

Post-operative wound assessment non-blinded (13 RCTs): the OR was 0.91 (95% CI: 0.71, 1.17; P=0.10).

Multiple dose regimes of greater than 24 hours (16 RCTs): the OR was 1.03 (95% CI: 0.77, 1.36).

Multiple dose regimes of less than 24 hours (12 RCTs): the OR was 1.03 (95% CI: 0.76, 1.40; P=0.95).

Overall rate of infection in each study: the expected OR (random effects) for the single- vs multiple-dose comparison increased by a factor of 1.12 (95% CI: 0.89, 1.42; P=0.33) for each increment of 5% on the overall infection rate.

Authors’ conclusions
This review provided evidence of no clear superiority of either single- or multiple-dose antimicrobial prophylaxis in the prevention SSI. Continued use of single-dose antimicrobial prophylaxis for major surgery is recommended. Further studies are required, especially in previously neglected surgical disciplines.
CRD commentary
This review was clearly written and presented review. It included the inclusion criteria with details of the definitions of
the terms used, information on the primary studies, a description of the methods used to extract the data, and an
assessment and investigation of heterogeneity. The authors mentioned the potential for reference bias towards obstetrics
and gynaecological surgery. They also discussed the following problems encountered in the primary studies: inadequate
numbers; inadequate randomisation methods; lack of intention to treat analysis; difficulties with interpretation of the
definition of SSI; differing periods of follow-up; a lack of data on the follow-up period; and low infection rates in a
number of studies.

By limiting the literature search to English language studies retrieved from one database, some relevant studies may
have been omitted. More comprehensive details of the publications searched would have been helpful. Details relevant
to study validity were extracted from the primary studies but validity, other than the blinding of wound assessment, was
not investigated in the sensitivity analysis. Data were also extracted on potential antimicrobial-associated complications,
but no further mention was made of this aspect of treatment.

The strength of the evidence supporting the authors' conclusions would have been increased by reporting a validity
assessment and considering antimicrobial-associated complications.

Implications of the review for practice and research
The authors recommend the continued use of single- rather than multiple-dose prophylaxis for the time being.

The authors consider that more studies are now required especially high-quality trials in previously neglected surgical
disciplines, such as neurosurgery, head and neck, plastic, orthopaedic and endoscopic.

Bibliographic details

PubMedID
9623456

Other publications of related interest
1. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections,

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Bacterial Agents /administration & dosage /therapeutic use; Antibiotic Prophylaxis /methods; Clinical Trials as
Topic; Drug Therapy, Combination; Humans; Odds Ratio; Surgical Wound Infection /prevention & control

AccessionNumber
11998001122

Date bibliographic record published
30/11/1999

Date abstract record published
30/11/1999
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.