Serotonin receptor antagonists for the prevention and treatment of pruritus, nausea, and vomiting in women undergoing cesarean delivery with intrathecal morphine: a systematic review and meta-analysis

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CRD summary
This review found that prophylactic serotonin (5-HT\textsubscript{3}) receptor antagonists did not reduce pruritus incidence, but significantly reduced severity and need for pruritus treatment, postoperative nausea and vomiting and need for antiemetic therapy, and effectively treated established pruritus, in women who received intrathecal morphine for caesarean delivery. Methodological concerns and potential for missed studies made the reliability of the conclusions unclear.

Authors' objectives
To evaluate the efficacy of serotonin (5-HT\textsubscript{3}) receptor antagonists for the prevention and treatment of pruritus, nausea and vomiting in women receiving spinal anaesthesia with intrathecal morphine for caesarean delivery.

Searching
MEDLINE (from 1966), EMBASE, Web of Science, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for publications in any language. The latest search was June 2008. Search terms were reported. Only full reports were considered; abstracts, letters and unpublished studies were excluded. The bibliography of each retrieved article and review was handsearched.

Study selection
Randomised controlled trials (RCTs) that compared prophylaxis or treatment using a serotonin (5-HT\textsubscript{3}) receptor antagonist (ondansetron, granisetron, tropisetron and dolasetron) versus placebo in women who underwent caesarean delivery under spinal anaesthesia with standardised intrathecal morphine were eligible for inclusion. Eligible trials had to report the main endpoints of incidence of pruritus and/or nausea and/or vomiting in all study groups.

Most of the included studies reported on prophylaxis against pruritus and/or nausea and vomiting, mostly with an observation period of 24 hours. No studies were of treatment of nausea and vomiting. Severity of nausea and vomiting was also assessed; studies used three different scales (details were provided). The 5-HT\textsubscript{3} receptor antagonists used in the included studies were ondansetron (4mg and 8mg), granisetron (1mg and 3mg) and tropisetron (5mg). Placebo was normal saline. Dose of intrathecal morphine ranged from 0.1mg to 0.2mg. Side effects were reported (such as headache).

The authors did not state how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed by two reviewers independently using the four-item seven-point Modified Oxford Scale. Any discrepancies were resolved by discussion with a third reviewer. Criteria used included: randomisation, allocation concealment, blinding and flow of patients.

Data extraction
Dichotomous data were extracted independently by three reviewers to calculate relative risks (RR) and 95% confidence intervals (CI). If event rates were reported over multiple time intervals and not over the entire duration of the study, authors were contacted for the relevant information and any other missing information. If the authors did not respond, the highest recorded incidence over the duration of the study was used in analysis. If the studies included groups other than those who took 5-HT\textsubscript{3} receptor antagonists or placebo, these groups were omitted from the analysis.

Methods of synthesis
Relative risks were pooled using a fixed-effects model. Between-study heterogeneity was determined using \(X^2\) test, \(I^2\)
statistic and $T^2$. Where there was significant heterogeneity ($p<0.1$), a random-effects model was used. Forrest plots were generated. Number needed to treat (NNT) was calculated to estimate the overall clinical impact of statistically significant interventions. Subgroup analyses were performed: type of 5-HT$_3$ receptor antagonist; postoperative pruritis using the studies that used intrathecal morphine without lipophilic opioids; and to investigate dose responsiveness. Publication bias was not assessed due to the small number of studies.

**Results of the review**

Nine RCTs were identified ($n=1,232$, range 60 to 240). Mean validity score was 5.4 (range 3 to 7). Two hundred patients received other antiemetics and were excluded from the analysis. The authors give the total number of patients as 1,152.

Incidence of pruritus was not significantly reduced with 5-HT$_3$ receptor antagonists compared to placebo (RR 0.94, 95% CI 0.81 to 1.09, $I^2=65$%; five RCTs), but their use significantly reduced incidence of severe pruritus (RR 0.79, 95% CI 0.65 to 0.97, NNT=13; four RCTs) and need for treatment of pruritus (RR 0.80, 95% CI 0.64 to 0.96, NNT=15; six RCTs). One RCT assessed treatment success for established pruritis and reported that ondansetron significantly reduced the pruritis severity score (RR 0.30, 95% CI 0.16 to 0.59, NNT=3).

Use of 5-HT$_3$ receptor antagonists significantly reduced incidence of postoperative nausea (RR 0.75, 95% CI 0.58 to 0.96, NNT=9, $I^2=23$%; four RCTs), vomiting (RR 0.49, 95% CI 0.30 to 0.81, NNT=12, $I^2=33$%; four RCTs), need for postoperative rescue antiemetic treatment (RR 0.38, 95% CI 0.21 to 0.68, NNT=7; three RCTs) and incidence of severe postoperative nausea and vomiting (RR 0.55, 95% CI 0.33 to 0.76, NNT=9; four RCTs) compared to placebo.

Subgroup analyses indicated that only treatment with ondansetron resulted in statistically significant results (as reported in the review). There was no evidence for dose responsiveness for ondansetron for prophylaxis of pruritis or severity of pruritis. There was no significant effect for 5-HT$_3$ receptor antagonists compared to placebo on incidence of postoperative pruritis when the analysis was limited to trials that used intrathecal morphine without lipophilic drugs.

No significant differences between 5-HT$_3$ receptor antagonists and placebo were reported for side effects; these included headache, cardiac arrhythmias and extrapyramidal side effects.

**Authors' conclusions**

Although prophylactic 5-HT$_3$ receptor antagonists did not reduce incidence of pruritus, they significantly reduced the severity and need for treatment of pruritus, incidence of postoperative nausea and vomiting, need for antiemetic therapy, and effectively treated established pruritus, in women who received intrathecal morphine for caesarean delivery. Their use in this patient population should be considered, but further research was needed.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched in any language. Unpublished studies were not considered and publication bias was not assessed. Study quality was assessed using suitable criteria. Validity assessment and data extraction were carried out with efforts to reduce error and bias; it was unclear whether this applied to study selection. Relevant study details were reported, but there were no details of the age of the participants. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. Analyses by type of 5-HT$_3$ receptor antagonist included only one study for some comparisons. Only a small number of studies and participants were included (acknowledged by the authors). Most studies were of good quality. The authors had concerns about differences in methodology between some studies.

In view of potential for missed studies, concerns about the suitability of the meta-analysis and the authors' concerns about the methodology of some studies, the extent to which the authors' conclusions are reliable is unclear.

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

**Practice**: The authors did not state any implications for practice.
Research: The authors identified a need for larger studies with adequate power to further investigate use of 5-HT3 serotonin receptor antagonists for prophylaxis against pruritus, intraoperative and postoperative nausea and vomiting in obstetrics and for treatment of established pruritus. They recommended use of validated and consistent scoring systems for assessing severity of pruritus and nausea and clearly defined and consistent endpoints for treatment of pruritus. Nausea and vomiting should be reported separately and clear differentiation made between events before, during or after delivery.

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