Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review

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Authors' objectives
To define the anti-emetic efficacy and safety of dexamethasone in the prevention of post-operative nausea and vomiting (PONV).

Searching
The authors searched MEDLINE from 1966, the Cochrane Library (Issue 2, 1999) and EMBASE from 1982, using the following free text terms: 'dexamethasone', 'nausea', 'vomiting' or 'emesis'; 'randomized' or 'randomised'; 'surgery', 'surgical' or 'postoperative'; and combinations of these words. The last search was performed in April 1999. There were no language restrictions. Additional trials were identified from reference lists of retrieved reports and by manually searching locally available anaesthesia journals. Abstracts, letters, review articles and studies on animals were not considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Dexamethasone was compared with any comparator, either active (i.e. other anti-emetics) or placebo. Sixteen different regimens of dexamethasone were tested, the most frequent of which were: for adults, 8 or 10 mg intravenously (i.v.), and for children, 1 or 1.5 mg/kg i.v. In all trials, dexamethasone was given as a single prophylactic dose, either orally as a premedication or i.v. at induction.

Specific interventions found in the included studies were: dexamethasone, ondansetron, granisetron, droperidol, metoclopramide, perphenazine, a combination of dexamethasone with a 5HT3 receptor antagonist (either ondansetron or granisetron), and placebo.

Participants included in the review
Surgical patients, both adults and children, undergoing general anaesthesia were included.

Outcomes assessed in the review
Prevention of early PONV, i.e. 0 to 6 hours post-operatively; late PONV, i.e. 0 to 24 hours post-operatively; and adverse effects. In most paediatric trials, the incidence of vomiting was the only end point.

How were decisions on the relevance of primary studies made?
All authors independently read all the reports and performed the study selection. Any disagreements were resolved through discussion.

Assessment of study quality
The authors used the 3-item, 5-point Oxford scoring system of Jadad et al. (see Other Publications of Related Interest) to assess the included studies for inclusion and methodological validity. All authors independently performed the validity assessment, and any disagreements were resolved through discussion.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted for the categories of: patients, surgery, dose and route of administration of
dexamethasone and comparators, study end points, and adverse effects. The cumulative incidence of PONV within 6 hours and 24 hours after surgery were extracted. Incidences of PONV during the two time periods were used as indicators of 'early' (0 to 6 hours) and 'late' (0 to 24 hours) anti-emetic efficacy, respectively. The anti-emetic efficacy on 'delayed' (6 to 24 hours) PONV was not analysed because the data were inconsistently reported. When several incidences of events were reported at different times, the cumulative values nearest to the 6th and 24th post-operative hours were analysed. Two different PONV events, nausea and vomiting (including retching), both early and late, were extracted in dichotomous form and treated separately.

Relative benefit and the number-needed-to-treat (NNT), both with 95% confidence intervals (CIs) were calculated for each individual trial.

**Methods of synthesis**

**How were the studies combined?**

The studies were combined using the weighted means of the experimental and control event rates. The pooled relative benefit and number-needed-to-treat (NNT), along with 95% confidence intervals (CIs), were then calculated using a fixed-effect model where there was no heterogeneity and a random-effects model where heterogeneity was present.

To estimate the additional risk of drug-related adverse effects, the relative risk and number-needed-to-harm were calculated with their 95% CIs.

**How were differences between studies investigated?**

The authors state that heterogeneity was assessed, but they do not report the method or results of the heterogeneity assessment.

**Results of the review**

Seventeen RCTs were included in the review with 1,946 participants: 598 received dexamethasone; 582 received ondansetron, granisetron, droperidol, metoclopramide or perphenazine; 423 received a placebo; and 343 received a combination of dexamethasone with a receptor antagonist, i.e. either ondansetron or granisetron. The average number of participants was 108 in each trial (range: 49 - 270) and 55 per group (range: 22 - 135). Ten trials involved adults and 7 involved children.

The median validity score was 3 (range: 2 - 5).

**Dexamethasone versus placebo (7 trials).**

In the 4 trials in adults and 3 trials in children, all results were statistically significant in favour of dexamethasone, with the exception of the following: early nausea with 8 mg dexamethasone i.v. in a small trial of 25 treated adults, and late vomiting with 0.5 mg/kg i.v. dexamethasone in a trial with a very low control event rate in children. In the pooled results, the NNT to prevent early and late vomiting with any dose of dexamethasone, compared with placebo, was 7.1 (95% CI: 4.5, 18) in adults and 3.8 (95% CI: 2.9, 5) in children. Two adult trials analysed dexamethasone's antinausea effect; the NNT was 4.3 (95% CI: 2.3, 26).

**Dexamethasone versus other anti-emetics (2 trials).**

Two trials were statistically significant in favour of the comparator anti-emetic. The combined data from the comparisons of dexamethasone with ondansetron and granisetron suggested superiority of the 5HT3 receptor antagonists in the prevention of early vomiting: NNT -5.9 (95% CI: -3.5, -20). In one large trial in children, 70 microg/kg perphenazine was significantly more effective in preventing early vomiting than 150 microg/kg dexamethasone: NNT -4.4 (95% CI: -3.0, -8.5).

**Concomitant use of dexamethasone with other anti-emetics (10 trials).**

Only the concomitant use of dexamethasone with a 5HT3 receptor antagonist showed a statistically-significant improvement. The pooled data from adults and children suggested a long-term benefit with 8 mg dexamethasone plus 4
mg ondansetron, or 40 microg/kg or 3 mg granisetron, compared with the respective 5HT3 receptor alone: the NNT to prevent late nausea (adult data only) and vomiting (data from adults and children) were 7.8 (95% CI: 4.1, 66), and 7.7 (95% CI: 4.8, 19), respectively.

Dexamethasone added to a 5HT3 receptor antagonist versus placebo (2 trials).

Event rates with the combination therapy were very low, between 2 and 5% for both early and late outcomes. Compared with placebo, the NNT point estimate to prevent early nausea and vomiting was approximately 4, and to prevent late nausea and vomiting was 3.7 and 5.5.

Adverse effects.

There was no statistically-significant difference between dexamethasone, 5HT3 receptor antagonists and placebo for these adverse effects.

Authors' conclusions
The authors state that, in the surgical setting, a single prophylactic dose of dexamethasone showed anti-emetic efficacy compared with placebo, without evidence of any clinically-relevant toxicity in otherwise healthy patients. Late, i.e. up to 24 hours, efficacy seems to be most pronounced. It is likely that the best prophylaxis of PONV currently available is achieved by combining dexamethasone with a 5HT3 receptor antagonist. Optimal doses of this combination need to be identified.

CRD commentary
This was a poorly reported systematic review. The authors have stated the research question clearly but their predetermined inclusion and exclusion criteria are limited. The literature search was quite thorough, although it was limited to published data and there were no tests for publication bias.

The quality of the included studies was assessed using a well-known quality scoring system, but the results of the scoring were not used in further sensitivity analyses or to exclude poor quality studies from the review. The authors have reported how the articles were selected, and who performed the selection, quality assessment, and data extraction.

The data extraction is reported in tables and discussed in the text of the review. The studies were statistically combined, and although heterogeneity was assessed the method of assessment and the results of that assessment are not reported. The authors' conclusions appear to follow from the results, but should be viewed with caution since the methods used in calculating the results are unclear.

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

Research: The authors imply that further research should be performed to (1) determine the optimal dose of combining dexamethasone with a 5HT3 receptor antagonist, and (2) to test the combination of dexamethasone with 5HT3 receptor antagonist using the true end points of increase in patient's comfort, shortened stays in the recovery room, and prevention of unplanned hospital admission caused by intractable PONV.

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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.