Dexamethasone for the Prophylaxis of Postoperative Nausea and Vomiting Associated with Neuraxial Morphine Administration: A Systematic Review and Meta-Analysis

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BACKGROUND: We performed a systematic review to assess the efficacy of dexamethasone in reducing postoperative nausea, vomiting (PONV), pruritus, and enhancing postoperative analgesia in patients receiving neuraxial anesthesia with neuraxial morphine.

METHODS: We searched Medline (1966–2011), the Cochrane Central Register of Controlled Trials, EMBASE, and Web of Science for all randomized controlled trials comparing dexamethasone with placebo for the prevention of PONV and/or pruritus in patients receiving neuraxial morphine as part of a neuraxial anesthetic technique. Data were extracted independently by the authors on the incidence of PONV, pruritus, pain scores at 4 and 24 hours, and use of rescue antiemetics, antipruritics, and analgesics.

RESULTS: Eight randomized controlled trials (4 cesarean deliveries, 4 total abdominal hysterectomies) were included. From these trials, 768 patients were analyzed with 473 receiving dexamethasone and 295 receiving placebo. The doses of dexamethasone investigated ranged from 2.5 to 10 mg. Dexamethasone reduced the incidence of postoperative nausea (relative risk, RR [95% confidence interval, CI] = 0.57 [0.45, 0.72]), vomiting (RR [95% CI] = 0.56 [0.43, 0.72]), and the use of rescue antiemetic therapy (RR [95% CI] = 0.47 [0.36, 0.61]) compared with placebo. There was no evidence of dose responsiveness with respect to its antiemetic effect. Dexamethasone also reduced 24-hour visual analog pain scores (measured on an 11-point scale [0–10]) (mean difference [95% CI] = −0.30 [−0.46, −0.13]) and the use of rescue analgesics (RR [95% CI] = 0.72 [0.52, 0.98]). Dexamethasone did not reduce the incidence of pruritus (RR [95% CI] = 0.98 [0.84, 1.15]). Examination of the funnel plots and Egger’s test revealed evidence of publication bias in the primary outcomes.
CONCLUSION: Dexamethasone is an effective antiemetic for patients receiving neuraxial morphine for cesarean delivery and abdominal hysterectomy. In addition, the doses used for antiemetic prophylaxis enhanced postoperative analgesia compared with placebo. However, dexamethasone was not effective for the prophylaxis against neuraxial morphine–induced pruritus. (Anesth Analg 2012;114:813–22)

Dexamethasone is an effective antiemetic when administered prophylactically in patients receiving general anesthesia. However, its role as an antiemetic in patients receiving neuraxial anesthesia is not well described. Neuraxial anesthesia is frequently used for cesarean delivery and other lower abdominal and lower limb procedures. The addition of neuraxial morphine to local anesthetics provides effective long-lasting postoperative analgesia. However, neuraxial morphine has been associated with a frequent incidence of postoperative nausea, vomiting (PONV) and pruritus.

We performed this systematic review and meta-analysis primarily to assess the efficacy of dexamethasone prophylaxis in reducing the overall incidence of postoperative nausea (PON) and postoperative vomiting (POV). Secondarily, we also planned to assess its role in preventing pruritus and enhancing postoperative analgesia in patients receiving neuraxial morphine as a part of a neuraxial anesthetic technique.

METHODS
We followed the recommendations of the PRISMA statement.

Eligibility Criteria
We performed a literature search of all published reports of randomized controlled trials that compared a single dose of IV dexamethasone with placebo primarily for the prevention of PONV in patients who received a single dose of neuraxial preservative-free morphine as an adjunct to a neuraxial anesthetic technique. In addition, we collected data on the incidence of pruritus and/or need for rescue antipruritic treatment, as well as pain scores and/or the need for rescue analgesics. The primary anesthetic technique had to be neuraxial anesthesia.

Literature Search and Study Selection
We searched Medline (1966–2011), the Cochrane Central Register of Controlled Trials, EMBASE, and Web of Science using the terms “dexamethasone,” “postoperative,” “nausea,” “vomiting,” “emesis,” “morphine,” “epidural,” “extradural,” “spinal,” “intrathecal,” “neuraxial,” “an(a)esthesia,” “analgesia” and/or “pruritus,” and their combinations in all fields without language restriction up to February 2011. The bibliographies of retrieved trials were used to identify other relevant articles.

The methodological quality of the included studies was assessed using the risk of bias tool recommended by the Cochrane Collaboration. Two of the authors
scored the included studies independently (TKA and CAJ). Any discrepancies were resolved by discussion with the third author (ASH).

**Data Collection and Presentation**

One author (TKA) extracted the data. A data collection sheet was used to collect the following data: (i) authors, (ii) year of publication, (iii) primary country of origin, (iv) type of surgery, (v) anesthetic technique, (vi) dose, timing, and route of administration of neuraxial morphine, (vii) dose and time of administration of dexamethasone, (viii) outcome measures including the incidence of PONV, pruritus, pain intensity, and the use of rescue antiemetics, antipruritics, and analgesics postoperatively, and (ix) side effects. Two authors (CAJ and ASH) independently checked the extracted data for accuracy. When studies included multiple group comparisons, only data from the dexamethasone and placebo groups were extracted. For studies not reporting an overall incidence of PONV but instead reporting PON and POV at different time intervals, we recorded the highest incidence for both outcomes. Pain intensity was recorded at 4 hours (early) and 24 hours (late) or the closest reported time intervals in the included studies. Pain scores were assumed to be at rest unless stated otherwise. We also collected the highest pain scores reported in each study regardless of the reported time interval. Pain scores reported as a 0- to 100-mm visual analog scale were converted to an 11-point scale (0 = no pain to 10 = worst pain). We also performed a subgroup analysis of different dexamethasone doses, surgical procedures, and route of administration of neuraxial morphine for the relevant outcomes when reported by 2 or more studies. Authors were contacted to provide additional information or clarification when necessary.

**Meta-Analysis**

Dichotomous data were extracted and summarized using relative risks (RRs) with 95% confidence intervals (CIs). If the 95% CI included a value of 1, it was assumed that there was no statistically significant difference between dexamethasone and placebo. Continuous data were extracted as mean and standard deviations and summarized using mean difference (MD) with 95% CI. If the 95% CI included a value of 0, it was assumed that there was no difference between the groups. Mean and standard deviations were estimated from studies reporting outcomes as median and range as recommended by Hozo et al.9 A fixed effects model was used by default. Significant heterogeneity was defined as $I^2 > 50\%$, and in such cases, the reason for heterogeneity was explored. Forest plots were used to graphically represent and evaluate treatment effects. The number needed to treat was calculated to estimate the overall clinical impact of any statistically significant interventions for dichotomous data for the primary outcomes. To assess whether there was a dose-response relationship for the antiemetic efficacy of dexamethasone, we performed a meta-regression in which the outcome variable was the log (RR) for PON or POV and the predictor variable was dexamethasone dose. A fixed effect regression
model was used. Publication bias was assessed using funnel plots for the primary outcomes and the regression test described by Egger et al.\textsuperscript{10} When outcomes were not consistently reported and quantitative analysis was inappropriate, they were reviewed qualitatively.

Analyses were performed using Review Manager Software (Review Manager [Revman] Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008), and Comprehensive Meta-Analysis software (Version 2.2.050).

**RESULTS**

We initially identified 191 publications but subsequently excluded 178 articles (Fig. 1). Of the remaining 13 potentially relevant articles, 8 were eventually analyzed.\textsuperscript{11–18} Of the excluded studies, no neuraxial morphine was administered in 2 studies,\textsuperscript{19,20} intrathecal neostigmine was administered in 1 study,\textsuperscript{21} intrathecal meperidine was administered in another,\textsuperscript{22} and there was no placebo group in the remaining study.\textsuperscript{23} Seven of the studies were performed in Taiwan, Republic

**Figure 1.** Flow chart of screened, excluded, and included trials. The included trials investigated dexamethasone as an antiemetic in patients receiving neuraxial morphine who also had neuraxial anesthesia as the primary anesthetic technique. RCTs = randomized controlled trials.
of China\textsuperscript{11-16,18} and the remaining study in the United Kingdom.\textsuperscript{17} Authors of 2 publications were contacted and provided missing data.\textsuperscript{14,17} The details of the included trials are shown in Table 1. The methodological quality of the included studies is summarized in the risk of bias table (Table 2). There were no discrepancies between the authors in the assessment of the methodological quality of the included studies. The 8 randomized controlled trials included 1014 patients; 246 of these patients received another antiemetic (tropisetron\textsuperscript{12}, droperidol\textsuperscript{11,15,18}, cyclizine\textsuperscript{17}, and metoclopramide\textsuperscript{16}) either alone or in combination with dexamethasone. These patients were not included in the analysis. Of the remaining 768 patients, 473 received IV dexamethasone and 295 received a placebo. Neuraxial morphine was administered for abdominal hysterectomies in 4 studies\textsuperscript{12,14,16,18} and cesarean deliveries in the remaining 4 studies.\textsuperscript{11,13,15,17} Epidural anesthesia was the primary anesthetic technique in 6 studies,\textsuperscript{12-16,18} combined spinal-epidural anesthesia in 1 study,\textsuperscript{17} and spinal anesthesia in the remaining study.\textsuperscript{11} The dose of epidural morphine was 3 mg\textsuperscript{12-16,18} and the dose of intrathecal morphine was 0.2 mg.\textsuperscript{11,17} The doses and time of administration of dexamethasone in each individual trial are listed in Table 1. Six studies investigated a single dose of dexamethasone\textsuperscript{11,12,14-17} whereas 2 dose ranging studies compared 3 doses with a placebo group.\textsuperscript{13,18} Dexamethasone was used at a dose of 2.5 mg in 2 studies,\textsuperscript{13,18} 5 mg in 4 studies,\textsuperscript{12,13,16,18} 8 mg in 4 studies,\textsuperscript{11,14,15,17} and 10 mg in 2 studies\textsuperscript{13,18} (Tables 1 and 3). Dexamethasone was administered before neuraxial morphine in 6 studies\textsuperscript{12-16,18} and after in 2 studies.\textsuperscript{11,17} In 7 of the 8 studies,\textsuperscript{11,16,18} dexamethasone was administered as an IV bolus, and in the remaining study,\textsuperscript{17} the drug was administered as an infusion. Visual examination of the funnel plots for both PON (Fig. 2) and POV (not shown) revealed evidence of publication bias. Egger’s test was also statistically significant for both PON (intercept [95% CI] = −2.84 [−4.26, −1.42], \(P = 0.002\)) and POV (intercept [95% CI] = −2.80 [−3.87, −1.73], \(P < 0.001\)).

**Postoperative Nausea and Vomiting**

**Postoperative Nausea**

All 8 studies reported on the incidence of PON (Table 3).\textsuperscript{11-18} Overall, when all doses of dexamethasone for all included studies were combined, there was a significant reduction in the incidence of PON compared with placebo (19% vs 36%, RR [95% CI] = 0.57 [0.45, 0.72]). Doses of 5, 8, and 10 mg significantly reduced the incidence of PON compared with placebo. However, the lowest dose of 2.5 mg did not significantly reduce the incidence of PON. There was no evidence of heterogeneity observed with this outcome (\(I^2\) [95% CI] = 32% [0%, 70%]). A fixed effect meta-regression demonstrated no evidence of dose-responsiveness for PON. The slope (95% CI) was 0.01160 (−0.09684, 0.12003) log RR per milligram of dexamethasone (\(P = 0.83\)). In a subgroup analysis by type of surgery, dexamethasone significantly reduced the incidence of PON compared with placebo in patients having abdominal hysterectomy (15% vs 32%, RR [95% CI] = 0.46 [0.31, 0.68]) and cesarean delivery (23% vs 41%, RR [95% CI] = 0.68 [0.51, 0.90]). In a subgroup analysis by route of
### Table 1. Characteristics of Included Trials

<table>
<thead>
<tr>
<th>First author, year of publication</th>
<th>Study groups (n)</th>
<th>Time of administration of study drug</th>
<th>Timing of dexamethasone administration in relation to neuraxial morphine</th>
<th>Type of surgery</th>
<th>Anesthetic technique</th>
<th>Dose and route of neuraxial morphine</th>
<th>Postoperative rescue antiemetic</th>
<th>Postoperative rescue antipruritic</th>
<th>Postoperative rescue analgesic</th>
<th>Outcomes analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 199914</td>
<td>Dexamethasone 8 mg (38), saline (36)</td>
<td>End of surgery</td>
<td>Before TAH</td>
<td>Epidural</td>
<td>3 mg epidural</td>
<td>Metoclopramide 10 mg IV</td>
<td>Diphenhydramine 20 mg IM</td>
<td>Diclofenac 75 mg IM</td>
<td>PON, POV, use of rescue antiemetics, VAS pain scores, use of rescue analgesics, incidence of pruritus, use of rescue antipruritics, incidence of side effects</td>
<td></td>
</tr>
<tr>
<td>Tzeng, 200015</td>
<td>Dexamethasone 8 mg (38), droperidol 1.25 mg (38), saline (37)</td>
<td>End of surgery</td>
<td>Before Cesarean delivery</td>
<td>Epidural</td>
<td>3 mg epidural</td>
<td>Metoclopramide 10 mg IV</td>
<td>Diphenhydramine 20 mg IM</td>
<td>Diclofenac 75 mg IM</td>
<td>PON, POV, use of rescue antemetics, use of rescue analgesics, incidence of pruritus, incidence of side effects</td>
<td></td>
</tr>
<tr>
<td>Ho, 200118</td>
<td>Dexamethasone 2.5 mg (43), dexamethasone 5 mg (42), dexamethasone 10 mg (44), droperidol 1.25 mg (42), saline (43)</td>
<td>End of surgery</td>
<td>Before TAH</td>
<td>Epidural</td>
<td>3 mg epidural</td>
<td>Ondansetron 4 mg IV</td>
<td>Diclofenac 75 mg IM</td>
<td>Diclofenac 75 mg IM</td>
<td>PON, POV, use of rescue antiemetics, VAS pain scores, use of rescue analgesics, incidence of pruritus, incidence of side effects</td>
<td></td>
</tr>
<tr>
<td>Wang, 200113</td>
<td>Dexamethasone 2.5 mg (44), dexamethasone 5 mg (44), dexamethasone 10 mg (43), saline (44)</td>
<td>End of surgery</td>
<td>Before Cesarean delivery</td>
<td>Epidural</td>
<td>3 mg epidural</td>
<td>Ondansetron 4 mg IV</td>
<td>Diphenhydramine 20 mg IV</td>
<td>Tenoxicam 20 mg IV</td>
<td>PON, POV, use of rescue antiemetics, VAS pain scores, use of rescue analgesics, incidence of pruritus, use of rescue antipruritics, incidence of side effects</td>
<td></td>
</tr>
<tr>
<td>Tzeng, 200216</td>
<td>Dexamethasone 5 mg (38), metoclopramide 10 mg (39), saline (38)</td>
<td>End of surgery</td>
<td>Before TAH</td>
<td>Epidural</td>
<td>3 mg epidural</td>
<td>Ondansetron 4 mg IV</td>
<td>Diclofenac 75 mg IM</td>
<td>Diclofenac 75 mg IM</td>
<td>PON, POV, use of rescue antiemetics, VAS pain scores, use of rescue analgesics, incidence of pruritus, incidence of side effects</td>
<td></td>
</tr>
<tr>
<td>Wang, 200212</td>
<td>Dexamethasone 5 mg (38), tropisetron 5 mg (39), saline (37)</td>
<td>End of surgery</td>
<td>Before TAH</td>
<td>Epidural</td>
<td>3 mg epidural</td>
<td>Droperidol 1.25 mg IV</td>
<td>Diphenhydramine 20 mg IV</td>
<td>Diclofenac 75 mg IM</td>
<td>PON, POV, use of rescue antiemetics, VAS pain scores, use of rescue analgesics, incidence of pruritus, use of rescue antipruritics, incidence of side effects</td>
<td></td>
</tr>
<tr>
<td>Nortcliffe, 200317</td>
<td>Dexamethasone 8 mg (30), cyclizine 50 mg (30), saline (30)</td>
<td>In recovery room</td>
<td>After Cesarean delivery</td>
<td>CSE</td>
<td>0.2 mg intrathecal</td>
<td>Prochlorperazine 12.5 mg IM</td>
<td>Chlorpheniramine 4 mg orally</td>
<td>Acetaminophen 500 mg/codeine 30 mg orally</td>
<td>PON, POV, use of rescue antiemetics, VAS pain scores, use of rescue analgesics, incidence of pruritus, incidence of side effects</td>
<td></td>
</tr>
<tr>
<td>Wu, 200711</td>
<td>Dexamethasone 8 mg (30), droperidol 1.25 mg (30), dexamethasone 8 mg + droperidol 1.25 mg (30), saline (30)</td>
<td>Before skin incision</td>
<td>After Cesarean delivery</td>
<td>Spinal</td>
<td>0.2 mg intrathecal</td>
<td>Ondansetron 4 mg</td>
<td>Diphenhydramine 20 mg IV</td>
<td>Diclofenac 75 mg IM</td>
<td>PON, POV, use of rescue antiemetics, VAS pain scores, use of rescue analgesics, incidence of pruritus, incidence of side effects</td>
<td></td>
</tr>
</tbody>
</table>

TAH = total abdominal hysterectomy; CSE = combined spinal-epidural; PON = postoperative nausea; POV = postoperative vomiting; VAS = visual analog scale.

*Additional data obtained from authors.*
Dexamethasone and Neuraxial Morphine–Induced PONV

administration of neuraxial morphine, dexamethasone significantly reduced PON compared with placebo in patients receiving epidural morphine (14% vs 31%, RR [95% CI] = 0.45 [0.32, 0.62]). In these studies, dexamethasone was also administered before epidural morphine. In the studies in which intrathecal morphine was administered, there was no difference in PON between the groups (52% vs 58%, RR [95% CI] = 0.89 [0.64, 1.22]).

**Postoperative Vomiting**

POV was investigated in all 8 studies (Table 3). Overall, when all doses of dexamethasone were combined, there was a significant reduction in the incidence of POV compared with placebo (15% vs 30%, RR [95% CI] = 0.56 [0.43, 0.72]). Doses investigated significantly reduced the incidence of POV when compared with placebo (Table 1). There was no evidence of heterogeneity among the trials ($I^2$ [95% CI] = 44% [0%, 75%]). A fixed effect meta-regression demonstrated no evidence of a dose-response relationship. The slope (95% CI) was 0.1127 (−0.0244, 0.2498) log

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**Table 2. Risk of Bias**

<table>
<thead>
<tr>
<th>Included studies</th>
<th>Adequate sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Incomplete data addressed</th>
<th>Free of selective reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 199914</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tzeng, 200015</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ho, 200118</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wang, 200113</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Tzeng, 200216</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wang, 200212</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nortcliffe, 200317</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wu, 200711</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Each study risk of bias was assessed as Yes (low risk of bias), No (high risk of bias), or Unclear for each question-based entry.

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**Table 3. The Effect of Dexamethasone on the Incidence of Postoperative Nausea, Vomiting, Pruritus, and the Use of Rescue Antiemetics and Antipruritics**

<table>
<thead>
<tr>
<th>Incidence of postoperative nausea</th>
<th>Risk of treatment group</th>
<th>Risk of control group</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone 2.5 mg12,13,16,18</td>
<td>19/87 (22%)</td>
<td>26/87 (30%)</td>
<td>0.73 (0.44, 1.22)</td>
<td>—</td>
</tr>
<tr>
<td>Dexamethasone 5 mg12,13,16,18</td>
<td>21/163 (13%)</td>
<td>50/162 (31%)</td>
<td>0.42 (0.26, 0.66)</td>
<td>6 (4, 11)</td>
</tr>
<tr>
<td>Dexamethasone 8 mg12,13,14,15,17</td>
<td>39/136 (29%)</td>
<td>57/133 (43%)</td>
<td>0.68 (0.50, 0.92)</td>
<td>8 (4, 35)</td>
</tr>
<tr>
<td>Dexamethasone 10 mg12,13,18</td>
<td>10/87 (12%)</td>
<td>26/87 (30%)</td>
<td>0.38 (0.20, 0.75)</td>
<td>5 (3, 15)</td>
</tr>
<tr>
<td>All studies combined11–18</td>
<td>89/473 (19%)</td>
<td>107/295 (36%)</td>
<td>0.57 (0.45, 0.72)</td>
<td>6 (4, 9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence of postoperative vomiting</th>
<th>Risk of treatment group</th>
<th>Risk of control group</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone 2.5 mg13,18</td>
<td>14/87 (16%)</td>
<td>20/87 (23%)</td>
<td>0.70 (0.38, 1.29)</td>
<td>—</td>
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<tr>
<td>Dexamethasone 5 mg12,13,16,18</td>
<td>14/163 (9%)</td>
<td>39/162 (24%)</td>
<td>0.36 (0.20, 0.63)</td>
<td>7 (4, 13)</td>
</tr>
<tr>
<td>Dexamethasone 8 mg12,13,14,15,17</td>
<td>35/136 (26%)</td>
<td>50/133 (38%)</td>
<td>0.69 (0.50, 0.96)</td>
<td>9 (4, 121)</td>
</tr>
<tr>
<td>Dexamethasone 10 mg13,18</td>
<td>6/87 (7%)</td>
<td>20/87 (23%)</td>
<td>0.30 (0.13, 0.71)</td>
<td>7 (4, 17)</td>
</tr>
<tr>
<td>All studies combined11–18</td>
<td>69/473 (15%)</td>
<td>89/295 (30%)</td>
<td>0.56 (0.43, 0.72)</td>
<td>7 (5, 11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Use of rescue antiemetics</th>
<th>Risk of treatment group</th>
<th>Risk of control group</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone 2.5 mg13,18</td>
<td>19/87 (22%)</td>
<td>28/87 (32%)</td>
<td>0.68 (0.41, 1.12)</td>
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<tr>
<td>Dexamethasone 5 mg12,13,16,18</td>
<td>20/163 (12%)</td>
<td>56/162 (35%)</td>
<td>0.35 (0.22, 0.56)</td>
<td>5 (3, 8)</td>
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<tr>
<td>Dexamethasone 8 mg12,13,14,15,17</td>
<td>26/136 (19%)</td>
<td>46/133 (35%)</td>
<td>0.56 (0.38, 0.82)</td>
<td>6 (4, 15)</td>
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<td>Dexamethasone 10 mg13,18</td>
<td>9/87 (10%)</td>
<td>28/87 (32%)</td>
<td>0.32 (0.16, 0.64)</td>
<td>5 (3, 10)</td>
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<td>All studies combined11–18</td>
<td>74/473 (16%)</td>
<td>102/295 (35%)</td>
<td>0.47 (0.32, 0.69)</td>
<td>6 (4, 8)</td>
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<table>
<thead>
<tr>
<th>Incidence of pruritus</th>
<th>Risk of treatment group</th>
<th>Risk of control group</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>All studies combined11–15,17</td>
<td>158/306 (52%)</td>
<td>120/214 (56%)</td>
<td>0.98 (0.84, 1.15)</td>
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</table>

<table>
<thead>
<tr>
<th>Use of rescue antipruritics</th>
<th>Risk of treatment group</th>
<th>Risk of control group</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies combined12–14,17</td>
<td>29/238 (12%)</td>
<td>26/147 (18%)</td>
<td>0.71 (0.43, 1.18)</td>
<td>—</td>
</tr>
</tbody>
</table>

RR = relative risk; CI = confidence interval; NNT = number needed to treat.
Dexamethasone and Neuraxial Morphine–Induced PONV

RR per milligram of dexamethasone \((P = 0.11)\). In a subgroup analysis by the type of surgery, dexamethasone significantly reduced the incidence of POV compared with placebo in patients having total abdominal hysterectomy (9% vs 25%, RR [95% CI] = 0.36 [0.26, 0.52]) and cesarean delivery (20% vs 36%, RR [95% CI] = 0.70 [0.52, 0.96]). In a subgroup analysis by route of administration of neuraxial morphine, dexamethasone significantly reduced the incidence of POV in those patients receiving epidural morphine compared with placebo (9% vs 24%, RR [95% CI] = 0.38 [0.25, 0.57]). However, in the studies in which intrathecal morphine was administered, there was no difference in POV between the groups (50% vs 55%, RR [95% CI = 0.91 [0.65, 1.28]).

**Use of Postoperative Rescue Antiemetic Treatment**

All 8 studies investigated the use of postoperative rescue antiemetic therapy (Table 3).\(^{11-18}\) Ondansetron 4 mg was the rescue antiemetic used in 4 studies,\(^{11,13,16,18}\) metoclopramide 10 mg in 2 studies,\(^{14,15}\) droperidol 1.25 mg in 1 study,\(^{12}\) and prochlorperazine 12.5 mg in the remaining study.\(^{17}\) Overall, when all doses of dexamethasone were combined, there was a significant reduction in the use of postoperative rescue antiemetic therapy when compared with placebo (16% vs 35%, RR [95% CI] = 0.47 [0.36, 0.61]). There was no evidence of significant heterogeneity \((I^2 = 47\%)\). Dexamethasone at doses of 5, 8, and 10 mg also significantly reduced the need for a rescue antiemetic therapy (Table 2). In a subgroup analysis by the type of surgery, dexamethasone reduced the need for postoperative rescue antiemetic therapy in patients undergoing total abdominal hysterectomy (13% vs 31%, RR [95% CI] = 0.38 [0.25, 0.59]) and cesarean delivery (18% vs 38%, RR [95% CI] = 0.53 [0.29, 0.98]) compared with placebo. In a subgroup analysis by route of administration of neuraxial morphine, dexamethasone significantly reduced the use of postoperative rescue antiemetic therapy in those patients receiving epidural morphine compared with placebo (12.8% vs 32.8%, RR [95% CI] = 0.37 [0.26, 0.52]). A similar effect was
not observed in patients receiving intrathecal morphine (35% vs 42%, RR [95% CI = 0.84 [0.56, 1.26]).

Postoperative Pain

Postoperative Pain Intensity

Seven studies reported on postoperative pain intensity in patients receiving dexamethasone for PONV prophylaxis.11–14,16–18 Six of these studies reported early pain scores at or around 4 hours (Fig. 3A).11–14,16,18 Five studies reported late postoperative pain scores at 24 hours (Fig. 3B).11–13,16,18 One study reported highest and lowest pain scores only, without specifying a time period.17 There were no differences in early pain scores in patients receiving dexamethasone compared with those receiving placebo. Overall, when all doses were combined, dexamethasone reduced postoperative pain scores at 24 hours when compared with the placebo group (MD [95% CI] = −0.30 [−0.46, −0.13]). There was evidence of significant heterogeneity among the included trials ($I^2 = 72\%$). Removing the only study11 in which intrathecal morphine was administered abolished this heterogeneity ($I^2 = 0$). When combining the

![Figure 3. Forest plots showing the effect of dexamethasone on (A) early pain scores (4 hours), (B) late pain scores (24 hours) (measured on an 11-point scale [0–10]), and (C) use of rescue analgesics. M-H = Mantel-Haenszel; IV = inverse variance.](image-url)
remaining studies, there was still a reduction in pain scores (MD [95% CI] = −0.20 [−0.37, −0.02]). Doses of dexamethasone of 5 mg (MD [95% CI] = −0.19 [−0.37, −0.01]) and 8 mg (MD [95% CI] = −1.00 [−1.45, −0.55]) significantly reduced pain scores at 24 hours compared with placebo. No conclusion could be drawn for the comparison of the highest reported pain scores between patients receiving dexamethasone and those in the placebo group because of the wide CIs of the pooled results (MD [95% CI] = −1.87 [−4.16, 0.41]).

**Use of Postoperative Rescue Analgesics**

All 8 studies reported on the use of rescue analgesics in patients receiving dexamethasone for PONV prophylaxis. In 6 of the studies, diclofenac 75 mg IM was used as the rescue analgesic. IV tenoxicam 20 mg was administered in 1 study and oral acetaminophen 500 mg/codeine 30 mg in the other. Overall, dexamethasone reduced the use of postoperative rescue analgesics compared with placebo (27% vs 38%, RR [95% CI] = 0.76 [0.62, 0.93]) (Fig. 3C). In subgroup analysis by dexamethasone dose, only dexamethasone at a dose of 5 mg significantly reduced the need for rescue analgesia when compared with placebo (27% vs 38%, RR [95% CI] = 0.72 [0.52, 0.98]). There was no evidence of heterogeneity among the trials ($I^2 = 0$). In a subgroup analysis by type of surgery, dexamethasone compared with placebo reduced the need for postoperative rescue analgesia in patients undergoing total abdominal hysterectomy (28% vs 40%, RR [95% CI] = 0.74 [0.56, 0.99]) but not after cesarean delivery. In a subgroup analysis by route of administration, dexamethasone was effective in significantly reducing the use of postoperative rescue analgesia after epidural morphine administration (26% vs 37%, RR [95% CI] = 0.74 [0.59, 0.95]). However, in patients receiving intrathecal morphine, no conclusion could be made regarding the use of postoperative rescue analgesics between the treatment and placebo groups (35% vs 43%, RR [95% CI] = 0.81 [0.55, 1.18]).

**Pruritus**

Six studies reported the incidence of pruritus associated with neuraxial morphine in patients receiving dexamethasone or placebo. Overall, dexamethasone did not significantly reduce the incidence of pruritus when compared with placebo (Table 3).

Four studies reported the use of rescue antipruritic medication after the administration of neuraxial morphine. IM diphenhydramine 20 mg was the rescue antipruritic in 3 studies and oral chlorpheniramine 4 mg was the rescue drug in the remaining study. Overall, no conclusion could be made regarding the impact of dexamethasone on the use of rescue antipruritic medication when compared with placebo because of the wide CIs of pooled results (Table 3). There was no evidence of heterogeneity for the trials included for both outcomes.
Side Effects
Seven of the 8 studies investigated and reported possible side effects of dexamethasone.11–13,15–18 Side effects were not consistently reported quantitatively and so were reviewed qualitatively. Five studies investigated delayed wound healing as a possible side effect during the patient’s postoperative stay.11,13,15,16,18 There were no reported cases in either the treatment or placebo groups. Similarly, there were 5 studies investigating wound infection,11,13,15,16,18 with no reported cases in either the treatment or intervention group. Other less relevant side effects investigated depended on the antiemetics being investigated in conjunction with dexamethasone. Three studies comparing the antiemetic efficacy of droperidol alone or in combination with dexamethasone reported no difference in the incidence of restlessness between the dexamethasone and placebo groups.11,15,18 In 2 of these studies, there was no reported incidence of this side effect in any patient.11,15 Two studies assessed and reported postoperative sedation.11,17 One study compared droperidol alone or in combination with dexamethasone11 whereas the other used cyclizine.17 Both studies used a 4-point sedation scale and reported no difference in sedation scores over the study period between the dexamethasone and placebo groups. One study investigating the antiemetic efficacy of tropisetron reported an incidence of headaches of 5% in both the dexamethasone and placebo groups.12 Another study comparing dexamethasone with metoclopramide reported no cases of extrapyramidal side effects in the dexamethasone and placebo groups.16

DISCUSSION
The results of this systematic review indicate that a single dose of IV dexamethasone is an effective antiemetic in patients receiving neuraxial morphine as part of a neuraxial anesthetic technique. In addition, dexamethasone produced a small but statistically significant reduction in 24-hour postoperative pain scores and reduced the need for rescue analgesics when compared with placebo. Dexamethasone, however, did not reduce the incidence of neuraxial morphine–induced pruritus when compared with placebo.

Dexamethasone has a well-established role as a prophylactic antiemetic in children and adults receiving general anesthesia.1–4,24 However, PON and POV are also frequent adverse effects after neuraxial morphine administration. Dahl et al.6 reported that the number needed to harm for PON and POW in patients receiving intrathecal morphine for cesarean delivery under spinal anesthesia was 6.3 and 10.1, respectively. The mechanism for the antiemetic effect of dexamethasone remains unknown. The ability of dexamethasone to deplete γ-aminobutyric acid stores, reduce the blood-brain barrier’s permeability to emetic toxins, inhibit brain-stem enkephalin release, central prostaglandin synthesis, and serotonin synthesis and release are among the proposed mechanisms.25,26 Its long duration of action makes it an ideal drug for prophylaxis in patients receiving long-acting neuraxial opioids.1 In this patient population, dexamethasone reduced the overall incidence of PON. The lowest effective dose for the prevention of PON and POW was 5 mg.
The lowest effective dose of dexamethasone for PONV prophylaxis in patients receiving neuraxial morphine has not been established but at least one other study found doses as low as 2.5 mg to be an effective antiemetic in adult patients receiving general anesthesia. Published consensus guidelines for the management of PONV recommend doses of 4 to 5 mg for antiemetic prophylaxis.

Interestingly, dexamethasone was an effective antiemetic in patients receiving epidural morphine but ineffective in patients receiving intrathecal morphine. However, based on the small sample size of the pooled results in the intrathecal morphine subgroup analysis, the power to detect a difference may have been inadequate (type II error). We pooled both epidural and intrathecal administration of morphine for this meta-analysis based on studies that reported no difference in the incidence of PONV when comparing comparable doses using both routes. In this review, the overall incidence of PON and POV in the control groups in both trials in which intrathecal morphine was administered was 58% and 55%, respectively, which is much higher than the corresponding incidence of 31% and 24%, respectively, in the trials investigating epidural morphine. It is possible that the mechanism of PONV in patients receiving intrathecal and epidural opioids may not be similar. In addition, the pharmacokinetics of both routes of administration differs significantly, potentially leading to more rapid rostral spread and higher intrathecal concentrations after direct intrathecal administration compared with administration by the epidural route. The intrathecal morphine dose may also have had a role. Doses of intrathecal morphine as high as 0.2 mg are associated with an increase in the incidence of PONV, compared with lower doses, without providing any additional analgesic efficacy. The timing of administration of dexamethasone in relation to the administration of neuraxial morphine may also have accounted for the observed difference. Dexamethasone was administered before morphine in the epidural studies but after its administration in the intrathecal studies. With the onset of action of the antiemetic effect of dexamethasone estimated to be 2 hours and the possibility of a more rapid onset of emetic symptoms after intrathecal morphine administration, it may have been more prudent to administer the prophylactic drug before initiation of spinal anesthesia.

Dexamethasone reduced pain scores and need for rescue analgesics in this systematic review. None of the trials individually reported any reduction in postoperative pain intensity or need for rescue analgesia between the treatment and placebo groups. However, analgesic outcomes were not a primary end point in any of the studies and the studies were probably not powered to detect this end point. The reduction in 24-hour pain scores highlights the slow onset and long duration of action of dexamethasone and a possible synergistic action between neuraxial morphine and dexamethasone. The administration of a single dose of dexamethasone has been associated with a reduction in tissue inflammatory mediators, including bradykinin, prostaglandins, and other nociception-promoting neuropeptides; this may contribute to its analgesic properties. Dexamethasone has been shown to significantly reduce postoperative peritoneal inflammation and abdominal pain.
after colectomy.\textsuperscript{35} However, although the overall reduction in late pain scores was statistically significant, it was small and may not be clinically relevant, especially in patient populations in which the pain scores were low.

Pruritus is a common adverse effect of neuraxial morphine but currently there seem to be no consistently effective therapies.\textsuperscript{36} The lack of an antipruritic effect of dexamethasone is disappointing in light of its antiemetic and antiinflammatory properties. However, dexamethasone administration has been associated with perineal pruritus, a poorly understood phenomenon that is associated with bolus administration and more frequently reported in females.\textsuperscript{37,38}

This meta-analysis has several limitations. We identified evidence of publication bias. Of the 8 trials included in this review, 6 were able to demonstrate some degree of antiemetic efficacy of single-dose dexamethasone. The causes of publication bias have been highlighted in previous publications and its presence may make the validity of the findings of this review questionable.\textsuperscript{3,10} However, tests of publication bias are unreliable in meta-analyses based exclusively on multiple small trials and therefore the results of these tests should be interpreted with caution.\textsuperscript{10} Another limitation is that 7 of the 8 studies were performed in Taiwan, Republic of China. In fact, the studies seemed to have been performed at the same institution and the study population also only included female patients. The results may therefore not be applicable to the male population or those of different ethnicity. With respect to the study design, in the majority of the studies, dexamethasone was administered at the end of surgery or postoperatively. This is in contradiction to evidence suggesting a superior antiemetic efficacy of dexamethasone when administered at the induction of anesthesia rather than at the end of surgery in patients receiving general anesthesia.\textsuperscript{24,34} The optimal timing of administration of dexamethasone in patients receiving neuraxial anesthesia has not been determined but is likely similar to general anesthesia given the slow onset of action of dexamethasone. Pain was a secondary end point in the included trials and details about postoperative analgesia were mainly reported as number of patients requiring rescue and not consistently as doses of rescue drugs given. Overall, side effects were poorly reported in the included trials. Adverse effects such as wound infection and delayed wound healing are of interest but were inadequately reported. Increased risk of bleeding after a single dose of dexamethasone in pediatric tonsillectomies has also been reported, but this risk was not explored in any of the studies.\textsuperscript{39} Future studies should accurately report side effects so that the overall safety of dexamethasone can be established.

Further research is needed to determine the role of dexamethasone as an antiemetic in patients receiving intrathecal morphine after neuraxial anesthesia. With the popularity of intrathecal morphine for postcesarean analgesia, the efficacy of dexamethasone as an antiemetic, particularly in this at-risk population, needs further investigation. Studies investigating dexamethasone in combination with other pharmacological and nonpharmacological antiemetic therapy are also needed.
Dexamethasone’s role as an analgesic has been extensively investigated in patients receiving general anesthesia but its role as an analgesic adjunct in patients receiving neuraxial anesthesia remains less clear. Studies investigating the analgesic effect of dexamethasone in this patient population as a primary outcome are needed.

In conclusion this systematic review presents relatively strong evidence that a single IV dose of dexamethasone 5 to 10 mg was an effective antiemetic for women receiving neuraxial morphine for cesarean delivery or abdominal hysterectomy. Although this review suggests that dexamethasone may not be effective in patients receiving intrathecal morphine, this should be interpreted with caution because of the small number of patients receiving intrathecal morphine that were included in the analysis. There is also some evidence that the doses used for antiemetic prophylaxis also improved postoperative analgesia, although the reduction in pain scores was small and may not be clinically significant. There was no evidence that dexamethasone was an effective antipruritic. Further studies are needed to investigate this drug’s safety profile and its efficacy in patients receiving intrathecal morphine. In light of possible publication bias, these findings need to be interpreted with caution.

**DISCLOSURES**

**Name:** Terrence K. Allen, MBBS, FRCA.

**Contribution:** This author helped design the study, analyze the data, and write the manuscript.

**Attestation:** Terrence K. Allen has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

**Name:** Cheryl A. Jones, MD, DVM.

**Contribution:** This author helped conduct the study and write the manuscript.

**Attestation:** Cheryl A. Jones has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

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**Contribution:** This author helped design the study, conduct the study, and write the manuscript.

**Attestation:** Ashraf S. Habib has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

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**REFERENCES**


