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Dexamethasone to Prevent Postoperative Nausea and Vomiting: An Updated Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Dexamethasone has an established role in decreasing postoperative nausea and vomiting (PONV); however, the optimal dexamethasone dose for reducing PONV when it is used as a single or combination prophylactic strategy has not been clearly defined. In this study, we evaluated the use of 4 mg to 5 mg and 8 mg to 10 mg IV doses of dexamethasone to prevent PONV when used as a single drug or as part of a combination preventive therapy.

METHODS: A wide search was performed to identify randomized clinical trials that evaluated systemic dexamethasone as a prophylactic drug to reduce postoperative nausea and/or vomiting. The effects of dexamethasone dose were evaluated by pooling studies into 2 groups: 4 mg to 5 mg and 8 mg to 10 mg. The first group represents the suggested dexamethasone dose to prevent PONV by the Society for Ambulatory Anesthesia (SAMBA) guidelines, and the second group represents twice the dose range recommended by the guidelines. The SAMBA guidelines were developed in response to studies, which have been performed to examine different dosages of dexamethasone.

RESULTS: Sixty randomized clinical trials with 6696 subjects were included. The 4-mg to 5-mg dose dexamethasone group experienced reduced 24-hour PONV compared with control, odds ratio (OR, 0.31; 95% confidence interval [CI], 0.23–0.41), and number needed to treat (NNT, 3.7; 95% CI, 3.0–4.7). When used together with a second antiemetic, the 4-mg to 5-mg dexamethasone group also experienced reduced 24-hour PONV compared with control (OR, 0.50; 95% CI, 0.35–0.72; NNT, 6.6; 95% CI, 4.3–12.8). The 8-mg to 10-mg dose dexamethasone group experienced decreased 24-hour PONV compared with control (OR, 0.26; 95% CI, 0.20–0.32; NNT, 3.8; 95% CI, 3.0–4.3). Asymmetric funnel plots were observed in the 8-mg to 10-mg dose analysis, suggesting the possibility of publication bias. When used together with a second antiemetic, the 8-mg to 10-mg dose group also experienced reduced incidence of 24-hour PONV (OR, 0.35; 95% CI, 0.22–0.53; NNT, 6.2; 95% CI, 4.5–10). In studies that provided a direct comparison between groups, there was no clinical advantage of the 8-mg to 10-mg dexamethasone dose compared with the 4-mg to 5-mg dose on the incidence of postoperative nausea and/or vomiting.

CONCLUSIONS: Our results showed that a 4-mg to 5-mg dose of dexamethasone seems to have similar clinical effects in the reduction of PONV as the 8-mg to 10-mg dose when dexamethasone was used as a single drug or as a combination therapy. These findings support the current recommendation of the SAMBA guidelines for PONV, which favors the 4-mg to 5-mg dose regimen of systemic dexamethasone. (Anesth Analg 2013;116:58–74)

Dexamethasone is a corticosteroid antiinflammatory drug with an established role for the prevention of postoperative nausea and vomiting (PONV). The Society for Ambulatory Anesthesia (SAMBA) guidelines for the management of PONV recommends a prophylactic dose of 4 mg to 5 mg for patients at high risk of PONV regardless of the surgical procedure.[1] A previous systematic review, evaluating patients undergoing various surgical procedures, did not address the effect of varying doses of dexamethasone on PONV.[2] Using a meta-analysis, Karanicolas et al.[3] evaluated patients undergoing laparoscopic cholecystectomy and suggested a greater efficacy to reduce PONV from a systemic dose of dexamethasone 8 mg to 16 mg compared with 2 mg to 5 mg. The generalizability of these findings to patients undergoing other surgical procedures has not been established. It also remains unclear whether varying doses of dexamethasone may have different efficacy when administered alone or in conjunction with other antiemetic drugs.

The primary objective of this study was to examine the effects of 4 mg to 5 mg and 8 mg to 10 mg single dose systemic dexamethasone on the incidence of PONV. A secondary objective was to evaluate whether the effect changed when dexamethasone was administered alone or in a combination regimen with another antiemetic drug.

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METHODS

This quantitative systematic review was conducted following the guidelines of the PRISMA statement.[4]

Systematic Search

Published reports of randomized trials evaluating the effects of dexamethasone on postoperative nausea and/or vomiting were searched using the National Library of Medicine's PubMed database, EMBASE, the Cochrane Database of Systematic Reviews, and Google Scholar inclusive to October 1, 2011. The initial search was performed using the free-text and MeSH terms "dexamethasone." The "and" function was used to combine the initial search with the MeSH terms "postoperative" and "nausea." No language restriction was used. The search was then limited to randomized controlled clinical trials in subjects older than 18 years. An attempt to identify additional studies not found by the primary search methods was performed by reviewing the reference lists from identified studies. No search was performed for unpublished studies. This initial search yielded 163 randomized clinical trials.

Selection of Included Studies

The study's inclusion and exclusion criteria were determined before the systematic search. Two authors (GDO and LJCA) independently evaluated the abstracts and results of the 163 articles obtained by the initial search. Seventy-four articles that were clearly not relevant based on our inclusion and exclusion criteria were excluded at this phase. Disagreements on inclusion of the articles were resolved by discussion among the evaluators. If an agreement could not be reached, the dispute was resolved with the help of a third investigator (SA).

Inclusion and Exclusion Criteria

We included randomized controlled trials of a single perioperative IV dexamethasone administration with an inactive (placebo or "no treatment") control group. Excluded were trials reporting nausea and vomiting after emergency medicine and nonsurgical patients. Trials in which the same subject received more than a single systemic dose of perioperative dexamethasone were also excluded to maximize clinical homogeneity. Studies involving a comparison of the combination of dexamethasone with a second antiemetic versus that of other antiemetic alone were included, with the combination group being the active group and the other antiemetic serving as control. Included studies had to report at least on early (≤6 hours) or 24-hour incidence of postoperative nausea and/or vomiting. Since we estimated the effects of a fixed dose regimen of dexamethasone, we excluded studies that used weight-dependent–based dosage. We also excluded comparisons or studies that were outside the dosage range examined. Studies performed by the author Yoshitaka Fujii have been excluded because of the questioned validity of these studies' findings.[5] No minimum sample size was required for inclusion in the meta-analysis.

Validity Scoring

Two authors (GSD and LJCA) independently read the included reports and assessed their methodologic validity using a modified Jadad 5-point quality scale.[6] The scale evaluates the study for the following: randomization, double-blind evaluation, concealment of study group to evaluator, valid randomization method, and completeness of data at follow-up. Discrepancies in rating of the trials were resolved by discussion among the evaluators. If an agreement could not be reached, the dispute was resolved with the help of a third investigator (SA). Because only randomized trials were included in the analysis, the minimum possible score of an included trial was 1, and the maximum was 5. Trials were not excluded or weighted in the analysis based on quality assessment scores.

Data Extraction

Two authors (GDO and LJCA) independently evaluated the full manuscripts of all included trials and performed data extraction using a data collection form specifically developed for this review.

Discrepancies were resolved by discussion between the 2 investigators. If an agreement could not be reached, the decision was made by a third investigator (SA). In addition, one author (MCK) cross-checked the data extraction to assure accuracy. Data extracted from trials included dexamethasone dose and time of administration, sample size, number of subjects in treatment groups, follow-up period, type of surgery, nausea and/or vomiting over 24 hours, early nausea and/or vomiting (≤6 hours), need for rescue antiemetics, and type of drug intervention (single regimen versus combination therapy).

Data were initially extracted from tables. For data not available in tables, attempts to contact authors were made; if the authors did not respond or did not have current contact information, the data were abstracted from available figures. Dichotomous data were extracted and converted to incidence while continuous data were recorded using mean and standard deviation. Data presented only as median and range were converted to mean and standard deviation using previously described methodology.[7] If studies reported the proportion of patients free of nausea and/or vomiting, the actual proportion of nausea and/or vomiting was obtained by subtracting the proportion of patients not experiencing nausea and/or vomiting from one.

To perform a quantitative analysis and to examine dose dependency of the outcomes, comparisons were stratified by dose into 2 groups: 4-mg to 5-mg and 8-mg to 10-mg dose groups. The dosage ranges were derived from clinical guidelines for PONV, which suggests a 4-mg to 5-mg dose for antiemetic prophylaxis.[1] As stated in the PONV guidelines, "The corticosteroid, dexamethasone, effectively prevents nausea and vomiting. It is recommended at a prophylactic dose of 4–5 mg IV (depending on the dosage formulation in different countries) for patients at increased risk for PONV." The other dosage group represents twice the dosage range of systemic dexamethasone recommended by SAMBA guidelines for PONV. The SAMBA guidelines were developed in response to studies that have been performed to examine different dosages of dexamethasone.

Definition of Relevant Outcome Data

Our primary outcomes were 24-hour incidence of PONV (defined as nausea and/or vomiting), early (≤6 hours

postoperatively) incidence of PONV, early and 24-hour incidence of nausea, and early and 24-hour incidence of vomiting (including retching). Our secondary outcomes were early (≤6 hours) and 24 hours need for rescue antiemetics.

Meta-Analyses

For dichotomous data, odds ratio (OR) and 95% confidence interval (CI) are reported. The weighted mean differences with 95% CI were determined and reported for continuous data. We calculated the number needed to treat (NNT) based on the absolute risk reduction, with 95% CI as an estimate of a beneficial effect. Because of the different surgical procedures, a random-effects model was used in an attempt to generalize our findings to studies not included in our meta-analysis.[8] A random-effects meta-analysis to estimate the NNT was performed by combining absolute risk differences of individual studies and also using the method of moments to estimate the variance component. Publication bias was evaluated by examining for asymmetric funnel plots using Egger regression test.[9] A one-sided $P < 0.05$ was considered an indication of an asymmetric funnel plot. The heterogeneity of the included studies was considered to be present if the I^2 statistic was >30%. Further analysis was planned a priori to explore relevant heterogeneity. Subgroup analysis was performed to investigate the effect of type of antiemetic intervention (single therapy versus combination therapy) and the type of anesthesia (general versus regional/local). In studies that involved more than one dose group comparison with a single control group, the control group was split according to the number of comparisons. A Q statistic was used to compare the effects between subgroups. The proportion of the total variance explained by the covariates (R^2) was calculated by dividing the random-effects pooled estimates of variance (I^2) within studies by total variance (total I^2). The value obtained was then subtracted from 1. When values were outside the range of 0% to 100%, they were set to the closest value (0% or 100%). Comparisons between the different dosage groups of dexamethasone were made using a Z test. Analysis was performed using Stata version 11 (Stata Corp, College Station, TX) and Comprehensive Meta-analysis software version 2 (Biostat, Englewood, NJ).

RESULTS

Of the 163 initially evaluated abstracts, 89 studies initially met the inclusion criteria (Fig. 1). Twenty-nine studies were subsequently excluded: 12 did not provide a direct comparison between dexamethasone and placebo,[10–21] 9 did not report on the evaluated outcomes,[22–30] 3 examined multiple doses of dexamethasone,[31–33] 3 used a weight-based dosage,[34–36] and 2 used a dose range outside the predetermined dosage groups.[37,38] Among the excluded trials, exclusion of 4 trials was performed after discussion between 2 investigators (GDO and LJCA).[26–29] The characteristics of included studies are listed in Table 1. The evaluated trials included data from 6696 subjects and were published between 1994 and 2011.[39–98] The median number of patients in the included studies receiving dexamethasone was 40. The median modified Jadad scale score was 4. The trials tested single dose dexamethasone given either preoperatively or intraoperatively for a large variety of surgical procedures. All 60 studies reported on nausea and/or vomiting. Discrepancies on data extraction were resolved with discussion between 2 investigators (GDO and LJCA) for 8 trials.[39,40,48,52,70,81,83,93] For 2 trials, data extraction discrepancies were resolved with the help of a third investigator (SA).[60,87]

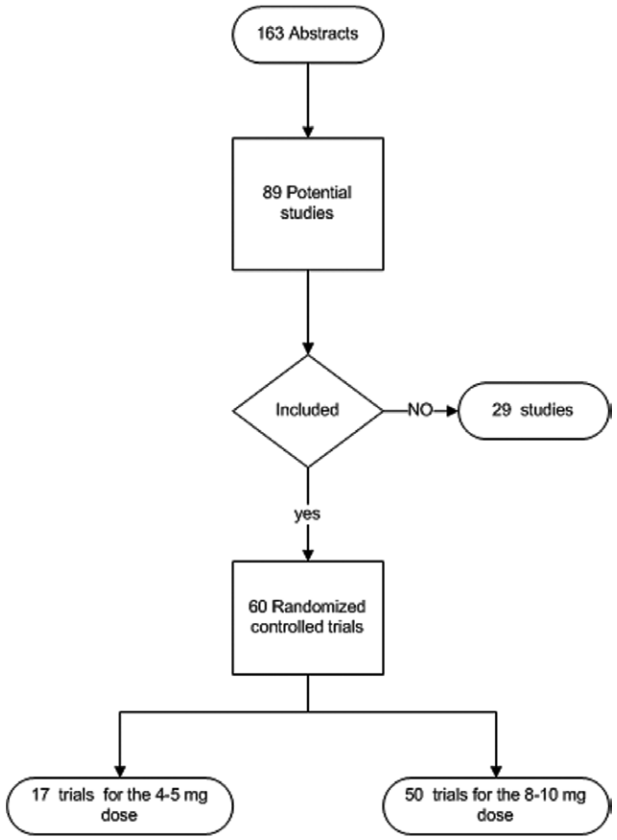

Figure 1. Flow chart outlining retrieved, excluded, and evaluated randomized controlled trials. Some trials evaluated multiple doses of dexamethasone.

Twenty-Four–Hour Nausea and/or Vomiting (PONV)

The effect of dexamethasone on PONV by dosing groups is presented in Figure 2. Heterogeneity was low for both dose group comparisons ($I^2 < 30\%$).

The calculated NNT values for the aggregated effect of the 4-mg to 5-mg and the 8-mg to 10-mg dose groups compared with control were 3.7 (95% CI, 3.0–4.7) and 3.8 (95% CI, 3.0–4.3), respectively. The funnel plot did not demonstrate asymmetry ($P = 0.06$) for the 4-mg to 5-mg group comparison but it did for the 8-mg to 10-mg dose group comparison ($P = 0.003$). Five studies directly compared the effect of the 8-mg to 10-mg dose group with 4-mg to 5-mg dose group on the incidence of 24-hour PONV.[63,81,84,85,89] The combined effect showed a wide CI relative to a significant clinical benefit (OR, 0.72; 95% CI, 0.45–1.17).

Three studies provided 3 comparisons of the 4-mg to 5-mg dose used as a second antiemetic to prevent 24-hour PONV.[54,74,93] The studies used 2 mg IV haloperidol,[54] 12.5

Table 1. Summary of Studies Included in Analysis

Authors	Year of publication	Procedures	Total number treatment/control	Treatment	Drug used as combination therapy (number of active/control subjects involved in the combination comparison)	Type of anesthesia	Modified Jadad score (1–5)	Method of data extraction
Murphy et al.[39]	2011	Laparoscopic cholecystectomy	56/59	Dexamethasone 8 mg IV before induction (combination therapy)	4 mg IV ondansetron (56/59)	Fentanyl/propofol/sevoflurane	4	Table
Mathiesen et al.[40]	2011	Tonsillectomy	43/45	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Alfentanil/propofol/sufentanil	5	Table
Gómez-Hernández et al.[41]	2010	Mastectomy	35/35	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol/nitrous oxide/sevoflurane	4	Table/text
Sánchez-Rodríguez et al.[42]	2010	Laparoscopic Cholecystectomy	105/105	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol/sevoflurane	3	Table/text/Figure
Thangaswamy et al.[43]	2010	Laparoscopic hysterectomy	37/18	Dexamethasone 4 mg and 8 mg before induction. (single drug)	Not applicable	Fentanyl/propofol/isoflurane/nitrous oxide	5	Table/text
Mattila et al.[44]	2010	Osteotomy	26/25	Dexamethasone 9 mg IV before induction (single drug)	Not applicable	Spinal bupivacaine 7.5 mg	4	Table
Entezariasl et al.[45]	2010	Cataract	50/50	Dexamethasone 8 mg IV before induction (single drug and combination therapy)	Metoclopramide 10 mg IV (25/25)	Fentanyl/propofol/nitrous oxide	4	Table/text
Alghanem et al.[46]	2010	Laparoscopic cholecystectomy	60/60	Dexamethasone 8 mg IV after induction (single drug)	Not applicable	Propofol/tramadol	5	Table/text
Sistla et al.[47]	2009	Laparoscopic Cholecystectomy	36/34	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Thiopenthal/suxamethonium/isoflurane/nitrous oxide	4	Table
Wu et al.[48]	2009	Anorectal Surgery	30/30	Dexamethasone 5 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol/sevoflurane/nitrous oxide	4	Table
Yeo et al.[49]	2009	Middle ear surgery	40/40	Dexamethasone 10 mg IV after induction (single drug)	Not applicable	Propofol/isoflurane/nitrous oxide	4	Table
Makhdoom and Farid[50]	2009	Middle ear surgery	40/40	Dexamethasone 10 mg IV before induction (single drug and combination therapy)	Midazolam 0.075 mg/kg IV (20/20)	Fentanyl/propofol/isoflurane	3	Table
Fukami et al.[51]	2009	Laparoscopic cholecystectomy	40/40	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol/sevoflurane/nitrous oxide	3	Table/text
Mathiesen et al.[52]	2008	Hip Arthroplasty	42/40	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Spinal bupivacaine 15 mg	4	Table
Gautam et al.[53]	2008	Laparoscopic cholecystectomy	47/48	Dexamethasone 8 mg IV before induction (combination therapy)	Ondansetron 4 mg IV (47/48)	Meperidine/thiopental/halothane	5	Table
Chu et al.[54]	2008	Laparoscopic vaginal hysterectomy	148/147	Dexamethasone 5 mg IV after induction (single drug and combination therapy)	Haloperidol 2 mg IV (74/74)	Fentanyl/propofol/desflurane	5	Table/text

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Table 1. (*Continued*)

Authors	Year of publication	Procedures	Total number treatment/control	Treatment	Drug used as combination therapy (number of active/control subjects involved in the combination comparison)	Type of anesthesia	Modified Jadad score (1–5)	Method of data extraction
Erhan et al.[55]	2008	Laparoscopic cholecystectomy	20/20	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Propofol/fentanyl/isoflurane	4	Table
Koc et al.[56]	2007	Varicocele	40/40	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Remifentanil/propofol/nitrous oxide	5	Table
Moussa and Oregan[57]	2007	Laparoscopic bariatric surgery	30/30	Dexamethasone 8 mg IV before induction (combination therapy)	Granisetron 1 mg IV (30/30)	Propofol/sevoflurane	3	Table
Bianchin et al.[58]	2007	Laparoscopic cholecystectomy	36/37	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol/sevoflurane/nitrous oxide	5	Table
Nesek-Adam et al.[59]	2007	Laparoscopic cholecystectomy	80/80	Dexamethasone 8 mg IV after induction (single drug and combination therapy)	Metoclopramide 10 mg IV (40/40)	Fentanyl/thiopental/isoflurane	4	Table/text
Wu et al.[60]	2007	cesarean delivery	30/30	Dexamethasone 8 mg before induction (single drug)	Not applicable	Spinal bupivacaine 10 mg and morphine 0.2 mg	4	Table/text
Kashmiri et al.[61]	2006	Laparoscopic cholecystectomy	30/30	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Thiopental/nalbuphine	2	Table
Chen et al.[62]	2006	Multiple types of surgery	350/350	Dexamethasone 10 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol/sevoflurane	3	Table/text
Numazaki and Fujii[63]	2005	Dental surgery	90/30	Dexamethasone 4, 8, and 16 mg IV after induction (single drug)	Not applicable	Fentanyl/propofol/sevoflurane/nitrous oxide	5	Table
Mckean et al.[64]	2006	Tonsillectomy	24/22	Dexamethasone 10 mg IV before induction (combination therapy)	Ondansetron 4 mg IV	Propofol/isoflurane/nitrous oxide	4	Table
Feo et al.[65]	2006	Laparoscopic cholecystectomy	49/52	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol/sevoflurane	4	Table/text
Laiq et al.[66]	2005	Laparoscopic gynecologycal	50/50	Dexamethasone 10 mg IV at induction (single drug)	Not applicable	Fentanyl/thiopental/halothane	3	Table
Yuksek et al.[67]	2003	Laparoscopic gynecological	20/20	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol/sevoflurane	4	Table
Bisgaard et al.[68]	2003	Laparoscopic cholecystectomy	40/40	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol	5	Table/text
Nortcliffe et al.[69]	2003	cesarean delivery	30/30	Dexamethasone 8 mg IV after induction (single drug)	Not applicable	Spinal bupivacaine 10 mg + fentanyl 10 mcg + morphine 0.2 mg	4	Table/text
Piper et al.[70]	2003	Hysterectomy/Breast surgery	75/75	Dexamethasone 8 mg IV before induction (combination therapy)	50 mg dolasetron orally (75/75)	Fentanyl/thiopental/desflurane	4	Table

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Table 1. (*Continued*)

Authors	Year of publication	Procedures	Total number treatment/control	Treatment	Drug used as combination therapy (number of active/control subjects involved in the combination comparison)	Type of anesthesia	Modified Jadad score (1–5)	Method of data extraction
Biswas et al.[71]	2003	Laparoscopic cholecystectomy	60/60	Dexamethasone 8 mg IV before induction (combination therapy)	Granisetron 40 mcg/kg IV (60/60)	Meperidine/thiopental/halothane/nitrous oxide	5	Table
Elhakim et al.[72]	2002	Laparoscopic cholecystectomy	120/30	Dexamethasone 2, 4, 8, and 16 mg IV before induction (combination therapy)	Ondasetron 4 mg IV (60/30)	Fentanyl/propofol/isoflurane/nitrous oxide	4	Tables
Wang et al.[73]	2002	Middle ear surgery	40/40	Dexamethasone 5 mg IV after induction (single drug)	Not applicable	Fentanyl/thiopental/sevoflurane/desflurane	3	Table
Coloma et al.[74]	2002	Laparoscopic cholecystectomy	70/70	Dexamethasone 4 mg IV after induction (combination therapy)	Dolasetron 12.5 mg IV (70/70)	Fentanyl/propofol/sevoflurane/nitrous oxide	3	Table
Goksu et al.[75]	2002	Otologic Surgery	20/20	Dexamethasone 8 mg IV after induction (combination therapy)	Granisetron 3 mg IV (20/20)	Thiopental//isoflurane	4	Table
Wang et al.[76]	2002	Laparoscopic Cholecystectomy	38/39	Dexamethasone 5 mg IV after induction (single drug)	Not applicable	Fentanyl/propofol/isoflurane	5	Table
Tzeng et al.[77]	2002	Abdominal hysterectomy	38/38	Dexamethasone 5 mg IV after induction (single drug)	Not applicable	Epidural lidocaine	3	Table
Wang et al.[78]	2002	Total Hysterectomy	39/37	Dexamethasone 5 mg IV after induction (single drug)	Not applicable	Epidural lidocaine	5	Table
Tzeng et al.[79]	2000	cesarean delivery	38/37	Dexamethasone 8 mg IV after induction (single drug)	Not applicable	Epidural lidocaine	3	Table
Thomas and Jones[80]	2001	Laparoscopic gynecologic	58/59	Dexamethasone 8 mg IV after induction (combination therapy)	Ondansetron 4 mg IV (58/59)	Fentanyl/propofol/sevoflurane/nitrous oxide	3	Table
Lee et al.[81]	2001	Thyroidectomy	88/44	Dexamethasone 5 mg and 8 mg IV before induction (single drug)	Not applicable	Fentanyl/thiopental/desflurane/nitrous oxide	3	Table
Huang et al.[82]	2001	Laparoscopic tubal ligation	39/38	Dexamethasone 5 mg IV after induction (single drug)	Not applicable	Fentanyl/propofol/isoflurane	3	Table
Liu et al.[83]	2001	Middle ear surgery	40/40	Dexamethasone 10 mg IV after induction (single drug)	Not applicable	Fentanyl/propofol/isoflurane	4	Table
Ho et al.[84]	2001	Total abdominal hysterectomy	129/43	Dexamethasone 2.5, 5, and 10 mg IV after induction (single drug)	Not applicable	Epidural lidocaine	4	Table/text
Wang et al.[85]	2001	Cesarean delivery	131/44	Dexamethasone 2.5, 5, and 10 mg IV after induction (single drug)	Not applicable	Epidural lidocaine	4	Table/text
Tan et al.[86]	2001	Inguinal hernia repair	30/30	Dexamethasone 10 mg IV before induction (single drug)	Not applicable	Spinal tetracaine 15 mg + neostigmine 100 μg	4	Table

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Table 1. (*Continued*)

Authors	Year of publication	Procedures	Total number treatment/control	Treatment	Drug used as combination therapy (number of active/control subjects involved in the combination comparison)	Type of anesthesia	Modified Jadad score (1–5)	Method of data extraction
Coloma et al.[87]	2001	Anorectal surgery	40/40	Dexamethasone 4 mg IV before induction (single drug)	Not applicable	Propofol/fentanyl	2	Table/text
Tzeng et al.[88]	2000	Dilation and Curettage	75/76	Dexamethasone 8 mg IV before induction (single drug and combination therapy)	Droperidol 1.25 mg IV (37/36)	Propofol/fentanyl	3	Table
Wang et al.[89]	2000	Thyroidectomy	173/44	Dexamethasone 1.25, 2.5, 5, and 10 mg IV after induction (single drug)	Not applicable	Fentanyl/propofol/isoflurane	4	Table
Wang et al.[90]	2000	Abdominal Hysterectomy	80/40	Dexamethasone 10 mg IV before and after induction (single drug)	Not applicable	Fentanyl/propofol/isoflurane	3	Table
Wang et al.[91]	2000	Laparoscopic tubal ligation	41/40	Dexamethasone 10 mg IV, no time specification (single drug)	Not applicable	Fentanyl/thiopental/isoflurane	4	Table
Wang et al.[92]	1999	Laparoscopic cholecystectomy	40/40	Dexamethasone 8 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol/isoflurane	5	Table
Janknegt et al.[93]	1999	Multiple surgery types	130/130	Dexamethasone 5 mg IV before induction (combination therapy)	Granisetron 1 mg IV (130/130)	Not standardized	2	Table
Wang et al.[94]	1999	Thyroidectomy	38/38	Dexamethasone 10 mg IV before induction (single drug)	Not applicable	Fentanyl/propofol/isoflurane	4	Table
Wang et al.[95]	1999	Abdominal hysterectomy	36/36	Dexamethasone 8 mg IV after induction (single drug)	Not applicable	Epidural lidocaine	3	Table/text
Rajeeva et al.[96]	1999	Diagnostic laparoscopic	25/26	Dexamethasone 8 mg IV after induction (combination therapy)	Ondansetron 4 mg IV (25/26)	Thiopental/nitrous oxide	3	Table/text
López-Olaondo et al.[97]	1996	Major gynecological surgery	50/50	Dexamethasone 8 mg IV before induction (single drug and combination therapy)	Ondansetron 4 mg IV (25/25)	Fentanyl/thiopental/isoflurane/nitrous oxide	3	Table
Mckenzie et al.[98]	1994	Major gynecological surgery	91/89	Dexamethasone 8 mg IV after induction (combination therapy)	Ondansetron 4 mg IV (91/89)	Not standardized	3	Text

mg IV dolasetron,[74] and 1 mg IV granisentron[93] as the first antiemetic. The 4-mg to 5-mg dose dexamethasone group showed a benefit compared with the control group when used with a second antiemetic (OR, 0.50; 95% CI, 0.35–0.72; NNT, 6.6; 95% CI, 4.3–12.8). Seven studies provided 7 comparisons of 8-mg to 10-mg dose used with a second antiemetic to prevent 24-hour PONV.[50,53,57,59,70,71,88] The studies used 0.075 mg/kg IV midazolam,[50] 4 mg IV ondasentron,[53] 1 mg IV granisetron,[57] 10 mg IV metoclopramide,[59] 50 mg per os dolasetron,[70] 40 μg/kg granisetron,[71] and 1.25 mg IV droperidol[88] as the first antiemetic. The 8-mg to 10-mg dexamethasone dose group also showed a benefit compared with control when used with a second antiemetic (OR, 0.35; 95% CI, 0.22–0.53; NNT, 6.2; 95% CI, 4.5–10).

The effect of dexamethasone on 24-hour incidence of PONV was not significantly different for studies performed under general anesthesia (OR, 0.29; 95% CI, 0.24–0.35) compared with studies performed under regional/local anesthesia (OR, 0.26; 95% CI, 0.17–0.38; $P = 0.10$).

Early (0–6 Hours) Nausea and/or Vomiting

The effect of dexamethasone on early PONV by dosing groups is shown in Figure 3. The calculated NNT values for the aggregated effects of the 4-mg to 5-mg and the 8-mg

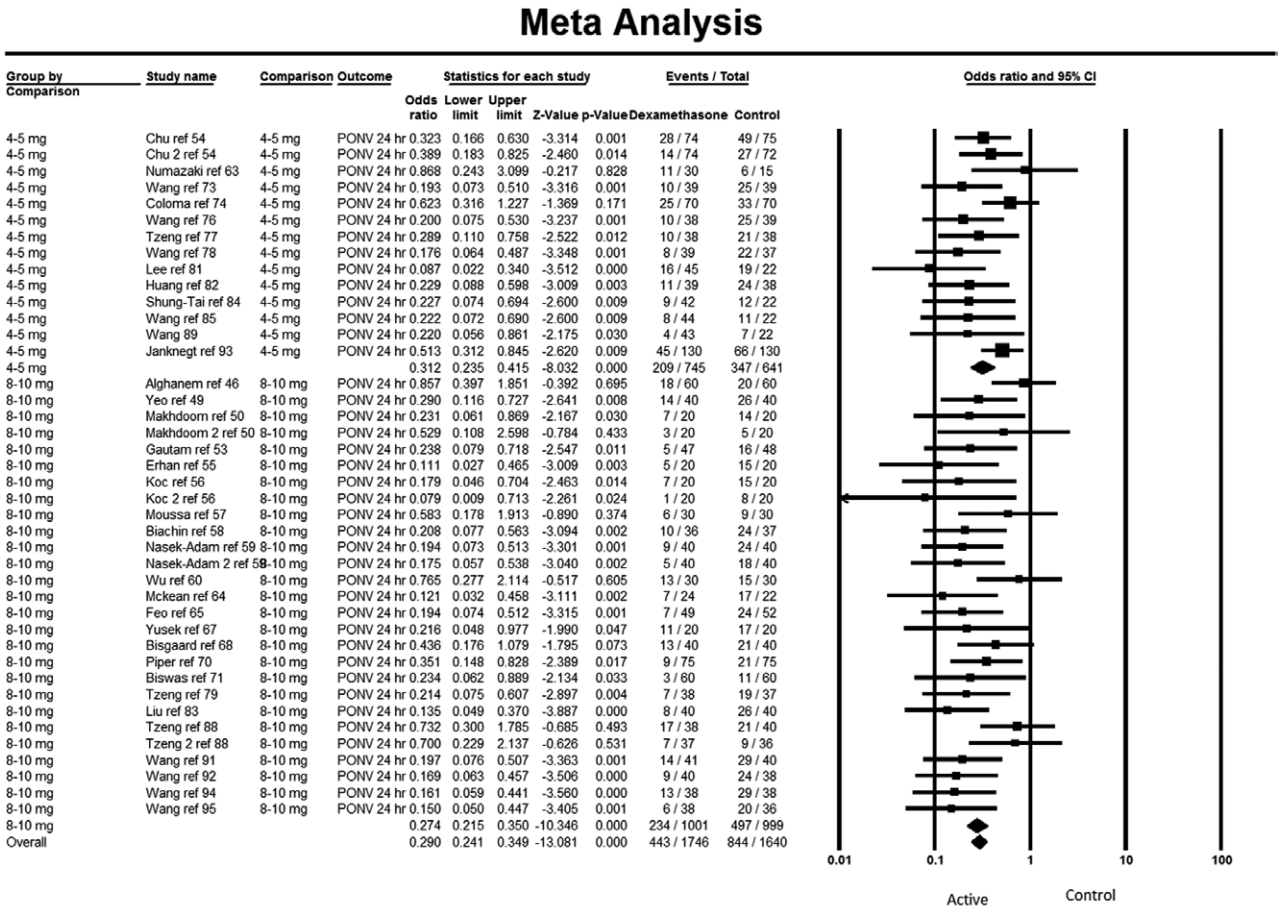

Figure 2. Pooled data evaluating the effect of systemic dexamethasone on the 24-hour incidence of postoperative nausea and vomiting (PONV) compared with control. Data were evaluated by calculating the odds ratio. The point estimate for the overall effect was 0.29 (95% confidence interval [CI], 0.24–0.34). Thirty studies examined dexamethasone used as a single prophylactic drug. The odds ratio for individual studies is represented by a square on forest plot with 95% CI of the difference shown as a solid line. Larger-sized square and thicker 95% CI line denote larger sample size. The diamonds represent the pooled estimate and uncertainty for the effects of the 4-mg to 5-mg dexamethasone dose group, the 8-mg to 10-mg dexamethasone dose group, and the overall effect.

to 10-mg dose groups were 10 (95% CI, 5.5–76.9) and 5.5 (95% CI, 4.0–9.0), respectively. Heterogeneity was low for the 4-mg to 5-mg dose group (I^2 = 0) and mild for the 8-mg to 10-mg dose group (I^2 = 33%). Heterogeneity could not be explained by studies evaluating dexamethasone with a second antiemetic. An examination of the funnel plot did not reveal asymmetry for the 4-mg to 5-mg dose group (P = 0.16) but it did for the 8-mg to 10-mg dose group (P = 0.01), suggesting the possibility of publication bias.

Eight studies provided 8 comparisons of 8-mg to 10-mg doses of dexamethasone to prevent early PONV when used with a second antiemetic.[53,57,70,71,72,75,80,88] The studies used 4 mg IV ondansetron,[53,72,80] 1 mg IV granisetron,[57] 50 mg per os dolasetron,[70] 40 μg/kg granisetron,[71] 3 mg IV granisetron,[75] and 1.25 mg IV droperidol[88] as the other antiemetic. Subgroup analysis showed a statistically significant reduction in the incidence of early PONV in the 8-mg to 10-mg dexamethasone dosage with a second antiemetic group (NNT, 12.5; 95% CI, 8.3–33.3). Two studies examined the effect of the 4-mg to 5-mg doses used with a second antiemetic, but neither showed a significant benefit compared with control.[54,72] The studies used 2 mg IV haloperidol[54] and 4 mg IV ondansetron[72] as the first antiemetic.

Twenty-Four–Hour Incidence of Nausea

The overall effect of dexamethasone (as a single drug or as part of a combined regimen) on the 24-hour incidence of nausea compared with control is presented in Figure 4. Heterogeneity was low (I^2 = 0) for both dose group comparisons.

The calculated NNT values for the combined effect of the 4-mg to 5-mg and the 8-mg to 10-mg dose groups were 7.1 (95% CI, 5.3–11.1) and 7.5 (95% CI, 6.0–10.2), respectively. The funnel plot did not show asymmetry for the 4-mg to 5-mg dose (P = 0.08) but it did for the 8-mg to 10-mg dose group (P = 0.003). Five studies directly compared the 8-mg to 10-mg with the 4-mg to 5-mg dose groups on the incidence of the 24-hour nausea.[63,81,84,85,89] The combined effect showed a wide CI relative to a significant clinical benefit (OR, 0.86; 95% CI, 0.47–1.55).

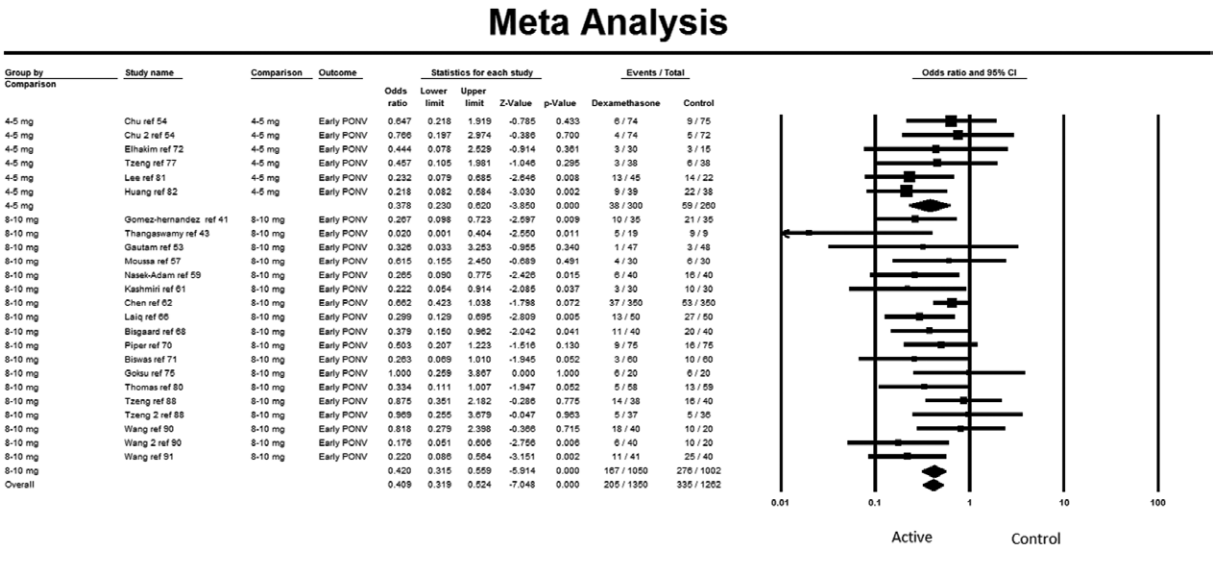

Figure 3. Pooled data evaluating the effect of systemic dexamethasone on the early (≤6 hours) incidence of postoperative nausea and vomiting (PONV) compared with control. Data were evaluated by calculating the odds ratio. The point estimate for the overall effect was 0.40 (95% confidence interval [CI], 0.31–0.52). Fourteen studies examined dexamethasone used as a single prophylactic drug. The odds ratio for individual studies is represented by a square on the forest plot with 95% CI of the difference shown as a solid line. Larger-sized square and thicker 95% CI line denote larger sample size. The diamonds represent the pooled estimate and uncertainty for the effects of the 4-mg to 5-mg dexamethasone dose group, the 8-mg to 10-mg dexamethasone dose group, and the overall effect.

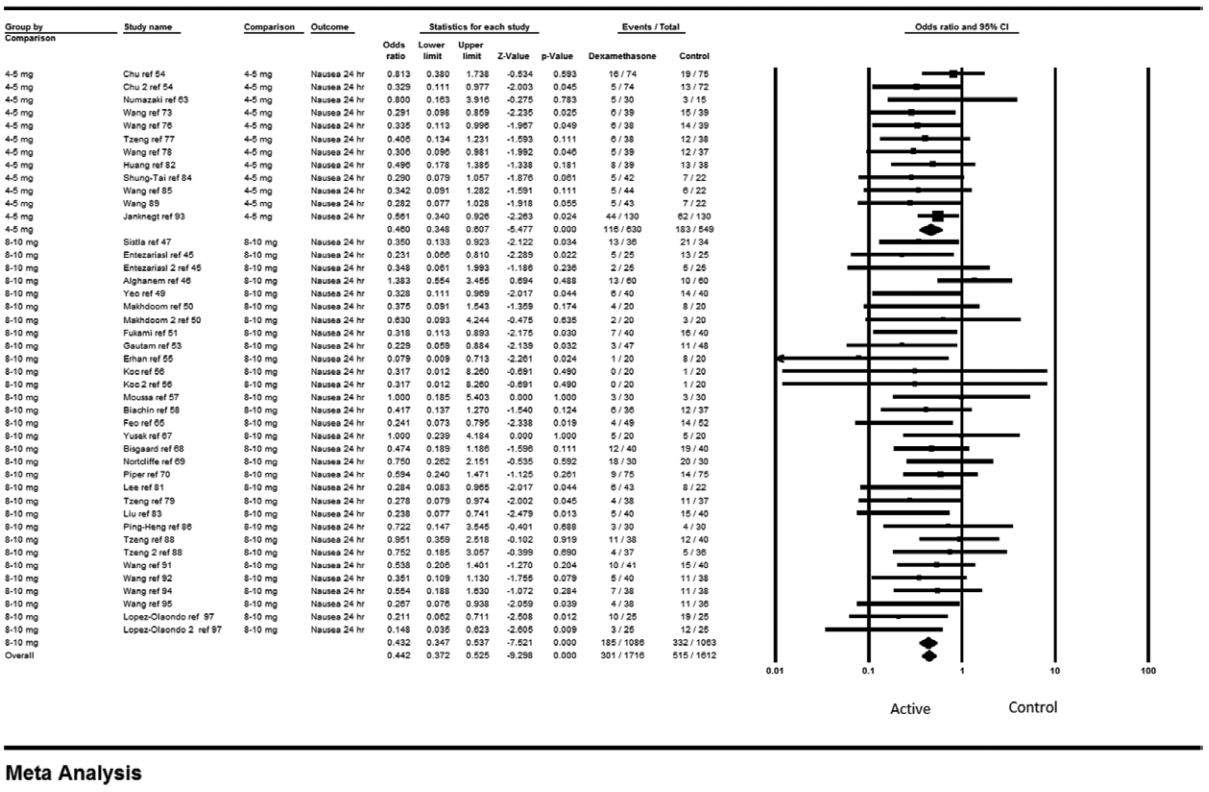

Figure 4. Pooled data evaluating the effect of systemic dexamethasone on the 24-hour incidence of nausea compared with control. Data were evaluated by calculating the odds ratio. The point estimate for the overall effect was 0.42 (95% confidence interval [CI], 0.37–0.52). Thirty-three studies examined dexamethasone used as a single prophylactic drug. The odds ratio for individual studies is represented by a square on the forest plot with 95% CI of the difference shown as a solid line. Larger-sized square and thicker 95% CI line denote larger sample size. The diamonds represent the pooled estimate and uncertainty for the effects of the 4-mg to 5-mg dexamethasone dose group, the 8-mg to 10-mg dexamethasone dose group, and the overall effect.

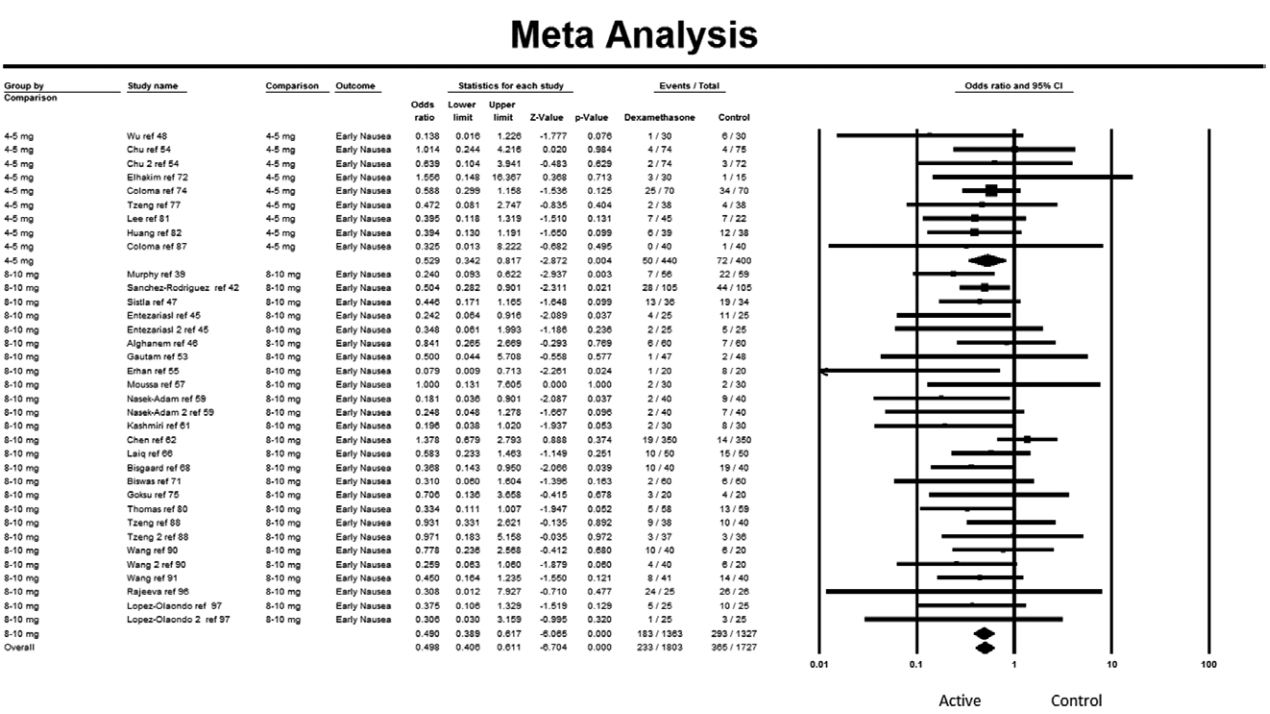

Figure 5. Pooled data evaluating the effect of systemic dexamethasone on the early (≤6 hours) incidence of nausea compared with control. Data were evaluated by calculating the odds ratio. The point estimate for the overall effect was 0.49 (95% confidence interval [CI], 0.40–0.61). Twenty-one studies evaluated dexamethasone as a single prophylactic drug. The odds ratio for individual studies is represented by a square on the forest plot with 95% CI of the difference shown as a solid line. Larger-sized square and thicker 95% CI line denote larger sample size. The diamonds represent the pooled estimate and uncertainty for the effects of the 4-mg to 5-mg dexamethasone dose group, the 8-mg to 10-mg dexamethasone dose group, and the overall effect.

Two studies provided 2 comparisons of the 4-mg to 5-mg dexamethasone dose used with a second antiemetic to prevent 24-hour nausea.[54,93] The studies used 2 mg IV haloperidol[54] and 1 mg IV granisetron [93] as the first antiemetic. The effect of the 4-mg to 5-mg dexamethasone dose was detected when administered with a second antiemetic (OR, 0.51; 95% CI, 0.32–0.80; NNT, 8.0; 95% CI, 5.3–10.9). Seven studies provided 7 comparisons of the 8-mg to 10-mg dexamethasone dose used with a second antiemetic to prevent 24-hour nausea.[45,50,53,57,70,88,97] The studies used 10 mg IV metoclopramide,[45] 0.075 mg/kg IV midazolam,[50] 4 mg IV ondasentron,[53,97] 1 mg IV granisetron,[57] 50 mg per os dolasetron,[70] and 1.25 mg IV droperidol[88] as the other antiemetic. A significant effect was also detected for the 8-mg to 10-mg dose group when dexamethasone was used with a second antiemetic (OR, 0.44; 95% CI, 0.26–0.75; NNT, 10.4; 95% CI, 5.9–43.4).

The effect of dexamethasone on the 24-hour incidence of nausea was not significantly different for studies performed under general anesthesia (OR, 0.43; 95% CI, 0.35–0.53) compared with studies performed under regional/local anesthesia (OR, 0.38; 95% CI, 0.25–0.60; $P = 0.54$).

Early (0–6 Hours) Incidence of Nausea

The effect of dexamethasone on the incidence of early nausea by dosing groups is presented in Figure 5. Heterogeneity was low for both dose group comparisons ($I^2 = 0$).

The calculated NNT values for the combined effect of the 4-mg to 5-mg and the 8-mg to 10-mg dose groups were 26.1 (95% CI, 13.1–1000) and 10.3 (95% CI, 7.4–16.6), respectively. The funnel plot did not demonstrate asymmetry for the 4-mg to 5-mg dose group ($P = 0.37$), but it showed some asymmetry for the 8-mg to 10-mg dose group ($P = 0.02$).

Three studies examined a 4-mg to 5-mg dexamethasone group used with a second antiemetic.[54,72,74] The studies used 2 mg IV haloperidol,[54] 4 mg IV ondansetron,[72] and 12.5 mg IV dolasetron[74] as the other antiemetic. The combined effect did not show a benefit compared with control on the incidence of early nausea (OR, 0.63; 95% CI, 0.34–1.17). Twelve studies provided 11 comparisons of the 8-mg to 10-mg dexamethasone used with a second antiemetic to prevent early nausea.[39,45,53,57,59,71,72,75,80,88,96,97] The studies used 4 mg IVondansetron,[39,53,72,80,96,97] 10 mg IV metoclopramide,[45,59] 1 mg IV granisetron,[57]40 μg/kg granisetron,[71] 3 mg IV granisetron,[75] and 1.25 mg IV droperidol[88] as the other antiemetic. When evaluated as combination therapy, the 8-mg to 10-mg dexamethasone dose reduced early nausea (OR, 0.37; 95% CI, 0.23–0.60) but the clinical effect was not significant (NNT, 16.6; 95% CI, 10.1–20.8).

Vomiting Od24 Hours

The effect of dexamethasone on vomiting over 24 hours by dosing groups is presented in Figure 6. Heterogeneity was low for both dose group comparisons ($I^2 = 0$).

The calculated NNT values for the combined effect of the 4-mg to 5-mg and 8-mg to 10-mg dose groups were 7.2 (95% CI, 5.5–10.7) and 6.9 (95% CI, 5.8–8.6), respectively. The

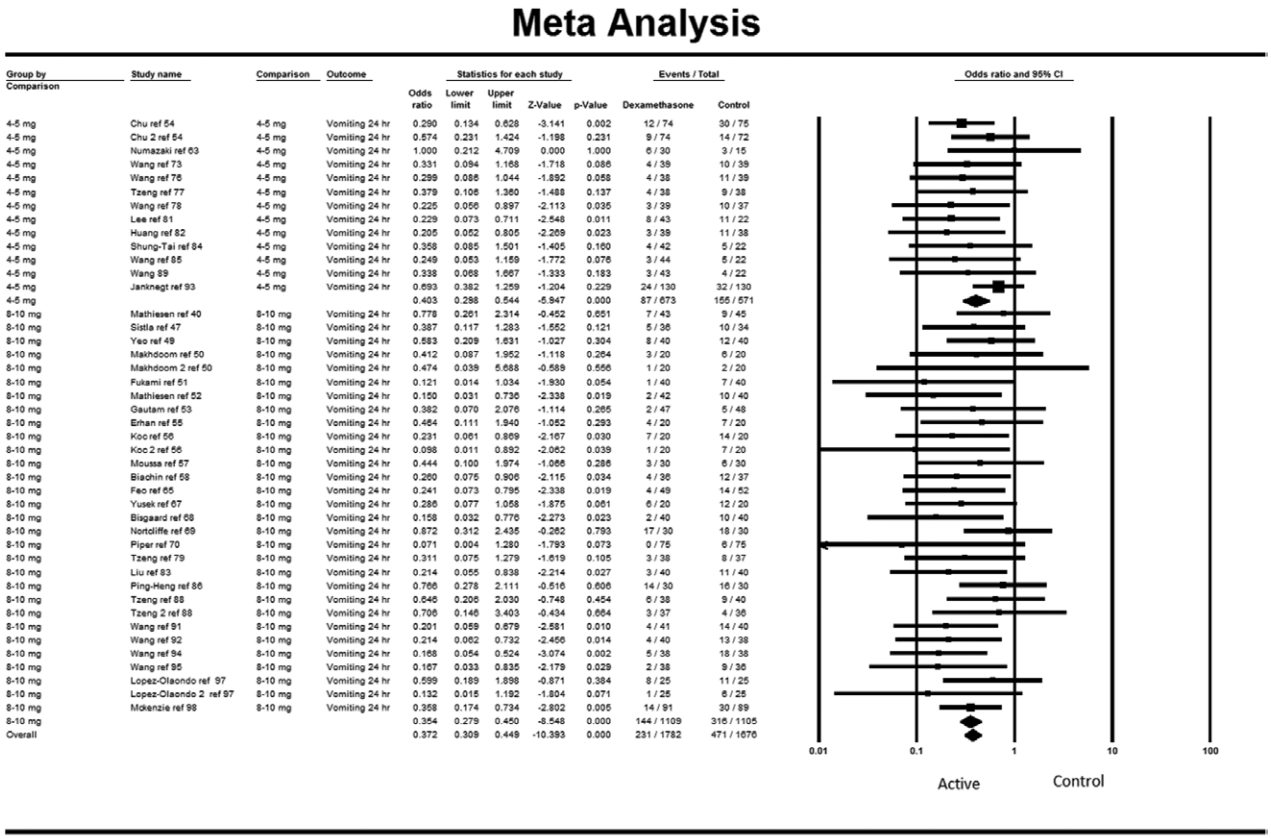

Figure 6. Pooled data evaluating the effect of systemic dexamethasone on the 24-hour incidence of vomiting compared with control. Data were evaluated by calculating the odds ratio. The point estimate for the overall effect was 0.37 (95% confidence interval [CI], 0.30–0.44). Thirty-three studies examined dexamethasone used as a single prophylactic drug. The odds ratio for individual studies is represented by a square on the forest plot with 95% CI of the difference shown as a solid line. Larger-sized square and thicker 95% CI line denote larger sample size. The diamonds represent the pooled estimate and uncertainty for the effects of the 4-mg to 5-mg dexamethasone dose group, the 8-mg to 10-mg dexamethasone dose group, and the overall effect.

funnel plot demonstrated some asymmetry ($P = 0.04$) for the 4-mg to 5-mg dose group and for the 8-mg to 10-mg dose group ($P = 0.004$). Five studies directly compared the effect of the 8-mg to 10-mg dose group with the 4-mg to 5-mg dose group on the incidence of vomiting over 24 hours.[63,81,84,85,89] The combined effect showed a wide CI relative to a significant clinical benefit (OR, 0.64; 95% CI, 0.33–1.27).

Two studies evaluated the effect of the 4-mg to 5-mg dexamethasone dose when used with a second antiemetic;[54,93] both studies did not demonstrate a beneficial effect of the 4-mg to 5-mg dexamethasone compared with the control group ($P > 0.05$). The studies used 2 mg IV haloperidol[54] and 1 mg IV granisentron[93] as the other antiemetic. Seven studies provided 7 comparisons of 8-mg to 10-mg dexamethasone dose used with a second antiemetic to reduce the incidence of vomiting over 24 hours.[50,53,57,70,88,97,98] The effect of the 8-mg to 10-mg dexamethasone on the incidence of vomiting over 24 hours was significant when dexamethasone was examined with a second antiemetic (OR, 0.36; 95% CI, 0.21–0.61; NNT, 11.1; 95% CI, 7.5–21.2).The studies used 0.075 mg IV midazolam,[50] 4 mg IV ondansetron,[53,97,98] 1 mg IV granisetron,[57] 10 mg IV metoclopramide,[59] 50 mg per os dolasetron,[70] and 1.25 mg IV droperidol[88] as the other antiemetic.

The effect of dexamethasone on 24-hour incidence of vomiting was not significantly different for studies performed under general anesthesia (OR, 0.35; 95% CI, 0.17–0.73) compared with studies performed under regional/local anesthesia (OR, 0.33; 95% CI, 0.26–0.42; $P = 0.17$).

Early (0–6 Hours) Vomiting

The effect of dexamethasone on early vomiting by dosing groups is presented in Figure 7. Heterogeneity was low for both dose group comparisons ($I^2 = 0$). The calculated NNT values for the aggregated effect of the 4-mg to 5-mg and the 8-mg to 10-mg dose groups were 17.5 (95% CI, 9.8–90.9) and 16.9 (95% CI, 12.5–25.6), respectively. The funnel plot did not demonstrate asymmetry ($P = 0.48$) for the 4-mg to 5-mg dose, but it showed some asymmetry for the 8-mg to 10-mg dose ($P = 0.04$).

Postoperative Need for Rescue Antiemetics (24 Hours)

The effect of dexamethasone on the 24-hour need for postoperative antiemetics by dosing groups is presented in Figure 8. Heterogeneity was low for both dose group comparisons ($I^2 < 10\%$).

The calculated NNT values for the combined effect of the 4-mg to 5-mg and the 8-mg to 10-mg dose groups were

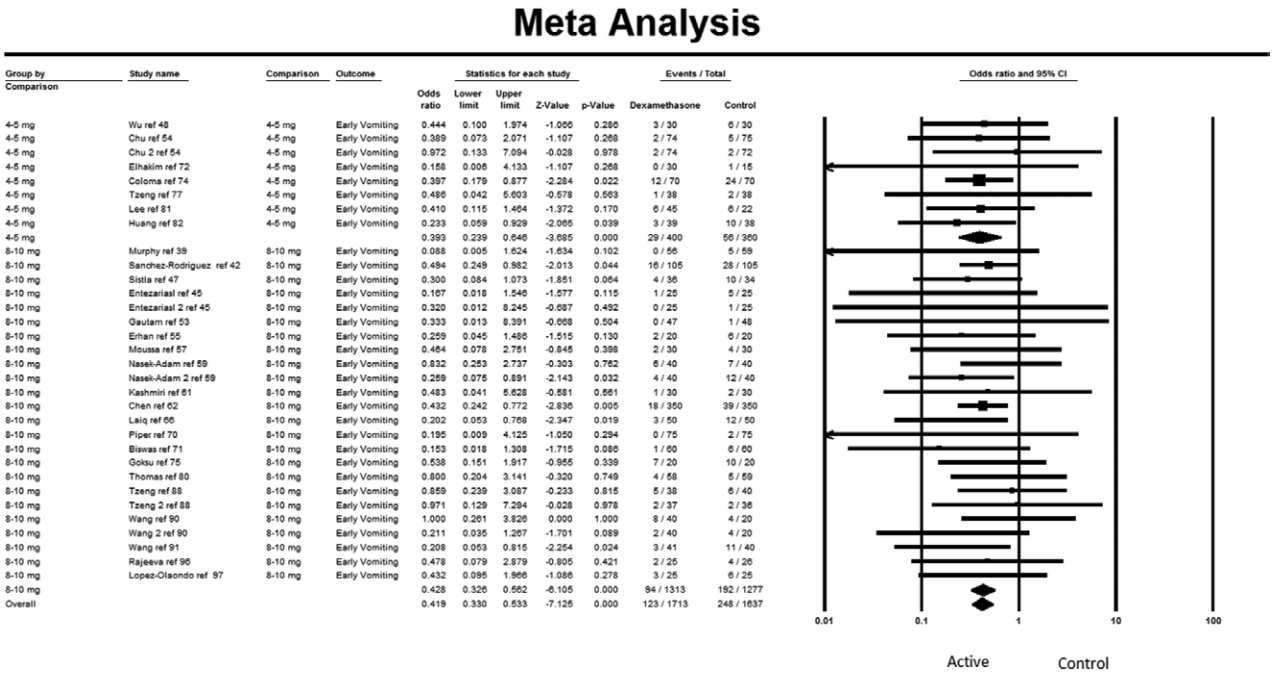

Figure 7. Pooled data evaluating the effect of systemic dexamethasone on the early (≤6 hours) incidence of vomiting compared with control. Data were evaluated by calculating the odds ratio. The point estimate for the overall effect was 0.41 (95% confidence interval [CI], 0.33–0.53). Nineteen studies examined dexamethasone as a single prophylactic drug. The odds ratio for individual studies is represented by a square on the forest plot with 95% CI of the difference shown as a solid line. Larger-sized square and thicker 95% CI line denote larger sample size. The diamonds represent the pooled estimate and uncertainty for the effects of the 4-mg to 5-mg dexamethasone dose group, the 8-mg to 10-mg dexamethasone dose group, and the overall effect.

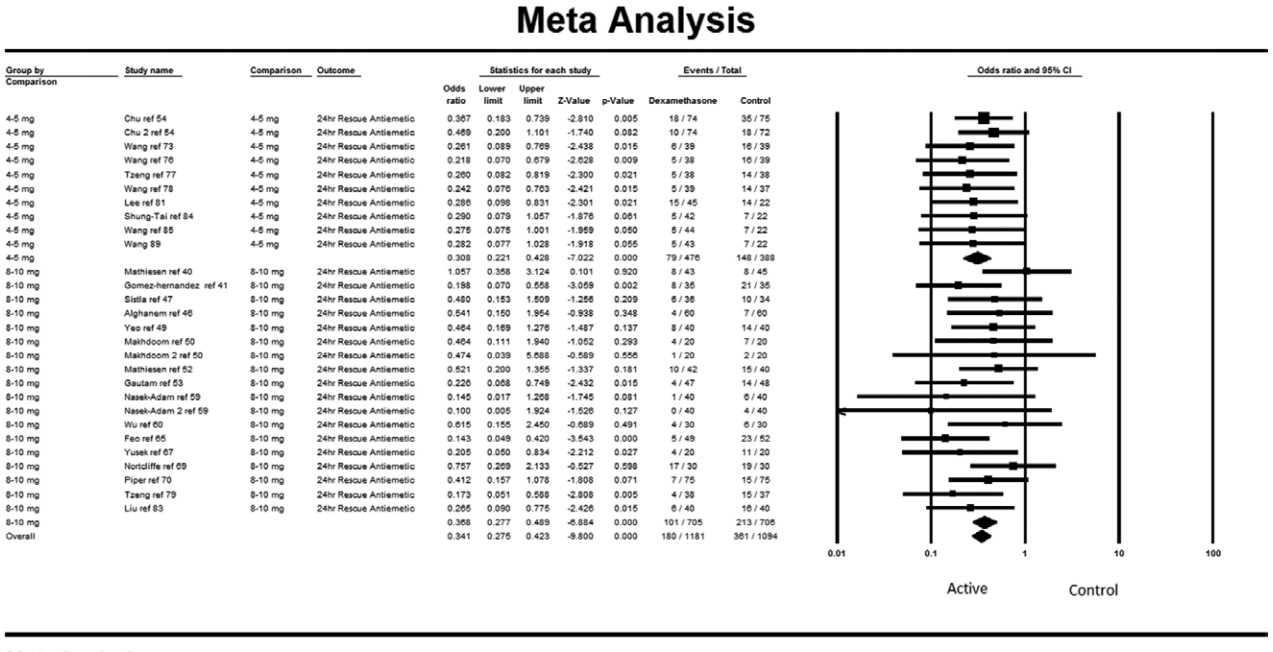

Figure 8. Pooled data evaluating the effect of systemic dexamethasone on the 24-hour need for rescue antiemetics compared with control. Data were evaluated by calculating the odds ratio. The point estimate for the overall effect was 0.34 (95% confidence interval [CI], 0.27–0.42). Twenty-three studies examined dexamethasone as a single prophylactic drug. The odds ratio for individual studies is represented by a square on the forest plot with 95% CI of the difference shown as a solid line. Larger-sized square and thicker 95% CI line denote larger sample size. The diamonds represent the pooled estimate and uncertainty for the effects of the 4-mg to 5-mg dexamethasone dose group, the 8-mg to 10-mg dexamethasone dose group, and the overall effect.

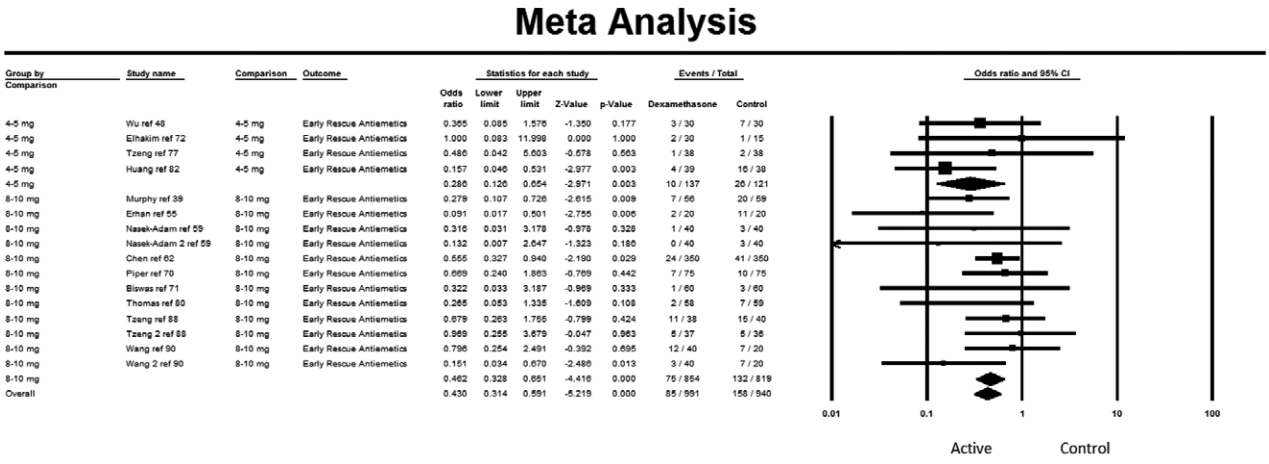

Figure 9. Pooled data evaluating the effect of systemic dexamethasone on the early (≤6 hours) need of rescue antiemetics compared with control. Data were evaluated by calculating odds ratio. The point estimate for the overall effect was 0.43 (95% confidence interval [CI], 0.31–0.59). Nine studies examined dexamethasone as a single prophylactic drug. The odds ratio for individual studies is represented by a square on the forest plot with 95% CI of the difference shown as a solid line. Larger-sized square and thicker 95% CI line denote larger sample size. The diamonds represent the pooled estimate and uncertainty for the effects of the 4-mg to 5-mg dexamethasone dose group, the 8-mg to 10-mg dexamethasone dose group, and the overall effect.

4.6 (95% CI, 3.6–6.4) and 5.8 (95% CI, 4.5–8.3), respectively. The analysis for the 4-mg to 5-mg and the 8-mg to 10-mg doses were limited by asymmetric funnel plots, indicating the possibility of publication bias (P = 0.01 and P = 0.008, respectively).

Only 1 study evaluated the effect of the 4-mg to 5-mg dexamethasone when used with a second antiemetic (OR, 0.46; 95% CI, 0.20–1.11).[54] The study used 2 mg IV haloperidol as the other antiemetic.[54] Four studies provided 4 comparisons for the 8-mg to 10-mg dexamethasone dose group on the 24-hour need for rescue antiemetics.[50,53,59,70] The effect of dexamethasone on the postoperative need for rescue antiemetics was detected when the 8-mg to 10-mg dexamethasone dose group was examined with a second antiemetic (OR, 0.31; 95% CI, 0.15–0.63; NNT, 8.8; 95% CI, 5.7–19.6). The studies used 0.075 mg IV midazolam,[50] 4 mg IV ondansetron,[53] 10 mg IV metoclopramide,[59] and 50 mg per os dolasetron[70] as the other antiemetic.

Early Postoperative Need for Rescue Antiemetics (0–6 Hours)

The effect of dexamethasone on the early (≤6 hours) need for postoperative antiemetics by dosing groups is presented in Figure 9. Heterogeneity was low for both dose group comparisons (I^2 = 0). The calculated NNT values for the aggregated effect of the 4-mg to 5-mg and the 8-mg to 10-mg dose groups on the need for early rescue antiemetics were 9.4 (95% CI, 4.2–41.6) and 13.3 (95% CI, 8.7–27.0), respectively. The funnel plot did not demonstrate asymmetry for the 4-mg to 5-mg dose group (P = 0.06), but it did for the 8-mg to 10-mg dose group (P = 0.03).

DISCUSSION

Several important findings have emerged from this current meta-analysis on the effect of dexamethasone for the prevention of postoperative nausea and/or vomiting. Different from Karanicolas et al.,[3] who detected dose effects of dexamethasone on the incidence of PONV, we did not observe a clinical advantage of the 8-mg to 10-mg systemic dexamethasone dose compared with the 4-mg to 5-mg dose in the prevention of PONV. In addition, when used with a second antiemetic, the 4-mg to 5-mg dose of dexamethasone offered similar clinical benefits as the 8-mg to 10-mg dose, suggesting a lack of clinical advantage for the 8-mg to 10-mg dose. Our results support the SAMBA guidelines–recommended 4-mg to 5-mg dexamethasone dose for the prevention of PONV.[1]

There may be several reasons responsible for the different findings between the current meta-analysis and the one previously performed by Karanicolas et al.[3] First, Karanicolas et al. arbitrarily compared a 2-mg to 5-mg dose group with an 8-mg to 16-mg dose group, while we based our group analysis on the SAMBA guidelines–recommended dexamethasone dose. Second, we excluded studies performed by the author Yoshitaka Fujii as suggested by Carlisle.[5] Last, we examined a much larger number of patients, undergoing different surgical procedures, whereas Karanicolas et al.[3] only examined patients undergoing laparoscopic cholecystectomy. Nonetheless, we observed less heterogeneity in our comparisons than Karanicolas et al.[3] observed in their study, suggesting the generalizability of our findings.

We did not observe differences in the clinical effect of dexamethasone on the prevention of nausea or vomiting when these outcomes were examined separately. In contrast, Tramèr and Walder[99] reported greater antivomiting than antinausea properties of ondasentron, another commonly used medication to prevent PONV. Nevertheless, it seems that previous comparisons between these individual drugs did not show a significant benefit in favor of a specific drug.[100]

Others have performed systematic reviews on the effect of dexamethasone to prevent PONV. Henzi et al.[2] did not

examine the dose-dependent effects of dexamethasone on PONV. Karanicolas et al.[3] showed differences in PONV reduction between extreme doses of dexamethasone (2–5 mg vs 8–16 mg) in patients undergoing laparoscopic cholecystectomy. However, some of the doses included in the group comparisons of Karanicolas et al.[3] are rarely used by clinical practitioners. Our findings are more generalizable because we included a wide range of surgical procedures, and we performed group comparisons based on common dosages used by clinical practitioners. We also did not detect a clinical benefit of the 8-mg to 10-mg dose compared with the 4-mg to 5-mg dose on the reduction of PONV when dexamethasone was used with a second antiemetic.

Our study is only valid when interpreted according to its limitations. To generalize our findings, we included several types of surgical procedures, allowing the possibility for a greater degree of heterogeneity. However, heterogeneity was low for the vast majority comparisons, which in fact suggests a generalizable effect of dexamethasone to prevent PONV. The funnel plots demonstrated asymmetry for some of the primary analysis involving the 8-mg to 10-mg dose group. The detection of negative studies that were not published due to negative results could decrease the combined effect for the 8-mg to 10-mg dose group in the affected comparisons.[101]

In summary, we demonstrated that when given as a single drug or when used in combination therapy, 4 mg to 5 mg of dexamethasone seems to have comparable clinical effects on the prevention of PONV as the 8-mg to 10-mg dose. Our findings confirm the recommendation of the SAMBA guidelines for the prevention of PONV, which favors the 4-mg to 5-mg dexamethasone dose.

DISCLOSURES

Name: Gildasio S. De Oliveira Jr., MD, MSCI.
Contribution: This author helped design and conduct the study, analyze the data, and prepare the manuscript.
Attestation: This author attests to the integrity of the data.
Name: Lucas J. Santana Castro-Alves, MD.
Contribution: This author helped conduct the study and prepare the manuscript.
Name: Shireen Ahmad, MD.
Contribution: This author helped conduct the study and prepare the manuscript.
Name: Mark C. Kendall, MD.
Contribution: This author helped conduct the study and prepare the manuscript.
Name: Robert J. McCarthy, PharmD.
Contribution: This author helped conduct the study, analyze the data, and prepare the manuscript.
Attestation: This author attests to the integrity of the data.
This manuscript was handled by: Peter S. A. Glass, MB, ChB.

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