The efficacy of the 5-HT3 receptor antagonists combined with droperidol for PONV prophylaxis is similar to their combination with dexamethasone: a meta-analysis of randomized controlled trials

Habib A S, El-Moalem H E, Gan T J

CRD summary
This review compared 5-HT3 receptor antagonists (5-HT) plus droperidol with 5-HT plus dexamethasone for the prevention of post-operative nausea and vomiting. The authors concluded that there was no statistically significant difference between the treatments in efficacy or safety, and that both combinations were significantly more effective than 5-HT alone. The authors' conclusions are likely to be reliable.

Authors' objectives
To compare the efficacy and safety of 5-HT3 receptor antagonists (5-HT) plus droperidol with 5-HT plus dexamethasone for the prevention of post-operative nausea and vomiting (PONV).

Searching
MEDLINE, EMBASE and the Cochrane Library were searched to April 2003 for studies published in any language; the search terms were stated. The reference lists of identified reports and reviews were also checked. Abstracts and unpublished data were excluded.

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

Specific interventions included in the review
Studies that compared currently used 5-HT receptor antagonists (ondansetron, granisetron, tropisetron or dolasetron) in combination with either droperidol or dexamethasone to 5-HT alone were eligible for inclusion.

Participants included in the review
It was clear that patients undergoing surgery were included. The participants were children and adults.

Outcomes assessed in the review
Studies that reported the incidence of nausea and vomiting in all treatment groups were eligible for inclusion. The review assessed cumulative early PONV (0 to 6 hours after surgery) and overall PONV (0 to 24 hours after surgery). Nausea and vomiting were assessed separately. Adverse effects (i.e. dizziness, headache and drowsiness) were also assessed.

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
The studies were assessed using the 3-item 5-point Oxford scale, which assesses randomisation, blinding, and the handling of drop-outs and withdrawals. The authors did not state who performed the validity assessment.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements through re-examination of the original reports and discussion. Data for nausea and vomiting were extracted separately. When several events were reported at
different times, the outcome data were extracted for the time nearest to 6 and 24 hours after surgery. For each study, relative risks (RRs) and 95% confidence intervals (CIs) were extracted.

**Methods of synthesis**

*How were the studies combined?*

The studies were combined using a random-effects meta-analysis. Pooled RRs and the number-needed-to-treat were calculated, along with the respective 95% CIs, for the two comparisons: 5-HT plus droperidol versus 5-HT alone and 5-HT plus dexamethasone versus 5-HT alone. Data were pooled from studies with an early PONV rate of less than 55% and an overall event rate of less than 75% in the 5-HT alone treatment arm. The review considered the difference between 5-HT plus droperidol and 5-HT plus dexamethasone to be significant if the 95% CI for the pooled RR of each combination compared with 5-HT alone did not overlap.

*How were differences between studies investigated?*

Statistical heterogeneity was assessed. Where statistical heterogeneity was found, the studies responsible for this heterogeneity were sought. The data were reanalysed after excluding 16 studies conducted by Fujii et al. that had been criticised in the literature. A test of interaction was performed to examine differences between studies of adults and children and studies with and without the 16 studies conducted by Fujii et al.

**Results of the review**

Thirty-three RCTs (n=3,447) were included.

No significant statistical heterogeneity was detected for any meta-analysis other than that for overall vomiting for 5-HT plus droperidol. When excluding one study with a lower event rate for this outcome, the meta-analysis showed no significant statistical heterogeneity.

**Efficacy.**

5-HT plus droperidol significantly improved the prevention of PONV, apart from early nausea, compared with 5-HT alone. 5-HT plus dexamethasone also significantly improved the prevention of PONV in comparison with 5-HT alone. The RRs for these analyses were presented graphically in the paper, with further details reported on the Canadian Journal of Anesthesia website (accessed 26/09/2005). See Web Address at end of abstract. Only RRs for meta-analyses excluding the 16 studies conducted by Fujii et al. were presented in the paper. Since the 95% CI of the RRs of the two combination treatments versus control overlapped, it was concluded that there was no significant difference in efficacy between the two combinations.

After omitting the 16 studies by Fujii et al., the difference in efficacy outcomes between 5-HT plus droperidol and 5-HT alone was no longer statistically significant for any of the efficacy outcomes, and was no longer significant for early nausea for 5-HT plus dexamethasone versus 5-HT alone.

**Side-effects.**

There was no significant difference between 5-HT plus droperidol and 5-HT alone for dizziness (RR 1.01, 95% CI: 0.38, 2.68; 4 RCTs with 420 patients), headache (RR 1, 95% CI: 0.63, 1.58; 7 RCTs with 650 patients), or drowsiness (RR 1.21, 95% CI: 0.61, 2.38; 5 RCTs with 500 patients).

There was also no significant difference between 5-HT plus dexamethasone and 5-HT alone for dizziness (RR 0.92, 95% CI: 0.68, 1.25; 12 RCTs with 1,399 patients), headache (RR 0.90, 95% CI: 0.70, 1.15; 13 RCTs with 1,389 patients), or drowsiness (RR 1.19, 95% CI: 0.68, 2.07; 13 RCTs with 605 patients). (In the table it was reported that the results for drowsiness were based on 53 studies, but it is likely that this was a misprint since the text reported that only 13 studies were included in this analysis.)

The 95% CI of the RRs of the two combination treatments versus control overlapped, thus it was concluded that there was no significant difference in safety between the two combinations.
Authors' conclusions
There was no statistically significant difference in PONV or side-effects between 5-HT combined with either droperidol or dexamethasone. Both combinations of drugs were significantly more effective than 5-HT alone.

CRD commentary
The review question was clear in terms of the study design, intervention and outcomes. Several relevant sources were searched and the search terms were stated. Attempts were made to minimise language bias but no attempts were made to minimise publication bias. The methods used to select the studies and assess validity were not described, so it is not known whether any efforts were made to reduce errors and bias. However, methods were used to minimise bias in the extraction of data. Validity was assessed using specified established criteria.

The studies were appropriately combined in a meta-analysis and statistical heterogeneity was assessed. The conclusion regarding the relative effect of the two combinations was based on indirect comparisons between subgroups of trials, rather than direct comparisons within trials. However, the authors only included studies with similar event rates in the control group and, under these circumstances, the comparison was considered valid. The authors' conclusions are likely to be reliable.

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

Bibliographic details
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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.