The efficacy of 5-HT3 receptor antagonists for the prevention of postoperative nausea and vomiting after craniotomy: a meta-analysis

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CRD summary
The authors concluded that the risk of vomiting at 24 and 48+ hours post-operatively was reduced by prophylactic 5-hydroxytryptamine type 3 receptor antagonists in patients undergoing craniotomy, but nausea was not reduced. This was a well-conducted review and the authors’ conclusions are likely to be reliable.

Authors' objectives
To evaluate the efficacy and safety of 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists for the prevention of post-operative nausea and vomiting (PONV) in patients undergoing craniotomy.

Searching
MEDLINE (1990 to 2005), PubMed, EMBASE (1988 to 2005), CINAHL (1990 to 2005), the Cochrane Library, DARE, Web of Science and Dissertation Abstracts were searched; the search terms were reported. In addition, unpublished studies were sought using OCLC Conference Papers, Proceedings Indexes and Google Scholar, and the reference lists in retrieved studies and reviews were screened. Pharmaceutical companies were contacted for details of unpublished data and ongoing trials.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that scored 3 or more points on the Jadad quality scale were eligible for inclusion in the meta-analysis.

Specific interventions included in the review
Studies that compared any type of intra-operative 5-HT3 receptor antagonist with placebo were eligible for inclusion. The included studies evaluated intravenous ondansetron (4 or 8 mg), granisetron (3 mg or 20 microg/kg) and tropisetron (2 mg). Over half of the included studies used 10 mg intravenous metoclopramide as a rescue anti-emetic following two episodes of vomiting; the remainder, where reported, used trimethobenzamide followed by ondansetron if nausea and/or vomiting exceeded 1 hour. Some studies reported the use of pre-operative, intra-operative or post-operative dexamethasone; 2 studies did not report whether dexamethasone was used or not. The studies were conducted in India, the USA, China, Egypt and Turkey.

Participants included in the review
Studies of adults undergoing craniotomy (regardless of location of surgery) were eligible for inclusion. The participants in the included studies were aged from 13 to 76 years and were undergoing infratentorial or supratentorial surgery. All of the included studies excluded patients presenting with nausea and/or vomiting and patients who had already taken an anti-emetic.

Outcomes assessed in the review
Studies that evaluated PONV were eligible for inclusion. The review assessed the cumulative incidence (number of new cases/total number of cases) of nausea, vomiting, and the use of rescue medication over 24 and 48+ hours. The review also assessed adverse events.

How were decisions on the relevance of primary studies made?
One reviewed initially screened abstracts and excluded irrelevant papers. Two reviewers then independently screened the remaining studies. Any disagreements were resolved by consensus.
Assessment of study quality
Two reviewers independently assessed validity using the Jadad scale, which considers randomisation, blinding, and the reporting of withdrawals and drop-outs. The maximum possible score was 5 points.

Data extraction
Two reviewers independently extracted the outcome data onto a standardised form. One reviewer entered the data for analysis, and one reviewer identified and resolved any discrepancies.

Methods of synthesis
How were the studies combined?
The pooled relative risks of harm (RRs; the risk of an event in the treatment group relative to the risk in the control group) were calculated with 95% confidence intervals (CIs) using a random-effects model. The number-needed-to-treat was also calculated. Publication bias was assessed using a funnel plot. Patient age, gender and duration of anaesthesia were compared between treatment groups.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic. Where heterogeneity was found, exploratory analysis was performed.

Results of the review
Seven RCTs were included (n=448 in the meta-analysis).

Three studies received a Jadad quality score of 3, two received a score of 4, and two received a maximum score of 5.

There was no significant difference between the 5-HT3 receptor antagonist treatment groups and control groups with regards to age, gender or length of administration of anaesthetic.

Cumulative post-operative emesis was significantly less common in 5-HT3 receptor antagonist treatment groups than in control groups at 24 hours (RR 0.50, 95% CI: 0.38, 0.66, p<0.00001; 6 RCTs) and 48+ hours (RR 0.52, 95% CI: 0.36, 0.75, p=0.0005; 5 RCTs). No significant heterogeneity was detected.

There was no statistically significant difference in post-operative nausea between 5-HT3 receptor antagonist treatment groups compared with control groups at 24 hours (RR 0.76, 95% CI: 0.54, 1.06, p=0.11; 5 RCTs) or 48+ hours (RR 0.81, 95% CI: 0.62, 1.06, p=0.13; 5 RCTs). Moderate heterogeneity was found at 24 hours (I-squared 48%).

The funnel plot did not exclude the possibility of publication bias.

The use of rescue anti-emetic medication was significantly reduced in 5-HT3 receptor antagonist treatment groups compared with control groups at 24 hours (RR 0.49, 95% CI: 0.27, 0.87; 4 RCTs), but there was no significant difference at 48+ hours (4 RCTs). Moderate heterogeneity was found at 24 hours (I-squared 59%).

None of the studies reported significant adverse events in either treatment group.

Authors’ conclusions
The risk of vomiting at 24 and 48+ hours post-operatively was reduced by prophylactic 5-HT3 receptor antagonists in patients undergoing craniotomy, but nausea was not reduced.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Many potential sources were searched and extensive attempts were made to minimise publication bias. However, it was not clear whether any language restrictions had been applied, so the potential for language bias cannot be assessed. Methods were used to minimise reviewer error and bias in the study.
selection, validity assessment and data extraction processes. Validity was assessed using established criteria and only higher quality studies were included in the analyses.

Details of the included studies were tabulated, and the authors compared baseline data between the treatment and control groups. Statistical heterogeneity was assessed and the pooling of data on post-operative emesis appeared appropriate. Potential reasons for the significant heterogeneity among studies reporting post-operative nausea were examined. This was a well-conducted review and the authors’ conclusions are likely to be reliable.

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

Research: The authors stated the need for further research into interventions to control post-operative nausea and to further reduce post-operative vomiting.

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Other publications of related interest
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