Effect estimates and methodological quality of randomized controlled trials about prevention of alveolar osteitis following tooth extraction: a systematic review
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CRD summary
This review concluded that treatment with local tetracycline and 0.12% chlorhexidine mouth rinse have significant and clinically relevant effects on the prevention of alveolar osteitis following the surgical removal of lower third molars. Overall, the data support the authors’ conclusions, but the poor quality of many of the studies may limit its reliability.

Authors’ objectives
To evaluate randomised controlled trials (RCTs) for the prevention of alveolar osteitis (AO) following tooth extraction.

Searching
MEDLINE and the Cochrane Library were searched from October 2004 to October 2005; the search terms were reported. The reference lists of retrieved publications were screened for additional studies. Only studies written in English, French, German or any of the Nordic languages (Danish, Finnish, Icelandic, Norwegian, Swedish) were eligible for inclusion in the review.

Study selection
Study designs of evaluations included in the review
RCTs were eligible for inclusion in the review. Trials with flawed analyses (e.g. using patients as the unit of randomisation, but teeth as the unit of analysis) were excluded from the review.

Specific interventions included in the review
Studies of interventions to prevent AO were eligible for inclusion. The included trials assessed antibiotics (tetracycline, amoxicillin, clindamycin and metronidazole), 0.12% chlorhexidine mouth rinse, propylic ester of para-hydrobenzoic acid (PEPH), and other interventions (e.g. saline rinses, local anaesthetics, gloves, coronectomy, iodine washes). Trials assessing other interventions usually compared different interventions, whilst trials of antibiotics, chlorhexidine and PEPH usually compared interventions with placebo or in some cases no treatment.

Participants included in the review
Studies of patients undergoing tooth extractions were eligible for inclusion. The majority of the included studies and the review’s conclusions focused on the surgical removal of lower third molars. Nearly half of the studies originated from Nordic countries; 31% originated from North America, with the remainder from the UK, New Zealand, Italy, Turkey, Nigeria and China.

Outcomes assessed in the review
The frequency of AO was assessed. The included studies followed up patients from 4 days to 3 weeks. AO was defined in 75% of the studies and 16% used the definition of Birn. Studies which primarily assessed post-operative complications were excluded from the review.

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

Assessment of study quality
Two authors rated the quality of each study twice using the Jadad scale. An overall total of up to 5 points were awarded according to the method of random allocation, double-blinding, and the reporting of withdrawals and drop-outs. Studies scoring 0 to 2 points were poor quality and those scoring 3 to 5 points were high quality. In addition the reporting of a definition of AO and an a priori power calculation were also assessed.
**Data extraction**
Two reviewers independently extracted the data and any disagreements were resolved through consensus. Absolute risk reductions (ARR) and numbers-needed-to-treat (NNT) were calculated, along with 95% confidence intervals (CIs). Data from split-mouth trials were considered paired data.

**Methods of synthesis**
How were the studies combined?
The authors reported that differences in study design and the reporting of study methods precluded meta-analysis; therefore the studies were combined in a narrative.

How were differences between studies investigated?
Some differences between the studies were evident from the data tables and were discussed in the text.

**Results of the review**
Thirty-two RCTs (n=8,462) were included in the review.

The mean Jadad score was 2.7 points (range: 1 to 5); half of the studies were considered poor quality. Half of the studies failed to report the method of randomisation used, while an appropriate method of double-blinding was only reported in 47%. The reporting of withdrawals and drop-outs was only complete in 22% of the studies. Only 13% of studies reported a priori power calculations.

**Antibiotic trials (8 RCTs).**
The ARR ranged from 0.8 to 31% and the NNT from 3 to 125 treated individuals. All 3 tetracycline trials (two poor quality and one high quality) showed statistically significant effects in favour of the treatment group compared with the control (the ARR ranged from 12 to 31% and the NNT from 3.2 to 8.3). However, of the remaining trials of amoxicillin (1 RCT), clindamycin (1 RCT) and metronidazole (3 RCTs), only the RCT of clindamycin showed a significant effect in favour of the intervention group.

**Chlorhexidine (5 RCTs).**
The ARR ranged from 2.8 to 25% and the NNT from 4 to 36 treated individuals. Two high-quality RCTs showed statistically significant differences after 7 days in favour of the 0.12% chlorhexidine rinse compared with placebo (ARR 11.2% and 25%; NNTs 8.9 and 4, respectively). However, 3 poor-quality RCTs of 0.2% chlorhexidine rinse in comparison with no treatment (2 RCTs) or saline rinse (1 RCT) failed to show any significant difference between the intervention and control groups.

**PEPH trials (3 RCTs).**
The ARR ranged from 6 to 26% and the NNT from 4.2 to 16.7 treated individuals. Two high-quality RCTs showed significant differences in favour of PEPH in comparison with placebo (ARRs 26% and 24%; NNTs 3.8 and 4.2, respectively), but the largest high-quality RCT failed to show a statistically significant difference between the treatment and control groups. All 3 trials were conducted by the same research group.

**Other trials (18 RCTs).**
Two poor-quality RCTs showed significant effects in favour of chlorhexidine, amoxicillin and clavulanic acid (ARR 14.8%, NNT 6.8) and chloraseptic (ARR 3.1% and NNT 32.3), in comparison with saline rinse and no treatment, respectively. In 2 further high-quality RCTs diflunisal (ARR -29.7% and NNT -3.4) and polylactic acid (ARR -10% and NNT -10) granules were shown to have significantly worse effects than no treatment. The remaining trials failed to show any significant differences between the treatment and control groups.

**Authors’ conclusions**
Local tetracycline treatment and 0.12% chlorhexidine mouth rinse showed significant and clinically relevant preventive effects on AO following the surgical removal of lower third molars.

**CRD commentary**
This review answered a clear research question that included a broad range of interventions and study populations. The literature search did not appear to make specific attempts to locate unpublished material and, given that no assessment of publication bias was reported, such bias cannot be ruled out. There may also be a risk of language bias since restrictions were placed on the study languages included. In general, the review methods attempted to reduce the risk of reviewer error and bias, although it is unclear how the studies were assessed for inclusion. Study quality was assessed and considered in the analysis, as were differences between the studies. The analysis focused only on the incidence of AO; the possible adverse effects of the interventions were not considered. Given that the authors highlighted a number of potential serious adverse effects from tetracycline, the clinical implications of their findings should be interpreted with caution. Overall, the authors’ conclusions appear to be supported by the data presented, but the paucity of studies assessing tetracycline and chlorhexidine, the small sample sizes and the poor quality of some of the studies, limits the reliability of these conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research in the form of high-quality, preferably double-blinded, RCTs with a priori power calculations are required to assess clinically relevant treatment effects and possible adverse effects of the interventions. In particular, the authors highlighted the requirement for further trials of PEPH from other independent research groups and for trials of ‘other’ interventions that show clinically relevant or significant preventive effects.

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