Safety of Perioperative Glucocorticoids in Elective Noncardiac Surgery

A Systematic Review and Meta-analysis

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ABSTRACT

Background: Glucocorticoids are increasingly used perioperatively, principally to prevent nausea and vomiting. Safety concerns focus on the potential for hyperglycemia and increased infection. The authors hypothesized that glucocorticoids predispose to such adverse outcomes in a dose-dependent fashion after elective noncardiac surgery.

Methods: The authors conducted a systematic literature search of the major medical databases from their inception to April 2016. Randomized glucocorticoid trials in adults specifically reporting on a safety outcome were included and meta-analyzed with Peto odds ratio method or the quality effects model. Subanalyses were performed according to a dexamethasone dose equivalent of low (less than 8 mg), medium (8 to 16 mg), and high (more than 16 mg). The primary endpoints of any wound infection and peak perioperative glucose concentrations were subject to meta-regression.

Results: Fifty-six trials from 18 countries were identified, predominantly assessing dexamethasone. Glucocorticoids did not impact on any wound infection (odds ratio, 0.8; 95% CI, 0.6 to 1.2) but did result in a clinically unimportant increase in peak perioperative glucose concentration (weighted mean difference, 20.0 mg/dl; CI, 11.4 to 28.6; $P < 0.001$ or 1.1 mM; CI, 0.6 to 1.6). Glucocorticoids reduced peak postoperative C-reactive protein concentrations (weighted mean difference, −22.1 mg/l; CI, −31.7 to −12.5; $P < 0.001$), but other adverse outcomes and length of stay were unchanged. No dose–effect relationships were apparent.

Conclusions: The evidence at present does not highlight any safety concerns with respect to the use of perioperative glucocorticoids and subsequent infection, hyperglycemia, or other adverse outcomes. Nevertheless, collated trials lacked sufficient surveillance and power to detect clinically important differences in complications such as wound infection. **(ANESTHESIOLOGY 2017; 126:234-48)**

WE are witnessing an exponential growth in the perioperative use of glucocorticoids for an expanding number of indications. When used in cardiac surgery patients, they improve pulmonary function, decrease rates of atrial fibrillation, and reduce the incidence of infection.[1,2] In hip and knee surgery, they are recommended to confer analgesic benefit,[3] and they decrease sore throat in intubated patients[4,5] and swelling in maxillofacial surgery.[6] The principal anesthesia indication is in the prevention of postoperative nausea and vomiting.[7]

Glucocorticoids are not, however, without harm.[8] They are associated with atypical or opportunistic infections in either short-term high-dose or chronic long-term (more than 21 days) administration. Recognized complications include hyperglycemia, psychosis, peptic ulceration, and poor bone healing.[9,10] Although high-quality studies have shown glucocorticoid use in cardiac surgery to be both beneficial and

What We Already Know about This Topic

- Glucocorticoids are commonly given to prevent nausea and vomiting
- However, glucocorticoids are immunosuppressive and may promote infection
- The authors conducted a meta-analysis of 56 trials (n = 5,607) that evaluated infection, hospital duration, and intraoperative glucose concentration

What This Article Tells Us That Is New

- Glucocorticoids did not impact on any wound infection (odds ratio, 0.84; 95% CI, 0.62 to 1.15) or length of stay (weighted mean difference, −0.27 days; CI, −1.37 to 0.84)
- Glucocorticoids slightly increased peak postoperative glucose concentrations by 20 mg/dl (CI, 11 to 29; $P < 0.001$), an amount that is probably not clinically important
- Single-dose steroid administration for prevention of nausea appears safe

This article is featured in "This Month in Anesthesiology," page 1A. This article has an audio podcast.

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safe,[1] there are three major safety concerns regarding the perioperative use of glucocorticoids in noncardiac surgical patients, including a possible increase in the risk of (1) hyperglycemia, (2) infection, and (3) perioperative bleeding.[9–11] None of the published trials in this field are of sufficient size to have adequate power to detect a meaningful effect upon these outcomes,[12] and there is a need to examine these questions with a meta-analysis. We, therefore, hypothesized that important adverse outcomes are related to the use of perioperative glucocorticoids, principally the occurrence of postoperative wound infection and hyperglycemia, and these relationships are dose-dependent.

Materials and Methods

Systematic Literature Search

This meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO 2016: CRD42016038280, http://www.crd.york.ac.uk/PROSPERO). We conducted a systematic literature search of MEDLINE and EMBASE *via* Ovid, PubMed, CINAHL, the Cochrane controlled trial register, and Web of Science from database inception to April 2, 2016. Each database was searched separately to improve functionality and to allow mapping to relevant subject headings. The strategy used validated methods of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[13] Search terms included combinations of the Medical Subject Headings: dexamethasone, methylprednisolone, glucocorticoid, steroid, perioperative period, perioperative care, and combinations with the key words: surgery, wound infection, surgical-site infection, pneumonia, infection, sepsis, sept*, pyrexia, febrile, C-reactive protein (CRP), wound dehiscence, anastomotic leak, blood glucose, hyperglycemia, malignancy, cancer, neoplasm, bleeding, hemorrhage, mortality, and death. Subject headings were exploded to include all relevant subheadings. Search limits included randomized trials, systematic reviews, and meta-analyses in adults (18 yr and older). There were no language restrictions. Two researchers (A.J.T. and V.G.) independently screened the articles by their titles and abstracts to identify studies specifically reporting on the primary outcomes of any wound infection or blood glucose concentration, as well as secondary outcomes relevant to an assessment of safety. The full text of these articles and the gray literature were then screened according to fixed eligibility criteria.

Study Selection, Data Extraction, and Quality Assessment

Published and unpublished studies that met all of the following criteria were eligible for inclusion: (1) randomized controlled trial; (2) evaluation of single or repeated doses of intravenous glucocorticoid against placebo, with the first dose commencing preoperatively or intraoperatively; (3) study population underwent elective noncardiac surgery; (4) the studies quantitatively defined at least one predetermined safety outcome as an endpoint and reported this in Results; and (5) an English translation of foreign language studies was available through our institutional library. The predetermined primary outcomes were any wound infection and blood glucose concentrations, and the secondary outcomes included wound healing, anastomotic leak, inflammatory response (as determined by CRP concentrations), length of stay, bleeding, and any other infection. Studies that reported no adverse effects or complications in either group were excluded unless systematic postoperative screening had taken place. Statements such as "no adverse events occurred" were insufficient in isolation to warrant inclusion. Reference lists of included articles were hand searched, and relevant trials were subjected to the same criteria.

Two researchers (A.J.T. and V.G.) independently examined and recorded trial characteristics and outcomes, using a predesigned data abstraction form. This abstraction form was used to record information regarding the quality of the trial such as allocation concealment, randomization, blinding, exclusion criteria, and systematic outcome measurement. The grading of allocation concealment was based on the Cochrane approach, that is, adequate, uncertain, or clearly inadequate. Quality assessment was performed using the Jadad scale.[14] Authors of the primary studies were contacted, when possible, if information was missing or unclear. There were no disagreements between the reviewers in relation to any of the data extracted.

Study Groups and Outcome Parameters

Studies reporting categorical adverse outcomes were grouped based on the following definitions: "any wound infection"—Centers for Disease Control and Prevention surgical-site infection criteria or no criteria provided; "deep wound infection"—Centers for Disease Control and Prevention deep/organ space surgical-site infection criteria or abdominal abscess at the site of surgery; "any infection"—specifically reported in results table (not amalgamated from individual complications, thereby avoiding double counting); "impaired wound healing" or "anastomotic leak" or "postoperative hemorrhage" or "malignancy recurrence"—specifically reported in results table. Studies were also grouped if the following continuous outcomes were measured perioperatively: blood glucose (mg/dl), CRP (mg/l), intraoperative blood loss (ml), and hospital length of stay measured in days.

The impact of glucocorticoid dose was assessed using dexamethasone as the reference drug; each outcome group was stratified according to dexamethasone dose equivalents in the first 24 h perioperatively into low (less than 8 mg), medium (8 to 16 mg), and high (more than 16 mg), using an online steroid equivalence converter (http://www.medcalc.com). These thresholds were selected to correspond to antiemetic doses,[15] doses to control swelling in maxillofacial surgery,[6] and doses aggressively targeting the systemic inflammatory response.[2] Studies assessing more than one dose of glucocorticoid against a single control group were

considered as a separate study for each dose. Studies reporting outcomes in diabetic and nondiabetic subgroups were also considered as separate studies where relevant.

Statistical Analysis

Statistical analyses were conducted using MetaXL version 3.1 (EpiGear International Pty Ltd, Australia). The presence and extent of heterogeneity between studies were assessed with Cochran Q and I^2 statistics. Pooled categorical outcomes incorporating studies with sparse event data were meta-analyzed using Peto odds ratio (OR) method with a 0.5 continuity correction where zero events occurred in both groups. Sensitivity analyses were subsequently performed using high-quality trials only (Jadad scale score, 4 to 5). Continuous outcomes were analyzed with the quality effects model incorporating the Jadad scale and expressed as weighted mean difference. Where median (range) data only were available, conversion to mean (SD) followed established guidance.[16]

For the primary outcome of blood glucose, the time point within each relevant study from the intraoperative or early postoperative (up to 12 h after surgery) periods with the highest mean values across both arms was used to compare peak perioperative glucose concentrations in the presence or absence of glucocorticoid. A similar approach was employed to assess peak perioperative CRP concentrations, using the time point within 3 days of surgery with the highest mean values across both arms. A sensitivity analysis with respect to blood glucose was conducted for trials with explicit exclusion criteria for diabetes. For the primary outcome of any wound infection, sensitivity analyses across all trials were performed using the Mantel–Haenszel, inverse variance, and quality effects models. Further sensitivity analyses were conducted for trials employing wound infection surveillance against Centers for Disease Control and Prevention criteria and for trials using dexamethasone as the glucocorticoid intervention.

Mixed meta-regression (methods of moment) was used to assess any potential interaction between dexamethasone dose (or equivalent) in the first 24 h and the risk of any wound infection and any interaction between the initial dexamethasone dose (or equivalent) and peak perioperative blood glucose concentrations (Comprehensive Meta-analysis version 2.2.034; Biostat, USA). $P < 0.05$ was used to denote statistical significance as this corresponded to an acceptable risk of false-positive results (type 1 error) for the primary outcomes within our specific meta-analysis design.[17]

Results

Characteristics of the Included Studies

The Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram outlining the study selection process is detailed in figure 1. Fifty-six randomized controlled trials employing perioperative glucocorticoids including 5,607 patients from 18 countries were identified and subject to meta-analysis (median sample size, 58; interquartile range, 36 to 106).[18–73] The median Jadad score was 4 (interquartile range, 3 to 5); 31 trials were ascribed a score of 4 or 5. The characteristics of the studies and their interventions are summarized in table 1. The number of studies and patients in each outcome group are summarized in table 2. Twenty-nine studies used dexamethasone, 24 used methylprednisolone, 2 used hydrocortisone, and 1 used betamethasone. The drug was administered intravenously in all trials, predominantly as a single preoperative or early intraoperative dose. Repeated doses were given in two studies using dexamethasone, two studies using methylprednisolone, and two studies using hydrocortisone. Eighteen trials reported on any wound infection as an outcome (table 3). Three used Centers for Disease Control and Prevention criteria, and three used clinical signs together with a positive culture and/or antibiotic therapy for diagnosis of wound infection. In only one trial was wound infection the primary outcome, and in one trial, wound infection was a component of a composite primary outcome. In 12 trials, the criteria for reaching a diagnosis of wound infection were either unclear or not stated.

Outcomes

There was no difference in the incidence of any wound infection in patients randomized to perioperative glucocorticoid (OR, 0.8; 95% CI, 0.6 to 1.2; $P = 0.80$; fig. 2A). This was unchanged after excluding low-quality trials (OR, 1.0; CI, 0.7 to 1.4) or including only trials that employed surveillance for wound infection against Centers for Disease Control and Prevention criteria (OR, 1.1; CI, 0.8 to 1.6; fig. 2B) or trials using dexamethasone (OR, 0.9; CI, 0.6 to 1.3). Across all trials, findings were unchanged with the Mantel–Haenszel model (OR, 0.9; CI, 0.6 to 1.2), the inverse variance model (OR, 0.9; CI, 0.7 to 1.3), and the quality effects model (OR, 0.9; CI, 0.7 to 1.3). Patients randomized to perioperative glucocorticoid had similar rates of deep wound infection (OR, 1.2; CI, 0.8 to 1.8; fig. 2C), impaired wound healing (OR, 1.0; CI, 0.5 to 2.1), any infection (OR, 0.9; CI, 0.6 to 1.3), anastomotic leak (OR, 1.0; CI, 0.5 to 2.2), and postoperative hemorrhage (OR, 1.4; CI, 0.7 to 2.7). These findings were unchanged restricting analyses to high-quality trials only or those using Centers for Disease Control and Prevention criteria (fig. 2D).

The highest glucose value measured at a specific time intraoperatively or within the first 12 h after surgery was greater in patients receiving glucocorticoids (weighted mean difference, 20.0 mg/dl; CI, 11.4 to 28.6; $P < 0.001$; fig. 3A). When studies excluding diabetic patients only were analyzed, a smaller but nonetheless statistically significant rise in blood glucose was observed (weighted mean difference, 14.0 mg/dl; CI, 2.0 to 25.9; $P = 0.02$). Hyperglycemia in studies with no diabetic exclusion criteria appeared more marked (weighted mean difference, 30.1 mg/dl; CI, 22.1 to 38.0; $P < 0.001$). The highest CRP value measured at a specific time within the first 3 postoperative days was lower in patients receiving

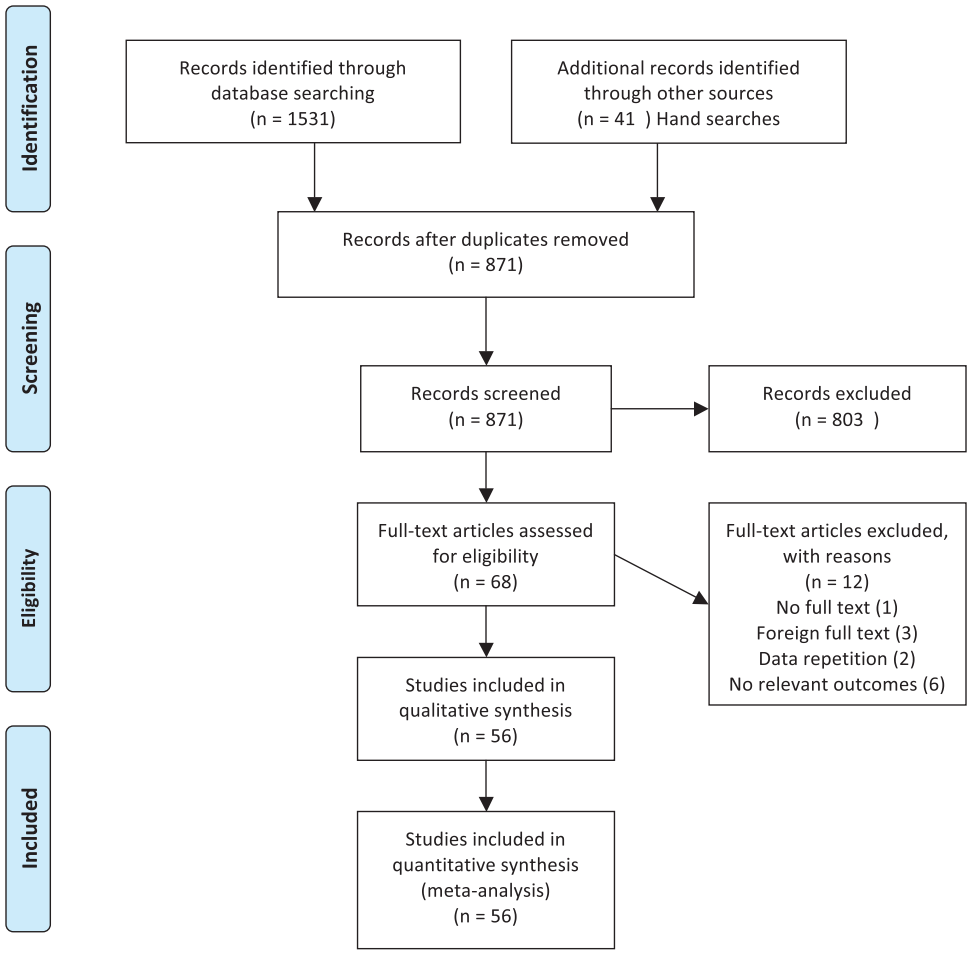


Fig. 1. Flowchart of systematic database search and trial identification.

glucocorticoids (weighted mean difference, −22.1 mg/l; CI, −31.7 to −12.5; $P < 0.001$; fig. 3B). The length of hospital stay was no different with perioperative glucocorticoids (weighted mean difference, −0.3 days; CI, −1.4 to 0.8; $P = 0.65$; fig. 3C). Intraoperative bleeding was unchanged after glucocorticoid administration (weighted mean difference, −6.4 ml; CI, −28.2 to 15.4; $P = 0.58$). Only a single study reported on malignancy recurrence, using follow-up data from a randomized trial of perioperative dexamethasone assessing the primary outcomes of peritoneal cytokines and fatigue.[49] Malignancy recurrence was, therefore, not subjected to meta-analysis. Stratification according to low-, medium-, or high-dose dexamethasone equivalents did not change the statistical significance of any of the categorical or continuous outcomes.

In a meta-regression analysis, there was no association between glucocorticoid dose and the subsequent risk of any wound infection (slope of regression line, −0.004; 95% CI, −0.001 to 0.003; $P = 0.30$; fig. 4A). There was also no association between the doses of dexamethasone and the difference in maximum glucose concentrations between the included studies (slope of regression line, 0.02; 95% CI, −0.01 to 0.05; $P = 0.21$; fig. 4B).

Bias

Funnel and Doi plot analyses suggest that less precise studies report greater reductions in any wound infection incidence after perioperative glucocorticoid administration (fig. 5, A and B). Blood glucose trials did not exhibit significant bias (fig. 5, C and D).

Discussion

The most important finding of this meta-analysis is that perioperative glucocorticoid administration does not result in an increased incidence of any wound infection, deep wound infection, anastomotic leak, impaired wound healing, or bleeding in patients undergoing noncardiac surgery. Glucocorticoids did not influence the length of stay but were associated with a clinically unimportant increase in blood glucose concentrations and a decrease in CRP concentrations. Although these findings appear to affirm the safety of short-term administration of glucocorticoids, the literature regarding safety outcomes is not particularly robust. Given the expanding use of these agents and the implications of harm for a large number of patients, this requires further discussion.

Table 1. Study Characteristics

Author, Country, Journal, Year	Surgery Type (n)	Glucocorticoid (Dexamethasone Equivalent Dose)	Primary Outcome(s)	Diabetics Excluded? (Criteria)
Abdelmalak *et al.*,[18] USA, Br J Anaesth, 2013 (DeLiT trial)	Major noncardiac (n = 381)	Dexamethasone, 14 mg more than 3 d	Composite of 15 major complications and 30-d mortality	No
Abdelmalak *et al.*,[74] USA, Anesth Analg, 2013 (DeLiT trial)	Major noncardiac (n = 185)	Dexamethasone, 8 mg	Blood glucose	Nondiabetics (a) Diabetics (b)
Aldrighetti *et al.*,[19] Italy, Liver Transpl, 2006	Liver resection (n = 76)	Methylprednisolone, 500 mg (dexamethasone, 100 mg)	Liver function tests/inflammatory mediators	No
Backes *et al.*,[20] USA, J Arthroplasty, 2013	Total joint arthroplasty (n = 120)	Dexamethasone, 10 mg	PONV/pain	Yes (Hba1c > 7.5%)
Bianchin *et al.*,[21] Italy, Minerva Anestesiol, 2007	Laparoscopic cholecystectomy (n = 80)	Dexamethasone, 8 mg	PONV	Yes (uncontrolled)
Bigler *et al.*,[22] Denmark, J Thorac Cardiovasc Surg, 1995	Pulmonary resection (n = 36)	Methylprednisolone, 25 mg/kg (dexamethasone, 5 mg/kg)	Pulmonary function/pain	Yes
Bisgaard *et al.*,[23] Denmark, Ann Surg, 2003	Laparoscopic cholecystectomy (n = 80)	Dexamethasone, 8 mg	Fatigue/pain	Yes (signs of endocrine disease)
Coloma *et al.*,[24] USA, Anesth Analg, 2001	Anorectal (n = 80)	Dexamethasone, 4 mg	Time to home readiness	No
Cowie *et al.*,[25] Australia, Anaesth Intensive Care, 2010	Laparoscopic cholecystectomy (n = 14)	Dexamethasone, 8 mg	Plasma cortisol	Yes
Doksrød *et al.*,[26] Norway, Acta Anaesthesiol Scan, 2012	Thyroid (n = 120)	Dexamethasone, 0.15 mg/kg (a) and 0.3 mg/kg (b)	Pain	No
Feo *et al.*,[59] Italy, Br J Surg, 2006	Laparoscopic cholecystectomy (n = 101)	Dexamethasone, 8 mg	PONV	Yes (endocrine disorder)
Fukami *et al.*,[60] Japan, J Hepatobiliary Pancreat Surg, 2009	Laparoscopic cholecystectomy (n = 80)	Dexamethasone, 8 mg	PONV	Yes (Hba1c > 8.5%)
Hayashi *et al.*,[27] Japan, Ann Surg, 2011	Liver resection (n = 210)	Hydrocortisone, 1,100 mg more than 3 d (dexamethasone, 44 mg)	Serum bilirubin	Yes (unstable diabetes)
Hyrkäs *et al.*,[61] Finland, Scand J Plast Reconstr Hand Surg, 1994	Dental extraction (n = 242)	Methylprednisolone, 40 mg (dexamethasone, 8 mg)	Wound healing	No
Jules-Elysee *et al.*,[73] USA, J Bone Joint Surg Am, 2012	Bilateral knee arthroplasty (n = 34)	Hydrocortisone, 300 mg more than 16 h (dexamethasone, 12 mg)	Interleukin-6	No
Kara *et al.*,[72] Turkey, Plast Reconstr Surg, 1999	Rhinoplasty (n = 55)	Dexamethasone, 10 mg	Unclear	Yes
Karaman *et al.*,[28] Turkey, Am J Surgery, 2013	Laparoscopic cholecystectomy (n = 80)	Dexamethasone, 8 mg	Unclear	Yes
Kardash *et al.*,[29] USA, Anesth Analg, 2008	Total hip arthroplasty (n = 50)	Dexamethasone, 40 mg	Pain	Yes
Kargi *et al.*,[62] Turkey, Ann Plast Surg, 2003	Rhinoplasty (n = 60)	Dexamethasone, 8 mg (plus repeat doses)	Unclear	Yes
Kirdak *et al.*,[30] Turkey, The American Surgeon, 2008	Colorectal (n = 30)	Dexamethasone, 8 mg	Unclear	No
Koc *et al.*,[63] Turkey, Am J Rhinol Allergy, 2011	Rhinoplasty (n = 40)	Methylprednisolone, 1 mg/kg (a) and 3 mg/kg (b) (dexamethasone, 0.2 mg/kg [a] and 0.6 mg/kg [b])	Unclear	Yes
Koh *et al.*,[31] Korea, Clin Orthop Relat Res, 2013	Total knee arthroplasty (n = 269)	Dexamethasone, 10 mg	PONV	No
Komori *et al.*,[32] Japan, Int Angiol, 1999	Aortic aneurysm repair (n = 20)	Methylprednisolone, 1 g (dexamethasone, 200 mg)	Interleukin-6	No
Kurz *et al.*,[33] USA, Br J Anaesth, 2015	Colorectal (n = 555)	Dexamethasone, 4 mg	Surgical-site infection	No
Lee *et al.*,[34] Korea, Surg Endosc, 2014	Endoscopic gastric (n = 36)	Dexamethasone, 0.15 mg/kg	Pain	Yes (severe diabetes)
Lunn *et al.*,[36] Denmark, BJA, 2013	Total hip arthroplasty (n = 48)	Methylprednisolone, 125 mg (dexamethasone, 25 mg)	Time to discharge readiness	Yes (diabetic neuropathy)
Lunn *et al.*,[36] Denmark, BJA, 2011	Total knee arthroplasty (n = 48)	Methylprednisolone, 125 mg (dexamethasone, 25 mg)	Pain	Yes (diabetic neuropathy)

(*Continued*)

Table 1. (Continued)

Author, Country, Journal, Year	Surgery Type (n)	Glucocorticoid (Dexamethasone Equivalent Dose)	Primary Outcome(s)	Diabetics Excluded? (Criteria)
Marion *et al.*,[64] USA, Neurosurgery, 1988	Microvascular decompression (n = 222)	Methylprednisolone, 40 mg (dexamethasone, 8 mg) plus repeat doses	Unclear	No
Mathiesen *et al.*,[65] Denmark, Acta Anaesthesiol Scand, 2011	Tonsillectomy (n = 131)	Dexamethasone, 8 mg	Pain	No
Muratore *et al.*,[37] Italy, Br J Surg, 2003	Liver resection (n = 53)	Methylprednisolone, 30 mg/kg (dexamethasone, 6 mg/kg)	Unclear	No
Murphy *et al.*,[38] USA, Anesth Analg, 2014	Hysterectomy (n = 200)	Dexamethasone, 4 mg (a, c) and 8 mg (b, d)	Blood glucose	Yes
Nagelschmidt *et al.*,[39] Germany, Eur J Surg, 1999	Abdominal (n = 20)	Methylprednisolone, 30 mg/kg (dexamethasone, 6 mg/kg)	Unclear	Yes
Nazar *et al.*,[40] Chile, Eur J Anaesthesiol, 2009	Gastric bypass (n = 30)	Dexamethasone, 8 mg	Blood glucose	No
Nielsen *et al.*,[66] Denmark, Pain, 2015	Lumbar disc repair (n = 160)	Dexamethasone, 16 mg	Pain	No
Pulitanò *et al.*,[41] Italy, HPB, 2007	Liver resection (n = 43)	Methylprednisolone, 500 mg (dexamethasone, 100 mg)	ALT	No
Rahimzadeh *et al.*,[42] Iran, J Clin Diagn Res, 2014	Hip fracture (n = 82)	Methylprednisolone, 125 mg (dexamethasone, 25 mg)	Pain	Yes
Reikerås *et al.*,[67] Norway, Eur J Trauma Emerg Surg, 2007	Lumbar osteotomy (n = 20)	Methylprednisolone, 10 mg/kg (dexamethasone, 2 mg/kg)	Unclear	No
Rendina *et al.*,[68] Italy, J Thorac Cardiovasc Surg, 1992	Lung resection (n = 20)	Methylprednisolone, 10 mg/kg (dexamethasone, 2 mg/kg) plus repeat doses	Bronchial healing	No
Sánchez-Rodríguez *et al.*,[69] Mexico, World J Surg, 2010	Laparoscopic cholecystectomy (n = 210)	Dexamethasone, 8 mg	PONV	Yes (Hba1c > 8%)
Sato *et al.*,[43] Japan, Ann Surg, 2002	Esophagectomy (n = 66)	Methylprednisolone, 10 mg/kg (dexamethasone, 2 mg/kg)	Organ system failure	Yes (insulin therapy)
Schietroma *et al.*,[44] Italy, JAMA Otolaryngol Head Neck Surg, 2013	Thyroid (n = 328)	Dexamethasone, 8 mg	Recurrent laryngeal nerve palsy	No
Schietroma *et al.*,[45] Italy, Updates Surg, 2010	Nissen fundoplication (n = 82)	Dexamethasone, 8 mg	Pain/fatigue	Yes (signs of endocrine disease)
Schmidt *et al.*,[46] Germany, J Hepatobiliary Pancreat Surg, 2007	Liver resection (n = 20)	Methylprednisolone, 30 mg/kg (dexamethasone, 6 mg/kg)	Interleukin-6	Yes (endocrine disorder)
Schulze *et al.*,[47] Denmark, Arch Surg, 1997	Colorectal (n = 24)	Methylprednisolone, 30 mg/kg (dexamethasone, 6 mg/kg)	Unclear	Yes
Simsa *et al.*,[48] Sweden, Eur J Pain, 2013	Inguinal hernia repair (n = 398)	Betamethasone, 12 mg (dexamethasone, 14.4 mg)	Pain	Yes
Singh *et al.*,[49] New Zealand, Br J Anaesth, 2014	Colorectal (n = 60)	Dexamethasone, 8 mg	Peritoneal cytokines/fatigue	No
Snäll *et al.*,[50] Finland, Br J Oral Maxillofac Surg, 2013	Mandible fracture (n = 41)	Dexamethasone, 30 mg/16 h	Impaired wound healing	No
Takeda *et al.*,[51] Japan, Eur J Surg, 1997	Esophagectomy (n = 30)	Methylprednisolone, 30 mg/kg (dexamethasone, 6 mg/kg)	Intensive care unit stay	Yes (metabolic disease)
Thangaswamy *et al.*,[70] India, J Anesth, 2010	Laparoscopic hysterectomy (n = 55)	Dexamethasone, 4 mg (a) and 8 mg (b)	Pain	Yes
Turner *et al.*,[52] United Kingdom, Br J Surg, 2008	Aortic aneurysm repair (n = 20)	Methylprednisolone, 10 mg/kg (dexamethasone, 2 mg/kg)	Renal function	Yes
Turner *et al.*,[53] United Kingdom, Anaesthesia, 2006	Liver transplantation (n = 34)	Methylprednisolone, 10 mg/kg (dexamethasone, 2 mg/kg)	Renal function	No
Vignali *et al.*,[54] Italy, Dis Colon Rectum, 2009	Colorectal (n = 52)	Methylprednisolone, 30 mg/kg (dexamethasone, 6 mg/kg)	Respiratory function	No
Worni *et al.*,[71] Switzerland, Ann Surg, 2008	Thyroidectomy (n = 72)	Dexamethasone, 8 mg	PONV	Yes (insulin therapy)
Yamashita *et al.*,[55] Japan, Arch Surg, 2001	Liver resection (n = 33)	Methylprednisolone, 500 mg (dexamethasone, 100 mg)	Interleukin-6	No
Yano *et al.*,[56] Japan, Hepatogastroenterology, 2005	Esophagectomy (n = 40)	Methylprednisolone, 500 mg (dexamethasone, 100 mg)	Unclear	No
Zargar-Shoshtari *et al.*,[57] New Zealand, Br J Surg, 2009	Colorectal (n = 60)	Dexamethasone, 8 mg	Peritoneal cytokines/fatigue	No
Zotti *et al.*,[58] Italy, Ital J Surg Sci, 1998	Hepatobiliary/vascular (n = 82)	Methylprednisolone, 30 mg/kg (dexamethasone, 6 mg/kg)	Pulmonary complication	Yes

DeLiT = dexamethasone, light anaesthesia, and tight glucose control; Hba1c = glycated hemoglobin; PONV = postoperative nausea and vomiting.

Table 2. Summary of Studies Grouped and Analyzed for Each Outcome Category

Adverse Outcome	Eligible Studies	Total Patients	Median Sample Size (IQR)	No. of Events (%)	I_2 %	Trials with Sparse Event Data?	Method (s) Used
Any wound infection[18,19,23,24,26,27,30,33,46,55,57,60,69–71,73]	18*	2,138	77 (36–80)	177 (8.3)	0	Yes	Peto/MH/IV/QE
Blood glucose[25,26,38,40,73,74]	11*	685	65 (42–74)	n/a	60	n/a	QE
Deep wound infection[18,27,30,33,55]	5	1,196	200 (33–381)	90 (7.5)	22	Yes	Peto
Any infection[19,33,41,43,54,56,61]	8*	992	59 (50–83)	136 (13.7)	41	Yes	Peto
Impaired wound healing[22,26,27,38,47,50,68]	11*	742	65 (39–73)	32 (4.3)	0	Yes	Peto
Anastomotic leak[18,43,54,56,57]	6*	599	50 (30–65)	26 (4.3)	0	Yes	Peto
Intraoperative blood loss[19,62,63,65,66,72,73]	11*	513	25 (20–54)	n/a	57	n/a	QE
Postoperative hemorrhage[19,21,24,34,41,48,61,66]	8	1,098	77 (66–175)	35 (3.2)	6	Yes	Peto
Length of stay[19–21,27,30,33–35,37,39,41,46,51,52,54,55,57,59,73]	20*	1,633	50 (32–74)	n/a	89	n/a	QE
CRP[18,28–30,32,35,42,46,55,57,67]	11	781	40 (24–55)	n/a	96	n/a	QE

*Studies with more than one drug dose compared to placebo or segregation of diabetic and nondiabetic patients were considered as separate studies.
CRP = C-reactive protein; I^2 = I-squared statistic for heterogeneity; IQR = interquartile range; IV = inverse variance; MH = Mantel–Haenszel; n/a = not applicable; QE = quality effects.

Table 3. Characteristics of Studies Reporting on Any Wound Infection

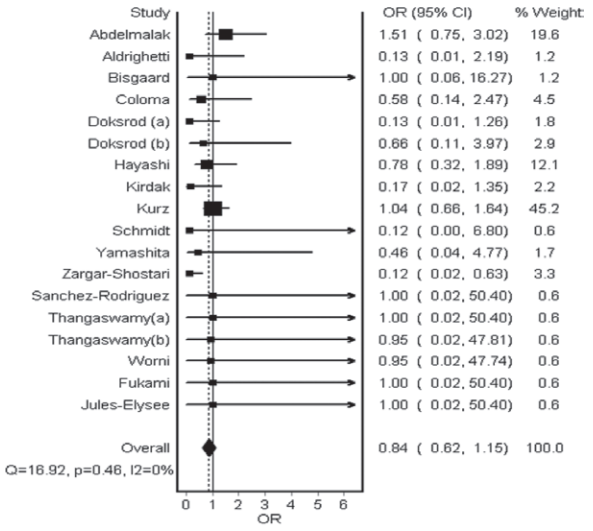
Author, Year	Criteria for Any Wound Infection	Surveillance Period	Glucocorticoid Event Rate	Control Event Rate
Abdelmalak *et al.*,[18] 2013	CDC for deep/organ space SSI*	Duration of hospitalization	21/193	14/188
Aldrighetti *et al.*,[19] 2006	Positive culture in the presence of clinical evidence of infection	Unclear	0/36	2/37
Bisgaard *et al.*,[23] 2003	Unclear	30 d	1/40	1/40
Coloma *et al.*,[24] 2001	Unclear	10 d	3/40	5/40
Doksrod *et al.*,[26] 2012	Unclear	30 d	0/40	3/40
Doksrod *et al.*,[26] 2012	Unclear	30 d	2/40	3/40
Fukami *et al.*,[60] 2009	Unclear	1 undefined postoperative visit	0/40	0/40
Hayashi *et al.*,[27] 2011	Positive culture in association with clinical signs and symptoms of infection	Unclear	10/102	12/98
Jules-Elysee *et al.*,[73] 2012	Unclear	Clinic at 3/6 mo	0/17	0/17
Kirdak *et al.*,[30] 2008	CDC for superficial/organ cavity SSI	30 d	0/14	3/13
Kurz *et al.*,[33] 2015	CDC for superficial/deep/peritoneal SSI†	30 d	45/283	42/272
Sánchez-Rodríguez *et al.*,[69] 2010	Unclear	30 d	0/105	0/105
Schmidt *et al.*,[46] 2007	Unclear	Unclear	0/10	1/10
Thangaswamy *et al.*,[70] 2010	Unclear	7 d	0/18	0/18
Thangaswamy *et al.*,[70] 2010	Unclear	7 d	0/19	0/18
Worni *et al.*,[71] 2008	Unclear	30 d	0/37	0/35
Yamashita *et al.*,[55] 2001	Unclear	Unclear	1/17	2/16
Zargar-Shoshtari *et al.*,[57] 2009	Documented erythema or discharge requiring antibiotic treatment	Unclear	0/29	6/31

*Primary outcome was a composite of major complications including surgical-site infection. †Primary outcome was surgical-site infection.
CDC = Centers for Disease Control and Prevention; SSI = surgical-site infection.

Postoperative infections, particularly surgical-site infections, are important as they prolong hospital stay, increase costs, and have an impact on postoperative mortality that extends to at least to 30 days.[75] Among the glucocorticoids, dexamethasone is the most commonly administered agent in the perioperative period being a potent, cheap, and effective antiemetic,[7,15] with analgesic properties and the capacity to improve the quality of recovery, facilitating early hospital discharge.[76–78] While several meta-analyses and practice guidelines have asserted the apparent safety of perioperative glucocorticoids in general and dexamethasone in particular in terms of infection risk,[3,15,79] the lack of definitions of adverse outcomes or use of postoperative surveillance has provoked much discussion.[11,80] Two small retrospective studies have produced conflicting results, with one suggesting that dexamethasone increases infection risk,[81] while a cohort study did not confirm these findings.[82] A large randomized controlled trial in cardiac surgery has reported a 4.9% absolute reduction in the risk of postoperative infection in patients receiving 1 mg/kg dexamethasone, principally

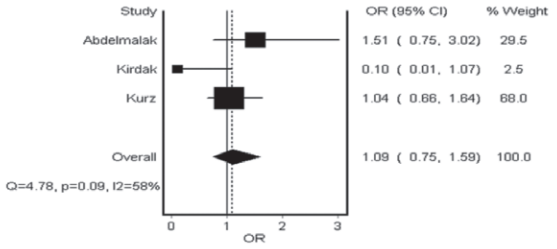
A

ALL STUDIES	Glucocorticoid		Placebo	
Study name	Events	Total	Events	Total
Abdelmalak	21	193	14	188
Aldrighetti	0	36	2	37
Bisgaard	1	40	1	40
Coloma	3	40	5	40
Doksrod(a)	0	40	3	40
Doksrod(b)	2	40	3	40
Hayashi	10	102	12	98
Kirdak	0	14	3	13
Kurz	45	283	42	272
Schmidt	0	10	1	10
Yamashita	1	17	2	16
Zargar-Shostari	0	29	6	31
Sanchez-Rodriguez	0	105	0	105
Thangaswamy(a)	0	18	0	18
Thangaswamy(b)	0	19	0	18
Worni	0	37	0	35
Fukami	0	40	0	40
Jules-Elysee	0	17	0	17
Total	83	1080	94	1058



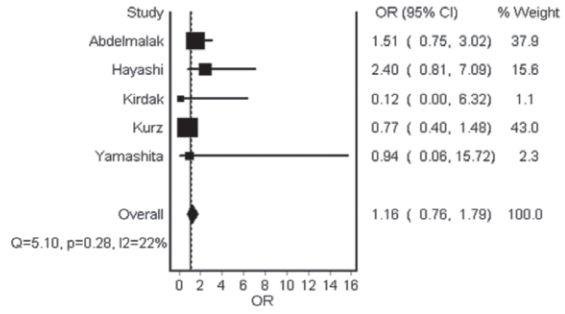
B

CDC STUDIES	Glucocorticoid		Placebo	
Study name	Events	Total	Events	Total
Abdelmalak	21	193	14	188
Kirdak	0	14	3	13
Kurz	45	283	42	272
Total	66	490	59	473



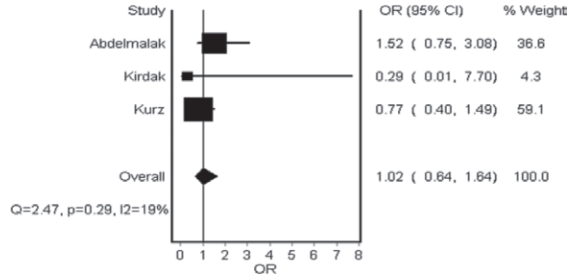
C

ALL STUDIES	Glucocorticoid		Placebo	
Study name	Events	Total	Events	Total
Abdelmalak	21	193	14	188
Hayashi	10	102	4	98
Kirdak	0	14	1	13
Kurz	17	283	21	272
Yamashita	1	17	1	16
Total	49	609	41	587



D

CDC STUDIES	Glucocorticoid		Placebo	
Study name	Events	Total	Events	Total
Abdelmalak	21	193	14	188
Kirdak	0	14	1	13
Kurz	17	283	21	272
Total	38	490	36	473



Favors glucocorticoid ← → Favors placebo

Fig. 2. The influence of perioperative glucocorticoid on the odds of any wound infection (*A*), any wound infection meeting Centers for Disease Control and Prevention criteria (CDC; *B*), deep wound infection (*C*), and deep wound infection meeting CDC criteria (*D*). OR = odds ratio.

related to the occurrence of pneumonia.[1] Our results do not suggest an effect of glucocorticoids on surgical-site infection, wound healing, and anastomotic leak nor a dose-related trend. When our analyses were restricted to high-quality trials that used objective criteria and postoperative surveillance to day 30, the results did not change. Hence, these results

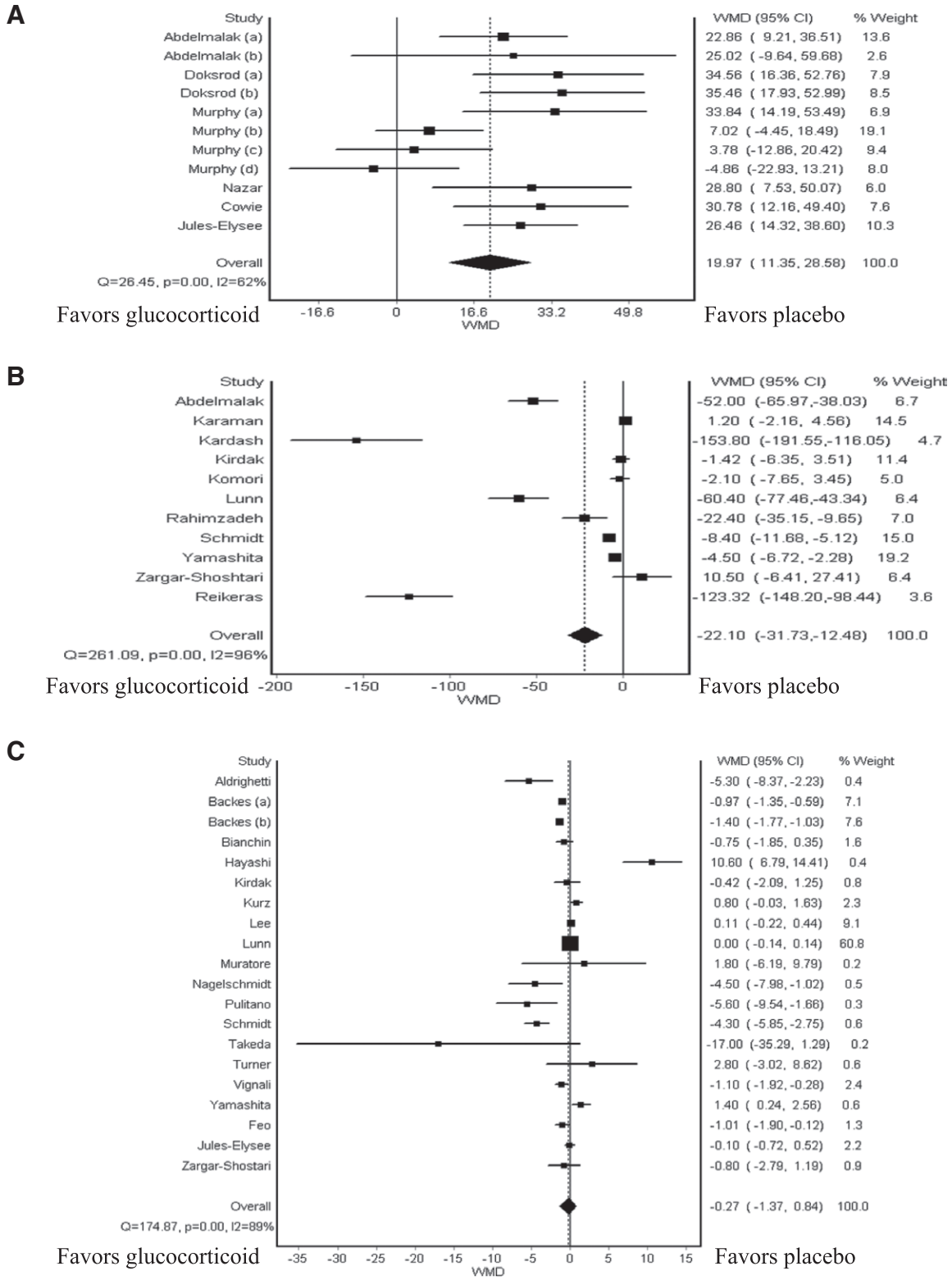


Fig. 3. The influence of perioperative glucocorticoid on peak perioperative blood glucose (mg/dl; *A*), peak perioperative C-reactive protein (mg/l; *B*), length of hospital stay (days; *C*). WMD = weighted mean difference.

are likely a robust finding. The Doi plot reveals that there is clear asymmetry, favoring the publication of small trials with lower rates of infection.

The hyperglycemic effect of perioperative glucocorticoids are real but small. Acute hyperglycemia may impair leukocyte functions[83] and wound healing,[84] these being worse

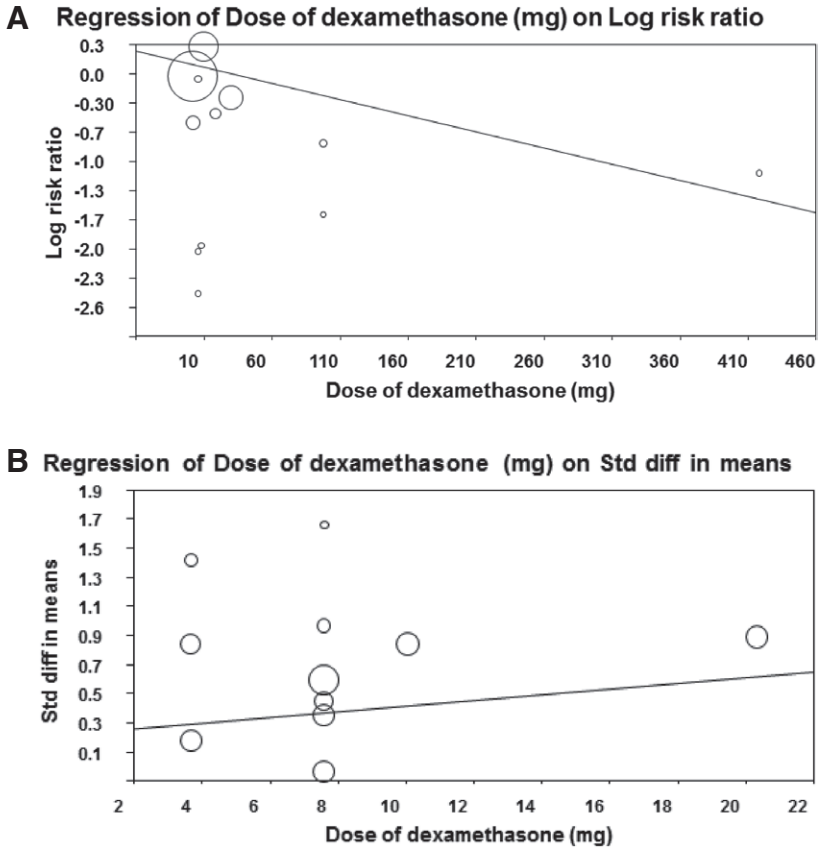


Fig. 4. Mixed meta-regression (methods of moment) to assess the interaction between dexamethasone dose equivalent and any wound infection (*A*; $P = 0.30$) and peak perioperative blood glucose (mg/dl; *B*; $P = 0.21$). The size of the markers is proportional to the size of the study. Std diff = standardized difference.

with surges of blood glucose rather than sustained hyperglycemia. While the clinical importance of perioperative hyperglycemia is as yet not fully evaluated, particularly in terms of causality, there is a growing body of observational data to support a strong relationship, especially in nondiabetic patients.[85,86] Studies have shown infectious and noninfectious complications to be directly related to the degree of hyperglycemia, with even a single elevation of blood glucose in the perioperative period being harmful.[87,88] Our results show that perioperative glucocorticoids increased blood glucose concentrations, but with the limited doses of dexamethasone used in the included trials in this meta-analysis (almost all less than or equal to 8 mg dexamethasone), the absolute difference in blood glucose (20.0 mg/dl) was modest and was only marginally less than that observed with a much larger dose in cardiac surgery patients.[1] We chose the maximal blood glucose concentration measured intraoperatively or postoperatively up to 12 h as this enabled the inclusion of the maximum number of trials. Whether this is the period in which a peak effect of glucocorticoid on blood glucose concentration is evident or not is unknown. Hyperglycemia after glucocorticoid was significant whether trials excluded diabetic patients or not, but the effect size appeared more marked in studies with no diabetic exclusion criteria. This observation was strongly influenced by a single, well-conducted trial reporting no significant hyperglycemia with dexamethasone after gynecologic surgery in nondiabetics.[38] In contrast, a separate analysis of the data from one of the included randomized trials[18] has been published, and it suggests that the hyperglycemic effect is more marked in nondiabetic patients, even when controlling for insulin treatment in the diabetes group.[74] Overall, the importance of small blood glucose increases is unknown[10] and remains to be established in a large, properly conducted trial. Beyond infection and hyperglycemia, the effect of glucocorticoids on postoperative CRP concentrations is consistent with their well-documented antiinflammatory actions[89] and is not surprising.

Some previous meta-analyses in noncardiac surgery have reported reductions in specific or composite postoperative complications and length of stay after glucocorticoid administration.[79,89] The limitations of these studies include summation of individual complications and an absence of adjustment for study quality or glucocorticoid dose.[90] Other systematic reviews have reported no impact on adverse events but were based on searches restricted to specific outcomes such as pain and were not suitable for a safety assessment.[3,78] Overall assertions of safety have been criticized as

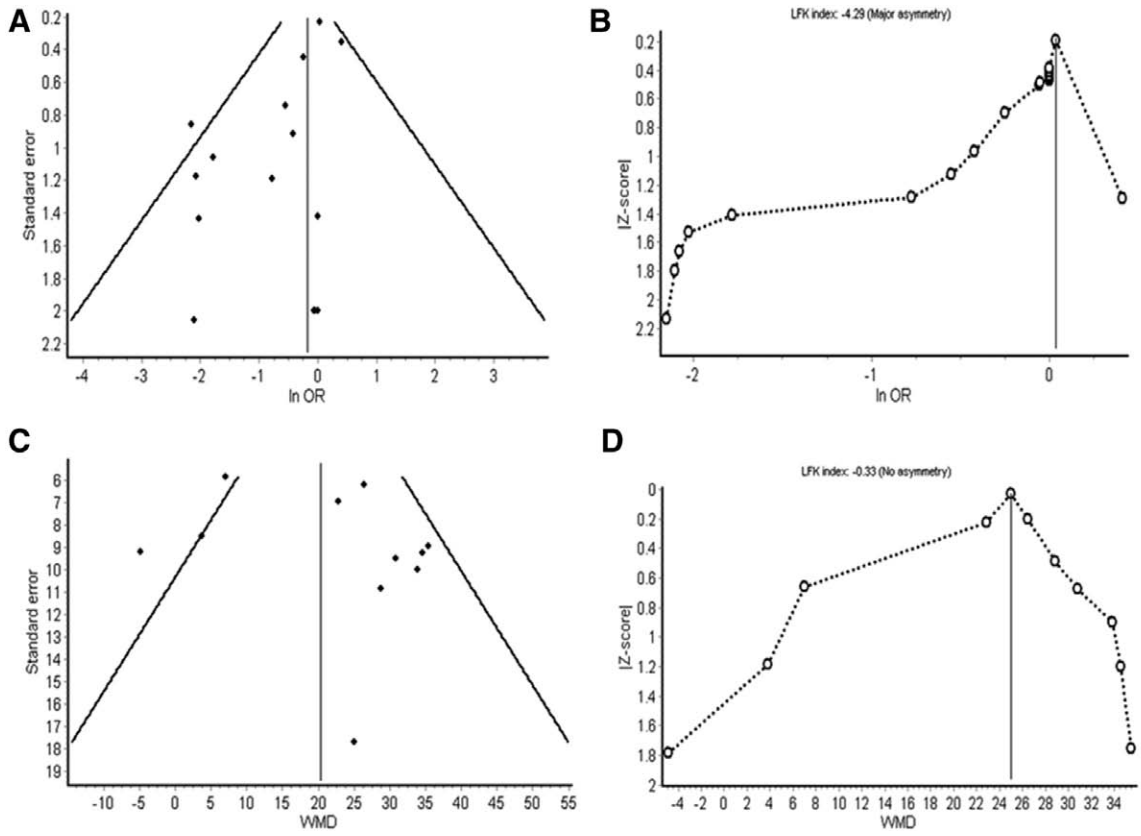


Fig. 5. Funnel and Doi plots for trials examining any wound infection (*A*, *B*) and perioperative blood glucose (*C*, *D*). LFK = Luis Furuya-Kanamari; OR = odds ratio; WMD = weighted mean difference.

few trials systematically defined or sought complications through postoperative surveillance. In this work, three recent high-quality trials with appropriate surveillance were included (and considered in isolation), and no impact on discrete complications was observed. Furthermore, trial quality and glucocorticoid dose were adequately adjusted for, lending further validity to the results.

Finally, we would like to acknowledge the limitations of this study, which are common to many meta-analyses[91] and which in our case are compounded by the poor quality of the definitions of the endpoints of interest. The qualitative outcomes (infection, anastomotic leak, and wound healing) lacked uniformity of approach and definition. In only one of the 18 trials reporting on infection rates was this a primary outcome, and in only six were any diagnostic definitions provided, a problem common to other fields.[92] The total number of patients included in this study was limited because we sought to specifically examine the effect of glucocorticoids in noncardiac surgery and nonobstetric patients as these patients represent the majority of patients undergoing general anesthesia globally every day. Combining the results of independent studies, with variable amounts of sampling error due to differing conditions, surgical populations, glucocorticoid type and dose, and sample size, is fraught with challenges.[90] The I^2 statistic (which was low) for infective outcomes may be underpowered to detect heterogeneity when the number of studies included in the meta-analysis is small ($k < 20$) and/or the average sample size of the studies is less than 80 (both conditions pertain to this meta-analysis).[93] To address this, we employed both quality effects and inverse variance heterogeneity models, which provide more reliable estimates than the random effects model.[94,95] Smaller, lower quality, and less precise trials tended to report larger effect sizes after glucocorticoid, but their influence was removed or attenuated by sensitivity analysis or the quality effects model, respectively. Our meta-analysis provides data on any wound infection rates in 2,138 patients and on deep wound infection rates in 1,196 patients. Based on these data, with any and deep wound infection rates in the control groups of 8.9% and 7.0 %, the detection of a small but clinically meaningful difference in infection rates of 2% between glucocorticoid and control groups at 90% power would require a trial with 3,543 patients in each arm.

In conclusion, our meta-analysis confirms many of the findings that have been asserted in previous meta-analyses and guideline documents. The administration of perioperative glucocorticoids to patients undergoing noncardiac and nonobstetric surgery appears to be safe in terms of postoperative infection risk, anastomotic leak, wound healing, and bleeding risk. They have a clear antiinflammatory effect without reducing the length of stay after surgery. Blood glucose concentrations do increase in the perioperative period

in patients receiving glucocorticoids, but the magnitude of changes is of questionable clinical importance especially since an increased risk of infection is not observed. An 8,800-patient trial of dexamethasone and surgical-site infection is in progress (Perioperative ADministration of Dexamethasone and Infection trial; ACTRN12614001226695). Pending those results, expected in 2019, available data suggest that single-dose perioperative dexamethasone does not provoke substantive complications. We can, therefore, be assured that the current literature does not raise any safety concerns that should rule out using low to moderate doses of glucocorticoids in the elective noncardiac surgical patient.

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Competing Interests

Drs. Ho and Corcoran are funded by WA Health and Raine Medical Research Foundation (Perth, Western Australia, Australia) through the Raine Clinical Research Fellowship. Drs. Chan and Ho are steering committee members for Perioperative ADministration of Dexamethasone and Infection (PADDI). Dr. Corcoran is the principal investigator for the PADDI trial. The other authors declare no competing interests.

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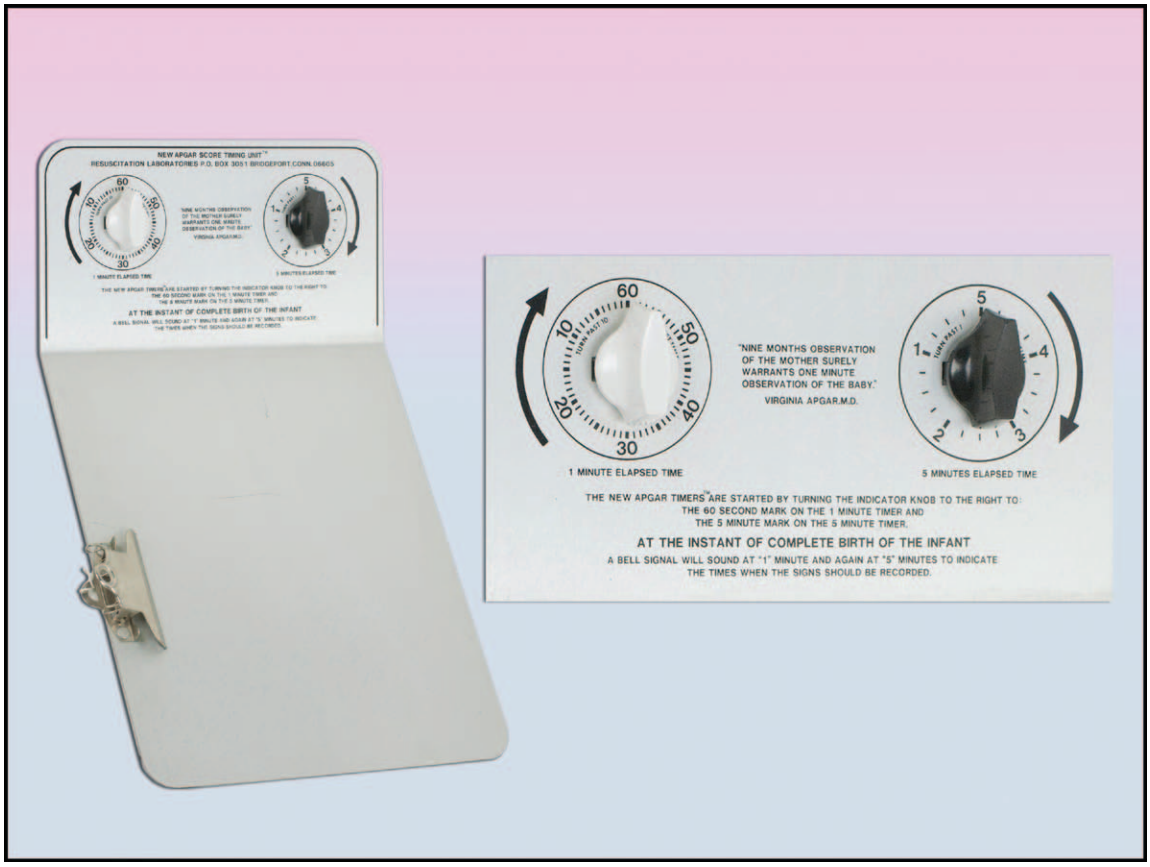
Colón-Morales and His Apgar Score Timing Units



Physicians and many laypeople are familiar with the 1- and 5-min Apgar scoring system for screening the health of newborns, a system named after anesthesiologist Virginia Apgar, M.D. Her original screening system was simplified in 1962 to the acronym APGAR for the neonate's Appearance (color), Pulse (heart rate), Grimace (reflex irritability), Activity (muscle tone), and Respiration. At a meeting in New York in 1968, an anesthesiologist named Miguel Angel Colón-Morales, M.D., displayed his "Apgar Score Timing Unit" as a single timer mounted on a clipboard. In June 1969, he filed a U.S. patent application for that invention as a "Device for monitoring physiological phenomenon." One year later, he was granted U.S. Patent No. 3517636. A later version of his invention featured not one, but two timers (*right*), and was dubbed (*left*) the "New Apgar Score Timing Unit." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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