Low-dose droperidol (<=1mg or <=15microg per kg) for the prevention of postoperative nausea and vomiting in adults: quantitative systematic review of randomised controlled trials

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CRD summary
This review concluded that low-dose droperidol (≤1mg or ≤15μgkg⁻¹) was clearly efficacious for prevention of postoperative nausea and vomiting and there was an argument to stop using doses of more than 1mg. The conclusions reflect the evidence but the restriction to published studies and limitations in the evidence base may mean that the conclusions are overly strong.

Authors' objectives
To determine the efficacy of low-dose droperidol in the prevention of postoperative nausea and vomiting in adults.

Searching
MEDLINE, EMBASE and Cochrane CENTRAL were searched to June 2011 for published studies of interest. No language restrictions were imposed. Search terms were reported. Bibliographies of retrieved papers were searched manually for further studies.

Study selection
Randomised controlled trials (RCTs) that reported on the efficacy of prophylactic intravenous single-dose droperidol regimens (≤1mg or ≤15μgkg⁻¹) in adults who underwent general anaesthetic were included. The primary outcome was prevention of postoperative nausea and vomiting; incidence of adverse effects was assessed as a secondary outcome. Eligible comparators included placebo or no treatment. Trials that used droperidol for the treatment of established postoperative nausea and vomiting were excluded. Also excluded were trials that combined droperidol with another antiemetic or used it as an antiemetic in a patient-controlled analgesia device.

Most studies were single centre (two were multicentre). Multicentre trials tested droperidol regimens of 0.625mg; droperidol regimens in single-centre trials ranged from 0.25mg to 1.0mg. Common comparators included placebo or saline; two studies administered droperidol alone and in combination with nitrous oxide or unbound oxygen. Types of surgery varied greatly across the studies (digestive, reproductive, ophthalmological, endocrine and oral/dental areas of health, where reported).

Multiple reviewers independently selected studies for inclusion in the review.

Assessment of study quality
Study quality was assessed independently by multiple reviewers who used a modified version of the Oxford scale to score trials from 1 to 6 (6 indicated the highest quality). Any discrepancies in assessment ratings were resolved by discussion.

Data extraction
Multiple reviewers extracted data on the outcomes (cumulative incidences of nausea and vomiting within six hours and within 24 hours of surgery and incidences of adverse effects). Cumulative incidences within zero to six hours of surgery were considered short-term or early indicators of antiemetic efficacy and those within zero to 24 hours indicated long-term or late efficacy (early events were included in late events). All variable doses (μgkg⁻¹) were extrapolated to fixed doses (mg) using the mean body weights of patients reported in the trials. Where body weight means were not reported, the median of all mean body weights from the trials was used instead.

Data were used to calculate relative risks and 95% confidence intervals. Numbers needed to treat (NNT) to benefit one individual were calculated; negative NNT were regarded as numbers needed to harm (details of the calculation methods fully reported in the review).
**Methods of synthesis**

Relative risks and 95% confidence intervals from individual studies were pooled. Statistical heterogeneity between the studies was assessed using the $X^2$ test ($p>0.1$ indicated significance) and the $I^2$ statistic. A fixed-effect model was used where significant heterogeneity was absent. A meta-regression analysis was performed to examine the influence of droperidol dose on the effects observed where significant heterogeneity was shown. Where heterogeneity remained unexplained, a random-effects model was used.

**Results of the review**

Twenty-four publications that described 25 RCTs (2,957 patients) were included in the review. The median quality score of the studies was 3 (range 1 to 6). Droperidol dose regimen ranges were 0.25mg to 0.94mg among studies that reported on early nausea, 0.25mg to 1.0mg in studies that reported on early vomiting, 0.63mg to 1.0mg for studies that reported on late nausea and 0.5mg to 1.0mg for those that reported on late vomiting.

Compared with placebo/no treatment, droperidol was associated with statistically significantly lower risks of early nausea (RR 0.45, 95% CI 0.35 to 0.58; eight RCTs; $I^2=0\%$), early vomiting (RR 0.65, 95% CI 0.57 to 0.74; 10 RCTs; $I^2=0\%$) and late nausea (RR 0.74, 95% CI 0.62 to 0.87; 12 RCTs; $I^2=63\%$). No evidence of dose responsiveness was found with the meta-analysis for late nausea. Droperidol was also associated with a statistically significantly lower risk of late vomiting, compared with placebo/no treatment (RR 0.61, 95% CI 0.47 to 0.80; 13 RCTs; $I^2=65\%$). Again, no evidence of dose responsiveness was found.

Removal of the two large multicentre RCTs from the meta-analyses for the outcomes of early vomiting, late nausea and late vomiting resulted in small reductions in the magnitudes of the effects observed (reported in the review paper). Six RCTs (droperidol dose range: 0.25mg to 0.75mg) reported on a composite nausea and vomiting endpoint; their data were not analysed within the review.

For both early and outcomes, NNT tended to be lower for nausea than vomiting. Compared with placebo/no treatment, significantly fewer patients treated with droperidol reportedly experienced headaches postoperatively (NNT=24) but significantly more were restless (number needed to harm=9). No statistically significant differences between groups were observed for incidences of sedation or dizziness. Results for NNT and adverse effects were reported in greater detail in the review paper.

**Authors’ conclusions**

Evidence from randomised controlled trials shows that low-dose droperidol ($\leq 1mg$ or $\leq 15\mu g kg^{-1}$) was clearly efficacious for the prevention of postoperative nausea and vomiting. Adverse drug reactions were likely to be dose-dependent and there was an argument to stop using doses of more than 1mg.

**CRD commentary**

The review question and inclusion criteria were clearly defined. Relevant electronic databases were searched and no language restrictions were imposed but the restriction to published studies means that some studies may have been missed. Multiple reviewers were involved in all of the review processes (minimising the risk of reviewer error and/or bias). Quality assessment revealed that the included studies were of variable quality. Study details (such as for surgery and patient characteristics) were limited. The statistical methods of synthesis were appropriate. Significant heterogeneity was observed in some meta-analyses. The authors acknowledged that most of the included studies had small sample sizes and reported large variability in control event rates; very few reported data for longer-term (24-hour) outcomes. They also acknowledged a lack of power to demonstrate a dose-response relationship.

The authors’ conclusions reflect the evidence but the restriction to published studies and limitations in the evidence base mean that these conclusions may be overly strong.

**Implications of the review for practice and research**

**Practice:** The authors stated that low-dose droperidol alone should not be regarded as a universal prophylaxis even in a high-risk setting.

**Research:** The authors stated that further research could investigate how often a prophylactic low-dose droperidol regimen might need to be repeated in order to maintain an adequate antinausea effect during a 24-hour period.
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contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on
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