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Adverse side effects of dexamethasone in surgical patients

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ABSTRACT

Background

In the perioperative period, dexamethasone is widely and effectively used for prophylaxis of postoperative nausea and vomiting (PONV), for pain management, and to facilitate early discharge after ambulatory surgery.

Long-term treatment with steroids has many side effects, such as adrenal insufficiency, increased infection risk, hyperglycaemia, high blood pressure, osteoporosis, and development of diabetes mellitus. However, whether a single steroid load during surgery has negative effects during the postoperative period has not yet been studied.

Objectives

To assess the effects of a steroid load of dexamethasone on postoperative systemic or wound infection, delayed wound healing, and blood glucose change in adult surgical patients (with planned subgroup analysis of patients with and without diabetes).

Search methods

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, and the Web of Science for relevant articles on 29 January 2018. We searched without language or date restriction two clinical trial registries to identify ongoing studies, and we handsearched the reference lists of relevant publications to identify all eligible trials.

Selection criteria

We searched for randomized controlled trials comparing an incidental steroid load of dexamethasone versus a control intervention for adult patients undergoing surgery. We required that studies include a follow-up of 30 days for proper assessment of the number of postoperative infections, delayed wound healing, and the glycaemic response.

Data collection and analysis

Two review authors independently screened studies for eligibility, extracted data from relevant studies, and assessed all included studies for bias. We resolved differences by discussion and pooled included studies in a meta-analysis. We calculated Peto odds ratios (ORs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes. Our primary outcomes were postoperative systemic or wound infection, delayed wound healing, and glycaemic response within 24 hours. We created a funnel plot for the primary outcome postoperative (wound or systemic) infection. We used GRADE to assess the quality of evidence for each outcome.

Main results

We included in the meta-analysis 38 studies that included adults undergoing a large variety of surgical procedures (i.e. abdominal surgery, cardiac surgery, neurosurgery, and orthopaedic surgery). Age range of participants was 18 to 80 years. There is probably little or no difference in the risk of postoperative (wound or systemic) infection with dexamethasone compared with no treatment, placebo, or active control (ramosetron, ondansetron, or tropisetron) (Peto OR 1.01, 95% confidence interval (CI) 0.80 to 1.27; 4931 participants, 27 studies; $I^2 = 27\%$; moderate-quality evidence). The effects of dexamethasone on delayed wound healing are unclear because the wide confidence interval includes both meaningful benefit and harm (Peto OR 0.99, 95% CI 0.28 to 3.43; 1072 participants, eight studies; $I^2 = 0\%$; low-quality evidence). Dexamethasone may produce a mild increase in glucose levels among participants without diabetes during the first 12 hours after surgery (MD 13 mg/dL, 95% CI 6 to 21; 10 studies; 595 participants; $I^2 = 50\%$; low-quality evidence). We identified two studies reporting on glycaemic response after dexamethasone in participants with diabetes within 24 hours after surgery (MD 32 mg/dL, 95% CI 15 to 49; 74 participants; $I^2 = 0\%$; very low-quality evidence).

Authors' conclusions

A single dose of dexamethasone probably does not increase the risk for postoperative infection. It is uncertain whether dexamethasone has an effect on delayed wound healing in the general surgical population owing to imprecision in trial results. Participants with increased risk for delayed wound healing (e.g. participants with diabetes, those taking immunosuppressive drugs) were not included in the randomized studies reporting on delayed wound healing included in this meta-analysis; therefore our findings should be extrapolated to the clinical setting with caution. Furthermore, one has to keep in mind that dexamethasone induces a mild increase in glucose. For patients with diabetes, very limited evidence suggests a more pronounced increase in glucose. Whether this influences wound healing in a clinically relevant way remains to be established. Once assessed, the three studies awaiting classification and two that are ongoing may alter the conclusions of this review.

PLAIN LANGUAGE SUMMARY

Adverse side effects of dexamethasone when administered to adult patients undergoing surgery

Background

In the presence of an infection, the body starts an inflammation process. Dexamethasone is a steroid drug that slows down this inflammation process. Long-term treatment with steroid drugs has many side effects such as increased risk of infection, high blood pressure, and development of diabetes. During surgery, dexamethasone is given to the patient to reduce the risk of nausea and vomiting after surgery, to relieve pain, and to make the patient feel better. However, whether short-term treatment with dexamethasone leads to any adverse side effects is not known.

Question

The reviewers examined current evidence on the adverse side effects of short-term treatment with dexamethasone during surgery. They compared patients receiving dexamethasone to patients not receiving dexamethasone. They particularly looked at the number of infections after surgery and the number of wounds that did not heal well. Furthermore, as long-term treatment with steroids can lead to high blood sugar, they looked at the response of blood sugar within the first 24 hours postoperatively.

What we found.

Study characteristics: the reviewers searched four digital databases to find all relevant studies on this topic. The evidence is current to 29 January 2018. In total, they retrieved 38 relevant studies. All studies included adults undergoing surgery. A total of 27 studies (4931 participants) had assessed the occurrence of infection after surgery, nine studies (1072 participants) had investigated delayed wound healing, and 10 studies (595 participants) had looked at the effect of dexamethasone on blood sugar.

Key results: after pooling results, reviewers found that dexamethasone had no effect on the development of an infection after surgery, and that wounds healed equally well in both groups. However, the quality of the studies was moderate to low, which means that more studies are needed to support a definitive conclusion. Finally, the mean blood sugar of patients without diabetes receiving dexamethasone was slightly higher than that of patients not receiving dexamethasone (low-quality evidence). In patients with diabetes, this effect seemed to be larger. However, blood sugar was measured in only 74 patients with diabetes, which means that reviewers did not obtain a very accurate estimate. They qualified this as very low-quality evidence.

Authors' conclusions: dexamethasone probably does not increase the risk of infection after surgery. Not enough information is available to determine whether dexamethasone has an effect on the time it takes for surgical wounds to heal. However, included studies did not focus on patients with high risk for delayed wound healing, for example, patients with diabetes or those taking steroids; thus more studies are needed on this topic. Additionally, one has to keep in mind that taking dexamethasone leads to a mild increase in blood sugar. For patients with diabetes, very limited evidence suggests a greater increase in blood sugar. Whether or not the small increase in blood sugar has any effect on healing of surgical wounds has yet to be established. Three studies awaiting classification and two ongoing trials may alter the conclusions of this review, once assessed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Dexamethasone compared to control in surgical patients						
Patient or population: surgical patients undergoing various types of surgery (e.g. abdominal, brain, cardiac, and orthopaedic surgery) Setting: adults undergoing surgery receiving either up to 20 mg dexamethasone or a control intervention. Studies were conducted in North America, Europe, and Asia. Intervention: dexamethasone 4 to 20 mg intravenous during induction Comparison: no treatment, placebo, or ramosetron						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with dexamethasone				
Postoperative wound or systemic infection Follow-up: mean 30 days	Study population		OR 1.01 (0.80 to 1.27)	4931 (27 RCTs)	⊕⊕⊕○ Moderate ^a	
	80 per 1000	81 per 1000 (65 to 100)				
Delayed wound healing Follow-up: mean 30 days	Study population		OR 0.99 (0.28 to 3.43)	642 (8 RCTs)	⊕⊕○○ Low ^b	
	70 per 1000	69 per 1000 (21 to 205)				
Glycaemic response - change from baseline to 2 to 12 hours postoperatively in patients without diabetes Follow-up: 1 day	Mean glycaemic response - change from baseline to 2 to 12 hours postoperatively in patients without diabetes: 48 mg/dL	MD 13 mg/dL higher (6 higher to 21 higher)	-	595 (10 RCTs)	⊕⊕○○ Low ^c	
Glycaemic response - change from baseline to 10 to 24 hours after surgery in patients with diabetes Follow-up: 1 day	Mean glycaemic response - change from baseline to 10 to 24 hours after surgery in patients with diabetes: 80 mg/dL	MD 32 mg/dL higher (15 higher to 49 higher)	-	74 (2 RCTs)	⊕○○○ Very low ^d	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomized controlled trial.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

^aDowngraded by one level owing to imprecision. We chose not to downgrade for risk of bias, as the sensitivity analysis showed that these studies had little effect on the outcome.

^bDowngraded by two levels owing to high risk of bias in the included studies and imprecision.

^cDowngraded by two levels owing to high risk of bias in the included studies and inconsistency.

^dDowngraded by three levels: one level for high risk of bias and two levels for serious imprecision.

BACKGROUND

Description of the condition

Dexamethasone has several indications and is frequently administered in the perioperative period. First, it has been shown to prevent postoperative nausea and vomiting (PONV) (De Oliveira 2013); however, PONV is still experienced by 20% to 30% of surgical patients (Habib 2012). It has been recommended that every person undergoing surgery should be given multi-modal PONV prophylaxis to achieve a PONV-free hospital (Kranke 2014). This would substantially increase the number of people exposed to dexamethasone in the perioperative period. Second, previous meta-analyses have shown significantly lower pain scores two and 24 hours after surgery, plus an opioid-sparing effect after administration of low-dose dexamethasone when used as a co-analgesic (De Oliveira 2011; Waldron 2013). Third, dexamethasone prolongs the duration of peripheral nerve blocks when given in combination with the local anaesthetic, or intravenously (Pehora 2017). Finally, dexamethasone improves postoperative recovery and promotes discharge after ambulatory surgery (Coloma 2001; Murphy 2011b). Therefore, giving every patient a perioperative dose of dexamethasone might be advisable. When general (multi-modal) prophylaxis using dexamethasone is considered, a comprehensive evaluation of associated potential adverse effects is needed (Bartlett 2013). This review therefore focused on the side effects of incidental dexamethasone application at a low dose in the perioperative period. The side effects considered in this review are postoperative systemic or wound infection, delayed wound healing, and hyperglycaemia.

Description of the intervention

Dexamethasone is most often administered for prophylaxis of PONV and is effective at a single dose (4 mg to 10 mg) given intravenously during surgery (De Oliveira 2013). It has been shown that doses of 1.25 mg to 20 mg administered during surgery lead to a significant reduction in postoperative pain scores (Waldron 2013). A single dose of 4 mg of dexamethasone has been shown to decrease the time to discharge after ambulatory surgery (Coloma 2001), and this is the recommended dose for PONV prophylaxis (Gan 2014). Thus, the dose given intravenously during surgery for the above mentioned reasons ranges between 4 mg and 20 mg. After administration of the drug, the concentration of dexamethasone rises quickly and peaks after two to 12 hours (Fauci 1976). However, dexamethasone has a rather long biological half-life of 36 to 72 hours, and it can suppress cortisol levels for up to one week (Fauci 1976).

How the intervention might work

It is known that long-term treatment with corticosteroids can produce many side effects, such as adrenal insufficiency, hyperglycaemia, and even development of diabetes mellitus (Liu 2014). It has been suggested that the anti-inflammatory and immunosuppressive properties (e.g. inhibition of pro-inflammatory cytokines, reduced ability of leucocytes to enter sites of infection, tissue injury, inhibitory effects on T and B cells) may have a negative effect on wound healing and might increase the risk of infection with long-term treatment (Busti 2005). Furthermore, dexamethasone induces hepatic gluconeogenesis and insulin resistance, thereby causing transient hyperglycaemia, which can lead to oxidative stress and endothelial and innate immune dysfunction (Dungan 2009; Qi 2004; Turina 2005). This has been associated with increased risk of wound infection in patients both with and without diabetes (Clement 2004; Smiley 2006). However, it is unknown whether a single dose of dexamethasone given in the perioperative period has the same adverse side effects as are seen with long-term treatment.

Why it is important to do this review

Although 32% to 45% of surgical patients will receive dexamethasone in the perioperative period as part of PONV prophylaxis or multi-modal pain treatment (Dahl 2014; Polderman 2015b), previous meta-analyses have only briefly mentioned the potential adverse effects of a single low dose of dexamethasone (De Oliveira 2013; Waldron 2013). Owing to multiple indications for dexamethasone, these meta-analyses might be subject to selective outcome reporting bias with regard to adverse side effects. Therefore, the current meta-analysis focused on the side effects of dexamethasone given once during the perioperative period for any of the indications mentioned above to guide clinical decision-making with regard to the risk-benefit ratio in patients both with and without diabetes.

OBJECTIVES

To assess the effects of a steroid load of dexamethasone on postoperative systemic or wound infection, delayed wound healing, and blood glucose change in adult surgical patients (with planned subgroup analysis of patients with and without diabetes).

METHODS

Criteria for considering studies for this review

Types of studies

We searched for randomized controlled trials (RCTs), irrespective of blinding status. We placed no restrictions on publication date or language. We did not include quasi-randomized, cross-over, or observational trials, as these types of studies are more subject to bias, and we expected that a sufficient number of RCTs could be included in this meta-analysis.

Types of participants

We considered studies with adult participants (according to the definitions of respective study authors) undergoing surgery, both inpatient and day-case surgery, under general or regional anaesthesia.

We excluded studies with paediatric participants (according to the definitions of respective study authors), as paediatric participants might have received different dosages and could respond differently to a steroid load. When the study population consisted of both paediatric and adult participants, the studies had to report results of the adult subgroup separately.

Types of interventions

We considered RCTs comparing intravenous dexamethasone given during surgery versus no treatment, placebo, or another antiemetic or analgesic drug given to a control group. However, the drug in the control group must not have had any glucocorticosteroid properties. We excluded studies that provided oral, intramuscular, or perineural administration of dexamethasone. As dexamethasone for PONV prophylaxis and pain treatment is rarely given at a high dose, we chose 20 mg as the maximum dose and included studies with repeated doses of dexamethasone up to 20 mg. We performed a subgroup analysis for single and multiple doses of dexamethasone.

Types of outcome measures

As several meta-analyses have shown possible beneficial effects of perioperative dexamethasone treatment ([De Oliveira 2013](#); [Waldron 2013](#)), we did not include treatment effects in the outcomes of this meta-analysis and focused only on the adverse side effects of dexamethasone. Consequently, we considered trials with intravenous dexamethasone administration for various indications and included trials with sufficient follow-up for assessment of postoperative infection or delayed wound healing and trials with glycaemic measurements. As this strategy might have led to selection bias, we documented all excluded studies based on lack of outcome data.

Primary outcomes

- Postoperative systemic or wound infection. Follow-up time for this outcome measure should be 30 days or longer. We used study authors' definitions of postoperative systemic and wound infection

- Delayed wound healing. Follow-up time for this outcome measure should be 30 days or longer. We measured the proportion of wounds that had not healed within 30 days
- Glycaemic response within 24 hours. We defined this as the difference between preoperative and postoperative blood glucose. As the peak serum level of dexamethasone is achieved two to 12 hours after injection, the postoperative glucose level had to be measured at least two hours but within 24 hours after dexamethasone administration. We looked at the change from baseline to 12 hours postoperatively and to 24 hours postoperatively on a continuous scale in patients without diabetes. We looked at the change from baseline to 24 hours postoperatively in patients with diabetes

Secondary outcomes

- Length of hospital stay, measured in days on a continuous scale
- Re-admission or unplanned hospital admission
- C-reactive protein (CRP), measured in the first 24 hours perioperatively
- 30-day all-cause mortality

Search methods for identification of studies

We searched for RCTs including surgical participants who received dexamethasone as an intervention and included a sufficient follow-up period (30 or more days) for adverse side effects. When it was stated in the results section that no adverse effects were found, but details of the assessment of adverse side effects (e.g. which adverse side effects, length of follow-up) were not described in the methods section, we contacted the corresponding author to retrieve data on details of the assessment of adverse side effects. We considered for inclusion in this meta-analysis only studies addressing at least one of our primary outcomes with sufficient duration of follow-up; however, as stated above, we documented all studies that we excluded for lack of outcome data. We placed no restrictions on time covered by the search. We excluded studies published by Yoshitaka Fuji because of the suggested invalidity of these results ([Carlisle 2012](#)). We did not apply any full-text language restrictions. We translated papers that were written in a language other than English.

Electronic searches

We identified RCTs through literature searching via systematic and sensitive search strategies as outlined in Chapter 6.4 of the *Cochrane Handbook for Systematic reviews of Interventions* ([Higgins 2011](#)). We searched the Cochrane Central Register of Controlled Trials (CENTRAL; January 2018, Issue 1 of 12), in the Cochrane Library ([Appendix 1](#)), MEDLINE (1946 to 29 January 2018; [Appendix 2](#)), Embase (1947 to 29 January 2018; [Appendix 3](#)), and the Web of Science (1900 to 29 January 2018; [Appendix 4](#)).

We searched the following websites for ongoing and unpublished studies on 28 February 2017.

- <https://clinicaltrials.gov/>.
- <http://www.controlled-trials.com>.

We developed the search strategy in consultation with the Information Specialist.

Searching other resources

We handsearched the reference lists of the original included articles to retrieve additional relevant studies. In addition, we handsearched the citations and reference lists of relevant reviews and meta-analyses. When necessary, we contacted trial authors for additional information.

Data collection and analysis

We used Cochrane's standard methods to select eligible studies (Higgins 2011), and we used a data extraction form to extract data from relevant trials. When no agreement was reached, we planned that a third review author should make the decision, but we found that this was not necessary during the review process. We used the Review Manager statistical package provided by Cochrane to analyse the data (Review Manager 2014).

Selection of studies

After merging the search results using EndNote software, we removed all duplicate records of the same report (Higgins 2011). Two review authors (JP and VFR) independently screened reports for eligibility based on title and abstract. When we encountered a difference in opinion, we resolved this by discussion between the two review authors (JP and VFR). When necessary, we consulted a third review author (JH). Subsequently, two review authors (JP and VFR) independently screened the full text of eligible studies for compliance with the eligibility criteria. If it remained unclear which adverse side effects were assessed, we contacted the authors of the respective studies to request the relevant information. We documented the studies excluded based on lack of outcome data.

Data extraction and management

Two review authors (JP and VFR) independently extracted data from the included studies. We recorded all relevant data on the data extraction form that had been developed for the purpose of this review (Appendix 5), and we documented for each trial the following data.

- Details of the study (when and where the study was executed and major sources of funding).
- Details of study participants (demographic characteristics, type and length of surgery).

- Details of the type of intervention (dose, timing, additional medication).
- Details of relevant outcomes (definitions and times of measurement).
- Details of relevant results.

Assessment of risk of bias in included studies

Two review authors (JP and VFR) independently assessed risk of bias using the Cochrane 'Risk of bias' domains detailed in Appendix 6 and discussed below.

Measures of treatment effect

When meta-analysis is used to combine results from several studies with binary outcomes, adverse effects may be rare but possibly serious, and thus important (Sutton 2002). As recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we used Peto's odds ratio (OR) to summarise study effects. This provides an unbiased estimate of the treatment effect and has been shown to be particularly appropriate for examining zero-event data.

For the glycaemic response, we retrieved the change from baseline results, which is more objective than the final postoperative glucose measurement, as this latter highly depends on the preoperative value.

Blood glucose and length of hospital stay often are not normally distributed and frequently are reported as median values with an interquartile range. We converted these data to mean values with standard deviations so we could pool the data (Hozo 2005).

Regarding secondary outcomes, we calculated Peto's OR for the number of unplanned admissions and for 30-day all-cause mortality, as we also expected these adverse effects to be rare.

Unit of analysis issues

For dichotomous outcomes, we documented for each group the total number of participants and the number of participants who experienced the outcome. For continuous glucose outcomes, we used the mean of the change from baseline along with the standard deviation for each group and the number of participants included in each group. For other continuous outcomes, we used mean, standard deviation, and number of participants in each group.

We did not extract graphically presented data, as we were unable to determine the exact mean and standard deviation from these figures. Instead, we described these results in the appropriate respective section.

Dealing with missing data

We attempted to retrieve relevant data by contacting the corresponding author of each study with missing data for the outcome of adverse side effects. Furthermore, when more outcomes were reported as a composite endpoint, we contacted investigators to

request the data for each outcome separately. When these data were nonetheless not available, we excluded the respective study.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity, which can lead to statistical heterogeneity. We considered a Chi^2 test $P < 0.05$ and an I^2 statistical value $> 60\%$ as cutoffs for statistical heterogeneity. When we identified heterogeneity, we explored possible causes. When we could not explain the heterogeneity, we proceeded with meta-analysis using a random-effects model. However, when we noted inconsistency in the direction of the effect, we did not perform a meta-analysis of the respective data. Studies might use different definitions for wound or systemic infection, leading to heterogeneity. We documented the definitions used by the included studies.

Assessment of reporting biases

We constructed a funnel plot for the primary outcome (postoperative systemic or wound infection) to assess reporting bias. Possible sources of asymmetry in funnel plots - which should be derived from at least 10 studies ([Egger 1997](#)) - include selection bias, poor methodological quality leading to inflated effects in smaller studies, and true heterogeneity - artefactual and chance.

Data synthesis

We used Review Manager software to perform the analysis ([Review Manager 2014](#)). When multi-arm studies were included, we used the placebo group as the control group. However, when no 'placebo' group was enrolled in the study, we merged the non-corticosteroid groups to one control group to make a two-arm comparison and to avoid double-counting of participants. We expected that the interventions would be comparable between trials. However, although the intervention might contribute to the observed adverse side effect, it will not be the sole cause of the adverse side effect. Therefore, we believed that it was more appropriate to use a random-effects model and to assess the average intervention effect.

Subgroup analysis and investigation of heterogeneity

We carried out a subgroup analysis for participants with and without diabetes for the glycaemic response, as patients with diabetes might respond differently to a steroid load compared to patients without diabetes.

We carried out a subgroup analysis for different doses (e.g. 4 mg to 5 mg vs 8 mg to 10 mg vs 20 mg of dexamethasone) to estimate whether the effect is robust for all doses. Furthermore, we carried

out a subgroup analysis for a single dose versus multiple doses of dexamethasone, to estimate whether the effect was comparable.

Sensitivity analysis

We included a sensitivity analysis for the following outcomes: postoperative risk of systemic or wound infection, delayed wound healing, and glycaemic control, while excluding studies with high risk of bias. Furthermore, we carried out a sensitivity analysis that excluded trials with non-normality glucose data, to assess whether these trials introduced a systematic bias.

'Summary of findings' table and GRADE

We used the GRADE system to assess the methodological quality of trials included in our review, to assess the quality of the body of evidence associated with specific outcomes in our review (postoperative systemic or wound infection; delayed wound healing; glycaemic response: change from baseline to 12 hours postoperatively and change from baseline to 24 hours postoperatively and change from baseline to 24 hours postoperatively in participants with diabetes; re-admission; length of hospital stay; CRP; and mortality), and to construct a 'Summary of findings' table by using [GradePro GDT](#) ([Guyatt 2008](#)). We constructed one 'Summary of findings' table for the comparison dexamethasone versus control, reporting on postoperative systemic or wound infection, delayed wound healing, and glycaemic control in all participants (change from baseline to 2 to 24 hours) and in participants with diabetes (change from baseline to 10 to 24 hours). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), directness of evidence, heterogeneity of data, precision of effect estimates, and risk of publication bias. We resolved differences of opinion by discussion.

RESULTS

Description of studies

See [Summary of findings for the main comparison](#) and [Characteristics of included studies](#).

Results of the search

(See [Figure 1.](#))

Figure 1. Flow diagram.

We screened 5764 articles on the basis of titles and abstracts; we identified 441 for full-text screening, of which we included 38 articles. We found that 274 studies reported the appropriate study design; however, follow-up for these studies was only 24 to 48 hours, and we therefore subsequently excluded them.

Included studies

We included 38 RCTs, of which 27 reported on postoperative (systemic or wound) infection, nine reported on delayed wound healing, and 12 reported on glycaemic control. In total, 2750 participants received dexamethasone, and 2640 participants received a control intervention. We have described details of these studies in the [Characteristics of included studies](#) table.

Settings

These RCTs were conducted in the following countries: Australia, Austria, Chile, China, Denmark, Ireland, Italy, Japan, Mexico, New Zealand, Norway, Romania, South Korea, Switzerland, Turkey, UK, and the USA. We have provided below an outline of study characteristics.

Populations and types of surgery

All of the included studies were conducted in adults undergoing the following different types of surgery.

- Acromioclavicular joint resection or arthroscopic subacromial decompression repair surgery ([Bjornholdt 2014](#)).
- Arthroscopy ([Kawanishi 2014](#)).
- Cardiac surgery ([Murphy 2011a](#); [Rafiq 2014](#)).
- Colorectal surgery ([DREAMS trial collaborators](#); [Kirdak 2008](#); [Kurz 2015](#); [Zargar-Shoshtari 2009](#)).
- Craniotomy ([Karacinar 2009](#)).
- Different types of elective surgeries ([Abdelmalak 2013a](#); [Abdelmalak 2013b](#); [Tien 2016](#); [Wang 2009](#)).
- Gastric bypass surgery ([Nazar 2009](#)).
- Hysterectomy ([Murphy 2014](#)).
- Laminectomy with or without fusion ([Choi 2013](#)).
- Laparoscopic appendectomy ([Kleif 2017](#)).
- Laparoscopic cholecystectomy ([Bisgaard 2003](#); [Cowie 2010](#); [Ionescu 2014](#); [Nazar 2011](#); [Sanchez-Rodriguez 2010](#); [Wakasugi 2015](#)).
- Laparoscopic gynaecological surgery ([Corocan 2017](#)).
- Lumbar discectomy ([Nielsen 2015](#)).
- Lumbosacral spine surgery ([Kalappa 2017](#)).
- Mastectomy ([Cortes-Flores 2018](#)).
- Nissen fundoplication ([Schietroma 2010](#)).
- Osteotomy ([Abukawa 2017](#)).
- Thyroid surgery ([Doksrod 2012](#); [Feroci 2011](#); [Schietroma 2013](#); [Worni 2008](#); [Zhang 2016](#); [Zhou 2012](#)).

- Total hip or knee arthroplasty ([Backes 2013](#); [Koh 2013](#); [Lei 2017](#)).

Diabetes

It was unclear whether participants with diabetes were included in most of the studies.

Of the following 21 studies, participants with diabetes were eligible for inclusion in their respective studies ([Abdelmalak 2013a](#); [Abdelmalak 2013b](#); [Backes 2013](#); [Cortes-Flores 2018](#); [Doksrod 2012](#); [Feroci 2011](#); [Kleif 2017](#); [Koh 2013](#); [Kurz 2015](#); [Lei 2017](#); [Murphy 2011a](#); [Nazar 2011](#); [Nielsen 2015](#); [Rafiq 2014](#); [Sanchez-Rodriguez 2010](#); [Schietroma 2013](#); [Tien 2016](#); [Wakasugi 2015](#); [Worni 2008](#); [Zargar-Shoshtari 2009](#); [Zhou 2012](#)).

Of those 21 studies, four excluded participants with poorly controlled diabetes. [Backes 2013](#) excluded glycosylated haemoglobin (HbA1c) > 7.5%; [Cortes-Flores 2018](#) excluded uncontrolled diabetes mellitus (serum glycated haemoglobin level > 8%); [Murphy 2011a](#) did not define poorly controlled diabetes; and [Sanchez-Rodriguez 2010](#) excluded HbA1c > 8%.

Four of the 21 studies excluded participants treated with insulin ([Feroci 2011](#); [Nazar 2011](#); [Worni 2008](#); [Zhou 2012](#)).

Interventions and comparisons

Different doses of dexamethasone were used in the perioperative period. Six of the included studies used a low dose (4 to 5 mg) of dexamethasone ([Corocan 2017](#); [Ionescu 2014](#); [Karacinar 2009](#); [Kawanishi 2014](#); [Kurz 2015](#); [Murphy 2014](#)). Twenty-seven included studies used an intermediate dose of dexamethasone (8 to 10 mg) ([Abdelmalak 2013b](#); [Abukawa 2017](#); [Backes 2013](#); [Bisgaard 2003](#); [Bjornholdt 2014](#); [Cortes-Flores 2018](#); [Cowie 2010](#); [DREAMS trial collaborators](#); [Feroci 2011](#); [Kalappa 2017](#); [Karacinar 2009](#); [Kirdak 2008](#); [Kleif 2017](#); [Koh 2013](#); [Murphy 2014](#); [Nazar 2009](#); [Nazar 2011](#); [Rafiq 2014](#); [Sanchez-Rodriguez 2010](#); [Schietroma 2010](#); [Schietroma 2013](#); [Tien 2016](#); [Wakasugi 2015](#); [Wang 2009](#); [Worni 2008](#); [Zargar-Shoshtari 2009](#); [Zhou 2012](#)). Seven groups studied a high dose of dexamethasone (12 to 20 mg) ([Abdelmalak 2013a](#); [Doksrod 2012](#); [Choi 2013](#); [Karacinar 2009](#); [Lei 2017](#); [Murphy 2011a](#); [Nielsen 2015](#)).

Three studies used multiple doses of dexamethasone according to their study design; however, the total dose of dexamethasone did not exceed 20 mg ([Abdelmalak 2013a](#); [Lei 2017](#); [Murphy 2011a](#)). Four studies were conducted with an active comparator in the control group: ramosetron ([Koh 2013](#)), ondansetron ([Rafiq 2014](#); [Tien 2016](#)), or tropisetron ([Zhou 2012](#)). Two studies were conducted with an open-label control group, which received a placebo ([Ionescu 2014](#); [Kawanishi 2014](#)). [Backes 2013](#) and [DREAMS trial collaborators](#) conducted their studies in a

blinded fashion; however, the control group did not receive a placebo. All other studies were blinded and were conducted with a placebo group (Abdelmalak 2013a; Abdelmalak 2013b; Bisgaard 2003; Bjornholdt 2014; Choi 2013; Corocan 2017; Cortes-Flores 2018; Cowie 2010; Doksrod 2012; Feroci 2011; Kalappa 2017; Karacinar 2009; Kirdak 2008; Kleif 2017; Kurz 2015; Lei 2017; Murphy 2011a; Murphy 2014; Nazar 2009; Nazar 2011; Nielsen 2015; Sanchez-Rodriguez 2010; Schietroma 2010; Schietroma 2013; Wakasugi 2015; Wang 2009; Worni 2008; Zargar-Shoshtari 2009).

Funding

Five studies (six articles) received commercial funding (Abdelmalak 2013a; Abdelmalak 2013b; Backes 2013; Bjornholdt 2014; Kleif 2017; Kurz 2015); nine trial groups received funds from research grants (Abukawa 2017; Bisgaard 2003; Corocan 2017; Doksrod 2012; DREAMS trial collaborators; Ionescu 2014; Karacinar 2009; Tien 2016; Zargar-Shoshtari 2009); five studies were supported by the hospital or research department (Doksrod 2012; Murphy 2014; Nazar 2011; Nielsen 2015; Rafiq 2014); and 15 studies did not report on the source of funding (Choi 2013; Cowie 2010; Feroci 2011; Kawanishi 2014; Kirdak 2008; Koh 2013; Murphy 2011a; Nazar 2009; Sanchez-Rodriguez 2010; Schietroma 2010; Schietroma 2013; Wang 2009; Worni 2008; Zhang 2016; Zhou 2012). Two of the co-authors of Backes 2013 reported that they received royalties from DePuy. Authors of Corocan 2017 reported the following conflicts of interest: T.C. is a member of the executive committee of the ANZCA Clinical Trials Network (Australia and New Zealand College of Anaesthetists (ANZCA) CTN). M.P. is an editor of *Anaesthesia and Intensive Care* and is on the Editorial Board for *International Journal of Obstetric Anesthesia*, *Obstetric Anesthesia Digest*, *Anesthesiology*, and *Pain Medicine*.

Outcomes

The definitions used for postoperative wound or systemic infection varied between included studies. Five studies - Abdelmalak 2013a; Ionescu 2014; Kirdak 2008; Kurz 2015; Wakasugi 2015 - scored this according to the Centers for Disease Control and Prevention (CDC) criteria (Horan 2008). Kleif 2017 used the Dindo-Clavien postoperative complications checklist (Dindo 2004). Koh 2013 used the Musculoskeletal Infection Society criteria (Parvizi 2011). Three studies used their own criteria, which included, for example, treatment with antibiotics (Backes 2013; Nielsen 2015; Zargar-Shoshtari 2009). Seventeen studies did not report the definition used for scoring a postoperative systemic or wound infection (Abukawa 2017; Bisgaard 2003; Bjornholdt 2014; Choi 2013; Corocan 2017; Cortes-Flores 2018; Doksrod 2012; DREAMS trial collaborators; Feroci 2011; Kawanishi 2014; Lei 2017; Rafiq 2014; Sanchez-Rodriguez 2010; Schietroma 2010; Schietroma 2013; Worni 2008; Zhou 2012).

Nine studies reported delayed wound healing (Bjornholdt 2014; Choi 2013; Doksrod 2012; Feroci 2011; Koh 2013; Kurz 2015; Rafiq 2014; Wakasugi 2015; Worni 2008), specifically assessed and reported by a surgeon performing follow-up, although the respective studies provided no definition for delayed wound healing. In Bjornholdt 2014, a physiotherapist, instead of the surgeon, was responsible for follow-up and diagnosis of delayed wound healing. Kurz 2015 used the Assessing Postoperative Wound Sepsis (ASEPSIS) system to quantify problems with delayed wound healing (Byrne 1989).

Sixteen studies reported glucose values in the perioperative period. However, they showed variability in the time points at which they measured glucose levels. Therefore, we chose to perform three subgroup analyses for the outcome glycaemic control: change from baseline to 2 to 12 hours postoperative, change from baseline to 24 hours postoperative, and change from baseline to 10 to 24 hours postoperative in participants with diabetes. Two studies reported change from baseline values (Abdelmalak 2013b; Tien 2016). Corocan 2017 and Murphy 2014 reported median glucose values with corresponding ranges and the median change from baseline, which we transformed to mean glucose values with standard deviations. Eight studies did not report the change from baseline (Cowie 2010; Doksrod 2012; Kalappa 2017; Murphy 2011a; Murphy 2014; Nazar 2009; Wang 2009; Zhang 2016). We therefore calculated the change from baseline using available data from these studies. We included nine studies in the meta-analysis for change from baseline within 12 hours after dexamethasone administration (Abdelmalak 2013b; Doksrod 2012; Kalappa 2017; Karacinar 2009; Murphy 2011a; Murphy 2014; Nazar 2009; Tien 2016; Wang 2009), as well as six studies for the analysis of change from baseline at 24 hours postoperatively (Corocan 2017; Cowie 2010; Kalappa 2017; Murphy 2014; Tien 2016; Zhang 2016). We performed a subgroup analysis for change from baseline 10 to 24 hours after surgery in participants with diabetes (Murphy 2014; Nazar 2009; Tien 2016).

Four studies evaluated the frequency of re-admission (Ionescu 2014; Kirdak 2008; Sanchez-Rodriguez 2010; Zargar-Shoshtari 2009).

Most often, study authors did not describe baseline CRP levels; however, we expected these levels to be low. Therefore, we assessed only the CRP level measured at 24 hours after surgery (Abdelmalak 2013a; Kirdak 2008; Lei 2017; Zargar-Shoshtari 2009).

We defined mortality as all-cause mortality at 30 days. Seven studies reported this outcome (Abdelmalak 2013a; Cortes-Flores 2018; DREAMS trial collaborators; Feroci 2011; Kirdak 2008; Kurz 2015; Rafiq 2014).

Excluded studies

We excluded 20 studies based on insufficient length of follow-up, most often between two and seven days (Abbaszadeh 2012; Al-Shehri 2004; Bianchin 2007; Coloma 2001; Halvorsen 2003;

Ho 2001; Jung 2013; Kara 1999; Lei 2018a; Liu 2001; Nasiri 2013; Pasternak 2004; Sethi 2016; Snall 2014; Thangaswamy 2010; Tolver 2012; Wang 2000; Wang 2001; Weber 1994; Wu 2007). In three studies, participants received dexamethasone based on a clinical decision (Pasternak 2004; Sethi 2016; Snall 2014). Thus these studies were not randomized; therefore we did not include them (Characteristics of excluded studies).

Studies awaiting classification

Two studies are awaiting classification (Ko-Iam 2015; Simogai 2016). We could not retrieve the full text of these articles (Characteristics of studies awaiting classification).

Ongoing studies

We identified three ongoing studies, which will contribute to the body of evidence when they have been completed (Kitcharanant 2016; Sidhu 2017; Wang 2018; Characteristics of ongoing studies).

Risk of bias in included studies

Figure 2 and Figure 3 show the overall risk of bias and the risk of bias for each study separately. We downgraded the level of evidence for studies that we judged to be at high risk of bias. An expression of concern has been issued for Schietroma 2013. Scientific and ethical concerns have been raised regarding this paper; therefore we have set all domains to high risk of bias (Piccirillo 2017).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdelmalak 2013a	?	?	?	?	?	?	?
Abdelmalak 2013b	?	?	?	?	?	?	?
Abukawa 2017	?	?	?	?	?	?	?
Backes 2013	?	?	?	?	?	?	?
Bisgaard 2003	?	?	?	?	?	?	?
Bjornholdt 2014	?	?	?	?	?	?	?
Choi 2013	?	?	?	?	?	?	?
Corocan 2017	?	?	?	?	?	?	?
Cortes-Flores 2018	?	?	?	?	?	?	?
Cowie 2010	?	?	?	?	?	?	?
Doksrod 2012	?	?	?	?	?	?	?
DREAMS trial collaborators	?	?	?	?	?	?	?
Feroci 2011	?	?	?	?	?	?	?
Ionescu 2014	?	?	?	?	?	?	?
Kalappa 2017	?	?	?	?	?	?	?
Karacinar 2009	?	?	?	?	?	?	?
Kawanishi 2014	?	?	?	?	?	?	?
Kirdak 2008	?	?	?	?	?	?	?
Kleif 2017	?	?	?	?	?	?	?
Koh 2013	?	?	?	?	?	?	?
Kurz 2015	?	?	?	?	?	?	?
Lei 2017	?	?	?	?	?	?	?
Murphy 2011a	?	?	?	?	?	?	?
Murphy 2014	?	?	?	?	?	?	?
Nazar 2009	?	?	?	?	?	?	?
Nazar 2011	?	?	?	?	?	?	?
Nielsen 2015	?	?	?	?	?	?	?
Rafiq 2014	?	?	?	?	?	?	?
Sanchez-Rodriguez 2010	?	?	?	?	?	?	?
Schietroma 2010	?	?	?	?	?	?	?
Schietroma 2013	?	?	?	?	?	?	?
Tien 2016	?	?	?	?	?	?	?
Wakasugi 2015	?	?	?	?	?	?	?
Wang 2009	?	?	?	?	?	?	?
Worni 2008	?	?	?	?	?	?	?
Zargar-Shoshtari 2009	?	?	?	?	?	?	?
Zhang 2016	?	?	?	?	?	?	?
Zhou 2012	?	?	?	?	?	?	?

Random sequence generation

Twenty-seven of the 38 studies used a computer-generated list for randomization (Abdelmalak 2013a; Abdelmalak 2013b; Backes 2013; Bisgaard 2003; Bjornholdt 2014; Choi 2013; Corocan 2017; Cowie 2010; Doksrod 2012; DREAMS trial collaborators; Feroci 2011; Ionescu 2014; Kalappa 2017; Kleif 2017; Koh 2013; Kurz 2015; Murphy 2011a; Murphy 2014; Nazar 2009; Nazar 2011; Nielsen 2015; Schietroma 2010; Tien 2016; Wakasugi 2015; Worni 2008; Zargar-Shoshtari 2009; Zhou 2012). Ten studies failed to report on the randomization process; therefore their risk of bias was unclear (Abukawa 2017; Cortes-Flores 2018; Karacinar 2009; Kawanishi 2014; Kirdak 2008; Lei 2017; Rafiq 2014; Sanchez-Rodriguez 2010; Wang 2009; Zhang 2016). However, overall we judged these studies to be at high risk of bias and downgraded their level of evidence (Abukawa 2017; Karacinar 2009; Schietroma 2013; Wang 2009; Zhang 2016).

Allocation

Twenty-four studies had adequate allocation concealment, usually with sequentially numbered opaque sealed envelopes (Abdelmalak 2013a; Abdelmalak 2013b; Backes 2013; Bisgaard 2003; Bjornholdt 2014; Corocan 2017; Doksrod 2012; DREAMS trial collaborators; Kawanishi 2014; Kirdak 2008; Kleif 2017; Kurz 2015; Lei 2017; Murphy 2011a; Murphy 2014; Nazar 2011; Nielsen 2015; Rafiq 2014; Sanchez-Rodriguez 2010; Schietroma 2010; Tien 2016; Wakasugi 2015; Worni 2008; Zargar-Shoshtari 2009). Nine studies did not describe the randomization and allocation process other than that the study was a randomized study (Abukawa 2017; Cortes-Flores 2018; Cowie 2010; Ionescu 2014; Kalappa 2017; Karacinar 2009; Nazar 2009; Wang 2009; Zhang 2016). We judged these studies to have unclear risk of selection bias. Five studies had high risk of selection bias (Choi 2013; Feroci 2011; Koh 2013; Schietroma 2013; Zhou 2012).

Blinding

Fifteen studies clearly stated the blinding process for patients and personnel and had low risk of performance bias (Bjornholdt 2014; Choi 2013; Corocan 2017; Doksrod 2012; Feroci 2011; Kirdak 2008; Kleif 2017; Kurz 2015; Murphy 2011a; Murphy 2014; Nielsen 2015; Schietroma 2010; Wakasugi 2015; Worni 2008; Zargar-Shoshtari 2009). All placebo-controlled studies used normal saline in an identical syringe as placebo. In 26 studies, the outcome assessor was adequately blinded to avoid detection bias (Abdelmalak 2013a; Abdelmalak 2013b; Backes 2013; Bisgaard 2003; Bjornholdt 2014; Choi 2013; Corocan 2017; Cowie 2010; DREAMS trial collaborators; Feroci 2011; Kirdak 2008; Kleif 2017; Koh 2013; Kurz 2015; Lei 2017; Murphy 2011a; Murphy

2014; Nazar 2009; Nazar 2011; Nielsen 2015; Schietroma 2010; Schietroma 2013; Wakasugi 2015; Worni 2008; Zargar-Shoshtari 2009; Zhou 2012). Of the 28 studies reporting on postoperative infections, four did not report whether the outcome assessor was blinded, and we judged them to have unclear risk of detection bias (Abukawa 2017; Cortes-Flores 2018; Doksrod 2012; Sanchez-Rodriguez 2010). We judged three studies to have high risk of detection bias, as study authors stated that the outcome assessors in these studies were not blinded (Ionescu 2014; Kawanishi 2014; Rafiq 2014).

Incomplete outcome data

Seven studies reported no information about dropouts or withdrawals during the study (and we therefore judged them to have high risk of attrition bias) (Abukawa 2017; Kalappa 2017; Karacinar 2009; Nazar 2011; Sanchez-Rodriguez 2010; Wang 2009; Zhang 2016). We judged three studies to have unclear risk of attrition bias; it appeared that no dropouts occurred (Nazar 2009; Cowie 2010), or that more dropouts occurred in the placebo group (Bjornholdt 2014). The remaining studies had low risk of attrition bias (Abdelmalak 2013a; Abdelmalak 2013b; Backes 2013; Bisgaard 2003; Choi 2013; Corocan 2017; Cortes-Flores 2018; Doksrod 2012; DREAMS trial collaborators; Feroci 2011; Ionescu 2014; Kawanishi 2014; Kirdak 2008; Kleif 2017; Koh 2013; Kurz 2015; Lei 2017; Murphy 2011a; Murphy 2014; Nielsen 2015; Rafiq 2014; Schietroma 2010; Tien 2016; Wakasugi 2015; Worni 2008; Zargar-Shoshtari 2009; Zhou 2012).

Selective reporting

Twenty-one studies had unclear risk of reporting bias, as the study protocol was not published or registered in a trial registry (Abukawa 2017; Backes 2013; Bisgaard 2003; Choi 2013; Cowie 2010; Ionescu 2014; Kalappa 2017; Karacinar 2009; Kawanishi 2014; Kirdak 2008; Koh 2013; Murphy 2011a; Nazar 2009; Nazar 2011; Sanchez-Rodriguez 2010; Schietroma 2010; Tien 2016; Wakasugi 2015; Wang 2009; Zhang 2016; Zhou 2012). Abdelmalak 2013b performed a subgroup analysis of the original data from Abdelmalak 2013a. This subgroup analysis was not prespecified in the study protocol, which was published at the start of the trial. We judged this study to have unclear risk of reporting bias. We identified Kurz 2015 as having high risk of reporting bias. The study protocol was registered; however, not all prespecified outcomes were reported in the final manuscript, and new secondary outcomes were added to the analyses. Furthermore, the study protocol of Cortes-Flores 2018 was registered after enrolment of participants. The primary outcome and the sample size calculation were changed during the course of the study. We judged this study to be at high risk of reporting bias.

Other potential sources of bias

We created a funnel plot for our primary outcome: postoperative wound or systemic infection. This plot showed a little asymmetry towards less infection in smaller studies. This could indicate a small risk of positive publication bias (Figure 4).

Figure 4. Funnel plot of comparison: 1 dexamethasone versus control, outcome: 1.1 Postoperative systemic or wound infection.

Effects of interventions

See: [Summary of findings for the main comparison Dexamethasone compared to control in surgical patients](#)
All included studies can be found in [Summary of findings for the main comparison](#). The assessment of the quality of evidence is shown in this table.

Primary outcomes

1. Postoperative wound or systemic infection

[Analysis 1.1](#) displays the effect of dexamethasone on postoperative wounds or systemic infection.

Two studies reported on postoperative wound or systemic infections but without sufficient length of follow-up; therefore we did not include these studies in the quantitative analysis of postoperative infections ([Murphy 2011a](#); [Zhang 2016](#)).

We pooled the results of 27 studies to estimate the effects of dexamethasone on postoperative wounds or systemic infection rates ([Abdelmalak 2013a](#); [Abukawa 2017](#); [Backes 2013](#); [Bisgaard 2003](#);

Bjornholdt 2014; Choi 2013; Corocan 2017; Cortes-Flores 2018; Doksrod 2012; DREAMS trial collaborators; Feroci 2011; Ionescu 2014; Kawanishi 2014; Kirdak 2008; Kleif 2017; Koh 2013; Kurz 2015; Lei 2017; Nielsen 2015; Rafiq 2014; Sanchez-Rodriguez 2010; Schietroma 2010; Schietroma 2013; Wakasugi 2015; Worni 2008; Zargar-Shoshtari 2009; Zhou 2012). These studies included 4931 participants in total: 2516 in the intervention group and 2415 in the control group. Researchers found no between-group differences in the rate of postoperative wounds or systemic infection (Peto odds ratio (OR) 1.01, 95% confidence interval (CI) 0.80 to 1.27; 4931 participants; $I^2 = 27\%$). In the subgroup analysis, we found no differences between different dosages (4 to 5 mg, 8 to 10 mg, and 12 to 20 mg) of dexamethasone. The sensitivity analysis, which excluded studies with high risk of bias, did not yield any different results (Analysis 1.7).

We downgraded the quality of evidence by one level to moderate owing to imprecision (few events). We decided not to downgrade for high risk of bias, as the sensitivity analysis showed that studies with high risk of bias had little effect on the results.

Two studies used multiple doses of dexamethasone in their study design (Analysis 1.2). Results show no differences between single (Peto OR 0.96, 95% CI 0.76 to 1.22; 4410 participants; 25 studies) and multiple doses of dexamethasone (Peto OR 1.51, 95% CI 0.75 to 3.02; 521 participants).

2. Delayed wound healing

Analysis 1.3 displays the effect of dexamethasone on delayed wound healing.

One study assessed delayed wound healing using a different scoring system and not as a dichotomous outcome; therefore we did not include this study in the quantitative analysis of delayed wound healing (Kurz 2015).

We included eight studies (Bjornholdt 2014; Choi 2013; Doksrod 2012; Feroci 2011; Koh 2013; Rafiq 2014; Wakasugi 2015; Worni 2008), and we pooled the results of 1072 participants: 542 in the intervention group and 530 in the control group. In four studies including 302 participants (Bjornholdt 2014; Choi 2013; Feroci 2011; Worni 2008), delayed wound healing did not occur in either group. Dexamethasone did not increase the incidence of delayed wound healing (Peto OR 0.99, 95% CI 0.28 to 3.43; 1072 participants, eight studies; $I^2 = 0\%$). We scored this outcome as having low-quality evidence. Three studies had high risk of bias in the selection, performance, or detection domain (Feroci 2011; Koh 2013; Rafiq 2014). Subsequently, we downgraded the quality of evidence by two levels - one level for high risk of bias and one level for imprecision (small number of events).

In the subgroup analysis, we did not find differences between different dosages of dexamethasone (8 to 10 mg dexamethasone: Peto OR 0.98, 95% CI 0.24 to 3.96; 912 participants, six studies; $I^2 = 0\%$ vs 12 to 20 mg dexamethasone: Peto OR 1.0, 95% CI 0.06 to 16.21; 160 participants, two studies; $I^2 =$ not applicable).

We were not able to perform a sensitivity analysis that excluded trials with high risk of bias. Only three trials without high risk of bias remained (Bjornholdt 2014; Doksrod 2012; Worni 2008). Two of these trials were zero-event trials (Bjornholdt 2014; Worni 2008), and Doksrod 2012 reported one event in either group.

3. Glycaemic response

We analysed glycaemic response in three subgroups (Analysis 1.4). We could not include four studies in the quantitative analyses (Backes 2013; Choi 2013; Feroci 2011; Nazar 2011).

Feroci 2011 reported only postoperative glucose values, without baseline levels. We contacted the corresponding author but did not receive a response. Backes 2013 reported glucose values for participants with and without diabetes receiving dexamethasone; however, researchers reported no glucose values for the control group. Again, we contacted the corresponding author but did not receive a response. Nazar 2011 showed only glucose values in a graph. We contacted the corresponding author, but we were unable to retrieve these results. One study reported glucose levels 18 hours postoperatively, which was outside the range of our prespecified outcome measures (not within 2 to 12 hours or 24 hours after dexamethasone administration); therefore we did not include it in the meta-analysis (Choi 2013).

3a. Glycaemic response within 2 to 12 hours

Change from baseline was significantly larger in the dexamethasone group than in the control group. We used a random-effects model owing to moderate heterogeneity. We included 10 studies for this outcome (mean difference (MD) 13 mg/dL, 95% CI 6 to 21; 595 participants; $I^2 = 50\%$) (Abdelmalak 2013b; Cowie 2010; Doksrod 2012; Kalappa 2017; Karacinar 2009; Murphy 2011a; Murphy 2014; Nazar 2009; Tien 2016; Wang 2009). The quality of evidence was low. We downgraded the quality of evidence for high risk of bias and imprecision (wide confidence intervals).

The sensitivity analysis excluding skewed data showed similar results: MD 17 mg/dL, 95% CI 9 to 25; eight studies, 419 participants; $I^2 = 47\%$.

We did not include Feroci 2011 in the meta-analysis owing to lack of baseline measurements. Researchers found significantly higher glucose values in the dexamethasone group than in the control group at eight hours postoperatively.

3b. Glycaemic response at 24 hours

Six studies including 355 participants reported on this outcome (Corocan 2017; Cowie 2010; Kalappa 2017; Murphy 2014; Tien 2016; Zhang 2016). Change from baseline was greater in the dexamethasone group than in the control group (MD 21 mg/dL, 95% CI -0.2 to 43; 450 participants; $I^2 = 92\%$). We downgraded the quality of evidence by three levels to very low quality owing to

high risk of bias, significant heterogeneity, and small sample sizes with large confidence intervals.

We classified [Zhang 2016](#) as having overall high risk of bias because study authors provided no information in the report about randomization strategy, blinding, and dropouts. This was the largest study for this outcome. When we excluded this study, the results did not change significantly (MD 23 mg/dL, 95% CI -5 to 51; 217 participants; $I^2 = 92\%$). [Murphy 2014](#) used a lower dosage (4 mg) of dexamethasone, and excluding this study resulted in a greater change from baseline (25 mg/dL, 95% CI 1 to 50; 383 participants; $I^2 = 93\%$).

[Choi 2013](#) found a 19 mg/dL increase in glucose 18 hours after surgery when dexamethasone was administered compared to 4 mg/dL in the control group. However, no statistical analysis was performed on these data. [Feroci 2011](#) found no differences in glucose values at 24 hours postoperatively between participants receiving dexamethasone and those given normal saline. [Backes 2013](#) found a reduction in glucose (5.0 mg/dL) 24 hours after surgery among participants without diabetes receiving dexamethasone.

3c. Glycaemic response within 10 to 24 hours in participants with diabetes

We found four studies reporting on glycaemic response within 10 to 24 hours among participants with diabetes ([Backes 2013](#); [Nazar 2009](#); [Nazar 2011](#); [Tien 2016](#)). [Nazar 2011](#) depicted glucose values only in a graph, and we did not include this study in the quantitative analysis. However, among participants with diabetes receiving dexamethasone, researchers found a maximum difference in glucose of 34 mg/dL at 10 hours after dexamethasone administration. The graph shows a smaller maximum difference in glucose for participants with diabetes not receiving dexamethasone. Study authors did not report whether this difference was significant. [Backes 2013](#) did not report glucose values for the control group and therefore could not be included in the quantitative analysis. However, researchers found that participants with diabetes receiving dexamethasone had a change from baseline of 4.8 mg/dL at 24 hours after the intervention.

Our meta-analysis showed that among participants with diabetes, the change from baseline was significantly greater in the dexamethasone group than in the control group (MD 32 mg/dL, 95% CI 15 to 49; 74 participants, two studies; $I^2 = 0\%$). We downgraded the quality of evidence by three levels to very low, as both studies had high risk of bias and included a very small sample size with very large confidence intervals.

Secondary outcomes

1. Length of hospital stay

Fourteen studies reported on length of hospital stay. We did not include three of these studies, as they did not report a standard deviation and we were unable to retrieve these results ([Schietroma 2010](#); [Schietroma 2013](#); [Zargar-Shoshtari 2009](#)). Thus, we were able to include 11 studies in the quantitative analysis with a total of 1794 participants for whom this outcome was reported ([Backes 2013](#); [Bisgaard 2003](#); [Feroci 2011](#); [Kirdak 2008](#); [Kurz 2015](#); [Lei 2017](#); [Murphy 2011a](#); [Rafiq 2014](#); [Sanchez-Rodriguez 2010](#); [Wakasugi 2015](#); [Worni 2008](#)). However, pooling these data showed high heterogeneity (81%) combined with inconsistency in the direction of effect. Therefore, we decided not to perform the meta-analysis. We downgraded the quality of evidence by three levels to very low quality owing to high risk of bias, imprecision, and inconsistency.

2. Re-admission

We pooled the data on 339 participants ([Ionescu 2014](#); [Kirdak 2008](#); [Sanchez-Rodriguez 2010](#); [Zargar-Shoshtari 2009](#)). Use of dexamethasone was not associated with greater risk of re-admission (risk ratio (RR) 1.18, 95% CI 0.43 to 3.25; 339 participants; $I^2 = 0\%$). The largest study contributing to this outcome had high risk of bias ([Sanchez-Rodriguez 2010](#)). We scored the quality of evidence for this outcome as very low (downgraded by three levels) owing to high risk of bias, imprecision, and significant heterogeneity (Analysis 1.5).

3. C-reactive protein (CRP) levels one day postoperatively

Six studies reported on CRP levels one day postoperatively ([Abdelmalak 2013a](#); [Bisgaard 2003](#); [Kirdak 2008](#); [Schietroma 2010](#); [Schietroma 2013](#); [Zargar-Shoshtari 2009](#)). Three of these studies displayed CRP levels only in a figure, without error bars ([Bisgaard 2003](#); [Schietroma 2010](#); [Schietroma 2013](#)). We contacted the corresponding authors to retrieve the original data, but we were unable to retrieve these data. All figures showed lower CRP levels in the dexamethasone group at day one postoperatively. The other four studies, with a total of 468 participants, reported CRP levels at one day postoperatively ([Abdelmalak 2013a](#); [Kirdak 2008](#); [Lei 2017](#); [Zargar-Shoshtari 2009](#)). Owing to the imprecise estimate, high heterogeneity, and inconsistency in the direction of effect, we decided not to conduct a meta-analysis for this outcome but only described the outcome data from the different trials. [Abdelmalak 2013a](#) and [Lei 2017](#) reported that CRP increased significantly more in the control group than in the dexamethasone group. [Kirdak 2008](#) and [Zargar-Shoshtari 2009](#) reported no differences in CRP levels between the dexamethasone and control groups at postoperative day one.

We downgraded the quality of evidence by three levels to very low owing to high risk of bias, inconsistency, and imprecision.

4. Mortality

Seven studies including 2646 participants reported 30-day mortality scores (Abdelmalak 2013a; Cortes-Flores 2018; DREAMS trial collaborators; Feroci 2011; Kirdak 2008; Kurz 2015; Rafiq 2014). Perioperative dexamethasone was not associated with higher 30-day mortality (Peto OR 0.80, 95% CI 0.38 to 1.66; $I^2 = 0\%$). Owing to high risk of bias and imprecision, we downgraded the quality of evidence to low (Analysis 1.6).

DISCUSSION

Summary of main results

The objective of this systematic review was to assess whether intraoperative use of a low dose of dexamethasone increased the risk of postoperative systemic or wound infection, delayed wound healing, and hyperglycaemia in surgical patients. We identified 27 randomized controlled trials (RCTs) that reported on postoperative systemic or wound infection, eight trials that reported on delayed wound healing, and 11 studies that reported on glycaemic response, to help us answer our questions. We found that a single dose of dexamethasone did not increase the risk of postoperative systemic or wound infection (Peto odds ratio (OR) 1.01, 95% confidence interval (CI) 0.80 to 1.27; 4931 participants, 27 studies; $I^2 = 27\%$, low-quality evidence) and did not increase the risk of delayed wound healing (Peto OR 0.99, 95% CI 0.28 to 3.43; 1072 participants, eight studies; $I^2 = 0\%$; low-quality evidence) but significantly increased glucose values in the first 12 hours after surgery (mean difference (MD) 13.31 mg/dL, 95% CI 5.91 to 20.71; 595 participants, 10 studies; $I^2 = 50\%$; low-quality evidence).

Overall completeness and applicability of evidence

Postoperative infection

We included studies with a wide spectrum of surgical interventions, and this increases the applicability of our findings to everyday practice. Infection rates differed between studies, ranging from 0% to 18% and reflecting the different surgical populations. We observed no statistical heterogeneity for this outcome; however, we noted a large variety of definitions for postoperative (wound or systemic) infection. Incidences of postoperative infection in the individual studies are likely to be an underestimation, as most studies were very small. However, larger studies and this sensitivity analysis also did not show any effect of dexamethasone on postoperative infection, indicating the validity of current results (Analysis 1.7; Abdelmalak 2013a; DREAMS trial collaborators). Nonetheless,

the required information size probably exceeds currently available evidence, and further studies are needed for a definitive conclusion.

Delayed wound healing

Only eight studies included in this meta-analysis reported on delayed wound healing, with an incidence of 0 to 2% (Bjornholdt 2014; Choi 2013; Doksrod 2012; Feroci 2011; Koh 2013; Rafiq 2014; Wakasugi 2015; Worni 2008), as opposed to incidences of 7% to 32% that have been reported in observational and retrospective studies (Althumairi 2016; SanGiovanni 2016). Participants at increased risk for delayed wound healing (e.g. participants with diabetes, those on immunosuppressive drugs) were not included in the randomized studies reporting on delayed wound healing included in this meta-analysis; therefore our findings should be extrapolated to the clinical setting with care.

Glycaemic response

Twelve studies measured blood glucose values in the perioperative period when dexamethasone was given (Abdelmalak 2013b; Corocan 2017; Cowie 2010; Doksrod 2012; Kalappa 2017; Karacinar 2009; Murphy 2011a; Murphy 2014; Nazar 2009; Tien 2016; Wang 2009; Zhang 2016). Only one study adequately reported on the relation between blood glucose values and the incidence of postoperative complications (Doksrod 2012). This meta-analysis showed that glucose was 13 mg/dL higher when participants had received dexamethasone than when participants had not received dexamethasone in the first 12 hours after surgery. In a clinical setting, we can therefore expect a mild increase in glucose values when dexamethasone is administered. However, as shown above, this mild increase in glucose is probably not associated with increased risk of postoperative infection.

For patients with diabetes, very limited evidence is available on the glycaemic response to dexamethasone. We could identify only two studies reporting on this outcome (74 participants) (Nazar 2009; Tien 2016). This group is too small to support definitive conclusions. However, data so far suggest an increase in glucose values when dexamethasone is administered in the perioperative period to patients with diabetes mellitus.

Quality of the evidence

We used the GRADE criteria to assess the quality of evidence per outcome measure. We scored evidence on postoperative infections as moderate quality. We downgraded the level of evidence by one level owing to imprecision. The sensitivity analysis showed little to no effect of studies at high risk of bias; therefore we chose not to downgrade for high risk of bias. We scored delayed wound healing and glycaemic response in the first 12 hours as low-quality evidence because of high risk of bias and limited events per study,

leading to imprecision. We downgraded glycaemic response in participants with diabetes to very low quality of evidence - two levels for imprecision and one for high risk of bias. For glycaemic response at 24 hours, we downgraded the level of evidence to very low quality owing to imprecision, risk of bias, and inconsistency. Although we do not question the estimated direction of the effect, we are not confident that we found a reliable effect size for these outcomes. Additionally, we did not perform a meta-analysis for length of hospital stay and C-reactive protein (CRP) values owing to high heterogeneity and inconsistency in the direction of effect.

Potential biases in the review process

During the review process, we adhered to the guidelines set by the Cochrane Review Group to minimise bias.

This systematic review assessed the adverse effects of an incidental steroid load of dexamethasone in the surgical population. The incidence of adverse effects reported in individual studies is generally low, which suggests that the incidence is actually low or that these effects are easily missed, especially in small studies. Pooling of data from small studies creates a much larger sample size. However, if adverse effects did not occur in the small studies, pooling results of these studies could reveal a falsely low incidence of adverse effects. In this systematic review, owing to the very low incidence of delayed wound healing and re-admission, the effect of dexamethasone on these outcomes might be underestimated.

We did an exploratory analysis and included [Murphy 2011a](#) and [Zhang 2016](#) in the analysis of postoperative wound or systemic infection, although follow-up for these studies was too short. This yielded similar results (Peto OR 1.01, 95% CI 0.80 to 1.27; 5273 participants, 29 studies; $I^2 = 23\%$; low-quality evidence, analysis not shown).

We included studies that reported on a large variety of surgical procedures. Each procedure has its own risk of postoperative infection. This could potentially bias our results. Two studies excluded patient groups with high risk of postoperative infection from analyses during the trial ([Choi 2013](#); [Rafiq 2014](#)). This could also bias the results of our meta-analysis.

Furthermore, the large variety of surgical procedures reported led to a large variety of surgical wounds, ranging from very small wounds (e.g. laparoscopy) to large wounds (sternotomy). Also the length of hospital stay depends significantly on the type of surgery performed.

When length of follow-up was not specifically stated in the full text of the article, we contacted the corresponding author, to minimise this bias. Still, we excluded 270 trials owing to insufficient follow-up for adverse events, which could have introduced selection bias. Also, four studies depicted glucose values and CRP only in a graph, not numerically ([Bisgaard 2003](#); [Nazar 2011](#); [Schietroma 2010](#); [Schietroma 2013](#)). We tried to obtain these results from the corresponding authors but learned that they are not available. Therefore, we reported these studies only descriptively.

Ongoing studies and those awaiting classification could have a potential impact on the body of evidence and thus are a potential source of bias ([Kitcharanant 2016](#); [Ko-lam 2015](#); [Sidhu 2017](#); [Simogai 2016](#); [Wang 2018](#)).

Finally, we think it is worth mentioning that an expression of concern has been issued for one of the included studies ([Schietroma 2013](#)). Scientific and ethical concerns surround this paper ([Piccirillo 2017](#)). As the paper is not retracted, we judged this paper to be at very high risk of bias.

Agreements and disagreements with other studies or reviews

The objective of this review was to assess the effects of a steroid load of dexamethasone on postoperative systemic or wound infection, delayed wound healing, and blood glucose change in adult surgical patients. Owing to the multiple indications for dexamethasone, previous systematic reviews on the beneficial effects of dexamethasone were subject to selective outcome reporting bias regarding the adverse effects. [Waldron 2013](#) and [De Oliveira 2011](#) conducted a systematic review on the effects of dexamethasone on postoperative pain; both assessed adverse effects as secondary outcomes and found no increase in the risk of infection. [Waldron 2013](#) also performed an analysis on delayed wound healing as a secondary outcome and found no increase in the risk of delayed wound healing. [De Oliveira 2011](#) was unable to perform an analysis on delayed wound healing, as review authors included only zero-event trials in this systematic review. [Waldron 2013](#) also looked at the glycaemic effect of dexamethasone after 24 hours, which showed mildly higher blood glucose levels in the dexamethasone group.

More recently, a meta-analysis was performed to examine the safety of glucocorticosteroids in non-cardiac surgery. This meta-analysis included studies with dexamethasone, methylprednisolone, or hydrocortisone. [Toner 2017](#) assessed the effect on the incidence of 'any infection' as a primary outcome and assessed glucose and length of hospital stay as secondary outcomes. Similar to our study, these review authors found no increase in the risk of infection (odds ratio (OR) 0.8, 95% CI 0.6 to 1.2), a higher glucose value 12 hours after surgery in patients without diabetes (weighted mean difference (WMD) 14 mg/dL, 95% CI 2.0 to 25.9), and no difference in length of stay (WMD -0.3 days, 95% CI -1.4 to 0.9). Given that the incidence of postoperative infection is low, and because it is easily missed in small studies, it could be helpful to review retrospective evidence on this topic. [Assante 2015](#) identified five large retrospective studies, which included from 235 to 3449 participants and assessed the effect of dexamethasone on postoperative infection. Four studies found no increase in the risk of postoperative infection in the dexamethasone group ([Bolac 2013](#); [Corcoran 2010](#); [Eberhart 2011a](#); [Gali 2012](#)). One study found an increased risk of postoperative infection; however, researchers excluded specific types of infections from the analysis ([Percival 2010](#)). In summary, available evidence from larger studies suggests

no harmful effect of an incidental steroid load of dexamethasone with respect to risk of postoperative infection.

In this systematic review, we assessed dexamethasone administered only via the intravenous route. Only two studies assessed the effects of oral dexamethasone on postoperative infection and glycaemic response (Eberhart 2006; Eberhart 2011b). Both studies have presented findings consistent with the conclusions provided in this systematic review. Adding these studies to the respective analysis showed the same results (postoperative systemic or wound infection: Peto OR 1.01, 95% CI 0.80 to 1.27; 5082 participants, 28 studies; $I^2 = 23\%$; low-quality evidence).

On the other hand, we consistently found that dexamethasone increased blood glucose levels, which could impair leucocyte function and formation of epithelia in the wound (Durmus 2003). However, as this meta-analysis now shows that a single dose of dexamethasone in patients without diabetes does not increase the risk of infection, mild transient hyperglycaemia induced by dexamethasone probably is not clinically relevant. One has to keep in mind that patients with higher risk of postoperative infection and delayed wound healing (e.g. patients with diabetes) probably were not included in most of the included trials. Therefore, further research is needed to establish the safety of dexamethasone, especially in high-risk patients. The PADDI trial is currently recruiting patients (Sidhu 2017). This trial aims to assess the impact of dexamethasone on surgical site infection 30 days after surgery, with stratification for diabetes status. Researchers randomize patients undergoing surgery under general anaesthesia to receive either 8 mg of dexamethasone or placebo during the perioperative period. They aim to include 8880 adults. As of 26 March 2018, 51 sites were recruiting and 4310 participants had been enrolled.

AUTHORS' CONCLUSIONS

Implications for practice

A single dose of dexamethasone probably does not increase the risk for postoperative infection. It is uncertain whether it has an effect on delayed wound healing in the general surgical population because of imprecision in trial results. Participants with increased

risk for delayed wound healing (e.g. participants with diabetes, those on immunosuppressive drugs) were not included in the randomized studies reporting on delayed wound healing included in this meta-analysis; therefore, our findings should be extrapolated to the clinical setting with caution. Furthermore one has to keep in mind that dexamethasone induces a mild increase in glucose. For patients with diabetes, very limited evidence suggests a more pronounced increase in glucose. Whether this influences wound healing in a clinically relevant way remains to be established. Three studies awaiting classification and two ongoing trials may alter the conclusions of this review, once assessed (Kitcharanant 2016; Ko-lam 2015; Sidhu 2017; Simogai 2016; Wang 2018).

Implications for research

Patients at high risk for delayed wound healing or postoperative infection are not adequately represented in the current body of evidence. Future research should focus on the clinical implications of dexamethasone-induced hyperglycaemia for patients with diabetes or at high risk for delayed wound healing. We are awaiting results of the PADDI trial, in which these patients are represented (Sidhu 2017).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abdelmalak 2013a

Methods	<ul style="list-style-type: none"> • Three-way factorial design randomized controlled trial • Enrolment was from 2007 to 2010. • Study was conducted in the USA.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patients over 40 years undergoing major elective surgery <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Intravenous or oral steroid therapy within 30 days • Any contraindications to the proposed interventions • ASA Physical Status (ASA PS) IV • Not fluent in English <p>381 patients (193 intervention and 188 placebo) over 40 years undergoing elective surgery were randomized</p> <ul style="list-style-type: none"> • Mean age: 64 years • 68% male • 26% with diabetes • 26% ASA II status • 63% ASA III status • 11% ASA IV status
Interventions	<p>Randomization for dexamethasone vs placebo, tight glycaemic control vs conventional control, deep anaesthetic depth vs light anaesthetic depth</p> <ul style="list-style-type: none"> • Intervention group received 8 mg dexamethasone 1 to 2 hours before surgery, 4 mg dexamethasone on day 1 postoperatively, and 2 mg dexamethasone on day 2 postoperatively. • Placebo group received normal saline at these time points.
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Composite endpoint of postoperative complications (sepsis, severe surgical site infection, myocardial infarction, heart failure, stroke, unstable ventricular arrhythmias, pulmonary embolism, pneumonia, respiratory failure, dialysis-dependent renal failure, large pleural or peritoneal effusions, major bleeding, major wound and surgical site healing complications, vascular graft thrombosis) • 30-day mortality • Postoperative infection assessed 30 days after surgery, according to Centers for Disease Control and Prevention (CDC) criteria <p>Secondary outcomes</p> <ul style="list-style-type: none"> • One-year mortality rates (obtained from electronic medical records) • CRP levels in the first 2 postoperative days. Blood samples were taken on day 1 and day 2 postoperatively. CRP was expressed as mg/L
Notes	<p>Sources of funding</p> <ul style="list-style-type: none"> • Aspect Medical (now Covidien) • Cleveland Clinic Research Project Committee

Abdelmalak 2013a (Continued)

	<ul style="list-style-type: none">• Anesthesiology Institute (departmental funds)• Abbott Laboratories Inc (limited support; supplied reagents for CRP analysis)• W.H.W.T. received grant support (money to the institution) in support of other studies from Abbott Laboratories• This is an investigator-initiated trial independent of the study sponsors. <p>Conflict of interest</p> <ul style="list-style-type: none">• None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer programme generated
Allocation concealment (selection bias)	Low risk	Web-based programme
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were blinded to dexamethasone. They were not blinded for randomization, result for tight glycaemic control, or anaesthetic depth
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Consistent with the protocol. Protocol was published.
Other bias	Unclear risk	Study was stopped early owing to futility.

Abdelmalak 2013b

Methods	<ul style="list-style-type: none"> Three-way factorial design randomized controlled trial Enrolment was from 2007 to 2010. Study was conducted in the USA.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Patients over 40 years undergoing major elective surgery <p>Exclusion criteria</p> <ul style="list-style-type: none"> Intravenous or oral steroid therapy within 30 days Any contraindications to proposed interventions ASA Physical Status (ASA PS) IV Not fluent in English <p>185 participants (90 intervention, 95 placebo) over 40 years old undergoing major</p>

	elective surgery were randomized to the conservative glycaemic control group <ul style="list-style-type: none">• 49 with diabetes (21 intervention, 28 placebo)• 136 without diabetes (69 intervention, 67 placebo)• Mean age: 64 years• 68% male• 30% ASA II status• 60% ASA III status• 10% ASA IV status	
Interventions	Randomization for dexamethasone vs placebo, tight glycaemic vs conventional control, deep anaesthetic depth vs light anaesthetic depth <ul style="list-style-type: none">• Intervention group received 8 mg dexamethasone 1 to 2 hours before surgery, 4 mg dexamethasone on day 1 postoperatively, and 2 mg dexamethasone on day 2 postoperatively.• Placebo group received normal saline at these time points.	
Outcomes	Primary outcome <ul style="list-style-type: none">• Hyperglycaemic surgical stress response, defined as the glucose change from preoperative to maximal intraoperative glucose concentration• Glycaemic response assessed in the subgroup that did not receive tight glycaemic control• Change from baseline to maximum intraoperative glucose	
Notes	Sources of funding <ul style="list-style-type: none">• Aspect Medical (now Covidien)• Cleveland Clinic Research Project Committee• Anesthesiology Institute (departmental funds)• Abbott Laboratories Inc (limited support; supplied reagents for CRP analysis)• W.H.W.T. received grant support (money to the institution) in support of other studies from Abbott Laboratories.• This is an investigator-initiated trial independent of the study sponsors. Conflict of interest <ul style="list-style-type: none">• None declared	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer programme generated
Allocation concealment (selection bias)	Low risk	Web-based programme
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were blinded for dexamethasone. They were not blinded for randomization, result for tight glycaemic control, or anaesthetic depth

Abdelmalak 2013b (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Unclear risk	Protocol was published. Glycaemic response during surgery was not a planned subanalysis
Other bias	Unclear risk	Study was stopped early owing to futility.

Abukawa 2017

Methods	<ul style="list-style-type: none"> Parallel-group randomized double-blind placebo-controlled trial All participants were operated on at Tokyo Medical University Hospital from 2007 to 2013.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ASA physical status I or II and agreement to participate in this study <p>Exclusion criteria</p> <ul style="list-style-type: none"> Underwent genioplasty and extraction of third molars in addition to BSSO Body mass index (BMI) > 25 Older than 50 years <p>24 adult patients undergoing bilateral sagittal split osteotomy were divided into 3 groups</p> <ul style="list-style-type: none"> 8 given 16 mg dexamethasone 8 given 8 mg dexamethasone 8 given 0 mg dexamethasone <p>Patients were not older than 50 years.</p> <ul style="list-style-type: none"> Patients with diabetes were eligible. Mean age: between 24 and 28 years Average surgery time: 226 to 263 minutes 8 given 8 mg dexamethasone 8 given 0 mg dexamethasone
Interventions	<p>16 mg dexamethasone vs 8 mg dexamethasone vs 0 mg dexamethasone</p> <ul style="list-style-type: none"> This was administered preoperatively; the exact time point was not described.
Outcomes	<p>Study endpoints were as follows.</p> <ul style="list-style-type: none"> Postoperative changes in buccal soft tissue thickness and masseter muscle thickness. Postoperative changes in MIO. Postoperative changes in sensation of the chin and lower lip region. Postoperative changes in blood test findings (CRP levels were measured at day 1 and day 2 postoperatively). Types of complications (steroid-induced psychosis, avascular osteonecrosis, non-union, and infection).

	Definition of postoperative infection was not stated. Length of follow-up: 2 years	
Notes	Sources of funding <ul style="list-style-type: none">Supported by Tokyo Medical University research grants Conflicts of interest <ul style="list-style-type: none">None of the study authors have any relevant financial relationship(s) with a commercial interest.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Inclusion period was 6 years; only 24 patients were included in the trial. No drop-outs were described
Selective reporting (reporting bias)	Unclear risk	Protocol was not published.
Other bias	Unclear risk	Unknown when postoperative infections were assessed and when they occurred

Backes 2013

Methods	<ul style="list-style-type: none"> Prospective randomized double-blind controlled trial Enrolment from 2011 to 2012 Conducted at a single centre in the USA
Participants	Inclusion criteria <ul style="list-style-type: none"> Patients undergoing elective, unilateral, total hip or knee arthroplasty Exclusion criteria <ul style="list-style-type: none"> Poorly controlled diabetes (HbA1c > 7.5% on pre-admission testing) Steroid or immunosuppressive drug use within 6 months of surgery Renal failure Hepatic failure

	<ul style="list-style-type: none">• Previous adverse effects from medications utilized in this study• 130 adult patients (41 intervention, 37 control) undergoing unilateral total hip or knee arthroplasty• Study had 3 treatment arms.<ul style="list-style-type: none">◦ One treatment arm (42 participants) was not included in meta-analysis owing to high dose of dexamethasone.• 10 patients with missing data• Mean age: 66 years	
Interventions	Dexamethasone (10 mg before induction and 4 mg ondansetron before skin closure) vs control (4 mg ondansetron before skin closure)	
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none">• Length of hospital stay (measured as number of calendar days patient was hospitalized)• Length of ambulation• Knee ROM• Cumulative hydromorphone PCA use• Daily hydrocodone consumption• Patient pain scores• Daily rescue anti-emetic consumption• Patient nausea/vomiting scores <p>Secondary outcomes</p> <ul style="list-style-type: none">• Changes in WBC• Changes in blood sugar• Wound complications• Other adverse effects <p>Definition of postoperative infection</p> <ul style="list-style-type: none">• Wound still draining at office follow-up, requiring any form of antibiotics or requiring return to the operating room <p>Total length of follow-up: 6 months</p>	
Notes	<p>Source of funding/Conflicts of interest</p> <ul style="list-style-type: none">• JP received funds from Depuy.• BC is a paid consultant for Smith and Nephew.	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomization
Allocation concealment (selection bias)	Low risk	Computer-based programme; person who was in charge of the randomization process was not involved in the follow-up of the trial

Backes 2013 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients, physiotherapists, and surgeons were blinded. Anaesthesiologists and nurses were not blinded No placebo was used. Therefore, surgeons could theoretically be aware of which study group participants belonged to
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 participants with incomplete data, equally divided over the groups
Selective reporting (reporting bias)	Unclear risk	Protocol not published. Glucose data were inconsistently reported
Other bias	Unclear risk	Not all expected data are reported.

Bisgaard 2003

Methods	<ul style="list-style-type: none"> Randomized double-blind placebo-controlled trial Enrolment from 1999 to 2000 at a single centre in Denmark
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Adult patients undergoing a laparoscopic cholecystectomy, ASA I-II <p>Exclusion criteria</p> <ul style="list-style-type: none"> ASA III-IV Age > 75 Pregnancy ECRP in history 1 month before operation Chronic pain disease Endocrine, liver, or renal disease Tranquillizer use 88 adult patients (40 intervention, 40 placebo, 8 excluded) undergoing laparoscopic cholecystectomy Mean age: 39 to 46 years Average duration of surgery: 68 to 78 minutes 75% female
Interventions	8 mg dexamethasone vs placebo (normal saline) 90 minutes before skin incision. Drug/placebo was drawn into a syringe and looked identical
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Fatigue/pain, measured as a VAS score <p>Secondary outcomes</p> <ul style="list-style-type: none"> PONV measured on a VRS Pulmonary function measured with a spirometer in sitting position before surgery

	and 1, 2, 3, 6, and 24 hours after surgery <ul style="list-style-type: none">• Convalescence measured as number of days away from work• CRP measured 6 and 24 hours after surgery• Body temperature measured 6 and 24 hours after surgery• 30-day morbidity follow-up was performed in all cases (no definition was given for the morbidity score).	
Notes	Source of funding <ul style="list-style-type: none">• Grants from the University of Copenhagen and the Danish Medical Research Council (journal no. 9902757) supported this study. Conflict of interest <ul style="list-style-type: none">• Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block-randomized computer-generated list
Allocation concealment (selection bias)	Low risk	Randomization code was kept separate and was not known to any of the investigators until the study was finished
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients and investigators were masked to group assignment. A nurse not participating in the study prepared and administered the study medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, treating physicians, and Investigators were masked to group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for dropouts were documented.
Selective reporting (reporting bias)	Unclear risk	No study protocol; however all outcome data consistently reported
Other bias	Unclear risk	Different analgesics and anaesthetics could be used; not standardized for all participants This has no effect on our primary outcome.

Methods	<ul style="list-style-type: none"> • Parallel-group placebo-controlled randomized controlled trial • Enrolment was conducted in 2011 at a single centre in Denmark.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Planned ambulatory shoulder surgery <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Planned nerve block • Concomitant other surgery • Age below 18 or above 90 years • Allergy to dexamethasone • Glaucoma • Untreated hypertension • Diabetes • Daily use of glucocorticoids • Daily use of strong opioids • Daily use of analgesics for reasons other than shoulder pain. • A secondary exclusion criterion was more extensive surgery than planned, such as repair of rotator cuff or labrum, biceps tenodesis, or arthrolysis <p>101 adult patients undergoing ambulatory acromioclavicular joint resection or arthroscopic subacromial decompression repair</p> <ul style="list-style-type: none"> • Study had 3 study arms. • <ul style="list-style-type: none"> ◦ 32 randomized to intervention, 26 analysed ◦ 37 randomized to placebo, 22 analysed ◦ Patients in the third study arm received too much dexamethasone and were not included in this meta-analysis (32 patients). • Mean age: 49 to 55 years • 50% male • 43% ASA classification status I • 57% ASA classification status II • Average duration of surgery: 55 to 56 minutes
Interventions	8 mg dexamethasone before induction vs placebo (normal saline) before induction
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Present pain intensity (NRS 0 to 10) 8 hours after surgery <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Pain intensity • Analgesic consumption and side effects recorded for 3 days after surgery • Complications such as infection or delayed wound healing were assessed after 2 months at outpatient follow-up with a hospital physiotherapist or by telephone <p>No definition was stated in the article for delayed wound healing or postoperative infection</p> <p>Follow-up: 2 months</p>
Notes	<p>Source of funding</p> <ul style="list-style-type: none"> • Supported by the Health Research Fund of Central Denmark Region • Family Hede Nielsen Foundation • Danish Rheumatism Association • Augustinus Foundation

Bjornholdt 2014 (Continued)

	Conflict of interest <ul style="list-style-type: none">• None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence table
Allocation concealment (selection bias)	Low risk	Pharmacy handled randomization and stored the randomization list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Pharmacy delivered identical bags with medication.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded. Pharmacy kept the list until follow-up was complete
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All dropouts were accounted for; however the group of dropouts in the placebo group was larger
Selective reporting (reporting bias)	Low risk	Protocol was published.
Other bias	Low risk	No apparent other bias

Choi 2013

Methods	<ul style="list-style-type: none"> Parallel randomized controlled trial Study was conducted in Korea. Unknown when enrolment took place
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Patients aged 20 and 70 years, with American Society of Anesthesiologists physical status I or II who were scheduled to undergo elective lumbar laminectomy with or without fusion <p>Exclusion criteria</p> <ul style="list-style-type: none"> Steroids administered within 24 hours before surgery or during 72 hours after surgery Any known allergy or contraindication to steroids or pregabalin Diabetes mellitus Previous lumbar spinal surgery Epidural injection for lumbosacral radiculopathy in the previous 6 weeks Preoperative use of antidepressants or anticonvulsants Body mass index > 35 kg/m²

	<ul style="list-style-type: none">● Impaired renal or hepatic function● Opioid dependent <p>.</p> <ul style="list-style-type: none">● 120 adult patients undergoing laminectomy with or without fusion were included.<ul style="list-style-type: none">○ 40 intervention○ 40 placebo○ The third intervention group (another placebo group) was not included in this meta-analysis (40 patients).● Mean age: 52 to 53 years● 50% male● 12 (16%) with diabetes included despite the exclusion criterion● Average duration of surgery: 134 to 151 minutes	
Interventions	16 mg dexamethasone plus pregabalin before induction vs 3.2 mL saline plus pregabalin before induction	
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none">● Postoperative pain intensity during rest and movement● Frequency of rescue analgesic administered during the first 72 hours after surgery <p>Secondary outcomes</p> <ul style="list-style-type: none">● Back and leg pain relief vs functional outcome in terms of daily activity performance over a 6-month period after surgery● Wound infection (definition for wound infection not described)● Delayed wound healing● Glucose values <p>Outcomes were assessed at 1, 3, and 6 months after surgery.</p>	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">● Not reported <p>Conflict of interest</p> <ul style="list-style-type: none">● None declared	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization table
Allocation concealment (selection bias)	High risk	Open table; unknown who kept this
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Staff nurse not participating in the study prepared study drugs - identical looking
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Surgeon assessing outcome was unaware of randomization.

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts and withdrawals were provided.
Selective reporting (reporting bias)	Unclear risk	Definition for wound infection is not documented.
Other bias	High risk	Reoperation excluded; reason for reoperation unknown - could be due to wound infection

Corocan 2017

Methods	<ul style="list-style-type: none"> • Prospective double-blind randomized trial • Enrolment took place in Australia.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Women were recruited at pre-assessment clinics and from preoperative wards. • Adult females, ASA I or II, age 18 to 60 years, undergoing elective major laparoscopic gynaecological surgery expected to require at least 90 minutes of operative time, requiring a hospital stay to include at least the first postoperative night <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Currently or recently taking immunosuppressive agents • Known or suspected malignancy • Hypertension • Diabetes mellitus • History of peptic ulceration • Chronic pain syndrome requiring regular opioid consumption • Predicted requirement for IV patient-controlled analgesia • Known hypersensitivity to dexamethasone or granisetron • 32 patients were included. <ul style="list-style-type: none"> ◦ 16 in the intervention group ◦ 16 in the control group
Interventions	<ul style="list-style-type: none"> • Intervention group received 4 mg dexamethasone after induction. • Control group received normal saline after induction.
Outcomes	<ul style="list-style-type: none"> • Serum glucose • IL-6 • Full blood count • Lymphocyte analysis and postoperative infection data assessed 6 weeks postoperatively
Notes	<p>Sources of funding</p> <ul style="list-style-type: none"> • Health Department of Western Australia (Raine Foundation Clinical Practitioner Fellowship to T.C.); University of Western Australia (T.C.) <p>Conflicts of interest</p> <ul style="list-style-type: none"> • T.C. is a member of the executive committee of the ANZCA Clinical Trials Network (Australia and New Zealand College of Anaesthetists (ANZCA) CTN).

	<ul style="list-style-type: none">• M.P. is an editor of <i>Anaesthesia and Intensive Care</i> and is on the Editorial Board for <i>International Journal of Obstetric Anaesthesia</i>, <i>Obstetric Anaesthesia Digest</i>, <i>Anesthesiology</i>, and <i>Pain Medicine</i>.• Other study authors declare no conflicts of interest.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drug was prepared by an observer who was not connected to the study and was diluted to a total volume of 4 mL with 0.9% sodium chloride in an unmarked syringe. The patient, the patient's anaesthetist, and all investigators were blinded to study drug identity
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study drug was prepared by an observer who was not connected to the study and was diluted to a total volume of 4 mL with 0.9% sodium chloride in an unmarked syringe. The patient, the patient's anaesthetist, and all investigators were blinded to study drug identity
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT flow diagram included; 1 dropout in intervention group
Selective reporting (reporting bias)	Low risk	Study was registered.
Other bias	Low risk	No other apparent form of bias

Cortes-Flores 2018

Methods	<ul style="list-style-type: none"> • Randomized double-blind trial • Enrolment took place in Mexico between June 2013 and October 2014.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • All ASA I or II patients scheduled to receive an elective partial mastectomy with or without axillary gland removal, according to the positivity or negativity of sentinel lymph nodes <p>Exclusion criteria</p> <ul style="list-style-type: none"> • American Society of Anesthesiologists class III or IV disease

	<ul style="list-style-type: none"> • Age > 70 years • Pregnancy • Previous steroid therapy • Uncontrolled diabetes mellitus (serum glycated haemoglobin level > 8%) • Use of opioids, sedatives, or analgesics within a week before surgery • Any history of alcohol or drug abuse • History of inner ear disease and/or uncontrollable severe PONV after any surgical procedure • 80 participants were included. <ul style="list-style-type: none"> ◦ 40 in the intervention group ◦ 40 in the control group
Interventions	<ul style="list-style-type: none"> • Intervention group received 8 mg dexamethasone 1 hour before surgery. • Control group received normal saline 1 hour before surgery.
Outcomes	Primary outcomes <ul style="list-style-type: none"> • Postoperative nausea and vomiting score • Pain scores • Spirometry parameters • Postoperative complications after 30 days
Notes	Sources of funding <ul style="list-style-type: none"> • Study authors did not receive any funding. Conflicts of interest <ul style="list-style-type: none"> • None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Procedure not described in report
Allocation concealment (selection bias)	Unclear risk	Procedure not described in report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Procedure not described in report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Procedure not described in report
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT flow diagram is included in the report.
Selective reporting (reporting bias)	High risk	Study was retrospectively registered at clinicaltrials.gov (NCT02305173). Furthermore, the primary outcome parameter was

		changed from spirometry parameters to PONV
Other bias	Low risk	No other apparent form of bias

Cowie 2010

Methods	<ul style="list-style-type: none"> Randomized placebo-controlled trial Study was conducted at a single centre in Australia.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Adult patients undergoing laparoscopic cholecystectomy <p>Exclusion criteria</p> <ul style="list-style-type: none"> Patients already on dexamethasone or with diabetes 14 adult patients undergoing a laparoscopic cholecystectomy <ul style="list-style-type: none"> 7 intervention 7 placebo Mean age: 35 to 49 years Average duration of surgery: 63 to 77 minutes
Interventions	8 mg dexamethasone plus 2 mg tropisetron before inductions vs placebo (normal saline) plus 2 mg tropisetron before induction
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Plasma glucose and cortisol levels measured at 5 and 24 hours after surgery <p>Study did not assess any secondary outcomes.</p>
Notes	<p>Sources of funding</p> <ul style="list-style-type: none"> Not reported <p>Conflict of interest</p> <ul style="list-style-type: none"> Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and investigators were masked to group assignment. How this was achieved is unknown. The anaesthesiologist was not blinded

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and investigators were masked to group assignment; objective outcome data
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description of dropouts or withdrawals, but very small sample size
Selective reporting (reporting bias)	Unclear risk	Outcome data are consistently reported. No study protocol has been published
Other bias	Unclear risk	Unknown

Doksrod 2012

Methods	<ul style="list-style-type: none"> • Parallel randomized controlled trial • Between 2008 and 2009, patients were enrolled at the Telemark Hospital in Norway.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adult patients ASA I-III, undergoing total thyroidectomy, hemithyroidectomy, or parathyroidectomy <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Body weight > 100 kg or body mass index > 35 • Regular or recent use of corticosteroids, anti-emetics, or opioids • 121 adult patients undergoing thyroid surgery <ul style="list-style-type: none"> ◦ 41 intervention ◦ 40 placebo ◦ Third study group not included in meta-analysis owing to high dose of dexamethasone (40 patients). • Patients with diabetes were eligible. • Baseline characteristics were not described in the article but were similar between groups.
Interventions	Dexamethasone 0.15 mg/kg ⁻¹ at induction vs placebo (normal saline 0.1 mL/kg ⁻¹). Study medication was prepared at the pharmacy in neutral ampoules
Outcomes	<ul style="list-style-type: none"> • NRS of pain (0 to 10) at rest and coughing • PONV (0 lowest with no symptoms and 5 maximum) • Consumption of opioids and antiemetics was recorded at 2 hours, 4 hours, 24 hours, 36 hours, 48 hours, 72 hours, and 30 days after surgery. • Blood glucose levels were measured at 2 hours and 4 hours after surgery. • Postoperative infection and wound healing were assessed by a questionnaire and by follow-up by a surgeon 30 days postoperatively. • No definition stated in article for postoperative infection or delayed wound healing

Notes	Sources of funding <ul style="list-style-type: none">• Telemark Hospital Conflict of interest <ul style="list-style-type: none">• None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated codes
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study medication was prepared at the pharmacy and delivered in identical-looking ampoules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified if surgeon doing the follow-up was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented
Selective reporting (reporting bias)	Low risk	Protocol was published (NCT00569920).
Other bias	Low risk	No apparent other bias

DREAMS trial collaborators

Methods	<ul style="list-style-type: none"> • Pragmatic blinded multi-centre randomized controlled trial at 45 centres in the UK • Inclusion period was from July 2011 to January 2014.
Participants	Inclusion criteria <ul style="list-style-type: none"> • Adults (aged 18 and over) • Ability to consent • Undergoing elective open or laparoscopic bowel surgery for malignant or benign pathology Exclusion criteria <ul style="list-style-type: none"> • Pregnancy • Gastrointestinal obstruction • Diabetes • Glaucoma • Active gastric ulceration confirmed by endoscopy • 1350 patients were recruited. <ul style="list-style-type: none"> ◦ 674 were allocated to 8 mg dexamethasone during induction.

	<ul style="list-style-type: none">◦ 676 were allocated to standard care.● 58% male● All underwent bowel surgery.	
Interventions	<ul style="list-style-type: none">● Intervention group received 8 mg dexamethasone after induction.● Control group received standard care.● Placebo was not used.	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">● Any vomiting within 24 hours postoperatively, defined as episodes of expulsion of gastric contents <p>Secondary outcomes</p> <ul style="list-style-type: none">● Number of episodes of vomiting postoperatively (with an interval of 5 minutes defining separate episodes)● Use of postoperative antiemetics● Severity of postoperative nausea and vomiting (measured with the PONV intensity scale)● Fatigue (measured with the FACIT-F (functional assessment of chronic illness-fatigue) questionnaire)● Time to toleration of oral diet● Length of hospital stay● Health-related quality of life (measured with EQ-5D-3L22 23) <p>Participants were seen 30 days postoperatively and assessments were made of wound and chest infections and other complications</p> <p>Attempts were made by telephone to contact participants who did not attend</p>	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">● This trial was supported in both development and delivery by the Birmingham Surgical Trials Consortium and the Royal College of Surgeons and Rosetrees Clinical Research Initiative.● Local support for the pilot phase was also provided by the Birmingham ECMC. <p>Conflicts of interest</p> <ul style="list-style-type: none">● All study authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following.<ul style="list-style-type: none">◦ No support from any organization for the submitted work beyond the study grants listed above◦ No financial relationships in the previous 3 years with any organizations that might have an interest in the submitted work◦ No other relationships or activities that could appear to have influenced the submitted work	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was made by a web-based central randomization service at the University of Birmingham clinical trials unit, with telephone backup

DREAMS trial collaborators (Continued)

Allocation concealment (selection bias)	Low risk	Computer-based, with algorithm
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only anaesthetist was not blinded, but administration of dexamethasone was noted only in the trial files, not in the anaesthetic record. However, no placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Research staff blinded. Anaesthetist not involved in postoperative care
Incomplete outcome data (attrition bias) All outcomes	Low risk	Detailed CONSORT flow diagram
Selective reporting (reporting bias)	Low risk	Trial was registered. All logical outcomes are reported.
Other bias	Low risk	No other apparent form of bias

Feroci 2011

Methods	<ul style="list-style-type: none"> • Double-blind randomized controlled trial • Enrolment took place at a single centre in Italy in 2009.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adult patients with ASA classification status I and II undergoing thyroid surgery <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Younger than 18 years • Previous malignant disease • Previous thyroid surgery • Previous neck surgery • Received antiemetic therapy within 48 hours before surgery • Chronic pain disorder • Insulin-dependent diabetes mellitus • History of severe and/or repeated PONV after previous minor surgery • Pregnancy • 102 adult patients were included. <ul style="list-style-type: none"> ◦ 51 intervention. ◦ 51 placebo. • Mean age: 54 to 57 years • 68% female • Duration of surgery: 84 to 89 minutes
Interventions	8 mg dexamethasone in 100 mL normal saline 20 minutes before surgery vs 100 mL normal saline before surgery

Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> PONV, measured as follows: 0: no nausea; 1: mild nausea; 2: severe nausea; 3: retching and/or vomiting <p>Use of postoperative antiemetics (frequency, amount of intake, and substance) was recorded during the observation period</p> <p>Secondary outcomes</p> <ul style="list-style-type: none"> Pain (assessed with a standardized visual analogue scale (VAS) that ranged from 0 (no pain) to 100 (worst pain imaginable)) Subjective voice disturbances (assessed by a voice visual analogue scale (VVAS: 100 ¼ normal voice, 0 ¼ worst voice imaginable)) Pain assessed with a standardized VAS that ranged from 0 (no pain) to 100 (worst pain imaginable) <p>Occurrence of side effects accompanying dexamethasone usage, such as transient insulin-dependent diabetes, wound infection, systemic infection, or delayed wound healing, was evaluated and reported. Glycaemia measurements were obtained 24 hours postoperatively</p> <p>Hospitalization time was also recorded.</p> <p>Postoperative wound infection and wound healing were assessed 30 days after surgery (no definition stated in the article)</p>
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Notes	<p>Sources of funding</p> <ul style="list-style-type: none"> Not reported <p>Conflict of interest</p> <ul style="list-style-type: none"> Not reported
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	High risk	Random number list; unclear how and where the list was stored and who had access
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Staff not participating in the trial prepared drugs; patients, anaesthesiologist, and researchers were blinded to the randomization process and outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators who collected postoperative data were blinded to the randomization process and to the types of drugs administered
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented

Feroci 2011 (Continued)

Selective reporting (reporting bias)	Low risk	Study was registered at trialregister.gov (NCT00888303).
Other bias	Low risk	No apparent other bias

Ionescu 2014

Methods	<ul style="list-style-type: none"> Parallel-group randomized controlled trial Enrolment took place at a single centre in Romania from 2008 to 2009.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ASA status I and II and undergoing a laparoscopic cholecystectomy <p>Exclusion criteria</p> <ul style="list-style-type: none"> Immune system disorders Known inflammatory disease (including acute cholecystitis) Abnormal white cell count Asthma Obesity (BMI > 30 kg/m²) Diabetes Gastric ulcer Allergies History of PONV Current steroid medication Anti-inflammatory medication 46 adult patients were included. <ul style="list-style-type: none"> 22 intervention 20 placebo 4 dropouts Mean age: 50 to 55 56% female. Average duration of surgery: 42 to 45 minutes
Interventions	Participants received 4 mg dexamethasone at induction (1 mL clear solution) vs normal saline at induction (1 mL clear solution)
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Plasma concentrations of both pro-inflammatory and anti-inflammatory interleukins measured by commercially available ELISA kits before surgery, after intubation, 2 hours after recovery, and 24 hours after anaesthesia Surgical site infection assessed according to SSI criteria, at 30 days after surgery
Notes	<p>Sources of funding</p> <ul style="list-style-type: none"> Research grant from the National Center for the Management of Project Romania <p>Conflict of interest</p> <ul style="list-style-type: none"> None declared
Risk of bias	

Ionescu 2014 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generator (computer)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were not blinded; however no expected influence on outcome parameter
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts described
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Other bias	Low risk	No apparent other bias

Kalappa 2017

Methods	<ul style="list-style-type: none"> • Prospective double-blind randomized trial • Enrolment took place in India in 2015 and 2016.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Undergoing lumbosacral spine surgeries (caudal to T12 spine) • Aged between 18 and 70 years • American Society of Anesthesiologists (ASA) Grades I and II • Under general anaesthesia <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Diabetes • Coagulopathy • Peptic ulcer disease • Anomalies of sacrum • On steroid medications within the past 6 months • 96 patients were included in this trial. • Randomly divided over 3 groups <ul style="list-style-type: none"> ◦ 32 in group A ◦ 32 in group B ◦ 32 in group C. Patients in group C were not included in this meta-analysis, as they received dexamethasone via the caudal route.
Interventions	<ul style="list-style-type: none"> • Group A received normal saline IV and ropivacaine via the caudal route. • Group B received 8 mg dexamethasone IV after induction and ropivacaine via the caudal route.

Kalappa 2017 (Continued)

Outcomes	<ul style="list-style-type: none">● Glucometric random blood sugar was recorded at baseline, 4 hours, 8 hours, 12 hours, and 24 hours after the caudal block.● Pain scores● Length of hospital stay	
Notes	Sources of funding <ul style="list-style-type: none">● None Conflicts of interest <ul style="list-style-type: none">● None reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	This is not described in the paper.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This is not described in the paper.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The senior registrar who assessed pain scores was blinded to group assignment. However, it is unclear if medication was registered in the anaesthesia records
Incomplete outcome data (attrition bias) All outcomes	High risk	No flow diagram or dropout rate reported.
Selective reporting (reporting bias)	Unclear risk	Study was not registered in a trial register.
Other bias	Low risk	No apparent other bias

Karacinar 2009

Methods	<ul style="list-style-type: none"> • Randomized double-blind placebo-controlled trial • Enrolment took place at a single centre in Turkey. 	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Adult patients undergoing a craniotomy Exclusion criteria <ul style="list-style-type: none"> • Diabetes • Glucose intolerance • Corticosteroid use • 68 ASA I or II patients were included. 	

	<ul style="list-style-type: none"> ○ 17 group D4. ○ 17 group D8. ○ 17 group D16. ○ 17 placebo. ● Mean age: 44 to 51 years ● 60% male ● Average duration of surgery: 229 to 243 minutes
Interventions	Participants received 4 mg, 8 mg, or 16 mg dexamethasone at induction vs 5 mL normal saline at induction
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> ● Glucose and electrolyte values, measured 1, 2, 3, and 4 hours after dexamethasone <p>Secondary outcomes</p> <ul style="list-style-type: none"> ● PONV measured on dichotomous scales ● Insufficient follow-up for complication data
Notes	<p>Sources of funding</p> <ul style="list-style-type: none"> ● This research was supported by the Research Fund of Erciyes University. <p>Conflict of interest</p> <ul style="list-style-type: none"> ● Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Unknown how allocation concealment was achieved
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Control group received a placebo; therefore participants were probably blinded. Unknown if personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unknown whether researchers were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No dropouts described
Selective reporting (reporting bias)	Unclear risk	Protocol was not published.
Other bias	Unclear risk	Report does not give a lot of information on the methods.

Methods	<ul style="list-style-type: none">• Randomized controlled trial• Enrolment took place at a single centre in Japan in 2012.	
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none">• Patients aged 20 to 75 undergoing an arthroscopy <p>Exclusion criteria</p> <ul style="list-style-type: none">• Refused consent• Diagnosed with a clinical condition in which ISB was contraindicated• History of coagulation disorder• International normalized ratio 1.5• Skin infection at the site of the block• Preexisting neuropathy involving the upper limb• Drug dependency• Systemic steroid use within the previous 6 months• Peptic ulcer disease• Diabetes mellitus• Renal disease• Hepatic disease• Pregnancy• 39 adult patients were included.<ul style="list-style-type: none">◦ 10 intervention.◦ 12 control.• In the third arm of the study, participants received perineural dexamethasone and therefore were not included in this meta-analysis.• Mean age: 55 to 59 years• 28% female• Average duration of surgery: 172 to 178 minutes	
Interventions	4 mg dexamethasone IV plus interscalene block vs interscalene block without placebo	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">• Length of the sensory block, defined as time between performance of the sensory block and first administration of analgesia <p>Secondary outcomes</p> <ul style="list-style-type: none">• NRS the morning after surgery• Analgesic need• Sleep disturbance• Overall satisfaction score, measuring patient comfort• Adverse events were evaluated 28 days after surgery.• No definition of wound infection was stated.	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">• Not reported <p>Conflict of interest</p> <ul style="list-style-type: none">• None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Kawanishi 2014 (Continued)

Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Low risk	Closed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or caregivers
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of researchers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Unknown

Kirdak 2008

Methods	<ul style="list-style-type: none"> • Double-blind randomized controlled trial • Enrolment took place at a single centre in Turkey in 2005.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adult patients undergoing elective colonic surgery <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Emergency surgery • Age < 18 or > 80 • Diabetes • Recent NSAID use • IBD • Renal failure • COPD • Ascites • Unresectable tumour • 30 adult patients were included. <ul style="list-style-type: none"> ◦ 14 intervention ◦ 13 control ◦ 3 dropouts • Mean age: 55 to 62 years • 59% male • Average duration of surgery: 149 to 157 minutes
Interventions	8 mg dexamethasone 60 to 90 minutes before surgery vs normal saline 60 to 90 minutes before surgery

Outcomes	Primary outcome Unclear. The following outcomes were assessed. <ul style="list-style-type: none">• CRP levels and IL-6 levels measured preoperatively and on days 1 and 2 postoperatively• Nausea and vomiting measured on a dichotomous scale assessed at days 1, 2, and 3 postoperatively• Pain measured with the VAS and as morphine consumption on days 1, 2, and 3 postoperatively• Morbidity or mortality occurring at operation or in the subsequent 30 days• Diagnosis of surgical site infection according to the definitions of the Centers for Disease Control and Prevention	
Notes	Sources of funding <ul style="list-style-type: none">• Not reported Conflicts of interest <ul style="list-style-type: none">• Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unknown
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Anaesthesiologists, surgeons, nurses administering study drugs, patients, other investigators who were involved in postoperative care, persons making laboratory measurements, and biostatisticians were unaware of patient group allocation until completion of statistical analysis
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators involved in postoperative care were unaware of participant group allocation until completion of statistical analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented
Selective reporting (reporting bias)	Unclear risk	Protocol not published
Other bias	Low risk	No apparent other bias

Methods	<ul style="list-style-type: none"> • Multi-centre parallel-group double-blind randomized placebo-controlled study • Enrolment took place at 2 centres in Denmark in 2015.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adults (aged at least 18 years) with ASA status I to III undergoing a diagnostic laparoscopy for suspected appendicitis between 30 April 2015 and 2 September 2015 <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Inflammatory bowel disease • Autoimmune disease • Chronic pain • Glaucoma • Ocular herpes simplex • Cushing's disease • Myasthenia gravis • Expected poor compliance with the study protocol • Systemic use of corticosteroids or other immunosuppressive drugs • Pregnant or breastfeeding women • Vaccinated within the last 14 days • 120 adult patients undergoing laparoscopic appendectomy were included. <ul style="list-style-type: none"> ◦ 59 intervention ◦ 57 placebo ◦ 4 lost to follow-up • Patients with diabetes were eligible. • Mean age: 38 to 41 years. • 53% female • 63% ASA status I • 34% ASA status II • Average duration of surgery: 47 to 49 minutes
Interventions	Dexamethasone 8 mg (2 mL) vs placebo (2 mL normal saline) 30 minutes before incision
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Incidence of PONV during first postoperative day (first 24 to 32 hours after surgery) <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Pain at rest • Pain when coughing • Fatigue • Quality of sleep • Quality of recovery • Duration of convalescence • Use of antiemetic and consumption of opioids during first postoperative day • Use of antiemetic and postoperative analgesics was recorded through the electronic patient medication system. • Adverse events and postoperative complications were recorded according to the Clavien-Dindo classification of surgical complications on the patient's medical chart and by patient interview 30 days after surgery.

Kleif 2017 (Continued)

Notes	Funding sources <ul style="list-style-type: none">• Work supported by the A.P. Møller Foundation for the Advancement of Medical Science• Hans and Nora Buchards Foundation• Axel Muusfeldts Foundation• J.K. received a research grant from Nordsjællands Hospital and financial support from the Department of Surgery, Nordsjællands Hospital, Copenhagen University Hospital. Conflict of interest <ul style="list-style-type: none">• None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Low risk	Pharmacy-based randomization
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Pharmacy prepared study drug in identical syringes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were not aware of study group until data analysis was completed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts are provided.
Selective reporting (reporting bias)	Low risk	Protocol was registered at clinicaltrials.gov (NCT02415335).
Other bias	Low risk	No apparent other bias

Koh 2013

Methods	<ul style="list-style-type: none"> • Multi-centre parallel randomized controlled trial • Enrolment took place in 2011 in Korea.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • 18 years or older who were scheduled for unilateral TKA for primary osteoarthritis <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of intolerance or allergy to any drug used in the current study • Severe impairment of bowel motility • Administration of another antiemetic drug or systemic steroid 24 hours before surgery

	<ul style="list-style-type: none">● History of cardiovascular or respiratory disease, or alcohol or opioid dependence● Impairment of renal or hepatic function● Regional anaesthesia contraindicated● Spinal anaesthesia failed● Femoral nerve block and/or intravenous patient-controlled analgesia (PCA) discontinued before the planned schedule● Declined to participate in the trial● Unable to provide informed consent● 290 adult patients undergoing TKA were included.<ul style="list-style-type: none">○ 146 randomized to intervention; 135 analysed○ 145 randomized to control; 134 analysed● Patients with diabetes were eligible.● Mean age: 72 years● 88% female● Average duration of surgery: 107 minutes	
Interventions	10 mg dexamethasone 1 hour before surgery vs 0.3 mg ramosetron at the end of surgery. No placebo was used	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">● Incidence of PONV assessed during 4 postoperative periods (0 to 6 hours, 6 to 24 hours, 24 to 48 hours, and 48 to 72 hours) <p>Secondary outcomes</p> <ul style="list-style-type: none">● Severity of nausea● Rescue antiemetic requirement and complete response● Pain level measured on a VAS ranging from 0 to 10 assessed during the 4 above mentioned periods● Amount of opioid consumption● Incidence of wound complications (Wound complications including periprosthetic joint infection and inadequate wound healing (including delayed wound healing or wound dehiscence) were evaluated by 1 of 2 surgeons at 2 weeks, 6 weeks, 3 months, 6 months, and 1 year after surgery at follow-up. Periprosthetic joint infection was diagnosed using the criteria outlined by the Musculoskeletal Infection Society.)	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">● Not reported <p>Conflict of interest</p> <ul style="list-style-type: none">● None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization table
Allocation concealment (selection bias)	High risk	No allocation concealment

Koh 2013 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were blinded; caregivers were not.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researcher was blinded until analysis was complete.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented
Selective reporting (reporting bias)	Unclear risk	Definitions of outcome measures were slightly altered since the protocol
Other bias	Unclear risk	Very extensive multi-modal pain treatment in both groups; influence on complication data unknown

Kurz 2015

Methods	<ul style="list-style-type: none"> • Multi-centre factorial randomized controlled trial • Patients were enrolled between 2002 and 2007 in Austria, USA, Ireland, and Switzerland.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adult patients under 80 years undergoing elective colorectal resection, expected to last 2 to 6 hours <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Chemotherapy within 6 months before surgery • Secondary wound closure anticipated • Fever or infection at admission • COPD • Unstable AP • Cardiomyopathy • Heart failure • MI within 6 months • Bowel obstruction • ASA IV or higher • 585 adult patients undergoing bowel surgery were included. <ul style="list-style-type: none"> ◦ 283 intervention ◦ 272 placebo • Patients with diabetes were eligible. • Mean age: 53 years • 53% male • 14% ASA status I • 60% ASA status II • 26% ASA status III • Average duration of surgery: 208 to 210 minutes

Interventions	Dexamethasone 4 mg during induction vs normal saline during induction	
Outcomes	Primary outcome <ul style="list-style-type: none">Incidence of SSI within 30 days of surgery Secondary outcomes <ul style="list-style-type: none">Wound-healing scores (ASEPSIS)Return of bowel functionDuration of hospitalization (measured in days) Wound infection and delayed wound healing were assessed, diagnosed according to CDC criteria. Assessed 30 days after surgery	
Notes	Fundings sources <ul style="list-style-type: none">This study was supported in part by the Gheens Foundation (Louisville, KY, USA) and the Mater College for Postgraduate Research (Ireland). Viasys Healthcare (Wheeling, IL, USA) provided the Hi-Ox oxygen masks. Conflicts of interest <ul style="list-style-type: none">Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes, sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgeons were blinded; anaesthesiologists were not. Anaesthetic records were sealed after surgery. Treatment was prepared by an independent investigator
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator assessing outcomes was blinded to who received treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study was ceased early owing to futility. Reasons for dropouts were documented
Selective reporting (reporting bias)	High risk	Protocol was published. Not all prespecified outcomes are reported
Other bias	Unclear risk	Participants were also randomized to receive 30% or 80% oxygen

Methods	<ul style="list-style-type: none">● Parallel randomized controlled clinical trial● Enrolment took place from April to September 2017 in China.	
Participants	Inclusion criteria <ul style="list-style-type: none">● Undergoing surgery in lateral decubitus position; primary total hip arthroplasty Exclusion criteria <ul style="list-style-type: none">● Revisions● Bilateral procedures● Allergy to dexamethasone● Administration of any glucocorticoids during the 3 months before surgery● Administration of any strong opioids during the past 7 days● Presence of rheumatoid disease● Presence of systemic lupus erythematosus● Presence of ankylosing spondylitis● Serious cardiac or cerebrovascular problems● Severe liver or kidney function deficiency● 210 participants were randomized.<ul style="list-style-type: none">○ 70 to group A○ 70 to group B○ 70 to group C	
Interventions	<ul style="list-style-type: none">● Group A received 3 doses of normal saline.● Group B received 10 mg dexamethasone at induction and 10 mg dexamethasone when discharged from recovery.● Group C received 3 doses of 10 mg dexamethasone and thus was excluded from this meta-analysis.	
Outcomes	<ul style="list-style-type: none">● Postoperative nausea and vomiting● Pain scores● Hip movement● Infection parameters	
Notes	Conflicts of interest <ul style="list-style-type: none">● None	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described
Allocation concealment (selection bias)	Low risk	Opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Anaesthetist and nurses not blinded but was not involved in the trial; rest of staff was blinded

Lei 2017 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Anaesthetist and nurses not blinded but not involved in the trial; rest of staff was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT flow diagram included in paper. No dropouts after randomization
Selective reporting (reporting bias)	Low risk	All outcomes reported; protocol was published in Chinese register
Other bias	Low risk	This research was funded by the National Health and Family Planning Commission of the People's Republic of China (CN) programme (201302007)

Murphy 2011a

Methods	<ul style="list-style-type: none"> • Parallel double-blind randomized placebo-controlled trial • Single centre in the USA • Dates of enrolment unknown
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Undergoing elective coronary artery bypass graft (CABG) surgery with CPB or single valvular repair/replacement surgery and anticipated early tracheal extubation <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Combined (CABG/valve) procedures • Ejection fraction 30% • Preoperative use of inotropic agents or an intra-aortic balloon pump • Preoperative use of steroids • Preoperative use of antiemetic agents • Acute or chronic renal failure • Pulmonary disease necessitating oxygen therapy • Potentially requiring prolonged postoperative mechanical lung ventilation • Poorly controlled diabetes • Poor English comprehension or psychiatric/central nervous system disturbances precluding completion of the QoR-40 questionnaire <p>.</p> <ul style="list-style-type: none"> • 117 adult patients undergoing CABG or valve repair <ul style="list-style-type: none"> ◦ 67 intervention ◦ 50 placebo • Mean age: 63 years • 71% female • 15% had diabetes. • Average duration of surgery: 322 to 338 minutes
Interventions	8 mg dexamethasone at induction plus 8 mg dexamethasone when cardiopulmonary bypass was initiated vs normal saline at induction and when cardiopulmonary bypass was initiated

Murphy 2011a (Continued)

Outcomes	Primary outcome variable of this <ul style="list-style-type: none">• Postoperative QoR-40 score• Postoperative infection assessed for 6 days postoperatively, defined as infection requiring surgical or antibiotic treatment (Postoperative infection data were not included in this meta-analysis owing to the short follow-up.)• Glucose measured 6 hours postoperatively	
Notes	Sources of funding <ul style="list-style-type: none">• Not reported Conflict of interest <ul style="list-style-type: none">• Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generation via computer
Allocation concealment (selection bias)	Low risk	Pharmacy-based randomization
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, investigators, and surgeons blinded; placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented; comparable between groups
Selective reporting (reporting bias)	Unclear risk	Reasonable outcome parameters; no protocol published
Other bias	Low risk	No apparent other bias

Murphy 2014

Methods	<ul style="list-style-type: none"> • Randomized controlled trial conducted • Single centre in the USA • Dates of enrolment unknown 	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Undergoing a hysterectomy • Aged 18 to 80 Exclusion criteria <ul style="list-style-type: none"> • Preoperative use of steroids or antiemetic drugs 	

	<ul style="list-style-type: none">● History of allergy to any study medications● Preoperative diagnosis of type 1 or 2 diabetes● Severe renal (serum creatinine > 1.6 mg/dL) or liver (liver enzymes > 2× normal values) disease● ASA physical status IV and V● 200 adult women undergoing a hysterectomy were randomized into 6 groups.● Three subgroups included in this meta-analysis<ul style="list-style-type: none">○ Late 8 mg: 33 participants○ Late 4 mg: 32 participants○ Late control: 34 participants● Mean age: 54 years● All participants were female.● Average duration of surgery: 213 to 243 minutes	
Interventions	8 mg dexamethasone at induction vs 4 mg dexamethasone at induction vs normal saline at induction	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">● Perioperative glucose concentrations, measured in all patients via a point-of-care device. Glucose values were measured 8 and 24 hours postoperatively. <p>Secondary outcomes</p> <ul style="list-style-type: none">● PONV scores assessed every 15 minutes at the PACU● Pain scores measured on a VAS evaluated when discharged from recovery● Total dose of hydromorphone during admission assessed● Postoperative fatigue, which may be reduced by steroids, assessed at PACU discharge on a 4-point ordinal scale (0 = none, 1 = mild fatigue, 2 = moderate fatigue, 3 = severe fatigue)● All participants were followed until the time of discharge from the hospital for any postoperative complications, including any evidence of postoperative wound infection or impaired wound healing (diagnosed by the surgical service). This follow-up period was too short for our meta-analysis.	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">● Support was provided solely by institutional and/or departmental sources. <p>Conflicts of interest</p> <ul style="list-style-type: none">● None	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated with block randomization
Allocation concealment (selection bias)	Low risk	Pharmacy based; blinding of all care providers, participants, and researchers

Murphy 2014 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Pharmacy provides blinded syringes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were blinded to group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented
Selective reporting (reporting bias)	Low risk	Consistent with published protocol
Other bias	Low risk	No apparent other bias

Nazar 2009

Methods	<ul style="list-style-type: none"> • Prospective double-blind randomized trial • Single centre in Chile • Dates of enrolment unknown
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • ASA physical status II or III • Did not receive premedication • Scheduled to undergo laparoscopic Roux-en-Y gastric bypass surgery <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Under treatment with corticosteroids • Oral hypoglycaemic drugs or insulin • Received glucose in the last 12 hours before surgery • 30 adult patients with glucose intolerance undergoing a Roux-en-Y anastomosis were included. <ul style="list-style-type: none"> ◦ 15 intervention ◦ 15 placebo • Mean age: 37 to 40 years • 20% male • Average duration of surgery: 103 to 107 minutes
Interventions	8 mg dexamethasone (2 mL) immediately after induction vs normal saline (2 mL) immediately after induction
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Glucose values, not specified at which time point. Glucose was measured at 2, 4, 6, 8, 10, and 12 hours after dexamethasone.
Notes	<p>Sources of funding</p> <ul style="list-style-type: none"> • Not reported <p>Conflict of interest</p> <ul style="list-style-type: none"> • Not reported

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers generated by a computer
Allocation concealment (selection bias)	Unclear risk	Not reported if there was a list with random numbers or if the computer randomized every participant separately
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear; not specifically stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researcher was unaware of group allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There appear to be no dropouts in this study.
Selective reporting (reporting bias)	Unclear risk	All expected outcomes are reported.
Other bias	Unclear risk	Unknown

Nazar 2011

Methods	<ul style="list-style-type: none"> • Randomized controlled trial • Single centre in Chile • Dates of enrolment unknown
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patients with and without diabetes type 2, with BMI of 20 to 30, undergoing a laparoscopic cholecystectomy <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Corticosteroids • Insulin • Vasoactive drugs • Oral antidiabetics on the day of surgery • 70 adult participants with and without diabetes undergoing laparoscopic cholecystectomy were randomized into 4 groups. <ul style="list-style-type: none"> ○ Healthy dexta: 20 participants ○ Healthy control: 20 participants ○ DMdexta: 15 participants ○ DMcontrol: 15 participants • Mean age: 41 to 56 years • 30% male

Nazar 2011 (Continued)

	<ul style="list-style-type: none"> • Average duration of surgery: 51 to 66 minutes
Interventions	8 mg dexamethasone after induction vs 2 mL normal saline after induction
Outcomes	Primary outcome <ul style="list-style-type: none"> • Glucose levels measured 12 hours postoperatively No secondary outcomes reported
Notes	Sources of funding <ul style="list-style-type: none"> • Department supported the study. Conflict of interest <ul style="list-style-type: none"> • None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Web-based randomization
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear who was in charge of preparing the study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	No information on dropouts reported
Selective reporting (reporting bias)	Unclear risk	Study protocol not published or registered. Expected outcomes reported
Other bias	Unclear risk	Unknown

Nielsen 2015

Methods	<ul style="list-style-type: none"> • Single-centre prospective randomized blinded trial • Enrolment took place in Denmark from 2012 to 2014.
Participants	Inclusion criteria <ul style="list-style-type: none"> • Adult patients 18 to 85 years • ASA status I to III • BMI 18 to 40 • Undergoing 1- to 2-level lumbar discectomy Exclusion criteria

	<ul style="list-style-type: none">• Unco-operative• Unable to speak Danish• Previous surgery• Pregnancy• Allergy to dexamethasone• Daily use of opioid or corticosteroids• Alcohol or drug abuse• 160 adult patients undergoing lumbar discectomy<ul style="list-style-type: none">◦ 77 intervention◦ 76 placebo◦ 7 dropouts• Patients with diabetes were eligible.• Mean age: 45 years• 60% male• Average duration of surgery: 51 to 60 minutes	
Interventions	16 mg dexamethasone after induction before incision vs 4 mL of normal saline after induction before incision	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">• Pain during mobilization 2 to 24 hours postoperatively calculated as a “weighted average level” area under the curve (AUC) (in millimetres) <p>Secondary outcomes</p> <ul style="list-style-type: none">• Pain at rest (AUC 2 to 24 hours)• Total morphine consumption (0 to 24 hours and 24 to 48 hours)• Pain at rest and during mobilization 48 hours postoperatively• Morphine-related adverse effects (nausea, vomiting, sedation, and postoperative use of antiemetics)<ul style="list-style-type: none">• Quality of sleep 24 hours postoperatively <p>Outcomes for 3-month follow-up</p> <ul style="list-style-type: none">• Back and leg pain (VAS 0 to 100 mm)• Use of analgesics• Postoperative complications including wound infections• Walking distance• Duration of sick leave• Working capability• Contentment with results of the operation• Wound infections self-reported and treated with antibiotics	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">• None <p>Conflict of interest</p> <ul style="list-style-type: none">• None	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

Nielsen 2015 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated, block randomization
Allocation concealment (selection bias)	Low risk	Pharmacy-based randomization. Pharmacy was in charge of preparing the study drugs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, surgeons, and clinical personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded. Unblinding was done after follow-up and exclusion of data and statistical handling were complete
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced between groups. Reasons for dropouts documented
Selective reporting (reporting bias)	Low risk	Study was registered. More secondary outcomes were reported.
Other bias	Low risk	No apparent other bias

Rafiq 2014

Methods	<ul style="list-style-type: none"> • Single-centre parallel randomized controlled trial • Enrolment took place from 2007 to 2009 in Denmark.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age over 18 years • Any cardiac procedure with sternotomy • Able to give informed consent <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Cardiac surgery without sternotomy • Peripheral neuropathy • Neurological disease • Psychiatric illness • History of gastrointestinal bleeding • Chronic pain (i.e. back pain, cancer, arthritis) • Serum creatinine > 150 $\mu\text{mol/L}$ • Hepatic disease with elevated liver enzymes (SGPT and SGOT elevated to 1.5 times maximum normal value) • Allergic to study medication • Alcohol abuse • Abuse of narcotics or medication • Pregnancy • Participation in other clinical trials • Insufficient language skill

	<ul style="list-style-type: none">● ICU stay longer than 24 hours (used as a predefined post-randomization exclusion criterion)● 180 adult participants undergoing cardiac surgery with sternotomy<ul style="list-style-type: none">○ 77 intervention○ 74 control○ 6 withdrawals○ 23 dropouts● Patients with diabetes were included.<ul style="list-style-type: none">○ 8 intervention○ 16 control● Mean age: 62 to 64 years● 21% female	
Interventions	8 mg dexamethasone at extubation vs 4 mg ondansetron at extubation	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">● Pain measured on the 11-NRS <p>Secondary outcomes (evaluated during hospital stay)</p> <ul style="list-style-type: none">● Additional analgesic consumption● Hospital stay in days● Evaluation of side effects by daily questionnaire. <p>Secondary outcomes (measured at 30 days)</p> <ul style="list-style-type: none">● Renal complications: increase in creatinine, dialysis, cardiac complications● Myocardial infarction (MI)● Postoperative pericardial effusion● Heart failure requiring inotropic support● Atrial fibrillation● Other complications: cerebral (stroke, bleeding)● Gastrointestinal bleeding● Blood component requirements and sternal complications● Death from all causes● Wound infection and wound dehiscence (no definition stated)	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">● None <p>Conflict of interest</p> <ul style="list-style-type: none">● None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation is not described.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes, sequentially numbered

Rafiq 2014 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants. Primary end-point of study (pain) might be biased. End-point of this meta-analysis (wound infection) might be biased by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts described
Selective reporting (reporting bias)	Low risk	Protocol published. Same outcomes reported as stated in the protocol
Other bias	High risk	Participants with prolonged ICU stay were excluded. These patients are vulnerable to developing wound infection

Sanchez-Rodriguez 2010

Methods	<ul style="list-style-type: none"> • Single-centre randomized controlled double-blind trial • Enrolment was from 2007 to 2008 in Mexico.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adult patients undergoing laparoscopic cholecystectomy <p>Exclusion criteria</p> <ul style="list-style-type: none"> • American Society of Anesthesiologists (ASA) status III and IV • Age > 80 years • Pregnancy • Treatment with steroids • Severe diabetes mellitus (haemoglobin A1c (HbA1c) > 8%) • Use of opioids • Sedatives or any kind of analgesics 1 week before LC • History of alcohol or drug abuse • Preoperative diagnosis of acute cholecystitis • Acute pancreatitis • Choledocholithiasis • Gallbladder carcinoma and/or conversion of the LC to an open procedure • 210 adult patients undergoing laparoscopic cholecystectomy were included. <ul style="list-style-type: none"> ◦ 105 intervention ◦ 105 placebo • Mean age: 36 to 38 years • 42% male • 59% ASA status I • 41% ASA status II • Average duration of surgery: 71 to 73 minutes

Interventions	8 mg dexamethasone before skin incision vs normal saline before skin incision	
Outcomes	Primary outcomes (6, 12, and 24 hours after surgery) <ul style="list-style-type: none">• Degree of postoperative nausea measured on a 4-point scale• Vomiting• Pain measured on VAS• Fatigue• Need for additional analgesic and antiemetic drugs• Postoperative complications were assessed until 30 days after surgery (no definition is stated).	
Notes	Sources of funding <ul style="list-style-type: none">• Not reported Conflict of interest <ul style="list-style-type: none">• Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Low risk	Opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described who prepared study drugs
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described how blinding of researcher was maintained
Incomplete outcome data (attrition bias) All outcomes	High risk	No dropouts described
Selective reporting (reporting bias)	Unclear risk	Protocol was not published, but expected outcomes are reported
Other bias	Unclear risk	Unknown

Methods	<ul style="list-style-type: none">• Single-centre randomized placebo-controlled double-blind trial• Enrolment was from March 2005 to April 2008 in Italy.	
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none">• Adult patients undergoing a laparoscopic Nissen fundoplication <p>Exclusion criteria</p> <ul style="list-style-type: none">• ASA physical class III or IV• Age > 75 years• Pregnancy• Chronic pain due to disease other than gastroesophageal reflux disease (GERD)• Endocrine, renal, hepatic, or immunological disease• Received opioids or tranquilizers (treatment 1 week before LFNF)• Spoke only a foreign language• Mental disorder• History of alcohol or drug abuse• If the operation was converted from LFNF to open procedure• If an additional fifth trocar was needed to complete the operation. Since development of surgical complications might influence chosen outcome parameters, these patients were excluded and results were analysed by protocol.• 82 adult patients undergoing laparoscopic Nissen fundoplication were randomized.<ul style="list-style-type: none">◦ 41 intervention◦ 41 placebo• Mean age: 46 to 49 years• 41% male• 22% ASA II status• Average duration of surgery: 56 to 57 minutes	
Interventions	8 mg dexamethasone before incision vs normal saline before incision	
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none">• Pain (measured on VAS and VRS daily during first postoperative week)• PONV (measured on VRS during first 6 hours and from 6 to 24 hours) <p>Secondary outcomes</p> <ul style="list-style-type: none">• CRP• IL-1 and IL-6 levels• Measured at 0, 30, 60, 90, 120, 180 minutes and 12 and 24 hours postoperatively• Wound infections were assessed 30 days after surgery (no definition stated).	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">• Not stated <p>Conflict of interest</p> <ul style="list-style-type: none">• None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Schietroma 2010 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Low risk	Opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Nurse not participating in the trial prepared drugs in identical-looking syringes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented
Selective reporting (reporting bias)	Unclear risk	No protocol published but all relevant outcomes reported
Other bias	Unclear risk	Unknown

Schietroma 2013

Methods	<ul style="list-style-type: none"> • Parallel randomized placebo-controlled trial • Enrolment took place at a single centre in Italy between 2008 and 2011.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adult patients aged 18 to 75 undergoing thyroidectomy <p>Exclusion criteria</p> <ul style="list-style-type: none"> • American Society of Anesthesiologists (ASA) physical class III or IV • Older than 75 years • Pregnancy • Chronic pain due to a disease other than thyroid disease • Any signs of renal, hepatic, and immunological disease • Received opioids or tranquillizers (1 week of treatment before thyroidectomy) • Spoke only a foreign language • Mental disorders • History of alcohol or drug abuse • 328 adult patients undergoing thyroidectomy were included. <ul style="list-style-type: none"> ◦ 163 intervention ◦ 165 placebo • Patients with diabetes were eligible. • Mean age: 46 to 49 years • 40% male • 64% ASA status I • Average duration of surgery: 56 to 57 minutes

Interventions	8 mg dexamethasone 90 minutes before induction vs normal saline 90 minutes before skin incision
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Temporary or permanent recurrent laryngeal nerve palsy, evaluated through flexible laryngoscopic examinations <p>Secondary outcomes</p> <ul style="list-style-type: none"> Pain, measured on VAS and VRS (0 = no pain; 1 = light pain; 2 = moderate pain; 3 = severe pain). Moreover, pain was recorded at rest (supine position) and during mobilization (supine to sitting position) preoperatively and at 1, 2, 3, 6, and 24 hours after surgery. Nausea and vomiting scores evaluated separately for the 0 through 6-hour period and the 6 through 24-hour period Blood was drawn at 0, 30, 60, 90, 120, and 180 minutes, at 12 and 24 hours, and on the first 6 postoperative days for CRP, IL-1, and IL-6 levels. A 30-day follow-up for morbidity was performed in all cases. Wound infection was assessed 30 days after surgery. No definition for wound infection was stated.
Notes	<p>Sources of funding</p> <ul style="list-style-type: none"> Not reported <p>Conflict of interest</p> <ul style="list-style-type: none"> None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Block randomization computer generated
Allocation concealment (selection bias)	High risk	Sealed opaque envelopes; researcher unaware of randomization sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	A nurse drew up the study medication in identical-looking syringes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Researchers were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts were reported, without reasons; evenly distributed across groups
Selective reporting (reporting bias)	High risk	Protocol was published without outcome measures.

Other bias	High risk	An expression of concern was issued. Scientific and ethical concerns surround this paper; therefore all domains have been set to high risk of bias (Piccirillo 2017).
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Tien 2016

Methods	<ul style="list-style-type: none">• Parallel randomized controlled trial• Dates of patient enrolment were not stated.• Single centre in the USA	
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none">• English-speaking adult patients scheduled for elective surgery under general anaesthesia that was expected to last for at least 1 hour and who were routinely admitted to hospital for at least 24 hours <p>Exclusion criteria</p> <ul style="list-style-type: none">• Pregnancy• Preoperative blood glucose levels > 11.1 mmol/L• Currently, or recently, receiving steroid treatment• 88 adult patients undergoing surgery lasting > 1 hour were randomized into 4 groups.<ul style="list-style-type: none">◦ NonDM-Dexa 20 participants◦ NonDM-Zofran 21 participants◦ DM-Dexa 20 participants◦ DM-Zofran 27 participants• Mean age: 44 to 63• 95% of non-diabetic participants were female compared to 43% of diabetic participants.• 85% of non-diabetic participants had ASA status II.• 75% of diabetic participants had ASA status III.• Average duration of surgery: 165 minutes in non-diabetic groups, 231 minutes in diabetic group	
Interventions	Dexamethasone 8 mg at induction vs ondansetron 4 mg toward the end of surgery	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">• Glucose values, not specifically stated at which time point. Glucose was measured 2, 4, and 24 hours after surgery.	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">• M. Tien was supported by the Foundation of Anesthesia Education and Research through the Medical Student Anesthesia Research Fellowship. <p>Conflict of interest</p> <ul style="list-style-type: none">• None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Tien 2016 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated random sequence software
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Anaesthetist not involved in the study prepared study drugs; not placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not described whether researchers were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented
Selective reporting (reporting bias)	Unclear risk	Protocol not registered; only glucose outcome parameters reported
Other bias	Unclear risk	Wide range of surgeries included, not evenly across the 4 groups

Wakasugi 2015

Methods	<ul style="list-style-type: none"> Multi-centre randomized double-blind placebo-controlled trial at 8 hospitals in Japan Enrolment was from 2010 to 2012.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Adult patients undergoing laparoscopic cholecystectomy with normal WBC, Hb, platelets, and liver function <p>Exclusion criteria</p> <ul style="list-style-type: none"> Emergency surgery ASA III/IV Previous abdominal surgery High risk of conversion Continuous corticoid treatment Opioid treatment Mental disorder Cardiac or respiratory disease Day surgery Contraindication for dexamethasone <p>.</p> <ul style="list-style-type: none"> 270 adult patients undergoing laparoscopic cholecystectomy <ul style="list-style-type: none"> 136 intervention 134 placebo Patients with diabetes were eligible. Mean age: 58 to 59 years

	<ul style="list-style-type: none">• 54% male• 54% ASA status I• Average operation time: 101 to 105 minutes	
Interventions	8 mg dexamethasone after induction vs normal saline after induction	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">• Degree of PONV and antiemetic requirements within 24 hours after surgery <p>Secondary outcomes</p> <ul style="list-style-type: none">• Postoperative complications• Postoperative hospital stay, cost of hospital stay• CRP levels measured preoperatively, not postoperatively• Postoperative infection and delayed wound healing assessed according to CDC criteria at 30 days postoperatively	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">• None <p>Conflict of interest</p> <ul style="list-style-type: none">• None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated en block randomization. Blocks of 4 were used (1:1), balanced by institution
Allocation concealment (selection bias)	Low risk	Sufficient allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were masked to group assignment. How this was done is unknown. It is not described how the medication was prepared
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented
Selective reporting (reporting bias)	Unclear risk	Study was not registered.
Other bias	Unclear risk	Different analgesics and anaesthetics could be used; not standardized for all participants This has no effect on the primary outcome of this review.

Methods	<ul style="list-style-type: none">• Single-centre randomized controlled trial conducted in China• Dates of enrolment are unknown.	
Participants	Inclusion criteria <ul style="list-style-type: none">• Adult patients scheduled for surgery under combined intravenous-inhalational anaesthesia with ASA status I or II Exclusion criteria <ul style="list-style-type: none">• Diabetes• Glucose intolerance• Use of corticosteroids• 30 adult patients were randomized into 3 groups.<ul style="list-style-type: none">◦ 10 to the intervention group◦ 10 to the control group◦ 10 received too much dexamethasone to be included in this review.• Mean age: 36 to 40 years• In the dexamethasone group, 50% were male.• In the saline group, 60% were male.• Average duration of surgery: 222 to 234 minutes	
Interventions	10 mg dexamethasone vs normal saline	
Outcomes	Primary outcome <ul style="list-style-type: none">• Glucose values, measured at baseline, 1, 2, and 3 hours after dexamethasone	
Notes	Sources of funding <ul style="list-style-type: none">• Not reported Conflict of interest <ul style="list-style-type: none">• Unknown	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unknown
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unknown
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unknown
Incomplete outcome data (attrition bias) All outcomes	High risk	No dropouts described

Wang 2009 (Continued)

Selective reporting (reporting bias)	Unclear risk	Protocol not published
Other bias	High risk	Very little information in report

Worni 2008

Methods	<ul style="list-style-type: none">• 2-arm, double-blind, randomized controlled study• Conducted at a single centre in Switzerland between 2005 and 2007	
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none">• Adult patients undergoing thyroidectomy <p>Exclusion criteria</p> <ul style="list-style-type: none">• Pregnancy• Antiemetic therapy• < 18 years old• Malignant disease• Thyroid or neck surgery• Depression• Chronic pain disorder• Insulin-dependent diabetes• 80 adult patients were included.<ul style="list-style-type: none">◦ 37 intervention◦ 35 placebo◦ 8 dropouts• Mean age: 52 years• 85% female.• Average duration of surgery: 172 to 195 minutes	
Interventions	8 mg dexamethasone (2 mL) vs normal saline (2 mL)	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">• Nausea (nausea and vomiting assessed on a 4-point scale: 0 no nausea, 1 mild nausea, 2 severe nausea, 3 vomiting) <p>Secondary outcomes</p> <ul style="list-style-type: none">• Pain (assessed with a VAS)• Voice disturbances (evaluated by laryngoscopy both preoperatively and 2 days postoperatively)• Postoperative wound infection measured at 30 days postoperatively	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">• Not reported <p>Conflict of interest</p> <ul style="list-style-type: none">• Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Worni 2008 (Continued)

Random sequence generation (selection bias)	Low risk	Computerized random number table
Allocation concealment (selection bias)	Low risk	The list was kept separate and was unknown to investigators.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs were prepared off the ward in identical syringes and were given by a blinded nurse
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts documented
Selective reporting (reporting bias)	Low risk	Protocol was registered: NCT00619086.
Other bias	Low risk	No apparent other bias

Zargar-Shoshtari 2009

Methods	<ul style="list-style-type: none"> • Single-centre randomized double-blind placebo-controlled trial • Conducted in New Zealand • Dates of enrolment were from 2006 to 2008.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adult patients undergoing open colonic resection <p>Exclusion criteria</p> <ul style="list-style-type: none"> • ASA status IV or higher • Stoma requirement • Not speaking English • Cognitive impairment • 60 adult patients undergoing colonic surgery <ul style="list-style-type: none"> ◦ 29 intervention ◦ 31 placebo • Patients with diabetes were eligible. • Mean age: 69 to 71 years • 58% female • 52% ASA II status
Interventions	8 mg dexamethasone vs normal saline 90 minutes before induction
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Fatigue, measured before surgery and on days 3, 7, 30, and 60 via the Identity-Consequence Fatigue Scale <p>Secondary outcomes</p>

	<ul style="list-style-type: none">• Cytokine, WBC, neutrophil, and CRP levels at day 1 postoperatively• VAS scores for nausea, vomiting, and pain on days 1 and 2 postoperatively• Postoperative complications, including wound infection and postoperative infection, assessed at 60 days (criteria for wound infection: documented erythema, discharge requiring antibiotic treatment, or wound dehiscence requiring closure)	
Notes	<p>Sources of funding</p> <ul style="list-style-type: none">• This research was conducted during tenure by K.Z.-S. of a Clinical Research Training Fellowship from the Health Research Council of New Zealand, and was supported by a research grant from the Auckland Medical Research Fund. <p>Conflicts of interest</p> <ul style="list-style-type: none">• None	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Individual not participating in the trial prepared identical study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for exclusions were documented.
Selective reporting (reporting bias)	Low risk	Protocol was published.
Other bias	Low risk	No apparent other bias

Zhang 2016

Methods	<ul style="list-style-type: none"> • Multi-centre parallel-group double-blind placebo-controlled study • Conducted in China • Enrolment of participants occurred in 2014. 	
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adult patients undergoing thyroidectomy • ASA status I or II • Age: 23 to 65 years • Intubation under direct vision 	

	Exclusion criteria <ul style="list-style-type: none"> • Dexamethasone allergy • Preoperative ulcer • Use of Shaw body type and analgesic drugs in patients with thyroid surgery • Hyperthyroidism with thyroid cancer • Hyperthyroidism • 233 adult patients undergoing thyroid surgery were included. <ul style="list-style-type: none"> ◦ 103 intervention ◦ 130 placebo • Patients with diabetes were eligible. • Mean age: 45 to 47 years • 23% male • 82% ASA status I • Average duration of surgery: 75 to 78 minutes
Interventions	0.1 mg/kg dexamethasone at induction vs normal saline at induction
Outcomes	<ul style="list-style-type: none"> • Wound pain and throat pain, measured on VAS • Incidence of PONV, assessed on VRS • Baseline and 24-hour postoperative glucose values • Postoperative infection assessed; however length of follow-up was 7 days. Criteria for wound infection were redness of the scar, swollen skin around the scar, and heat and pain around the scar. Owing to the short follow-up, data on postoperative infection were not included in this meta-analysis.
Notes	Sources of funding <ul style="list-style-type: none"> • Not reported in the article Conflicts of interests <ul style="list-style-type: none"> • Not reported in the article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	No dropouts documented

Selective reporting (reporting bias)	Unclear risk	Protocol was not published, and all expected outcomes were reported
Other bias	High risk	Very little information in the report

Zhou 2012

Methods	<ul style="list-style-type: none"> Randomized controlled trial conducted at a single centre in China Enrolment took place from 2009 to 2010.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Adult patients undergoing thyroid surgery <p>Exclusion criteria</p> <ul style="list-style-type: none"> Antiemetic therapy within 48 hours before surgery Depression Chronic pain disorder Gastrointestinal disease Insulin-dependent diabetes mellitus Pregnancy < 18 years of age Known malignant disease Previous thyroid or neck surgery <p>Per-protocol analysis</p> <ul style="list-style-type: none"> Patients who underwent extended lymphadenectomy because of positive findings in the fresh frozen tissue analysis and those who were not given standard anaesthesia and postoperative management were also excluded. <p>168 adult patients undergoing thyroid surgery were randomized into 3 groups</p> <ul style="list-style-type: none"> 56 patients to the dexamethasone group, 50 analysed; 56 to the tropisetron group, 50 analysed; 56 to the dexamethasone plus tropisetron group, 50 analysed Dexamethasone and dexamethasone plus tropisetron groups were combined as the intervention group in this meta-analysis. Mean age: 48 years 24% male Average duration of surgery: 74 to 82 minutes
Interventions	8 mg dexamethasone immediately before induction vs 5 mg tropisetron immediately before induction
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Nausea and vomiting (assessed on a 4-point scale at 0 to 6 hours postoperatively and at 6 to 48 hours postoperatively) Pain (postoperative pain assessed on VAS) <p>Secondary outcomes</p> <ul style="list-style-type: none"> Satisfaction scores at 24 hours postoperatively Postoperative complications like laryngeal nerve palsy Hypoparathyroidism Postoperative bleeding and wound infection Postoperative stay and hospital cost for first 24 hours

	<ul style="list-style-type: none">● Wound infection/wound healing assessed 30 days after surgery (no definition provided)	
Notes	Sources of funding <ul style="list-style-type: none">● Not stated Conflict of interest <ul style="list-style-type: none">● None declared	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	High risk	Random number list on a computer spread sheet
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Personnel not part of the study prepared study drug. Unknown if participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for drop-outs documented
Selective reporting (reporting bias)	Unclear risk	The study was registered at a Chinese trial register
Other bias	Unclear risk	Unknown

Acronyms and abbreviations used in this table

ANZCA: Australian and New Zealand Anaesthetic Counsel; **AP:** angina pectoris; **ASA PS:** American Association of Anesthesiologists Physical Status; **ASEPSIS:** name of scoring questionnaire of delayed wound healing; **AUC:** area under curve; **BMI:** body mass index; **BSSO:** bilateral split mouth osteotomy; **CABG:** coronary artery bypass graft operation; **CDC:** Centers for Disease Control and Prevention; **CPB:** cardiac pulmonary bypass; **COPD:** obstructive lung disease; **CRP:** C-reactive protein; **DM:** diabetes mellitus; **ECMC:** experimental cancer medicine centre; **ECRP:** endoscopic retrograde cholangiopancreatography; **ELISA:** enzyme-linked immuno sorbent assay; **EQ-5D-3L:** a standardized measure of health status; **FACIT-F:** Functional Assessment of Chronic Illness Therapy-Fatigue; **GERD:** gastro-oesophageal reflux disease; **Hb:** haemoglobin; **HbA1c:** glycated haemoglobin; **IBD:** inflammatory bowel disease; **ICMJE:** International Committee of Medical Journal Editors; **ICU:** intensive care unit; **IL:** interleukin; **ISB:** interscalene block; **LC:** laparoscopic cholecystectomy; **LFNF:** laparoscopic floppy Nissen fundoplication; **MI:** myocardial infarction; **MIO:** maximal interincisal opening; **NRS:** numeric rating scale; **NSAID:** non-steroidal anti-inflammatory drug; **PACU:** postoperative care unit; **PCA:** patient-controlled analgesia; **PONV:** postoperative nausea and vomiting; **QoR-40:** Quality of Recovery Questionnaire; **ROM:** range of motion; **SGOT:** liver enzymes; **SGPT:** liver enzymes; **SSI:** surgical site infection; **TKA:** total knee arthroplasty; **VAS:** visual analogue scale; **VRS:** verbal rating scale; **WBC:** white blood cell count.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbaszadeh 2012	Randomized controlled trial including 185 participants undergoing CABG surgery. Dexamethasone 6 mg + 6 mg vs placebo. Excluded: length of follow-up: 3 days
Al-Shehri 2004	Randomized placebo-controlled trial including 30 participants undergoing tonsillectomy. Dexamethasone 3 doses of 6 mg vs placebo. Excluded: length of follow-up: 14 days
Bianchin 2007	Randomized controlled trial including 80 participants undergoing cholecystectomy. Dexamethasone 8 mg vs placebo. Excluded: length of follow-up: 4 days
Coloma 2001	Randomized controlled trial including 80 participants undergoing outpatient anorectal surgery. Dexamethasone 4 mg vs placebo. Excluded: length of follow-up: 10 days
Halvorsen 2003	Randomized controlled trial including 300 participants undergoing CABG surgery. Dexamethasone 2 doses of 4 mg vs placebo. Excluded: length of follow-up: 6 days
Ho 2001	Randomized controlled trial including 225 women undergoing a hysterectomy. Dexamethasone 10 mg vs 5 mg vs 2.5 mg vs droperidol vs saline. Excluded: length of follow-up: 7 to 8 days
Jung 2013	Randomized controlled trial including 110 participants undergoing microlaryngeal surgery. Dexamethasone 0.2 mg/kg vs saline. Excluded: length of follow-up: until first visit in outpatient clinic, unclear after how many days
Kara 1999	Randomized controlled trial in 55 participants undergoing rhinoplasty. Dexamethasone 10 mg vs saline. Excluded: length of follow-up: 9 days
Lei 2018a	Randomized controlled trial including 110 participants undergoing total hip arthroplasty. Dexamethasone 10 mg vs saline. Excluded: length of follow-up: 14 days
Liu 2001	Randomized controlled trial including 80 participants undergoing tympanomastoid surgery. Dexamethasone 10 mg vs saline. Excluded: length of follow-up: during hospital stay
Nasiri 2013	Randomized controlled trial including 64 participants undergoing thyroid surgery, Dexamethasone vs saline. Excluded: length of follow-up: 6 days. Glucose measured once - unclear when
Pasternak 2004	Study in 20 participants undergoing a craniotomy. Dexamethasone vs placebo. Excluded: not a randomized study. Dexamethasone was administered based on a clinical decision
Sethi 2016	Study in 60 participants undergoing a craniotomy. Dexamethasone vs saline. Excluded: not a randomized study. Dexamethasone was administered based on a clinical decision
Snall 2014	Post hoc analyses of completed study. Participants were selected from a larger cohort including patients with facial fractures

(Continued)

Thangaswamy 2010	Randomized controlled trial including 55 participants undergoing a hysterectomy. Dexamethasone 4 mg vs 8 mg vs placebo. Excluded: length of follow-up: 7 days
Tolver 2012	Randomized controlled trial including 80 men undergoing a transabdominal, preperitoneal inguinal hernia repair. Dexamethasone 8 mg vs placebo Excluded: length of follow-up: 2 days
Wang 2000	Randomized controlled trial in 225 women undergoing thyroidectomy. Dexamethasone 10 mg vs 5 mg vs 2.5 mg vs 1.25 mg vs saline. Excluded: length of follow-up: 10 days
Wang 2001	Randomized controlled trial in 180 participants undergoing a caesarean section. Dexamethasone 10 mg vs 5 mg vs 2.5 mg. Excluded: length of follow-up: 6 days
Weber 1994	Randomized controlled trial in 23 participants undergoing orthognathic surgery. Dexamethasone 16 mg vs placebo. Excluded: length of follow-up: 3 days
Wu 2007	Randomized controlled trial in 120 women undergoing a caesarean section. Dexamethasone 8 mg vs 4 mg vs placebo. Excluded: length of follow-up: 6 days

Abbreviation used in this table

CABG: coronary artery bypass graft.

Characteristics of studies awaiting assessment [ordered by study ID]

Ko-Iam 2015

Methods	Double-blind randomized controlled trial (parallel design)
Participants	100 patients, ASA I or II undergoing elective laparoscopic cholecystectomy
Interventions	<ul style="list-style-type: none"> • Treatment group received 8 mg dexamethasone and 10 mg metoclopramide • Control group received 10 mg metoclopramide and normal saline solution 1.6 mL
Outcomes	<ul style="list-style-type: none"> • PONV • Pain Assessed at 2, 6, 12, and 24 hours postoperatively and at discharge
Notes	"No postoperative complications occurred in both groups". We were unable to retrieve the full text of this publication

Simogai 2016

Methods	Randomized trial
Participants	Patients undergoing surgery
Interventions	Participants received 0 mg, 1.65 mg, 3.3 mg, or 4.95 mg dexamethasone
Outcomes	<ul style="list-style-type: none">Postoperative nausea and vomiting
Notes	Full text requested but not retrieved

Acronyms and abbreviations used in this table

ASA: American Association of Anesthesiologists; PONV: postoperative nausea and vomiting.

Characteristics of ongoing studies [ordered by study ID]

Kitcharanant 2016

Trial name or title	Effects of perioperative intravenous dexamethasone on the severity of persistent postsurgical pain after total knee arthroplasty: a prospective, randomized, double-blind, placebo-controlled trial
Methods	Parallel randomized double-blind trial
Participants	70 patients with osteoarthritis of the knee
Interventions	Dexamethasone vs normal saline
Outcomes	<ul style="list-style-type: none">Postsurgical pain: modified WOMAC scores for pain at 12 weeks postoperative
Starting date	October 2016
Contact information	nk_win@hotmail.com
Notes	Expected end date: June 2017

Sidhu 2017

Trial name or title	Perioperative administration of dexamethasone and infection trial
Methods	Multi-centre prospective double-blind active-control parallel-assessment stratified pragmatic non-inferiority safety and efficacy study
Participants	<ul style="list-style-type: none">8880 adult patientsASA physical status I to IVUndergoing elective or expedited (non-cardiac) surgery of at least 2 hours' durationUsing general anaesthesia with or without regional block

Sidhu 2017 (Continued)

	<ul style="list-style-type: none"> • With a single (or multiple) surgical skin incision(s) > 5 cm in length and a minimum anticipated hospital stay of at least 1 night
Interventions	Dexamethasone vs active control
Outcomes	Primary outcome <ul style="list-style-type: none"> • Surgical site infection within 30 days of surgery
Starting date	Enrolling patients
Contact information	jaspreet.sidhu@monash.edu
Notes	www.paddi.org.au

Wang 2018

Trial name or title	Dexamethasone, flurbiprofen axetil, and delirium after lung cancer surgery
Methods	Randomized controlled trial
Participants	844 participants
Interventions	Dexamethasone and flurbiprofen axetil vs dexamethasone and lipid microsphere vs normal saline and flurbiprofen vs normal saline and lipid microsphere
Outcomes	<ul style="list-style-type: none"> • Delirium • Length of hospital stay • Postoperative complications
Starting date	27 June 2017
Contact information	wangdongxin@hotmail.com
Notes	ClinicalTrials.gov Identifier: NCT03200600

Acronyms and abbreviations used in this table

ASA: American Association of Anesthesiologists; **WOMAC:** Western Ontario and McMaster University Arthritis Index.

DATA AND ANALYSES

Comparison 1. Dexamethasone versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative systemic or wound infection	27	4931	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.80, 1.27]
1.1 Low dose (4 to 5 mg) of dexamethasone	4	641	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.62, 1.44]
1.2 Intermediate dose (8 to 10 mg) of dexamethasone	19	3637	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.69, 1.26]
1.3 High dose (12 to 20 mg) of dexamethasone	4	653	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [0.87, 2.95]
2 Subgroup analysis for postoperative systemic or wound infection: single vs multiple doses of dexamethasone	27	4931	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.80, 1.27]
2.1 Single dose of dexamethasone	25	4410	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.76, 1.22]
2.2 Multiple doses of dexamethasone	2	521	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.51 [0.75, 3.02]
3 Delayed wound healing	8	1072	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.28, 3.43]
3.1 Intermediate dose (8 to 10 mg) of dexamethasone	6	912	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.24, 3.96]
3.2 High dose (12 to 20 mg) of dexamethasone	2	160	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.06, 16.27]
4 Glycaemic response	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Change from baseline within 2 to 12 hours after surgery	10	595	Mean Difference (IV, Random, 95% CI)	13.31 [5.91, 20.71]
4.2 Change from baseline 24 hours after surgery	6	450	Mean Difference (IV, Random, 95% CI)	21.19 [-0.17, 42.55]
4.3 Change from baseline 10 to 24 hours after surgery in patients with diabetes	2	74	Mean Difference (IV, Random, 95% CI)	31.66 [14.54, 48.78]
5 Re-admission or unplanned hospital admission	4	339	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.39, 3.90]
6 Mortality	7	2646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.38, 1.66]
7 Sensitivity analysis excluding high risk of bias studies from Analysis 1.1	8	1860	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.75, 1.42]
7.1 Low dose (4 to 5 mg) of dexamethasone	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.12, 4.95]
7.2 Intermediate (8 to 10 mg) dose of dexamethasone	5	1646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.71, 1.39]

7.3 High dose (12 to 20 mg) of dexamethasone	2	192	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.99 [0.56, 7.10]
8 Sensitivity analysis excluding skewed glucose data	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Change from baseline to 2 to 12 hours after surgery	8	419	Mean Difference (IV, Random, 95% CI)	16.74 [8.88, 24.60]
8.2 Change from baseline to 24 hours after surgery	4	352	Mean Difference (IV, Random, 95% CI)	33.16 [6.56, 59.76]

Analysis 1.1. Comparison 1 Dexamethasone versus control, Outcome 1 Postoperative systemic or wound infection.

Review: Adverse side effects of dexamethasone in surgical patients

Comparison: 1 Dexamethasone versus control

Outcome: 1 Postoperative systemic or wound infection

(Continued . . .)

Analysis 1.2. Comparison 1 Dexamethasone versus control, Outcome 2 Subgroup analysis for postoperative systemic or wound infection: single vs multiple doses of dexamethasone.

Review: Adverse side effects of dexamethasone in surgical patients

Comparison: 1 Dexamethasone versus control

Outcome: 2 Subgroup analysis for postoperative systemic or wound infection: single vs multiple doses of dexamethasone

(Continued ...)

Analysis 1.3. Comparison 1 Dexamethasone versus control, Outcome 3 Delayed wound healing.

Review: Adverse side effects of dexamethasone in surgical patients

Comparison: 1 Dexamethasone versus control

Outcome: 3 Delayed wound healing

Analysis 1.4. Comparison 1 Dexamethasone versus control, Outcome 4 Glycaemic response.

Review: Adverse side effects of dexamethasone in surgical patients

Comparison: 1 Dexamethasone versus control

Outcome: 4 Glycaemic response

(Continued ...)

(... Continued)

Analysis 1.5. Comparison 1 Dexamethasone versus control, Outcome 5 Re-admission or unplanned hospital admission.

Review: Adverse side effects of dexamethasone in surgical patients

Comparison: 1 Dexamethasone versus control

Outcome: 5 Re-admission or unplanned hospital admission

Analysis 1.6. Comparison 1 Dexamethasone versus control, Outcome 6 Mortality.

Review: Adverse side effects of dexamethasone in surgical patients

Comparison: 1 Dexamethasone versus control

Outcome: 6 Mortality

Analysis I.7. Comparison I Dexamethasone versus control, Outcome 7 Sensitivity analysis excluding high risk of bias studies from Analysis I.1.

Review: Adverse side effects of dexamethasone in surgical patients

Comparison: I Dexamethasone versus control

Outcome: 7 Sensitivity analysis excluding high risk of bias studies from Analysis I.1

Analysis 1.8. Comparison 1 Dexamethasone versus control, Outcome 8 Sensitivity analysis excluding skewed glucose data.

Review: Adverse side effects of dexamethasone in surgical patients

Comparison: 1 Dexamethasone versus control

Outcome: 8 Sensitivity analysis excluding skewed glucose data

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor: [Dexamethasone] explode all trees
- #2 dexamethasone:ti,ab,kw (Word variations have been searched)
- #3 #1 or #2
- #4 MeSH descriptor: [Perioperative Period] explode all trees
- #5 MeSH descriptor: [Perioperative Care] explode all trees
- #6 MeSH descriptor: [Anesthesia, General] explode all trees
- #7 MeSH descriptor: [Postoperative Nausea and Vomiting] explode all trees
- #8 perioperat* or surgery or anesthesia or anaesthesia or postoperat* or PONV:ti,ab,kw (Word variations have been searched)
- #9 MeSH descriptor: [Wound Healing] explode all trees
- #10 MeSH descriptor: [Postoperative Care] explode all trees
- #11 MeSH descriptor: [Postoperative Period] explode all trees
- #12 MeSH descriptor: [Postoperative Complications] explode all trees
- #13 MeSH descriptor: [Blood Glucose] explode all trees
- #14 MeSH descriptor: [Analgesia] explode all trees
- #15 wound* near/5 healing:ti,ab,kw (Word variations have been searched)
- #16 postoperative near/5 infection*:ti,ab,kw (Word variations have been searched)
- #17 post-operative near/5 infection*:ti,ab,kw (Word variations have been searched)
- #18 surgery or surgical or an?esthesia or analgesia:ti,ab,kw (Word variations have been searched)
- #19 (hyp?rglyc?emic or glycy?emic) near/3 response:ti,ab,kw (Word variations have been searched)
- #20 blood glucose* or perioperative or postoperative:ti,ab,kw (Word variations have been searched)
- #21 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
- #22 #3 and #21 in Trials

Appendix 2. MEDLINE (Ovid SP) search strategy

- 1. exp Dexamethasone/ or dexamethasone.ti,ab.
- 2. exp Wound Healing/ or Postoperative Care/ or Postoperative Complications/ or Postoperative Period/ or "Postoperative Nausea and Vomiting"/ or Perioperative Care/ or Perioperative Period/ or Anesthesia, General/ or (wound* adj5 healing).mp. or (post?operative adj5 infection*).mp. or (surgery or surgical or an?esthesia or analgesia).ti,ab. or ((hyp?rglyc?emic or glycy?emic) adj3 response).ti,ab. or Blood Glucose/ or blood glucose*.ti,ab. or Analgesia/ or (perioperative or postoperative).ti,ab.
- 3. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh. (814437)
- 4. 1 and 2 and 3

Appendix 3. Embase search strategy

- #1
- 'dexamethasone'/exp OR dexamethasone.ti,ab
- #2
- 'wound healing'/exp OR 'postoperative period'/exp OR 'postoperative care'/exp OR 'postoperative complication'/de OR 'postoperative nausea and vomiting'/de OR 'perioperative period'/de OR 'general anesthesia'/de OR (wound* NEAR/5 healing) OR ((post-operative OR 'post operative') NEAR/5 infection*) OR surgery:ti,ab OR surgical:ti,ab OR an?esthesia:ti,ab OR analgesia:ti,ab OR (((hyp*rglyc*emic OR glycy*emic) NEAR/3 response):ti,ab) OR 'glucose blood level'/de OR 'blood glucose*:ti,ab OR 'analgesia'/de OR perioperative:ti,ab OR postoperative:ti,ab
- #3
- ('randomized controlled trial'/de OR 'controlled clinical trial'/de OR randomized:ab OR placebo:ab OR 'clinical trials as topic':de OR randomly:ab OR trial:ti) NOT ('animal'/de NOT ('human'/de AND 'animal'/de))
- #4

#1 AND #2 AND #3

Appendix 4. Web of Science search strategy

#3 AND #2 AND #1

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

TS=clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

TS=(post\$operative OR perioperative OR surgery OR surgical OR an\$esthesia OR analgesia OR blood glucose*) OR TS=(wound* NEAR/5 healing) OR TS=((hyperglyc\$emic OR glyc\$emic) NEAR/3 response)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

TS=Dexamethason*

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

Appendix 5. Data extraction form

Review title or ID

Study ID (*surname of first author and year first full report of study was published (e.g. Smith 2001)*)

Report IDs of other reports of this study (*e.g. duplicate publications, follow-up studies*)

Notes:

I. General information

Date form completed (<i>dd/mm/yyyy</i>)	
Name/ID of person extracting data	
Report title (<i>title of paper/abstract/report that data are extracted from</i>)	
Report ID (<i>ID for this paper/abstract/report</i>)	
Reference details	
Report author contact details	
Publication type (<i>e.g. full report, abstract, letter</i>)	
Study funding sources (<i>including role of funders</i>)	
Possible conflicts of interest (<i>for study authors</i>)	
Notes: +	

2. Study eligibility

Study characteristics	Eligibility criteria (<i>Insert eligibility criteria for each characteristic as defined in the Protocol</i>)	Yes	No	Unclear	Location in text (<i>pg & ¶/fig/table</i>)
Type of study	Randomized controlled trial				

(Continued)

Participants	Adult participants undergoing surgery under general or regional anaesthesia				
Types of interventions	One study arm randomized to dexamethasone (max 20 mg, including repeated doses) Other study arm randomized to no treatment/placebo/antiemetic/analgesic (no corticosteroid allowed as comparative arm)				
Types of outcome measures	Wound infection Delayed wound healing Glycaemic response				
INCLUDE		EXCLUDE			
When outcome measures are missing in the report: contact corresponding author					
Date of contact:					
Received information:					
Reason for exclusion					
Notes:					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

	Description <i>Include comparative information for each group (i.e. intervention and control), if available</i>	Location in text <i>(pg & ¶/fig/table)</i>
Population description <i>(from which study participants are drawn)</i>		
Setting <i>(type of surgery)</i>		
Inclusion criteria		

(Continued)

Exclusion criteria		
Design (e.g. parallel, cross-over, cluster)		
Unit of allocation (by individuals, cluster/groups, or body parts)		
Sufficient time of follow-up	Yes No Unclear	Length:
Notes:		

4. 'Risk of bias' assessment

See Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions.

Domain	Risk of bias			Support for judgement	Location in text (pg & #/fig/table)
	Low risk	High risk	Unclear risk		
Random sequence generation (selection bias)					
Allocation concealment (selection bias)					
Blinding of participants and personnel (performance bias)				Outcome group: all	
(if required)				Outcome group:	
Blinding of outcome assessment (detection bias)				Outcome group: all	
(if required)				Outcome group:	
Incomplete outcome data (attrition bias)					

(Continued)

Selective outcome reporting? (reporting bias)					
Other bias					
Notes:					

5. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Total no. randomized (or total pop. at start of study for NRCTs)		
Baseline imbalances		
Withdrawals and exclusions (if not provided below by outcome)		
Age		
Sex		
Race/ethnicity?		
ASA classification		
Co-morbidities?		
Other treatment received (additional to study intervention)		
Type of surgery		
Duration of surgery (min)		
Subgroups measured		
Subgroups reported		

(Continued)

Notes:

6. Intervention groups

Copy and paste table for each intervention and comparison group.

Intervention group 1

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Group name		
No. randomized to group (specify whether no. people or clusters)		
Description (include sufficient detail for replication, e.g. content, dose, components)		
Dose and timing (e.g. frequency, duration of each episode)		
Co-interventions		
Economic variables (i.e. intervention cost, changes in other costs as result of intervention)		
Notes:		

Comparison group 2

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Group name		
No. randomized to group (specify whether no. people or clusters)		
Description (include sufficient detail for replication, e.g. content, dose, components)		

(Continued)

Dose and timing (e.g. frequency, duration of each episode)		
Co-interventions		
Economic variables (i.e. intervention cost, changes in other costs as result of intervention)		
Notes:		

7. Outcomes

Copy and paste table for each outcome.

Outcome 1

	Reported in paper	Location in text (pg & 1/fig/table)
Postoperative infection		
Delayed wound healing		
Glycaemic response (preoperative and postoperative glucose)		
Length of hospital stay		
Re-admission		
C-reactive protein		
30-day all-cause mortality		
Quality of life		
Notes:		

8. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome

	Description as stated in report/paper				Location in text <i>(pg & ¶/fig/table)</i>
Comparison					
Outcome					
Subgroup					
Results	Intervention		Comparison		
	No. events	No. participants	No. events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis <i>(by individuals, cluster/groups, or body parts)</i>					
Notes:					

Continuous outcome

	Description as stated in report/paper				Location in text (pg & ¶/fig/table)
Comparison					
Outcome					
Subgroup					
Post intervention or change from base-line?					
Results	Intervention		Comparison		

(Continued)

	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							
Unit of analysis (by individuals, cluster/groups, or body parts)							
Statistical methods used and appropriateness of these methods (e. g. adjustment for correlation)							
Notes:							

Other outcome

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Comparison		
Outcome		
Subgroup		
Time point (specify whether from start or end of intervention)		

(Continued)

Results	Intervention result	SD (or other variance)	Control result	SD (or other variance)	
	Overall results		SE (or other variance)		
No. participants	Intervention		Control		
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis (<i>by individuals, cluster/ groups, or body parts</i>)					
Notes:					

9. Other information

	Description as stated in report/paper	Location in text (pg & Iffig/table)
References to other relevant studies		

Appendix 6. Cochrane risk of bias domains

Random sequence generation

- Assessment of randomization: the sufficiency of the method in producing two comparable groups before intervention
- Grading:
 - 'Low risk': a truly random process (e.g. random computer number generator, coin tossing, throwing dice)
 - 'High risk': any non-random process (e.g. date of birth; date of admission by hospital, by clinic record number, or by availability of the intervention)
 - 'Unclear risk': if information is insufficient to judge on risk of bias

Allocation concealment

- Allocation method prevented investigators or participants from foreseeing assignment
- Grading:
 - 'Low risk': central allocation or sealed envelopes
 - 'High risk': if an open allocation schedule or other unconcealed procedure was used
 - 'Unclear risk': if information is insufficient to judge on risk of bias

Blinding of participants and personnel

- Assessment of appropriate blinding of investigation team and participants: person responsible for participants' care, participants, and eventual others
- Grading:
 - 'Low risk': we considered blinding as adequate if participants and personnel were kept unaware of intervention allocations after inclusion of participants in the study and if the method of blinding involved a placebo or an intervention disguised in the same manner as a placebo
 - 'High risk': not double-blinded; categorized as an open-label study or without the use of a placebo or an intervention disguised in the same manner as a placebo
 - 'Unclear': blinding not described

Blinding of outcome assessor

- Assessment of appropriate blinding of outcome assessor. Outcomes should not be influenced by the method of blinding used
- Grading:
 - 'Low risk': we considered blinding as adequate if outcome assessors were kept unaware of intervention allocations after inclusion of participants in the study and if the method of blinding involved a placebo or an intervention disguised in the same manner as a placebo. Outcomes should not be influenced by the method of blinding used
 - 'High risk': not double-blinded; categorized as an open-label study or without the use of a placebo or an intervention disguised in the same manner as a placebo
 - 'Unclear risk': blinding not described

Incomplete outcome data

- Completeness of outcome data including attrition and exclusions
- Grading:
 - 'Low risk': if the numbers and the reasons for dropouts and withdrawals in the intervention groups were described and if the reasons for dropouts were not likely to be related to the true outcome, or if it was specified that no dropouts or withdrawals occurred
 - 'High risk': if no description of dropouts and withdrawals was provided and if missing data were likely to be related to true outcomes
 - 'Unclear risk': if nothing was specifically stated

Selective reporting

- The possibility of selective outcome reporting
- Grading:
 - 'Low risk': if the reported outcomes were those prespecified in an available study protocol or official trial registration, registered before trial initiation
 - 'High risk': if not all prespecified outcomes were reported, or if they were reported using non-prespecified subscales or were reported incompletely, or if the report failed to include a key outcome that would have been expected to have been reported for such a study
 - 'Unclear risk': when no study protocol or official trial registration was available. Retrospectively registered trials were considered as unclear risk

Other bias

- Assessment of any possible sources of bias not addressed in domains 1 to 5
- Grading:
 - 'Low risk': if the report appeared to be free of such bias
 - 'High risk': if at least one important bias related to study design was present, or there was early stopping due to some data dependent process, extreme baseline imbalance, claimed fraudulence, or other problems
 - 'Unclear risk': insufficient information or evidence that an identified problem would have introduced bias

WHAT'S NEW

Date	Event	Description
31 October 2018	Amended	One of the studies included in this review (Schietroma 2013), has now been retracted (Piccirillo 2018). This study will be excluded from the published Cochrane review. The updated review will be republished shortly. When the Cochrane review was originally published there was a published expression of concern regarding the study (Piccirillo 2017), which was regarded as at high risk of bias.

HISTORY

Protocol first published: Issue 11, 2015

Review first published: Issue 8, 2018

Date	Event	Description
4 October 2018	Amended	Acknowledgement section amended to include Co-ordinating Editor

CONTRIBUTIONS OF AUTHORS

Conceiving the review: JP, JH.
Co-ordinating the review: JP.
Undertaking manual searches: JP, VFR.
Screening search results: JP, VFR.
Organizing retrieval of papers: JP, VFR.
Screening retrieved papers against inclusion criteria: JP, VFR.
Appraising quality of papers: JP, VFR.
Abstracting data from papers: JP, VFR.
Writing to authors of papers for additional information: JP.
Providing additional data about papers: JP.
Obtaining and screening data on unpublished studies: JP.
Managing data for the review: JP, SVD.
Entering data into Review Manager ([Review Manager 2014](#)): JP.
Analysing RevMan statistical data: JP, SVD.
Performing other statistical analysis not using RevMan: JP, SVD, JH.
Interpreting data: JP, SVD, HDV, MH, PK, BP, JH.
Making statistical inferences: JP, SVD, HDV, MH, PK, BP, JH.
Writing the review: JP, HDV, MH, PK, BP, JH.
Securing funding for the review: BP.
Performing previous work that was the foundation of the present study: JP, JH.
Serving as guarantor for the review (one review author): JP.
Taking responsibility for reading and checking the review before submission: JP.

DECLARATIONS OF INTEREST

Jorinde AW Polderman: none declared.

Violet Farhang-Razi: none declared.

Susan Van Dieren: none declared.

Peter Kranke.

- Consultancy (money paid to author): MSD; Fresenius Kabi.
- Grants/grants pending (money to institution): Fresenius Kabi; Premier Research (Acacia Ltd).
- Payment for lectures including service on speakers bureaus (money paid to author): Fresenius Kabi; MSD.

None of the companies listed for Dr Kranke's COI have any relation to the current work.

J Hans DeVries.

- Consulting fee or honorarium: Johnson.
- Board membership (money to institution): Novo Nordisk; Johnson & Johnson; Roche Diagnostics.
- Consultancy (money to institution): Sanofi.
- Grants/grants pending (money to institution): Dexcom; Senseonics; Novartis; Novo Nordisk; ECHO Therapeutics.
- Payment for lectures including service on speakers bureaus (money to institution): Medtronic; Dexcom; Eli Lilly; Roche.
- Diagnostics: Novo Nordisk; Sanofi; MSD.
- Dr DeVries's institution received research support, fees for advice, and speaker's fees from Abbott Diabetes Care; Dexcom Inc; Eli Lilly; Medtronic; Novo Nordisk; Novartis; Roche Diagnostics; and Sanofi.

None of these bear any relation to the current work. None of the companies listed market products/drugs in this area.

Markus W Hollmann.

- Board membership: IARS; *Anesthesia & Analgesia*.
- Consultancy (money to institution): Pfizer; Eurocept; B Braun; ECHO; Fresenius; Merck.
- Grants/grants pending (money to institution): ZonMw.
- Payment for lectures including service on speakers bureaus (money to institution): Eurocept/Octapharm; Merck; B Braun; Pfizer.
- Payment for development of educational presentations (money to institution): Merck.

None of the above declared relationships have influenced this work in that all activities are completely unrelated to the work presented in this review. None of the companies listed market products/drugs in this area.

Benedikt Preckel.

- Grants/grants pending (money to institution): European Foundation for the Study of Diabetes; Society of Cardiovascular Anesthesia; Dutch Society of Anesthesia; ZonMw (Dutch Organization for Health Care).
- Payment for lectures including service on speakers bureaus (money to institution): Philips Germany; Abbott Netherlands.

None of the companies listed market products/drugs in this area.

Jeroen Hermanides.

- Research grants: European Foundation for the Study of Diabetes, European Society for Anaesthesiology. Pending funding (to institution) for investigator-initiated trial from NovoNordisk. Speaker fee: Eli Lilly.

None of the above declared relationships have influenced this work in that all activities are completely unrelated to the work presented in this review. None of the companies listed market products/drugs in this area.

SOURCES OF SUPPORT

Internal sources

- Academic Medical Centre, Netherlands.

The Department of Anaesthesiology provided sufficient time to work on the review.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol ([Polderman 2015a](#)).

- **Objectives:** we added 'a steroid load of' to the wording of the objectives. Furthermore, we changed time to wound healing to delayed wound healing to be consistent throughout the review.
- **Types of interventions:** we changed 'the control group can be...:' to 'which could be either.'
- **Outcomes:** the published protocol stated, 'measured within 30 days', and in the following sentence, 'should be at least 30 days'. To avoid confusion, this has been changed to 'there needs to be a sufficient follow-up period of 30 days or longer'. Furthermore, we elaborated on how we measured our primary and secondary outcomes.
- **Electronic searches:** we included information on our search strategy for unpublished studies in the electronic searches section and removed this from the searches in other resources section. We updated the search in the other resources section with information from our handsearching strategy (which was previously noted in the electronic search section).
- **Assessment of risk of bias in included studies:** our strategy for assessment of risk of bias domains has been moved to [Appendix 6](#), as apposed to the main text in the protocol.
- **Data collection and analysis:** we constructed one 'Summary of findings' table for the comparison dexamethasone versus control, reporting on postoperative systemic or wound infection, delayed wound healing, and glycaemic control.
- **Measures of treatment effect:** we changed the following sentence: "We will present results on delayed wound healing as a summary risk ratio (RR) with 95% CIs. We will calculate the MD of the change from baseline with corresponding 95% CIs in pre- and postoperative blood glucose between the dexamethasone and control group" to "As recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*, we used Peto's odds ratio to summarise study effects. This provides an unbiased estimate of the treatment effect and has been shown to be particularly appropriate in examining zero-event data. For the glycaemic response, we retrieved the change from baseline results, which is more objective than the final postoperative glucose measurement, as this latter highly depends on the preoperative value. Blood glucose and length of hospital stay often are not normally distributed and frequently are reported as median values with interquartile range. We converted these data to mean values with standard deviations to be able to pool the data ([Hozo 2005](#)). Regarding secondary outcomes, we calculated the MD with 95% CIs for length of stay and CRP between dexamethasone and control groups. We calculated Peto's odds ratio for the number of unplanned admissions and 30-day all-cause mortality".
- **Unit of analysis:** this section has been updated; we included more information about continuous outcomes and data presented as graphs, which was not included in the protocol. (For the continuous glucose outcomes, we used the mean of the change from baseline with the standard deviation of each group and the number of participants in each group. For the other continuous outcomes, we used mean, standard deviation, and the number of patients in each group. We did not extract data and included in our meta-analysis only data that were presented graphically, as we were unable to determine the exact mean and standard deviations from these figures. Instead, we described these results in the respective section.
- **Subgroup analysis and investigation of heterogeneity:** we moved the following sentences from the sensitivity analysis to the subgroup analysis section: "We carried out a subgroup analysis for different doses (e.g. 4 mg to 5 mg vs 8 mg to 20 mg) of

dexamethasone, to estimate whether the effect is robust for all doses. Furthermore, we carried out a subgroup analysis for a single dose versus multiple doses of dexamethasone, to estimate whether the effect was comparable”.

- **Sensitivity analysis:** we moved the following sentence from the subgroup analysis to the sensitivity analysis section: “Furthermore, we included a subgroup analysis for the following outcomes: postoperative risk of systemic or wound infection, delayed wound healing, and glycaemic control, while excluding studies with high risk of bias”. We added the following sentence to this section: “Furthermore, we carried out a sensitivity analysis while excluding trials with non-normality glucose data, to assess if these trials induced a systematic bias”.

- The following text: “We used the GRADE system to assess...differences of opinion by discussion” was moved to a subheading “Grade analysis”, below “Sensitivity analysis”. This text was first located under “Data collection and analysis”.

NOTES

31 October 2018

One of the studies included in this review ([Schietroma 2013](#)), has now been retracted ([Piccirillo 2018](#)). This study will be excluded from the published Cochrane review. The updated review will be republished shortly. When the Cochrane review was originally published there was a published expression of concern regarding the study ([Piccirillo 2017](#)), which was regarded as at high risk of bias.