5HT3 antagonists for prophylaxis of postoperative nausea and vomiting in breast surgery: a meta-analysis

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CRD summary
The authors concluded that 5-HT3 antagonists were superior to other pharmacological interventions for the prevention of post-operative nausea and vomiting in patients undergoing breast surgery under general anaesthesia. Given the small sample sizes and potential for an overstatement of findings due to double counting of participants, the authors’ conclusions should be interpreted with caution as they may not be reliable.

Authors’ objectives
To compare the effectiveness of 5-HT3 antagonists against all non 5-HT3 antagonists for the prevention of post-operative nausea and vomiting in women who underwent breast cancer surgery.

Searching
PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched up to June 2010 for relevant studies published in English. Search terms were reported. Reference lists of all included articles, reviews, correspondence and relevant abstracts were scanned for additional studies.

Study selection
Randomised controlled trials that compared 5-HT3 antagonists with placebo or active controls (any pharmacological intervention for post-operative nausea and vomiting apart from 5-HT3 antagonists), for prophylaxis against post-operative nausea and vomiting in women who underwent breast cancer surgery under general anaesthesia were included.

Studies were conducted in India, Sweden, USA, Japan, Hong Kong, Saudi Arabia, Korea, The Netherlands and Canada. Primary outcome of interest was incidence of post-operative nausea and vomiting and the secondary outcomes of interest were incidence of nausea alone, vomiting and the use of rescue medications for severe post-operative nausea and vomiting. In most studies, these outcomes were determined for 24 hours after surgery. The inhalation agents such as isoflurane, sevoflurane and halothane were used for general anaesthetics. Opioids were also used during intubation and maintenance in most trials. If included studies compared more than one regimen of a 5-HT3 antagonists against placebo, only the optimal dose was included in the meta-analysis. The included 5-HT3 antagonists drugs were ondansetron, granisetron, tropisetron, dolasetron and ramosetron; active controls were steroids (dexamethasone) and antiemetics (metoclopramide and droperidol). The time of drug administration varied from one hour before induction to end of surgery.

Two researchers independently screened studies for eligibility.

Assessment of study quality
Study quality was assessed using the Jadad scale which ranged from 0 to 5 (0 weakest score and 5 strongest).

Two reviewers evaluated study quality.

Data extraction
Data were extracted to calculate odds ratios (ORs) and their 95% confidence intervals (CIs).

Two reviewers independently extracted the studies data.

Methods of synthesis
A random-effects model was used to combine odds ratios and their 95% confidence intervals. Statistical heterogeneity was assessed by $I^2$ and $X^2$. Results were also pooled separately by comparator (placebo or active controls). Publication bias was assessed using funnel plot. L’Abbe plot and regression analysis was used to assess if the baseline risk was a
significant source of heterogeneity. Subgroup analyses were conducted for age (50 and younger versus 50 and older), duration of surgery (less than two hours, two to three and greater than three) and the timing of antiemetic prophylaxis (at induction versus end of anaesthesia). Sensitivity analyses was also conducted to determine the influence of each trial on the results.

Results of the review
Nineteen trials (28 treatment comparisons) were included in the review. According to the authors, 2,053 participants were included but there was some double counting in the control groups. All trials were of good methodological quality (Jadad score greater than 3); eleven trials reported adequate randomisation and seventeen trials reported double-blinding. Symmetrical funnel plots suggested no publication bias.

5-HT3 antagonists versus placebo (15 trials; 19 treatment comparisons): There was a statistically significant reduction in the incidence of post-operative nausea and vomiting with ondansetron compared with placebo (OR 0.20, 95% CI 0.09 to 0.46; six comparisons; $I^2=65\%$). Similar results were found for granisetron (OR 0.21, 95%CI 0.13 to 0.35; eight comparisons; $I^2=25\%$) and other 5HT3 antagonists (OR 0.13, 95% CI 0.09 to 0.19; five comparisons; $I^2=0\%$).

The overall effect of 5-HT3 antagonists were found to be superior to placebo (OR 0.18 95% CI 0.13 to 0.26; 19 comparisons; $I^2=44\%$). Significant heterogeneity was observed. Subgroup analyses showed that 5-HT3 antagonists were also found to be effective regardless of age, duration of surgery and timing of prophylaxis. Furthermore 5-HT3 antagonists reduced nausea, vomiting and the use of rescue antiemetics but had the same adverse effects compared with placebo. The L’Abbe plot suggested that the benefit of the 5-HT3 antagonist correlates positively with the baseline risk of post-operative nausea and vomiting.

5-HT3 antagonists versus active controls (seven trials; nine treatment comparisons): The overall effect of 5-HT3 antagonists significantly reduced the post-operative nausea and vomiting compared with active controls (OR 0.65, 95% CI 0.47 to 0.91; nine comparisons; $I^2=0\%$). Subgroup analyses could not perform due to the small number of trials available for ondansetron, granisetron and other 5-HT3 antagonists. Five trials, which were available for the analysis of the rescue antiemetic requirement, showed no significant difference between 5HT3 antagonists and active controls.

Granisetron alone versus combination (three trials; three treatment comparisons): The combination of granisetron with dexamethasone or droperidol showed significant greater effect on post-operative nausea and vomiting compared to granisetron alone (OR 0.25, 95% CI 0.12 to 0.53; three comparisons; $I^2=0\%$).

Further sensitivity results were reported.

Authors’ conclusions
5-HT3 antagonists were superior to other pharmacological interventions for the prevention of post-operative nausea and vomiting in patients who underwent breast surgery under general anaesthesia.

CRD commentary
The review question was clear and the inclusion criteria reported. Relevant sources were searched, but unpublished studies and studies in languages other than English were not searched for so relevant studies may have been missed. Attempts were made to minimise reviewer errors and bias in the review process. Included studies were quality assessed and appropriate methods were used for pooling data. However, the causal factors for statistical heterogeneity were not identified. For some analyses single placebo arms were used more than once to allow multiple comparisons from individual trials and this may have resulted in an overestimation of the findings.

The authors mention that evidence was strong for granisetron but was preliminary for other 5HT3 antagonists. Given the small sample sizes and potential for an overstatement of findings due to double counting of participants, the authors’ conclusions should be interpreted with caution as they may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that there was sufficient evidence to adopt 5HT3 antagonists as first line drugs for prophylaxis of post-operative nausea and vomiting in patients who underwent breast surgery under general anaesthesia.

Research: The authors stated that future studies should explore the combination therapy with different classes of
antiemetic for better control of post-operative nausea and vomiting in women who underwent breast surgery.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
22387645

**Original Paper URL**
http://www.jspgonline.com/article.asp?issn=0022-3859;year=2012;volume=58;issue=1;spage=23;epage=31;aulast=Singhal;type=0

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anesthesia /adverse effects; Antiemetics /therapeutic use; Breast Neoplasms /surgery; Female; Humans; Incidence; Mastectomy /adverse effects /methods; Postoperative Nausea and Vomiting /epidemiology /prevention & control; Randomized Controlled Trials as Topic; Risk Factors; Serotonin 5-HT3 Receptor Antagonists /therapeutic use; Treatment Outcome

**AccessionNumber**
12012019016

**Date bibliographic record published**
18/10/2012

**Date abstract record published**
06/12/2012

**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.