Steroids to Ameliorate Postoperative Pain

CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

SURGICAL tissue injury provokes a neuroendocrine stress response and inflammation.[1,2] The neuroendocrine response can be moderated by regional or neuraxial anesthesia.[3,4] However, the inflammatory response results largely from local release of mediators that then act systemically.[5] It is widely believed that the inflammatory response to surgical tissue injury is responsible for serious complications including prolonged fatigue,[6] atrial fibrillation,[7] delirium,[8] and prolonged intensive care unit stay.[9] It is also likely that inflammation contributes to acute postoperative pain.[10] A variety of antiinflammatory medications including lidocaine,[11] selective cyclooxygenase-2 inhibitors,[12] and other nonsteroidal antiinflammatory drugs[12] have thus been used in attempts to reduce surgical pain. The ultimate antiinflammatory drugs, however, are steroids. To the extent that inflammatory mechanisms contribute to postoperative pain, one might expect that preoperative or intraoperative steroid administration would ameliorate postoperative pain. Consistent with this theory, steroids peripherally inhibit phospholipase, thereby decreasing pain-aggravating products of the cyclooxygenase and lipoxygenase pathways.[13] Corticosteroids also inhibit expression of cytokine genes and release of proinflammatory enzymes, bradykinin, and neuropeptides from injured nerve terminals[14–16] — all of which also worsen pain. In addition, corticosteroids decrease perioperative proinflammatory mediators including interleukins 1, 6, and 8, along with tumor necrosis factor, C-reactive protein, and leukocyte adhesion molecules.[15,17] As might thus be expected, many studies have evaluated the effects of steroid administration on surgical pain. In this issue of ANESTHESIOLOGY, De Oliveira *et al.*[18] present a meta-analysis of studies that evaluated the effect of intravenous dexamethasone on postoperative pain.

"… dexamethasone ameliorates acute postoperative pain … [but] what remains unclear is the risk-benefit ratio."

The strength of the analysis by De Oliveira *et al.* is that it evaluates a wide range of doses. Their analysis suggests that higher doses of dexamethasone (more than 0.2 mg/kg) do not improve analgesia compared with medium or low doses. Less clear is whether medium doses are superior to low doses (less than 0.1 mg/kg). A typical 4-mg dose for prophylaxis of postoperative nausea and vomiting[19] thus may or may not be sufficient.

De Oliveira *et al.* also evaluated the effect of timing on postoperative pain. Unlike with most analgesics, many effects of corticosteroids require gene expression and protein production — and thus have a delayed onset. As might be expected, preoperative dosing appeared more effective then intraoperative administration. Edema and inflammation induced by surgery usually persist for days, far longer than the antiinflammatory effect of a single dose of dexamethasone. It is thus somewhat surprising that no studies evaluate the analgesic effect of repeated steroid doses. Persistent incisional pain (lasting longer than 3 months) is common especially after thoracotomy,[20] hysterectomy,[21] and breast surgery.[22] Persistent incisional pain is often preceded by severe perioperative pain,[23] suggesting that effective postoperative analgesia may help prevent conversion of acute pain to chronic pain. However, the potential effect of steroids on persistent incisional pain remains unknown.

Increasing evidence suggests that perioperative steroids provide short-term benefits. For example, it is beyond question that low-dose dexamethasone reduces postoperative nausea and vomiting.[19,24] Similarly, steroids reduce fatigue in the days after surgery.[6] The meta-analysis by De Oliveira *et al.*[18] provides considerable support for an analgesic effect of steroids. The difficulty is that the same basic antiinflammatory mechanisms that presumably provide these benefits may aggravate risk of surgical wound infection.

◆ This Editorial View accompanies the following article: De Oliveira Jr GS, Almeida MD, Benzon HT, McCarthy RJ: Perioperative single dose systemic dexamethasone for postoperative pain: A meta-analysis of randomized controlled trials. ANESTHESIOLOGY 2011; 115:575–88.

Illustration: A. Johnson/J. P. Rathmell.

Accepted for publication June 8, 2011. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

 Anesthesiology 2011; 115:457–9

The potential risk of administering perioperative steroids is far from trivial: surgical site infection remains a common and serious complication.[25] Furthermore, the transition from inevitable wound contamination to clinical infection occurs during a brief "decisive period" during and for several hours after surgery — and is thought to mostly depend on failure of immune defenses.[26] Clinicians thus need to seriously consider potential harm that could result from administration of drugs that specifically impair immune defenses during the decisive period.

De Oliveira *et al.* conclude that "a single dose of perioperative dexamethasone does not increase dose-limiting complications such as wound infection." However, this conclusion is based on reported infections in the underlying studies included in their analysis; reliance on these studies is a critical limitation because none used appropriate methodology to evaluate infection or was powered to detect clinically important increases in infection risk. A more accurate statement might be that the effect of perioperative steroid administration on wound infection risk remains unknown — and could well be substantial.

Hyperglycemia is another steroid-induced complication. The increase is modest[27] but has yet to be well characterized. Furthermore, there is little convincing evidence that small increases in perioperative plasma glucose concentration worsen outcomes.[28] At least in most patients, it thus seems unlikely that hyperglycemia is a compelling reason to avoid giving low- to moderate-dose steroids.

The analysis by De Oliveira *et al.* is certainly the most thorough quantitative literature review of perioperative dexamethasone for pain. However, all meta-analyses share basic limitations. A major concern is publication bias, which results from the tendency for positive studies to be published more often than negative ones. Although the authors used statistical methods to evaluate and limit the effects of publication bias, some unknown amount surely remains. Another major issue is the quality of available studies; a meta-analysis is only as good as the underlying studies. For example, pain and/or opioid consumption was not always the primary outcome of the underlying studies; consequently, it was not necessarily well evaluated. This is even more the case for potential steroid-induced complications that were never the primary outcome and thus inadequately evaluated.

In summary, the meta-analysis of De Oliveira *et al.* provides good evidence that dexamethasone ameliorates acute postoperative pain. Whether a low dose (less than 0.1 mg/kg) is sufficient remains unclear, but a dose exceeding 0.2 mg/kg does not appear necessary. The meta-analysis also shows that analgesia is enhanced when steroids are given preoperatively or at least shortly after induction. What remains unclear is the risk-benefit ratio because the underlying studies did not adequately evaluate the potential substantial effect of steroids on host resistance to the bacteria that cause surgical site infections.

Alparslan Turan, M.D., Daniel I. Sessler, M.D., Department of Outcomes Research, The Cleveland Clinic, Cleveland, Ohio. turana@ccf.org, www.OR.org

References

1. Udelsman R, Holbrook NJ: Endocrine and molecular responses to surgical stress. Curr Probl Surg 1994; 31:653–720
2. Kohl BA, Deutschman CS: The inflammatory response to surgery and trauma. Curr Opin Crit Care 2006; 12:325–32
3. Sessler DI, Ben-Eliyahu S, Mascha EJ, Parat MO, Buggy DJ: Can regional analgesia reduce the risk of recurrence after breast cancer? Methodology of a multicenter randomized trial. Contemp Clin Trials 2008; 29:517–26
4. Bagry H, de la Cuadra Fontaine JC, Asenjo JF, Bracco D, Carli F: Effect of a continuous peripheral nerve block on the inflammatory response in knee arthroplasty. Reg Anesth Pain Med 2008; 33:17–23
5. Buvanendran A, Kroin JS, Berger RA, Hallab NJ, Saha C, Negrescu C, Moric M, Caicedo MS, Tuman KJ: Upregulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. Anesthesiology 2006; 104:403–10
6. Lunn TH, Kristensen BB, Andersen LØ, Husted H, Otte KS, Gaarn-Larsen L, Kehlet H: Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: A randomized, placebo-controlled trial. Br J Anaesth 2011; 106:230–8
7. Anselmi A, Possati G, Gaudino M: Postoperative inflammatory reaction and atrial fibrillation: Simple correlation or causation? Ann Thorac Surg 2009; 88:326–33
8. Rudolph JL, Ramlawi B, Kuchel GA, McElhaney JE, Xie D, Sellke FW, Khabbaz K, Levkoff SE, Marcantonio ER: Chemokines are associated with delirium after cardiac surgery. J Gerontol A Biol Sci Med Sci 2008; 63:184–9
9. Kilger E, Heyn J, Beiras-Fernandez A, Luchting B, Weis F: Stress doses of hydrocortisone reduce systemic inflammatory response in patients undergoing cardiac surgery without cardiopulmonary bypass. Minerva Anestesiol 2011; 77: 268–74
10. Zhang JM, An J: Cytokines, inflammation, and pain. Int Anesthesiol Clin 2007; 45:27–37
11. Vigneault L, Turgeon AF, Côté D, Lauzier F, Zarychanski R, Moore L, McIntyre LA, Nicole PC, Fergusson DA: Perioperative intravenous lidocaine infusion for postoperative pain control: A meta-analysis of randomized controlled trials. Can J Anaesth 2011; 58:22–37
12. White PF: The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anesth Analg 2005; 101(5 Suppl):S5–22
13. Sapolsky RM, Romero LM, Munck AU: How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 2000; 21:55–89
14. Hargreaves KM, Costello A: Glucocorticoids suppress levels of immunoreactive bradykinin in inflamed tissue as evaluated by microdialysis probes. Clin Pharmacol Ther 1990; 48: 168–78
15. Czock D, Keller F, Rasche FM, Häussler U: Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clin Pharmacokinet 2005; 44:61–98
16. Hong D, Byers MR, Oswald RJ: Dexamethasone treatment reduces sensory neuropeptides and nerve sprouting reactions in injured teeth. Pain 1993; 55:171–81
17. Schurr UP, Zünd G, Hoerstrup SP, Grünenfelder J, Maly FE, Vogt PR, Turina MI: Preoperative administration of steroids: Influence on adhesion molecules and cytokines after cardiopulmonary bypass. Ann Thorac Surg 2001; 72:1316–20
18. De Oliveira Jr GS, Almeida MD, Benzon HT, McCarthy RJ: Perioperative single dose systemic dexamethasone for postoperative pain: A meta-analysis of randomized controlled trials. Anesthesiology 2011; 115:575–88
19. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, Zernak C, Danner K, Jokela R, Pocock SJ, Trenkler S,

Kredel M, Biedler A, Sessler DI, Roewer N, IMPACT Investigators: A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004; 350:2441–51

20. Wildgaard K, Ravn J, Kehlet H: Chronic post-thoracotomy pain: A critical review of pathogenic mechanisms and strategies for prevention. Eur J Cardiothorac Surg 2009; 36:170–80
21. Brandsborg B, Nikolajsen L, Hansen CT, Kehlet H, Jensen TS: Risk factors for chronic pain after hysterectomy: A nationwide questionnaire and database study. ANESTHESIOLOGY 2007; 106:1003–12
22. Gärtner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H: Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA 2009; 302:1985–92
23. Perkins FM, Kehlet H: Chronic pain as an outcome of surgery. A review of predictive factors. ANESTHESIOLOGY 2000; 93:1123–33
24. Henzi I, Walder B, Tramèr MR: Dexamethasone for the prevention of postoperative nausea and vomiting: A quantitative systematic review. Anesth Analg 2000; 90:186–94
25. Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P: Adverse impact of surgical site infections in English hospitals. J Hosp Infect 2005; 60:93–103
26. Burke JF: The effective period of preventive antibiotic action in experimental incisions and dermal lesions. Surgery 1961; 50:161–8
27. Maheshwari A, Abdelmalak B, Mascha EJ, Kirkova Y, Sessler DI: The Effect of Steroids on Surgery-Induced Hyperglycemia in Diabetics and Non-Diabetics. Presented at the Annual Meeting of American Society of Anesthesiologists 2010, San Diego, CA 1175
28. Duncan AE, Abd-Elsayed A, Maheshwari A, Xu M, Soltesz E, Koch CG: Role of intraoperative and postoperative blood glucose concentrations in predicting outcomes after cardiac surgery. ANESTHESIOLOGY 2010; 112:860–71

ANESTHESIOLOGY REFLECTIONS

Block-ing Pain with Jiffy Toothache Drops

Founded in Brooklyn, New York, in 1907 by Lithuanian-American pharmacist Alexander Block, the Block Drug Company shifted its headquarters in 1938 to nearby Jersey City, New Jersey. From there it produced or distributed dozens of products, including "Jiffy Toothache Drops" (*above*) which featured a topical anesthetic blend of benzocaine, eugenol, and menthol. (Of course the accompanying mix of chloroform in "54.2% Alcohol" also helped relieve dental pain in a "Jiffy" ….) After the founder's death in 1953, Block Drug was run by his family, then traded publicly from 1971–2001, and finally sold to a pharmaceutical giant. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.

Perioperative Single Dose Systemic Dexamethasone for Postoperative Pain

A Meta-analysis of Randomized Controlled Trials

Gildàsio S. De Oliveira, Jr., M.D.,* Marcela D. Almeida, M.D.,† Honorio T. Benzon, M.D.,‡ Robert J. McCarthy, Pharm.D.§

CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: Dexamethasone is frequently administered in the perioperative period to reduce postoperative nausea and vomiting. In contrast, the analgesic effects of dexamethasone are not well defined. The authors performed a meta-analysis to evaluate the dose-dependent analgesic effects of perioperative dexamethasone.

Methods: We followed the PRISMA statement guidelines. A wide search was performed to identify randomized controlled trials that evaluated the effects of a single dose systemic dexamethasone on postoperative pain and opioid consumption. Meta-analysis was performed using a random-effect model. Effects of dexamethasone dose were evaluated by pooling studies into three dosage groups: low (less than 0.1 mg/kg), intermediate (0.11–0.2 mg/kg) and high (≥0.21 mg/kg).

Results: Twenty-four randomized clinical trials with 2,751 subjects were included. The mean (95% CI) combined effects favored dexamethasone over placebo for pain at rest (≤4 h, −0.32 [0.47 to −0.18], 24 h, −0.49 [−0.67 to −0.31]) and with movement (≤ 4 h, −0.64 [−0.86 to −0.41], 24 h, −0.47 [−0.71 to −0.24]). Opioid consumption was decreased to a similar extent with moderate −0.82 (−1.30 to −0.42) and high −0.85 (−1.24 to −0.46) dexamethasone, but not decreased with low-dose dexamethasone −0.18 (−0.39–0.03). No increase in analgesic effectiveness or reduction in opioid use could be demonstrated between the high- and intermediate-dose dexamethasone. Preoperative administration of dexamethasone appears to produce a more consistent analgesic effect compared with intraoperative administration.

Conclusion: Dexamethasone at doses more than 0.1 mg/kg is an effective adjunct in multimodal strategies to reduce postoperative pain and opioid consumption after surgery. The preoperative administration of the drug produces less variation of effects on pain outcomes.

What We Already Know about This Topic

- Dexamethasone is often used to prevent postoperative nausea and vomiting, but its effects on pain are less well studied

What This Article Tells Us That Is New

- In a meta-analysis of approximately 2,500 patients, dexamethasone, >0.1 mg/kg, reduced postoperative pain and opioid consumption

ACUTE postoperative pain is an undesirable outcome that can delay functional recovery for patients undergoing surgical procedures. Multimodal analgesic approaches

◆ This article is accompanied by an Editorial View. Please see: Turan A, Sessler DI: Steroids to ameliorate postoperative pain. ANESTHESIOLOGY 2011; 115:457–9.

* Instructor, Department of Anesthesiology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois. † Clinical Associate, Department of Psychiatry, University of Chicago, Pritzker School of Medicine, Chicago, Illinois. ‡ Professor, Department of Anesthesiology, Northwestern University, Feinberg School of Medicine. § Research Professor, Department of Anesthesiology, Northwestern University, Feinberg School of Medicine.

Received from the Department of Anesthesiology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois. Submitted for publication January 28, 2011. Accepted for publication May 5, 2011. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. De Oliveira: Department of Anesthesiology, Northwestern Memorial Hospital, 251 E. Huron Street, F5-704, Chicago, Illinois 60611. g-jr@northwestern.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

 Anesthesiology 2011; 115:575–88

have been used as an important strategy to mitigate postoperative pain.[1] The effectiveness of adjunct agents, including ketamine,[2] gabapentin,[3] paracetamol, and nonsteroidal antiinflammatory drugs,[4] have been examined in systematic reviews that demonstrate their benefits in reducing postoperative pain and/or opioid consumption. These agents became useful multimodal analgesic strategies.[5] Dexamethasone is a corticosteroid commonly used perioperatively to reduce postoperative nausea and vomiting[6] and may have a beneficial role in postoperative analgesia. However, in a systematic review of dexamethasone after laparoscopic cholecystectomy, the postoperative analgesic effect of dexamethasone, examined as a secondary outcome was found to be inconclusive.[7] Therefore, the effect of dexamethasone on postoperative pain as well as the optimal dose to reduce pain has not been clearly defined. Currently, dexamethasone is not recommended as a component of a multimodal drug strategy to decrease postsurgical pain.

The objective of this quantitative systematic review was to assess the efficacy and dose dependency of single-dose perioperative dexamethasone on postsurgical pain outcomes. We also evaluated the dose-dependent side effects of single dose dexamethasone in the perioperative period.

Materials and Methods

This quantitative systematic review was conducted following the guidelines of the PRISMA statement.[8]

Systematic Search

Published reports of randomized trials evaluating the effects of dexamethasone on surgical postoperative pain were searched using the National Library of Medicine's PubMed database, the Cochrane Database of Systematic Reviews, and Google Scholar inclusive to September 1, 2010. Free text and MeSH terms "dexamethasone," "pain," "postoperative," "preoperative," "analgesia," and "opioid" were used individually and in various combinations. No language restriction was used. The search was limited to randomized controlled clinical trials in subjects older than 18 yr. An attempt to identify additional studies not found by the primary search methods was made by reviewing the reference lists from identified studies. No search was performed for unpublished studies. This initial search yielded 211 randomized clinical trials.

Selection of Included Studies

The study's inclusion and exclusion criteria were determined before the systematic search. Two authors (GDO and MDA) independently evaluated the abstract and results of the 211 articles obtained by the initial search. 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 (HTB).

Inclusion and Exclusion Criteria

We included randomized controlled trials of a single perioperative intravenous dexamethasone administration with an inactive (placebo or "no treatment") control group. Excluded were trials reporting analgesia after emergency medicine, dental, and nonsurgical pain. Trials evaluating more than one dose of perioperative dexamethasone were also excluded to maximize clinical homogeneity. Studies containing a concurrent use of an alternative multimodal analgesia regimen were excluded if a direct comparison of dexamethasone and placebo could not be established. Included studies had to report at least pain scores or opioid consumption on postoperative pain outcomes. No minimum sample size was required for inclusion in the meta-analysis.

Validity Scoring

Two authors (GSD and MDA) independently read the included reports and assessed their methodologic validity using a modified Jadad five-point quality scale.[9] 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 (HTB). 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 MDA) 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 two investigators (GDO and MDA). If an agreement could not be reached between the two investigators, the decision was made by a third investigator (HTB). 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, early pain scores ($\leq$4 h) at rest and at movement, late pain scores (24 h) at rest and at movement, cumulative opioid consumption, time to opioid administration (minutes), length of hospital stay (hours), and adverse events. Postoperative opioid consumption was converted to the equivalent dose of intravenous morphine.[10] Visual analog scale or numeric rating scale of pain were converted to a 0–10 numeric rating scale.

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 on the presence or absence of adverse effects was extracted and converted to incidence while continuous data were recorded using mean and SD. Data pre-

sented only as median and range were converted to means and SD using previously described methodology.[11] When required, the SD for pain scores was estimated using the most extreme values. The most conservative value was used when the same outcome was reported more than one time for a determined period. Dexamethasone dose was converted to units in mg/kg using the mean weight reported for the dexamethasone groups. When no information about group weight was available, 70 kg was used.

To facilitate a quantitative analysis and to examine dose dependency of the outcomes, comparisons were stratified by dose into three groups: low-dose (≤0.10 mg/kg), intermediate-dose (0.11–0.20 mg/kg), and high-dose (≥0.21 mg/kg) dexamethasone. The dosage ranges were derived from clinical guidelines for postoperative nausea and vomiting that favor low dose compared with intermediated dose dexamethasone for antiemetic prophylaxis.[6] The high-dose group represents doses greater than those routinely used for antiemetic prophylaxis.

Definition of Relevant Outcome Data

Primary Outcomes. Early acute postoperative pain scores (visual analog scale or numeric rating scale) at rest and at movement (0–4 h postoperatively); late acute postoperative pain scores (visual analog scale or numeric rating scale) at rest and at movement (24 h postoperatively); and cumulative opioid consumption (up to 24 h) in the postoperative period.

Secondary Outcomes. The time to first analgesic administration (minutes); time to hospital discharge (hours); and incidence and severity (visual analog scale or numeric rating scale) scores of chronic pain. In addition, adverse events including postoperative infection (wound, urinary tract, and pneumonia), hyperglycemic events, delayed healing, and pruritus were examined.

Meta-analyses

The standardized mean differences with 95% CI were determined and reported for continuous data. For dichotomous data (adverse effects), the Peto odds ratio (to account for the potential of zero counts in the cells for low-frequency outcomes) and 95% CI are reported. A significant effect compared with placebo required that the 95% CI for continuous data did not include 0 and for dichotomous data, the CI did not include 1.0. We calculated number needed to harm, based on the absolute risk reduction, with 95% CI as an estimate of a harmful effect. We used the lower 95% CI estimate of the number needed to harm to describe the largest increase in adverse events that could be excluded by our analysis. Because of the different surgical procedures, we used a random effect model in an attempt to generalize our findings to studies not included in our meta-analysis.[12] Publication bias was evaluated by examining for asymmetric funnel plots using the Egger regression test.[13] A one-sided $P < 0.05$ was considered an indication of an asymmetric funnel plot. A file drawer analysis described by Rosenthal[14] was performed in the case of an asymmetric funnel plot. The test estimates the lowest number of additional studies that if they would become available would reduce the combined effect to nonsignificance assuming the average z-value of the combined P values of these missing studies would be 0.[14] Sensitivity analysis was also performed to assess the effect of the elimination of a single trial on the outcome of the analysis.

Heterogeneity of the included studies was considered to be present if the I^2 statistic was greater than 30%. Further analysis was planned *a priori* to explore relevant heterogeneity. Subgroup analysis was performed to investigate the effect of time of dexamethasone administration (preoperative *vs.* intraoperative) on the pain outcomes. 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 random effects pooled estimates of variance (τ squared) within studies by total variance (total τ squared). The value obtained was then subtracted from 1. When values fall outside the range of 0–100%, they were set to the closest value (0% or 100%).

Comparisons between the different doses of dexamethasone and were made using a Z test with Bonferroni correction for multiple comparisons. Analysis was performed using Comprehensive Meta-analysis software version 2 (Biostat, Englewood, NJ).

Results

Of the 211 initially evaluated abstracts, 38 studies initially met the inclusion criteria (fig. 1). Fourteen studies were subsequently excluded: 12 either had no acute pain outcomes,

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

Table 1. Summary of Studies Included in Analysis

Authors	Year of Publication	Procedures	Number Treatment/ Control	Treatment
Al-Quadah *et al.*[29]	2010	Nasal sinus endoscopy	32/30	Dexamethasone 8 mg IV at induction
Sánchez-Rodríguez *et al.*[35]	2010	Laparoscopic cholecystectomy	105/105	Dexamethasone 8 mg IV 60 min preoperatively
Thangaswamy *et al.*[30]	2010	Laparoscopic hysterectomy	36/19	Dexamethasone 4 mg and 8 mg IV 2 h preoperatively
Fukami *et al.*[46]	2009	Laparoscopic cholecystectomy	40/40	Dexamethasone 8 mg IV 90 min before surgery
Jokela *et al.*[31]	2009	Laparoscopic hysterectomy	120/30	Dexamethasone 5 mg, 10 mg and 15 mg IV before induction
Yeo *et al.*[52]	2009	Middle ear surgery	40/40	Dexamethasone 10 mg IV after induction
Kardash *et al.*[43]	2008	Total hip arthroplasty	25/25	Dexamethasone 40 mg IV intraoperative
Worni *et al.*[36]	2008	Thyroidectomy	37/35	Dexamethasone 8 mg IV 45 min preoperatively
Bianchin *et al.*[40]	2007	Laparoscopic cholecystectomy	36/37	Dexamethasone 8 mg IV 2min before induction
Hval *et al.*[39]	2007	Breast segmental mastectomy	50/50	Dexamethasone 16 mg IV after induction
Wu *et al.*[32]	2007	Anorectal surgery	30/30	Dexamethasone 5 mg IV before induction
Aminmansour *et al.*[44]	2006	Lumbar discectomy	39/22	Dexamethasone 40 mg or 80 mg IV– time not specified
Chen *et al.*[41]	2006	Orthopedic, otolaryngologic, ophthalmologic, laparoscopy, laparotomy	350/350	Dexamethasone 10 mg before induction
Feo *et al.*[47]	2005	Laparoscopic cholecystectomy	49/52	Dexamethasone 8 mg 90 min before surgery
McKean *et al.*[37]	2005	Tonsillectomy	24/22	Dexamethasone 10 mg IV after induction
Bisgaard *et al.*[38]	2003	Laparoscopic cholecystectomy	40/40	Dexamethasone 8 mg IV 90 min preoperatively
Coloma *et al.*[50]	2002	Laparoscopic cholecystectomy	70/70	Dexamethasone 4 mg IV at induction
Elhakim *et al.*[45]	2002	Laparoscopic cholecystectomy	120/30	Dexamethasone 4 mg, 8 mg, 16 mg before induction
Lee *et al.*[48]	2002	Gynecologic laparoscopy	83/84	Dexamethasone 8 mg before induction
Wang *et al.*[33]	2002	Laparoscopic cholecystectomy	38/39	Dexamethasone 5 mg IV after induction
Coloma *et al.*[34]	2001	Anorectal surgery	40/40	Dexamethasone 4 mg IV intraoperative
Carr *et al.*[49]	1999	Tonsillectomy	15/14	Dexamethasone 20 mg IV intraoperatively
Wang *et al.*[51]	1999	Laparoscopic cholecystectomy	40/38	Dexamethasone 8 mg IV before induction
McKenzie *et al.*[42]	1997	Major gynecologic surgery	40/40	Dexamethasone IV 20 mg after induction

† Means and SDs for data used in analysis were extracted from tables and or text unless specified. ‡ Means and/or SDs were estimated from median and or range.

IM = intramuscularly; IV = intravenously; PCA = patient-controlled analgesia; po = per oral; PRN = as needed; q = every; SC = subcutaneously.

Table 1. Continued

Type of Anesthesia	Postoperative Analgesia	Modified Jadad Score (1–5)[9]	Method of Data Extraction†
Fentanyl/propofol/ isoflurane	Acetaminophen 1g po q 6 hr + tramadol (IM) PRN	4	Table/Figure
Fentanyl/propofol	Ketorolac 30 mg IV q 8 hr + buprenorphine (0.15–0.30 mcg) PRN	3	Table/text
Fentanyl/propofol/N_2O/ isoflurane	Fentanyl PCA	5	Figure/text
Fentanyl/propofol/N_2O/ sevoflurane	Diclofenac sodium 50 mg per rectum PRN	3	Table/text
Remifentanil/propofol/ N_2O	Oxycodone PCA	5	Table/Figure
Propofol/isoflurane/ N_2O	Ketorolac 30 mg IV q 6 h	4	Table/text
Spinal, L2-L3, 15 mg 0.5% bupivacaine	PCA morphine, acetaminophen 650 mg po q 6 h and ibuprofen 400 mg po q 6 h	5	Table/text
Fentanyl/propofol/thiopental/ isoflurane/sevoflurane	Acetaminophen 4g + metamizole + morphine IV or SC	5	Figure/text
Fentanyl/propofol/N_2O/ sevoflurane	Ketorolac 30 mg IV	5	Table/text‡
Remifentanil/fentanyl/ propofol	Oxycodone 5 mg po	5	Figures/text
Propofol/sevoflurane/ N_2O	Ketorolac 30 mg IV + meperidine 12.5–25 mg IV	4	Table/text
Anesthetic regimen not standardized	Morphine SC	3	Table/text
Fentanyl/propofol/ sevoflurane	Meperidine 50 mg IM q 4 hr PRN	4	Table/text
Fentanyl/propofol/ sevoflurane	Acetaminophen 1 g IV q 6 h + ketoprofen PRN	3	Figures/text
Morphine/propofol/N_2O/ isoflurane	Acetaminophen 1 g PO q 6 h + diclofenac 50 mg PO q 8 h	5	Tables/text‡
Fentanyl/propofol	Ibuprofen 600 mg po q 8 h + morphine 5–10 mg IV	5	Figures/table/text
Fentanyl/propofol/sevoflurane	Fentanyl 25mcg PRN pain	3	Table/text
Fentanyl/propofol/N_2O/ isoflurane	Nalbuphine 20 mg IM q 4 hr PRN	4	Table/text
Fentanyl/thiopental/ sevoflurane	Ketorolac 15 mg IV	3	Table/text
Fentanyl/propofol/ isoflurane	Tenoxicam 20 mg q 12 hr IV	5	Author
Sedation: midazolam, propofol, ketorolac, fentanyl, and local infiltration	Hydrocodone 2.5 mg –acetaminophen 500 mg	2	Table/text
Not described	Codeine elixir q 4 hr PRN	5	Figure
Fentanyl/propofol/ isoflurane	Morphine PCA IV	5	Table/text
Fentanyl/propofol/N_2O/ isoflurane	Morphine IV PCA	4	Table/text‡

Group	Study name	Comparison	Outcome	Statistics for each study						
				Std diff in mean	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
1	Al-quadad	0.01-0.1mg/kg	early pain	0.000	0.254	0.065	-0.498	0.498	0.000	1.000
1	Thangaswamy	0.01-0.1mg/kg	early pain	0.258	0.335	0.112	-0.398	0.914	0.771	0.441
1	Jokela	0.01-0.1mg/kg	early pain	-0.632	0.265	0.070	-1.151	-0.114	-2.390	0.017
1	Wu	0.01-0.1mg/kg	early pain	-1.177	0.280	0.078	-1.725	-0.629	-4.208	0.000
1	Wang 2002	0.01-0.1mg/kg	early pain	-0.230	0.229	0.052	-0.679	0.218	-1.007	0.314
1	Coloma 2001	0.01-0.1mg/kg	early pain	-0.167	0.224	0.050	-0.606	0.272	-0.744	0.457
1				-0.330	0.190	0.036	-0.702	0.043	-1.736	0.083
2	Sanchez-Rodriguez	0.11-0.2mg/kg	early pain	-0.424	0.140	0.019	-0.698	-0.151	-3.040	0.002
2	Thangaswamy	0.11-0.2mg/kg	early pain	0.129	0.329	0.108	-0.516	0.774	0.391	0.696
2	Jokela	0.11-0.2mg/kg	early pain	-0.748	0.267	0.071	-1.271	-0.224	-2.799	0.005
2	Woni	0.11-0.2mg/kg	early pain	-0.218	0.236	0.056	-0.682	0.245	-0.923	0.356
2	McKean	0.11-0.2mg/kg	early pain	-1.000	0.313	0.098	-1.614	-0.386	-3.195	0.001
2	Bisgaard	0.11-0.2mg/kg	early pain	-0.500	0.227	0.052	-0.945	-0.055	-2.202	0.028
2	Yeo	0.11-0.2mg/kg	early pain	0.300	0.225	0.051	-0.141	0.741	1.333	0.182
2	Bianchin	0.11-0.2mg/kg	early pain	-0.043	0.234	0.055	-0.502	0.415	-0.186	0.853
2	Fukami	0.11-0.2mg/kg	early pain	-0.415	0.226	0.051	-0.858	0.028	-1.837	0.066
2	Feo	0.11-0.2mg/kg	early pain	-0.245	0.200	0.040	-0.636	0.147	-1.224	0.221
2	Wang 1999	0.11-0.2mg/kg	early pain	-0.566	0.231	0.053	-1.019	-0.113	-2.450	0.014
2				-0.332	0.100	0.010	-0.528	-0.136	-3.322	0.001
3	Jokela	>0.2mg/kg	early pain	-0.857	0.270	0.073	-1.386	-0.328	-3.177	0.001
3	Kjetil	>0.2mg/kg	early pain	-0.500	0.203	0.041	-0.898	-0.102	-2.462	0.014
3	McKenzie	>0.2mg/kg	early pain	0.000	0.224	0.050	-0.438	0.438	0.000	1.000
3	Kardash	>0.2mg/kg	early pain	-0.195	0.284	0.080	-0.751	0.361	-0.688	0.491
3	Aminmasour 1	>0.2mg/kg	early pain	-0.192	0.314	0.099	-0.807	0.423	-0.612	0.540
3	Aminmasour 2	>0.2mg/kg	early pain	0.057	0.309	0.095	-0.548	0.663	0.186	0.852
3				-0.295	0.140	0.020	-0.570	-0.020	-2.104	0.035
Overall				-0.321	0.075	0.006	-0.468	-0.175	-4.292	0.000

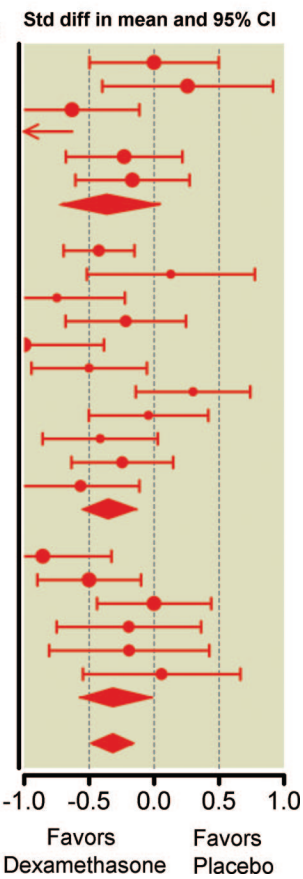

Fig. 2. Pooled data evaluating the effect of dexamethasone dose on early pain scores (4 h or less) at rest compared with placebo. Data evaluated using a random effects model. Point estimate (95% CI) for overall effect was −0.32 (−0.46 to −0.17). Standardized mean difference for individual study represented by *small circles* on Forrest plot with 95% CI of the difference shown as *solid line*. *Larger sized circle* and *thicker 95% CI line* denote larger sample size. The *diamond* represents the pooled estimate and uncertainty for the effects of low- (0.1 mg/kg or less), intermediate- (0.11–0.2 mg/kg), and high-dose (more than 0.2 mg/kg) dexamethasone, respectively. Sample heterogeneity as assessed by the I^2 for the low-, intermediate-, and high-dose grouping of studies was 68, 52, and 42, respectively.

data could not be extracted, or authors could not be reached[15–26]; one trial used multiple doses[27]; and one trial evaluated oral dexamethasone.[28] The characteristics of included studies are listed in table 1. The evaluated trials included data from 2,751 subjects and were published between 1997 and 2010.[29–52] The median number of patients in the included studies receiving dexamethasone was 40. The median modified Jadad scale score was 4. The trials tested a single dose of dexamethasone given either preoperatively or intraoperatively in a large variety of surgical procedures. All 24 studies reported on opioid consumption and/or pain scores. Six studies reported pain scores for both rest and activity.[30,31,38,39,43,45]

Early (0–4 h) Pain at Rest

The overall effect of dexamethasone on early pain at rest compared with placebo favored dexamethasone with a mean difference (95% CI) of −0.32 (−0.46 to −0.18) (fig. 2). The funnel plot did not demonstrate asymmetry, indicating that there was not substantial publication bias ($P = 0.43$) (fig. 3).

The aggregate effect of the six studies evaluating low-dose dexamethasone on early pain at rest[29–34] did not achieve statistical significance at −0.33 (−0.70 to 0.04) of dexamethasone compared with placebo (fig. 2). All the studies assessed dexamethasone given intraoperatively. *Post hoc* sensitivity analysis demonstrated that removal of the study of Thangaswamy *et al.*[30] would change the analysis to result in a significant effect of −0.42 (−0.81 to −0.03) for low-dose dexamethasone compared with placebo.

The effect of the combined 11 studies examining the effect of intermediate-dose dexamethasone on early pain at rest[29–31,35–42] suggests a decrease in early pain of −0.33 (−0.52 to −0.13) compared with placebo. There was no difference in the effect of time of drug administration on early pain and 38% of the total variance in the effect was explained by the time of drug administration.

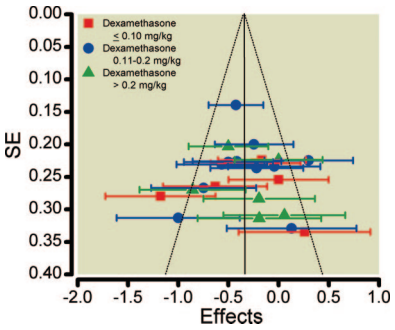

Fig. 3. Early pain at rest funnel plot assessing publication bias. Plotted is the SE *versus* standard difference in mean (Effects). *Vertical line* is the combined effect for early pain, with *diagonal lines* representing the expected 95% CI from the combined effect. Studies outside the funnel indicate heterogeneity. Eggers regression suggests absence of asymmetry ($P = 0.43$, one-sided).

The heterogeneity for studies evaluating the preoperative administration was low ($I^2 = 0$) but it was high for studies examining the intraoperative administration of the drug ($I^2 = 77$).

Five studies evaluated the effect of high-dose dexamethasone on early postoperative pain at rest.[31,39,42–44] One study[44] provided two comparisons that were included in the analysis. There was a beneficial effect of dexamethasone on early pain of −0.29 (−0.57 to −0.02). Dexamethasone was administered intraoperatively in all of these studies. No difference in effectiveness was found among the dexamethasone groups on early pain at rest.

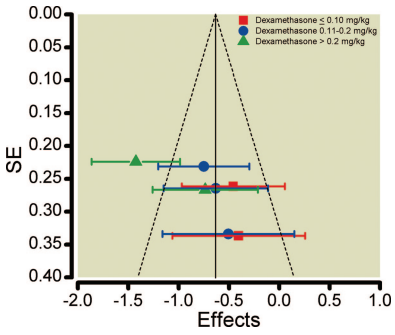

Fig. 5. Early pain at movement funnel plot assessing publication bias. Plotted is the SE *versus* standard difference in mean (Effects). *Vertical line* is the combined effect for early pain, with *diagonal lines* representing the expected 95% CI from the combined effect. Studies outside the funnel indicate heterogeneity. The funnel demonstrated some asymmetry ($P = 0.04$, one-sided) with one of the seven studies outside the 95% CI indicating some heterogeneity favoring dexamethasone; however, the low number of studies limits the potential for evaluating substantial publication bias.

Early (0–4 h) Pain at Movement

The overall effect of dexamethasone on early pain at movement compared with placebo favored dexamethasone with a mean difference (95% CI) of −0.64 (−0.86 to −0.41) (fig. 4) The funnel demonstrated some asymmetry ($P = 0.04$) with one of the seven studies outside the 95% CI, indicating some heterogeneity favoring dexamethasone; however, the low number of studies limits the potential for evaluating substantial publication bias (fig. 5).

Group	Study name	Comparison	Outcome	Statistics for each study						
				Std diff in mean	Std error	Variance	Lower limit	Upper limit	Z-value	P-value
1	Thangaswamy	0.01-0.1mg/kg	Early pain Mov	-0.403	0.337	0.113	-1.063	0.257	-1.198	0.231
1	Jokela	0.01-0.1mg/kg	Early pain Mov	-0.457	0.262	0.068	-0.970	0.056	-1.747	0.081
1				-0.437	0.207	0.043	-0.842	-0.032	-2.115	0.034
2	Thangaswamy	0.11-0.2 mg/kg	Early pain Mov	-0.506	0.334	0.112	-1.161	0.149	-1.514	0.130
2	Jokela	0.11-0.2 mg/kg	Early pain Mov	-0.631	0.265	0.070	-1.149	-0.112	-2.384	0.017
2	Bisgard	0.11-0.2 mg/kg	Early pain Mov	-0.750	0.231	0.054	-1.203	-0.297	-3.242	0.001
2				-0.657	0.154	0.024	-0.960	-0.355	-4.256	0.000
3	Jokela	>0.20mg/kg	Early pain Mov	-0.736	0.267	0.071	-1.259	-0.213	-2.758	0.006
3	Kjetil	>0.20mg/kg	Early pain Mov	-1.425	0.224	0.050	-1.864	-0.986	-6.363	0.000
3				-1.096	0.344	0.118	-1.770	-0.421	-3.183	0.001
Overall				-0.637	0.116	0.014	-0.865	-0.409	-5.475	0.000

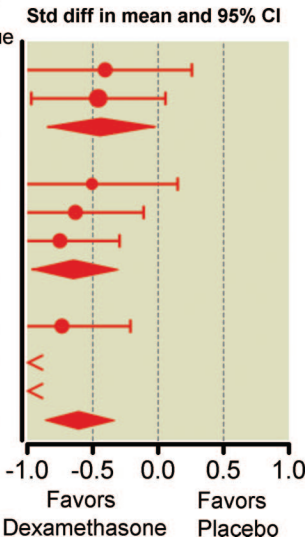

Fig. 4. Pooled data evaluating the effect of dexamethasone dose on early pain scores (4 h or less) with movement compared with placebo. Data evaluated using a random effects model. Point estimate (95% CI) for overall effect was −0.64 (−0.86 to −0.41). Standardized mean difference for individual study represented by square on Forrest plot with 95% CI of the difference shown as *solid line*. *Larger sized circle* and *thicker 95% CI line* denote larger sample size. The diamond represents the pooled estimate and uncertainty for the effects of low- (0.1 mg/kg or less), intermediate- (0.11–0.2 mg/kg), and high-dose (more than 0.2 mg/kg) dexamethasone, respectively. Sample heterogeneity as assessed by the I^2 for the low-, intermediate-, and high-dose grouping of studies was 0, 0 and 74, respectively.

Group	Study name	Comparison	Outcome	Statistics for each study						
				Std diff in mean	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
1	Al-quadad	0.01-0.1mg/kg	late pain	-0.416	0.257	0.066	-0.919	0.088	-1.619	0.106
1	Thangaswamy	0.01-0.1mg/kg	late pain	-0.341	0.336	0.113	-0.999	0.317	-1.016	0.309
1	Jokela	0.01-0.1mg/kg	late pain	-0.362	0.260	0.068	-0.872	0.148	-1.391	0.164
1	Elhakim	0.01-0.1mg/kg	late pain	-0.460	0.262	0.068	-0.973	0.053	-1.759	0.079
1	Wang 2002	0.01-0.1mg/kg	late pain	-0.847	0.238	0.057	-1.313	-0.381	-3.560	0.000
1	Elhakim 2	0.01-0.1mg/kg	late pain	-0.276	0.259	0.067	-0.784	0.233	-1.063	0.288
1				-0.471	0.108	0.012	-0.682	-0.259	-4.364	0.000
2	Sanchez-Rodriguez	0.11-0.2mg/kg	late pain	-1.888	0.166	0.028	-2.213	-1.563	-11.377	0.000
2	Thangaswamy	0.11-0.2mg/kg	late pain	0.145	0.329	0.108	-0.501	0.790	0.440	0.660
2	Jokela	0.11-0.2mg/kg	late pain	-1.373	0.287	0.082	-1.935	-0.810	-4.783	0.000
2	Woni	0.11-0.2mg/kg	late pain	-0.246	0.237	0.056	-0.709	0.218	-1.038	0.299
2	McKean	0.11-0.2mg/kg	late pain	-0.063	0.295	0.087	-0.641	0.516	-0.212	0.832
2	Bisgaard	0.11-0.2mg/kg	late pain	-0.625	0.229	0.052	-1.074	-0.176	-2.729	0.006
2	Bianchin	0.11-0.2mg/kg	late pain	0.148	0.234	0.055	-0.311	0.608	0.632	0.528
2	Fukami	0.11-0.2mg/kg	late pain	-0.360	0.225	0.051	-0.801	0.082	-1.595	0.111
2	Chen	0.11-0.2mg/kg	late pain	0.167	0.076	0.006	0.018	0.315	2.201	0.028
2	Feo	0.11-0.2mg/kg	late pain	-0.333	0.200	0.040	-0.726	0.060	-1.663	0.096
2	Lee 1	0.11-0.2mg/kg	late pain	-0.160	0.216	0.047	-0.583	0.264	-0.739	0.460
2	Lee 2	0.11-0.2mg/kg	late pain	-0.242	0.223	0.050	-0.679	0.196	-1.083	0.279
2	Elhakim	0.11-0.2mg/kg	late pain	-0.556	0.263	0.069	-1.072	-0.040	-2.113	0.035
2				-0.417	0.197	0.039	-0.804	-0.030	-2.113	0.035
3	Jokela	>0.2mg/kg	late pain	-0.500	0.262	0.069	-1.014	0.014	-1.907	0.057
3	Kjetil	>0.2mg/kg	late pain	-0.769	0.207	0.043	-1.175	-0.363	-3.711	0.000
3	Elhakim	>0.2mg/kg	late pain	-0.556	0.263	0.069	-1.072	-0.040	-2.113	0.035
3	Carr	>0.2mg/kg	late pain	-0.824	0.328	0.108	-1.467	-0.182	-2.514	0.012
3	McKenzie	>0.2mg/kg	late pain	-3.332	0.346	0.119	-4.009	-2.655	-9.643	0.000
3	Kardash	>0.2mg/kg	late pain	-0.268	0.284	0.081	-0.825	0.289	-0.944	0.345
3				-1.022	0.385	0.148	-1.776	-0.269	-2.659	0.008
Overall				-0.491	0.092	0.008	-0.671	-0.311	-5.338	0.000

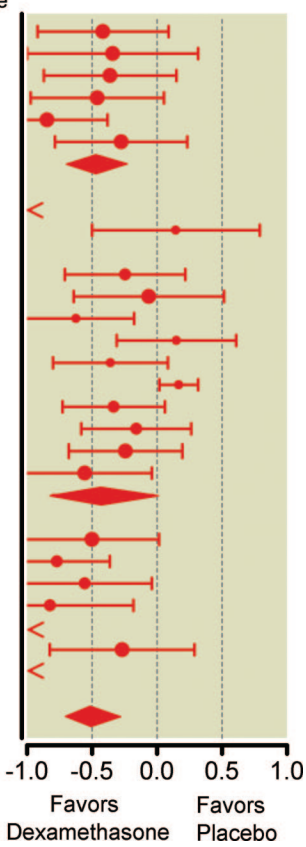

Fig. 6. Pooled data evaluating the effect of dexamethasone dose on late pain scores (24 h) at rest compared with placebo. Data evaluated using a random effects model. Point estimate (95% CI) for overall effect was −0.49 (−0.67 to −0.31). Standardized mean difference for individual study represented by *circle* on Forrest plot with 95% CI of the difference shown as *solid line*. *Larger sized circle* and *thicker 95% CI line* denote larger sample size. The *diamond* represents the pooled estimate and uncertainty for the effects of low- (0.1 mg/kg or less), intermediate- (0.11–0.2 mg/kg), and high-dose (more than 0.2 mg/kg) dexamethasone, respectively. Sample heterogeneity as assessed by the I^2 for the low-, intermediate- and high-dose grouping of studies was 0, 71, and 96, respectively.

Two studies evaluated the effect of low-dose dexamethasone on early pain at movement,[30,31] showing a reduction when compared with placebo, −0.43(−0.84 to −0.03). Three studies assessed the effect of moderate-dose dexamethasone on early pain at movement,[30,31,38] showing a reduction when compared with placebo, −0.65 (−0.96 to −0.35), and two studies evaluating high dose dexamethasone on early pain at movement[31,39] also demonstrated a decrease in pain when compared with placebo, −1.09 (−1.77 to −0.42). There was no difference between the effects of different doses of dexamethasone on early pain at movement.

Late (24 h) Pain at Rest

The overall effect of dexamethasone on late pain at rest compared with placebo favored dexamethasone with a mean difference (95% CI) of −0.49 (−0.67 to −0.31) (fig. 6). The funnel demonstrated moderate asymmetry ($P = 0.01$) with 5 of the 25 studies outside the 95% CI with 2[40,41] favoring placebo and 3[31,35,42] favoring dexamethasone (fig. 7).

The effects of dexamethasone (compared with placebo) on late pain at rest by dosing groups is presented in figure 6. Five studies examined the effects of low-dose dexamethasone on late pain at rest.[29,30,31,33,45] One study[45] provided two comparisons and both were included in the analysis. A positive effect on late pain at rest of −0.47 (−0.68 to −0.25) was observed. There was no evidence of asymmetry in the funnel plot ($P = 0.15$).

Twelve studies evaluated the effect of intermediate-dose dexamethasone on late pain at rest.[30,31,35–38,40,41,45–48] One study[48] provided two comparisons and both were included in the analysis. There was a decrease in late pain at rest of −0.41 (−0.80 to −0.03) compared with placebo. There was no evidence of asymmetry in the funnel plot ($P = 0.09$). There was a greater effect when dexamethasone was given preoperatively, −0.77 (−0.95–0.09) compared with intraoperative administration, −0.007 (−0.12–0.11) ($P < 0.001$).

The six studies examining the effect of high-dose dexamethasone on late pain at rest [31,39,42,43,45,49] demonstrated a

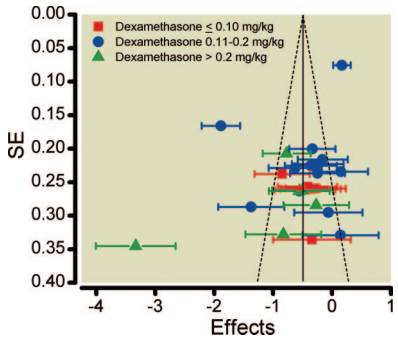

Fig. 7. Late pain (24 h) at rest funnel plot assessing publication bias. Plotted is the SE *versus* standard difference in mean (Effects). *Vertical line* is the combined effect for early pain with diagonal lines representing the expected 95% CI from the combined effect. Studies outside the funnel indicate heterogeneity. The funnel demonstrated moderate asymmetry ($P = 0.01$, one-sided) with 5 of the 25 studies outside the 95% CI, with 2 favoring placebo and 3 favoring dexamethasone. There was no asymmetry in funnel plots for low-, moderate-, or high-dose dexamethasone subgroups.

decrease in pain of −1.0 (−1.77 to −0.26) compared with placebo. There was no evidence of asymmetry on the funnel plot ($P = 0.14$). All studies assessed dexamethasone given intraoperatively. There was no difference in the effect on late pain when the high-dose dexamethasone was compared with the moderate- ($P = 0.13$) or the low-dose ($P = 0.14$) groups.

Late Pain at Movement

The overall effect of dexamethasone on late pain at movement compared with placebo favored dexamethasone with a mean difference (95% CI) of −0.47 (−0.71 to −0.24) (fig. 8). The funnel demonstrated asymmetry ($P = 0.003$) with one study[43] favoring dexamethasone outside the 95% CI (fig. 9).

Three studies examined the effect of low-dose dexamethasone.[30,31,45] One of the studies[45] provided data for two comparisons and both were included in the analysis. Low-dose dexamethasone demonstrated a reduction of −0.39 (−0.66 to −0.12) in late pain at movement. There was no evidence of asymmetry on the funnel plot ($P = 0.43$).

Four studies examining the effect of moderate-dose dexamethasone[30,31,38,45] also showed a reduction in pain of −0.52 (−1.02, −0.03). However, the analysis was limited by asymmetry ($P = 0.05$). Rosenthal analysis predicted that 14 missing studies would be required to change the analysis. There was no difference in the influence of time of drug administration on the dexamethasone effects ($P = 0.45$), with 18% of the total accounted variance due to time of administration. There was high heterogeneity in the effect when the drug was administered intraoperatively ($I^2 = 89$) and low heterogeneity when the drug was administered preoperatively ($I^2 = 0$).

Four studies evaluated the effect of high-dose dexamethasone on late pain at movement,[31,39,43,45] demonstrating a reduction in pain of −3.16 (−4.95 to −1.38). The analysis

Group	Study name	Comparison	Outcome	Statistics for each study						
				Std diff in mean	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
1	Thangaswamy	0.01-0.1mg/kg	Late pain Mov	-0.345	0.336	0.113	-1.003	0.313	-1.027	0.304
1	Jokela	0.01-0.1mg/kg	Late pain Mov	-0.351	0.260	0.068	-0.861	0.159	-1.348	0.178
1	Elhakim	0.01-0.1mg/kg	Late pain Mov	-0.581	0.264	0.069	-1.098	-0.065	-2.205	0.027
1	Elhakim 2	0.01-0.1mg/kg	Late pain Mov	-0.285	0.260	0.067	-0.794	0.224	-1.098	0.272
1				-0.394	0.138	0.019	-0.664	-0.125	-2.866	0.004
2	Thangaswamy	0.11-0.2 mg/kg	Late pain Mov	0.113	0.329	0.108	-0.532	0.758	0.343	0.732
2	Jokela	0.11-0.2 mg/kg	Late pain Mov	-0.351	0.260	0.068	-0.861	0.159	-1.348	0.178
2	Bisgard	0.11-0.2 mg/kg	Late pain Mov	-1.125	0.241	0.058	-1.597	-0.653	-4.675	0.000
2	Elhakim	0.11-0.2 mg/kg	Late pain Mov	-0.639	0.265	0.070	-1.158	-0.121	-2.416	0.016
2				-0.529	0.252	0.064	-1.024	-0.035	-2.098	0.036
3	Jokela	>0.20mg/kg	Late pain Mov	-1.151	0.279	0.078	-1.697	-0.604	-4.128	0.000
3	Elhakim	>0.20mg/kg	Late pain Mov	-0.664	0.265	0.070	-1.184	-0.145	-2.505	0.012
3	Kardash	>0.20mg/kg	Late pain Mov	-21.500	2.169	4.703	-25.750	-17.250	-9.915	0.000
3	Kjetil	>0.20mg/kg	Late pain Mov	-0.784	0.208	0.043	-1.191	-0.378	-3.780	0.000
3				-3.166	0.911	0.829	-4.951	-1.381	-3.477	0.001
Overall				-0.472	0.120	0.014	-0.707	-0.238	-3.946	0.000

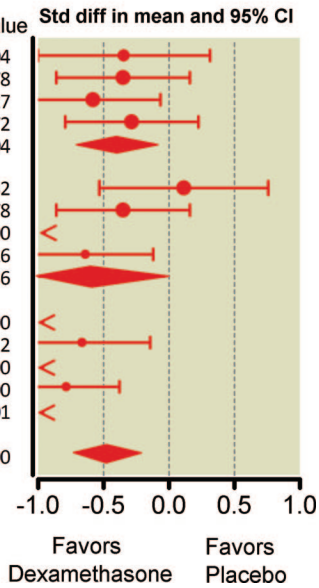

Fig. 8. Pooled data evaluating the effect of dexamethasone dose on late pain scores (24 h) with movement compared with placebo. Data evaluated using a random effects model. Point estimate (95% CI) for overall effect was −0.47 (−0.71 to −0.24). Standardized mean difference for individual study represented by *circle* on Forrest plot with 95% CI of the difference shown as *solid line*. *Larger sized circle* and *thicker 95% CI line* denote larger sample size. The *diamond* represents the pooled estimate and uncertainty for the effects of low- (0.1 mg/kg or less), intermediate- (0.11–0.2 mg/kg), and high-dose (more than 0.2 mg/kg) dexamethasone, respectively. Sample heterogeneity as assessed by the I^2 for the low, intermediate and high dose grouping of studies was 0, 71 and 96, respectively.

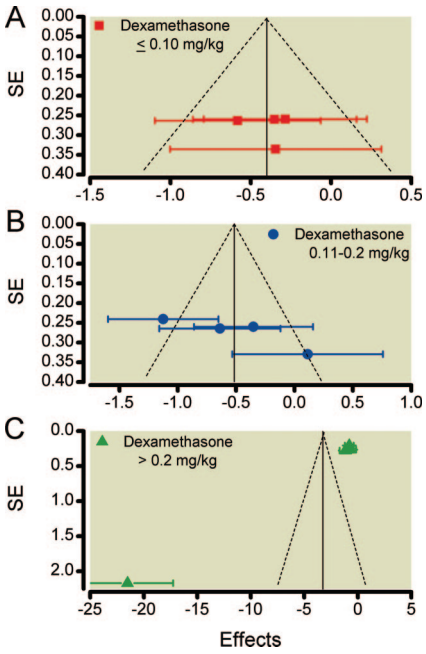

Fig. 9. Late pain (24 h) at movement funnel plots assessing publication bias. Plotted is the SE *versus* standard difference in mean (Effects). *Vertical line* is the combined effect for early pain, with *diagonal lines* representing the expected 95% CI from the combined effect. Studies outside the funnel indicate heterogeneity. (*A*) Funnel plot for dexamethasone less than 0.1 mg/kg. There was no evidence of asymmetry on the funnel plot ($P = 0.43$, one-sided). (*B*) Funnel plot for intermediate dose dexamethasone (0.11–0.2 mg/kg) and late pain with movement. Eggers regression demonstrated some asymmetry ($P = 0.05$, one-sided) with one study lying outside of the 95% CI. (*C*) Funnel plot for high-dose dexamethasone (more than 0.2 mg/kg) and late pain with movement. Eggers regression demonstrated asymmetry ($P = 0.01$, one sided) with one study lying outside of the 95% CI.

was potentially affected by asymmetry of the sample ($P = 0.01$), indicating a publication bias for positive studies. Rosenthal analysis suggested that 104 missing studies would be needed to increase the *P* value above 0.05. *Post hoc* sensitivity analysis demonstrated that removal of the Kardash *et al.*[43] study would result in a change in the effect of the high dose dexamethasone group on late pain to −0.84 (−1.12 to −0.56) when compared with placebo. With the Kardash *et al.*[43] study included high-dose dexamethasone showed improvement in late pain at movement compared with the low ($P = 0.003$) or intermediate ($P = 0.004$) dose; whereas with the Kardash *et al.* study removed high-dose dexamethasone showed improvement in late pain at movement compared with the low ($P = 0.01$) but not intermediate ($P = 0.26$) dose.

Postoperative Opioid Cconsumption

The overall effect of dexamethasone on postoperative opioid consumption compared with placebo favored dexamethasone with a mean difference (95% CI) of −0.41 (−0.58 to −0.24) (fig. 10). The funnel plot did not demonstrate asymmetry indicating that there was not substantial publication bias ($P = 0.35$) (fig. 11).

Four studies evaluated the effect of low-dose dexamethasone on postoperative opioid consumption.[30,31,45,50] One study provided data for two comparisons, and both were included in the analysis.[45] No difference in opioid consumption compared with placebo was found at −0.17 (−0.38 to 0.03). All of the studies evaluated dexamethasone administered during the intraoperative period.

Nine studies examined the effect of moderate dose dexamethasone on postoperative opioid consumption demonstrating an opioid-sparing effect of −0.82 (−1.22 to −0.42) compared with placebo.[30,31,35,36,38,40,41,45,51] Moderate-dose dexamethasone also decreased opioid consumption compared with low dose ($P = 0.003$). When given in the preoperative period, the mean effect of dexamethasone on opioid consumption was −0.9 (−1.15 to −0.72) compared with −0.48 (−1.04 to −0.07) when given intraoperatively ($P = 0.1$), suggesting an advantage for preoperative administration. In addition, 46% of the between-studies variation in effect was due to the time of drug administration.

Five studies assessed the effects of high-dose dexamethasone on postoperative opioid consumption.[31,39,43,44,45] One study[51] provided data for two comparisons, and both were included in the analysis. There was a reduction in postoperative opioid consumption of −0.84 (−1.24 to −0.45) compared with placebo. All studies included in the analysis evaluated dexamethasone administered intraoperatively. High- dose dexamethasone reduced opioid consumption compared with low dose ($P = 0.002$), but there was no difference in the opioid-sparing effect when comparing moderate-dose and high-dose dexamethasone ($P = 0.94$).

Chronic Pain (3 Months or Longer)

None of the included studies reported on chronic pain.

Time to First Analgesic Administration (Minutes)

Four studies evaluated the effects of low-dose dexamethasone on time to analgesic administration.[30,31,45,50] One study[45] provided data for two comparisons, and both were included in the analysis. There was a prolongation of the time to analgesic requirement when the low dexamethasone group was compared with placebo at 0.70 (0.01–1.39). There was no evidence of an asymmetric funnel plot ($P = 0.07$). The studies demonstrated high heterogeneity ($I^2 = 89$) but the between-studies variability could not be explained by the time of drug administration.

Three studies evaluated the effect of intermediate-dose dexamethasone on time to analgesic requirement,[30,31,45] showing no effect on the time to analgesic requirement: 1.09 (−0.2 to 2.41). There was no evidence of asymmetric funnel plots ($P = 0.21$). The analysis was limited by high heterogeneity that could not be explained by time of administration of dexamethasone ($I^2 = 92$). Only two studies evaluated the effect of high-dose dexamethasone on time to analgesic re-

Group	Study name	Comparison	Outcome	Statistics for each study: Std diff in mean	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
1	Thangaswamy	0.01-0.1mg/kg	opioid	0.120	0.334	0.111	-0.534	0.774	0.360	0.719
1	Jokela	0.01-0.1mg/kg	opioid	-0.616	0.264	0.070	-1.134	-0.098	-2.330	0.020
1	Elhakim	0.01-0.1mg/kg	opioid	-0.157	0.259	0.067	-0.664	0.350	-0.606	0.544
1	Coloma 2002	0.01-0.1mg/kg	opioid	-0.130	0.169	0.029	-0.461	0.202	-0.765	0.444
1	Elhakim 2	0.01-0.1mg/kg	opioid	-0.066	0.258	0.067	-0.572	0.440	-0.255	0.799
1				-0.177	0.106	0.011	-0.386	0.032	-1.661	0.097
2	Sanchez-Rodriguez	0.11-0.2mg/kg	opioid	-0.677	0.142	0.020	-0.956	-0.399	-4.774	0.000
2	Thangaswamy	0.11-0.2mg/kg	opioid	-1.356	0.365	0.133	-2.071	-0.641	-3.718	0.000
2	Jokela	0.11-0.2mg/kg	opioid	-0.574	0.263	0.069	-1.091	-0.058	-2.180	0.029
2	Woni	0.11-0.2mg/kg	opioid	-2.669	0.337	0.114	-3.329	-2.008	-7.921	0.000
2	Bisgaard	0.11-0.2mg/kg	opioid	-0.665	0.230	0.053	-1.115	-0.215	-2.894	0.004
2	Bianchin	0.11-0.2mg/kg	opioid	0.440	0.237	0.056	-0.024	0.904	1.857	0.063
2	Chen	0.11-0.2mg/kg	opioid	-0.873	0.079	0.006	-1.028	-0.718	-11.038	0.000
2	Elhakim	0.11-0.2mg/kg	opioid	-0.034	0.258	0.067	-0.540	0.472	-0.131	0.896
2	Wang 1999	0.11-0.2mg/kg	opioid	-1.330	0.250	0.063	-1.820	-0.839	-5.312	0.000
2				-0.824	0.206	0.043	-1.229	-0.420	-3.994	0.000
3	Jokela	>0.2mg/kg	opioid	-1.340	0.286	0.082	-1.900	-0.780	-4.691	0.000
3	Kjetil	>0.2mg/kg	opioid	-1.347	0.222	0.049	-1.781	-0.913	-6.082	0.000
3	Elhakim	>0.2mg/kg	opioid	-0.225	0.259	0.067	-0.732	0.283	-0.867	0.386
3	Kardash	>0.2mg/kg	opioid	-0.502	0.287	0.083	-1.065	0.061	-1.747	0.081
3	Aminmasour 1	>0.2mg/kg	opioid	-0.862	0.327	0.107	-1.503	-0.220	-2.633	0.008
3	Aminmasour 2	>0.2mg/kg	opioid	-0.774	0.320	0.103	-1.402	-0.146	-2.417	0.016
3				-0.849	0.200	0.040	-1.241	-0.457	-4.250	0.000
Overall				-0.411	0.086	0.007	-0.579	-0.244	-4.809	0.000

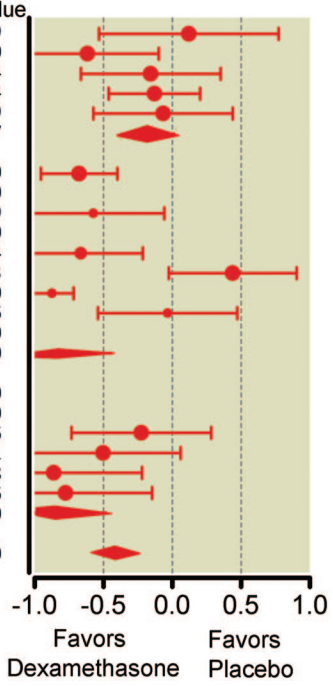

Fig. 10. Pooled data evaluating the effect of dexamethasone dose on opioid consumption (intravenous morphine equivalents) compared with placebo. Data evaluated using a random effects model. Point estimate (95% CI) for overall effect was −0.41 (−0.91 to −0.24). Standardized mean difference for individual study represented by *circle* on Forrest plot with 95% CI of the difference shown as *solid line*. *Larger sized circle* and *thicker 95% CI line* denote larger sample size. The *diamond* represents the pooled estimate and uncertainty for the effects of low- (0.1 mg/kg or less), intermediate- (0.11–0.2 mg/kg), and high-dose (more than 0.2 mg/kg) dexamethasone, respectively. Sample heterogeneity as assessed by the I^2 for the low-, intermediate-, and high-dose grouping of studies was 0, 89, and 67, respectively.

quirement, showing no delay on the time to analgesic requirement: 0.72 (−0.70 to 2.14).[31,45] The analysis was limited by the low number of studies and high heterogeneity ($I^2 = 92$). Both studies evaluated dexamethasone given during the intraoperative period.

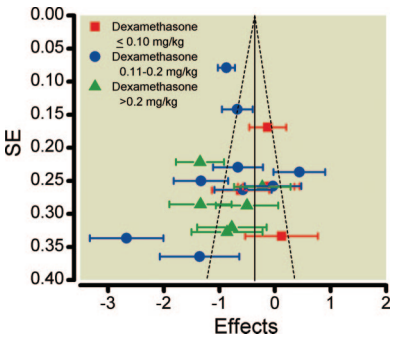

Fig. 11. Opioid-sparing effect of dexamethasone funnel plot assessing publication bias. Plotted is the SE *versus* standard difference in mean (Effects). *Vertical line* is the combined effect for early pain, with *diagonal lines* representing the expected 95% CI from the combined effect. Studies outside the funnel indicate heterogeneity. Eggers regression suggests absence of asymmetry ($P = 0.35$, one-sided).

Time to Hospital Discharge (Hours)

Five studies examined the effect of low-dose dexamethasone on time to hospital discharge compared with placebo.[30,32,34,45,50] One study[45] provided data for two comparisons, and both were included in the analysis. The combined data showed a decrease in time to hospital discharge: −0.47 (−0.72 to −0.2). The analysis was limited by the presence of an asymmetric funnel plot ($P = 0.04$), with Rosenthal analysis suggesting 30 missing studies would be needed to change the results.

Six studies assessed the effect of moderate-dose dexamethasone compared with placebo on time to hospital discharge.[30,35,36,40,45,47] There was a reduction in time to discharge, −0.47 (−0.91 to −0.04), and no evidence of an asymmetric funnel plot ($P = 0.40$). Heterogeneity was high ($I^2 = 89$), with 16% of the total variance attributable to the time of drug administration. Only one study[45] that evaluated the effect of high-dose dexamethasone on the time to hospital discharge demonstrated a 5.5-h reduction when compared with placebo ($P < 0.001$).

Safety Analysis

Among the studies evaluating low dose dexamethasone, two did not comment on adverse side effects.[29,32] Three studies reported no difference in adverse side effects,[33,45,50] two spe-

cifically reported no difference in postoperative wound infection,[30,34] and one study specifically reported no cases with delayed wound healing.[30] One study reported no difference in changes of blood glucose between the dexamethasone and placebo group.[30]

Among studies evaluating moderate doses of dexamethasone, two did not report on side effects,[37,51] two reported no differences in adverse side effects,[41,45] eight specifically reported no cases of postoperative wound infection,[30,35,36,40,46–48,52] and one reported the same incidence of wound infection in the dexamethasone and placebo groups,[38] resulting in a 0.2% (0.05% to 1%) incidence of postoperative infection for both the dexamethasone and placebo groups. These numbers resulted in an overall risk difference (95% CI) of 0% (−1.2% to 1.2%) between the moderate dose dexamethasone group and saline. The lower estimate of the 95% CI of the number needed to harm is 83, therefore indicating that we can exclude one additional case of wound infection in fewer than 83 patients. Two studies reported no difference in change of blood glucose[30,36] and four studies specifically reported no differences in wound healing.

Among studies evaluating high-dose dexamethasone, one study did not comment on side effects,[49] two reported no cases of serious side effects,[39,45] one specifically reported no cases of wound infection or delayed wound healing,[43] and one trial reported a single case of wound infection in the placebo group and no case in the dexamethasone groups[44]These numbers resulted in an overall risk difference (95% CI) of 0.3% (−2.5% to 3.1%). The lower estimate of the number needed to harm is 32, indicating that we can rule out one additional case of wound infection in fewer than 32 patients. Three studies[31,43,45] showed no decrease in the odds ratio (95% CI) for pruritus: 0.72 (0.2 to 2.1) compared with placebo.

Discussion

Several important findings emerged from our meta-analysis. First, intermediate-dose dexamethasone (0.11–0.2 mg/kg) had opioid-sparing effects. It also reduced early and late pain both at rest and at movement. Heterogeneity was partially explained by the time of drug administration (preoperative *vs.* intraoperative). High-dose dexamethasone (more than 0.2 mg/kg) had opioid-sparing effects and also decreased pain scores. We were unable to detect a difference in opioid use for the low-dose dexamethasone (less than 0.1 mg/kg) when given intraoperatively despite a reduction in late pain at rest and at movement. There is evidence that a single perioperative systemic dexamethasone dose can be used as part of a multimodal pain strategy to reduce postoperative pain.

Our findings have important clinical implications because lower dose dexamethasone is commonly given intraoperatively at the time of anesthesia induction to reduce postoperative nausea and vomiting.[6] By giving intermediate doses of dexamethasone (0.11–0.2 mg/kg), beneficial effects on postoperative pain and a reduction in opioid consumption in addition to decreased nausea and vomiting can be achieved.[7] The decreased variability in analgesic effectiveness when moderate-dose dexamethasone was administered preoperatively favors preoperative rather than intraoperative administration of the drug. This finding is consistent with the time to peak effect of dexamethasone (45 min to 1 h). A potential limitation to the preoperative administration of dexamethasone is that it can frequently (50–70%) produce extreme perineal pain when given rapidly in low volumes.[53] This effect can be avoided if the dexamethasone dose is diluted in 50 ml saline solution and infused over 10 min.[54]

In a comparison, the high-dose dexamethasone group reduced late pain at movement compared with the intermediate dose, but did not show a significant advantage in opioid-sparing effects, early pain at rest and at movement, and late pain at rest. Dexamethasone was administered intraoperatively for all of the studies evaluating the high-dose group, which limited our ability to investigate the influence of the time of drug administration on the outcome measures. In regard to early pain at rest, the three dexamethasone groups had similar point estimate reductions, but we were unable to demonstrate a statistically significant effect for the low dose group.

Our review provided evidence that a single dose of perioperative dexamethasone did not increase dose-limiting complications such as wound infection nor does it appear to delay wound healing. This conclusion is strongest for the moderate doses of dexamethasone because there are greater numbers of patients studied at this dosing level. Our study corroborates the safety assessment regarding postoperative wound infection and healing in a systematic review evaluating a single dose of a different corticosteroid (methylprednisolone).[55] Because we included several procedures and not only contaminated surgeries, our findings cannot be generalized to patients at high risk of developing postoperative wound infection. Blood glucose alterations were specifically mentioned in only two studies, limiting any safety assessment on this important side effect.

Time to hospital discharge, an important outcome due to its economic implications and affected by the presence of postoperative pain,[56] showed a similar positive effect in both low-dose and intermediate-dose groups. The analysis, however, was limited by the presence of publication bias in the low dexamethasone group, and by high heterogeneity in the moderate-dose group. It is conceivable that further reduction in postoperative pain could affect discharge time, although we were unable to demonstrate this in our current analysis.

Our meta-analysis had several limitations. In an attempt to generalize our findings to different surgical procedures, we included different types of surgeries that may have affected the heterogeneity in some of our analyses. Varying methods of postoperative pain management across the studies were another potential source of heterogeneity. We could not demonstrate a decrease in opioid-related side effects such as

pruritus because of the low number of studies by dosing group reporting on these side effects. We also did not examine the effect of dexamethasone on postoperative nausea and vomiting. We believe that this analysis would be biased by a large number of studies that evaluated postoperative nausea and vomiting but not postoperative pain and that were, therefore, excluded from our analysis.

Our quantitative review raises important questions that need to be addressed in future studies. First, the effect of low and high dose dexamethasone given preoperatively on postoperative pain needs further investigation. Second, side effects such as wound infection and healing with high-dose dexamethasone, especially in open surgical procedures, need additional evaluation. Third, because acute pain can contribute to the development of chronic pain,[57] studies assessing the effects of dexamethasone on chronic postoperative pain are also warranted. The data originated in the current study should be confirmed by large dose-ranging randomized clinical trials.

In summary, low-dose dexamethasone when given intraoperatively does not have opioid sparing effects after surgery. High-dose dexamethasone (more than 0.2 mg/kg) when given intraoperatively has opioid-sparing effects and decreased postoperative pain; however, it does not seem to be advantageous when compared with intermediate (0.11 to 0.2 mg/kg) doses. Intermediate dose dexamethasone (0.11 to 0.2 mg/kg) is a safe and effective multimodal pain strategy after surgical procedures. The preoperative administration of the drug provides a greater effect on postoperative pain.

References

1. White PF: The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anesth Analg 2005; 101:S5–22
2. Bell RF, Dahl JB, Moore RA, Kalso E: Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006 Jan 25;(1):CD004603
3. Ho KY, Gan TJ, Habib AS: Gabapentin and postoperative pain: A systematic review of randomized controlled trials. Pain 2006; 126:91–101
4. Ong CK, Seymour RA, Lirk P, Merry AF: Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: A qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg 2010; 110:1170–9
5. White PF: Multimodal analgesia: Its role in preventing postoperative pain. Curr Opin Investig Drugs 2008; 9:76–82
6. Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS, Hooper VD, Kovac AL, Kranke P, Myles P, Philip BK, Samsa G, Sessler DI, Temo J, Tramèr MR, Vander Kolk C, Watcha M, Society for Ambulatory Anesthesia: Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2007; 105: 1615–28
7. Karanicolas PJ, Smith SE, Kanbur B, Davies E, Guyatt GH: The impact of prophylactic dexamethasone on nausea and vomiting after laparoscopic cholecystectomy: A systematic review and meta-analysis. Ann Surg 2008; 248:751–62
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. J Clin Epidemiol 2009; 62:e1–34
9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996; 17:1–12
10. Macintyre PE, Ready LB: Pharmacology of opioids, Acute Pain Management: A Practical Guide. 2nd edition. Philadelphia, WB Saunders, 2001, pp 15–49
11. Hozo SP, Djulbegovic B, Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5:13
12. DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177–88
13. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629–34
14. Rosenthal R: The file drawer problem and tolerance for null results. Psychol Bull 1979; 86: 638–41
15. McKenzie R, Tantisira B, Karambelkar DJ, Riley TJ, Abdelhady H: Comparison of ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting. Anesth Analg 1994; 79:961–4
16. Liu YH, Li MJ, Wang PC, Ho ST, Chang CF, Ho CM, Wang JJ: Use of dexamethasone on the prophylaxis of nausea and vomiting after tympanomastoid surgery. Laryngoscope 2001; 111:1271–4
17. Fujii Y, Nakayama M: Reduction of postoperative nausea and vomiting and analgesic requirement with dexamethasone in women undergoing general anesthesia for mastectomy. Breast J 2007; 13:564–7
18. Fujii Y, Nakayama M: Dexamethasone for reduction of nausea, vomiting and analgesic use after gynecological laparoscopic surgery. Int J Gynaecol Obstet 2008; 100:27–30
19. Fujii Y, Itakura M: Reduction of postoperative nausea, vomiting, and analgesic requirement with dexamethasone for patients undergoing laparoscopic cholecystectomy. Surg Endosc 2010; 24:692–6
20. Fujii Y, Nakayama M: Dexamethasone for the reduction of postoperative nausea and vomiting and analgesic requirements after middle ear surgery in adult Japanese patients. Methods Find Exp Clin Pharmacol 2009; 31:337–40
21. Fujii Y, Nakayama M: Efficacy of dexamethasone for reducing postoperative nausea and vomiting and analgesic requirements after thyroidectomy. Otolaryngol Head Neck Surg 2007; 136:274–7
22. Zargar-Shoshtari K, Sammour T, Kahokehr A, Connolly AB, Hill AG: Randomized clinical trial of the effect of glucocorticoids on peritoneal inflammation and postoperative recovery after colectomy. Br J Surg 2009; 96:1253–61
23. López-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Sáez A: Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. Br J Anaesth 1996; 76:835–40
24. Wang JJ, Ho ST, Lee SC, Liu YC, Ho CM: The use of dexamethasone for preventing postoperative nausea and vomiting in females undergoing thyroidectomy: A dose-ranging study. Anesth Analg 2000; 91:1404–7
25. Movafegh A, Soroush AR, Navi A, Sadeghi M, Esfehani F, Akbarian-Tefaghi N: The effect of intravenous administration of dexamethasone on postoperative pain, nausea, and vomiting after intrathecal injection of meperidine. Anesth Analg 2007; 104:987–9
26. Bergeron SG, Kardash KJ, Huk OL, Zukor DJ, Antoniou J: Perioperative dexamethasone does not affect functional outcome in total hip arthroplasty. Clin Orthop Relat Res 2009; 467:1463–7
27. Lachance M, Lacroix Y, Audet N, Savard P, Thuot F: The use

of dexamethasone to reduce pain after tonsillectomy in adults: A double-blind prospective randomized trial. Laryngoscope 2008; 118:232–6

28. Mattila K, Kontinen VK, Kalso E, Hynynen MJ: Dexamethasone decreases oxycodone consumption following osteotomy of the first metatarsal bone: A randomized controlled trial in day surgery. Acta Anaesthesiol Scand 2010; 54: 268–76
29. Al-Qudah M, Rashdan Y: Role of dexamethasone in reducing pain after endoscopic sinus surgery in adults: A double-blind prospective randomized trial. Ann Otol Rhinol Laryngol 2010; 119:266–9
30. Thangaswamy CR, Rewari V, Trikha A, Dehran M, Chandralekha: Dexamethasone before total laparoscopic hysterectomy: A randomized controlled dose-response study. J Anesth 2010; 24:24–30
31. Jokela RM, Ahonen JV, Tallgren MK, Marjakangas PC, Korttila KT: The effective analgesic dose of dexamethasone after laparoscopic hysterectomy. Anesth Analg 2009; 109:607–15
32. Wu JI, Lu SF, Chia YY, Yang LC, Fong WP, Tan PH: Sevoflurane with or without antiemetic prophylaxis of dexamethasone in spontaneously breathing patients undergoing outpatient anorectal surgery. J Clin Anesth 2009; 21:469–73
33. Wang JJ, Ho ST, Uen YH, Lin MT, Chen KT, Huang JC, Tzeng JI: Small-dose dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy: A comparison of tropisetron with saline. Anesth Analg 2002; 95:229–32
34. Coloma M, Duffy LL, White PF, Kendall Tongier W, Huber PJ Jr: Dexamethasone facilitates discharge after outpatient anorectal surgery. Anesth Analg 2001; 92:85–8
35. Sánchez-Rodríguez PE, Fuentes-Orozco C, González-Ojeda A: Effect of dexamethasone on postoperative symptoms in patients undergoing elective laparoscopic cholecystectomy: Randomized clinical trial. World J Surg 2010; 34:895–900
36. Worni M, Schudel HH, Seifert E, Inglin R, Hagemann M, Vorburger SA, Candinas D: Randomized controlled trial on single dose steroid before thyroidectomy for benign disease to improve postoperative nausea, pain, and vocal function. Ann Surg 2008; 248:1060–6
37. McKean S, Kochilas X, Kelleher R, Dockery M: Use of intravenous steroids at induction of anaesthesia for adult tonsillectomy to reduce post-operative nausea and vomiting and pain: A double-blind randomized controlled trial. Clin Otolaryngol 2006; 31:36–40
38. Bisgaard T, Klarskov B, Kehlet H, Rosenberg J: Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: A randomized double-blind placebo-controlled trial. Ann Surg 2003; 238:651–60
39. Hval K, Thagaard KS, Sem TK, Schlichting E, Ellen S, Raeder J, Johan R: The prolonged postoperative analgesic effect when dexamethasone is added to a nonsteroidal antiinflammatory drug (rofecoxib) before breast surgery. Anesth Analg 2007; 105:481–6
40. Bianchin A, De Luca A, Caminiti A: Postoperative vomiting reduction after laparoscopic cholecystectomy with single dose of dexamethasone. Minerva Anestesiol 2007; 73:343–6
41. Chen MS, Hong CL, Chung HS, Tan PP, Tsai CC, Su HH, Wong CH: Dexamethasone effectively reduces postoperative nausea and vomiting in a general surgical adult patient population. Chang Gung Med J 2006; 29:175–81
42. McKenzie R, Riley TJ, Tantisira B, Hamilton DL: Effect of propofol for induction and ondansetron with or without dexamethasone for the prevention of nausea and vomiting after major gynecologic surgery. J Clin Anesth 1997; 9:15–20
43. Kardash KJ, Sarrazin F, Tessler MJ, Velly AM: Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. Anesth Analg 2008; 106:1253–7
44. Aminmansour B, Khalili HA, Ahmadi J, Nourian M: Effect of high-dose intravenous dexamethasone on postlumbar discectomy pain. Spine 2006; 31:2415–7
45. Elhakim M, Nafie M, Mahmoud K, Atef A: Dexamethasone 8 mg in combination with ondansetron 4 mg appears to be the optimal dose for the prevention of nausea and vomiting after laparoscopic cholecystectomy. Can J Anaesth 2002; 49:922–6
46. Fukami Y, Terasaki M, Okamoto Y, Sakaguchi K, Murata T, Ohkubo M, Nishimae K: Efficacy of preoperative dexamethasone in patients with laparoscopic cholecystectomy: A prospective randomized double-blind study. J Hepatobiliary Pancreat Surg 2009; 16:367–71
47. Feo CV, Sortini D, Ragazzi R, De Palma M, Liboni A: Randomized clinical trial of the effect of preoperative dexamethasone on nausea and vomiting after laparoscopic cholecystectomy. Br J Surg 2006; 93:295–9
48. Lee Y, Lai HY, Lin PC, Huang SJ, Lin YS: Dexamethasone prevents postoperative nausea and vomiting more effectively in women with motion sickness. Can J Anaesth 2003; 50:232–7
49. Carr MM, Williams JG, Carmichael L, Nasser JG: Effect of steroids on posttonsillectomy pain in adults. Arch Otolaryngol Head Neck Surg 1999; 125:1361–4
50. Coloma M, White PF, Markowitz SD, Whitten CW, Macaluso AR, Berrisford SB, Thornton KC: Dexamethasone in combination with dolasetron for prophylaxis in the ambulatory setting: Effect on outcome after laparoscopic cholecystectomy. ANESTHESIOLOGY 2002; 96:1346–50
51. Wang JJ, Ho ST, Liu YH, Lee SC, Liu YC, Liao YC, Ho CM: Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Br J Anaesth 1999; 83:772–5
52. Yeo J, Jung J, Ryu T, Jeon YH, Kim S, Baek W: Antiemetic efficacy of dexamethasone combined with midazolam after middle ear surgery. Otolaryngol Head Neck Surg 2009; 141: 684–8
53. Neff SP, Stapelberg F, Warmington A: Excruciating perineal pain after intravenous dexamethasone. Anaesth Intensive Care 2002; 30:370–1
54. Bell A: Preventing perineal burning from i.v. dexamethasone. Oncol Nurs Forum 1988; 15:199
55. Sauerland S, Nagelschmidt M, Mallmann P, Neugebauer EA: Risks and benefits of preoperative high dose methylprednisolone in surgical patients: A systematic review. Drug Saf 2000; 23:449–61
56. Elvir-Lazo OL, White PF: Postoperative pain management after ambulatory surgery: Role of multimodal analgesia. Anesthesiol Clin 2010; 28:217–24
57. Gärtner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H: Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA 2009; 302: 1985–92