Perioperative hyperglycaemia and its treatment in patients with diabetes mellitus

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ADVERSE SIDE EFFECTS OF DEXAMETHASONE IN SURGICAL PATIENTS

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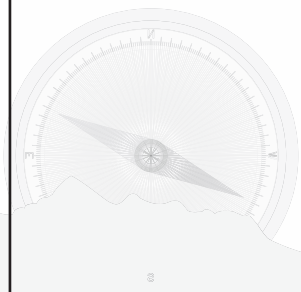

Abstract

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 the development of diabetes mellitus. However, whether a single steroid load during surgery has negative effects in the postoperative period has not yet been studied.

Objectives: We assessed the effects of an incidental steroid load of dexamethasone on postoperative infection, delayed wound healing and blood glucose change in adult surgical patients. We included a planned subgroup analysis for patients with and without diabetes.

Search methods: We searched MEDLINE, Embase, CENTRAL and the Web of Science for relevant articles on February 8th 2017. We searched without language or date restriction two clinical trial registries to identify ongoing studies and handsearched the reference lists of relevant publications to identify all eligible trials.

Selection criteria: We searched for randomised controlled trials comparing an incidental steroid load of dexamethasone with a control group not treated with steroids in adult patients undergoing surgery. The studies were required to have a sufficient follow-up of 30 days to properly assess the number of postoperative infections, delayed wound healing and the glycaemic response.

Data collection and analysis: Two authors independently screened the studies for eligibility, extracted data from relevant studies and assessed all included studies for bias. Differences were resolved by discussion. Included studies were pooled in a meta-analysis. We calculated odds ratio's (OR's) and risk ratio's (RR's) for dichotomous outcomes and mean differences (MD's) for continuous outcomes. A funnel plot was created for the primary outcome postoperative (wound or systemic) infection.

Main results: We included 32 studies in the meta-analysis, of which 23 studies (3339 participants) reported on postoperative (wound or systemic) infections, the sensitivity analysis, excluding zero event trials on postoperative infections, included 14 studies (2535 participants). Eight studies (1072 participants) reported on delayed wound healing, 10 studies (930 participants) reported on glycaemic control in all participants (majority without diabetes) and 2 studies (74 participants) reported on glycaemic control

in participants with diabetes. All studies were performed in adults undergoing a large variety of surgical procedures. We specifically looked at the comparison dexamethasone versus control. Pooling of the studies showed no increased risk of postoperative (wound or systemic) infections (sensitivity analysis 14 studies, 2535 participants, OR 0.94, 95% CI 0.65 to 1.34; I^2 = 8%) with a high level of evidence. In addition, no increased risk for delayed wound healing was found (low level of evidence). Patients at risk for delayed wound healing were not included in our meta-analysis. Lastly, a mild increase in glucose levels in participants without diabetes up to 24 hours after surgery was observed (MD 16 mg dl^{-1}, 95% CI 10 to 23; 910 participants; 10 studies; I^2= 47%) with a moderate level of evidence. We identified two studies reporting on glycaemic response after dexamethasone in participants with diabetes within 24 hours after surgery (MD 32 mg dl^{-1}, 95% CI 15 to 49; I2=0%, 74 participants). The evidence for patients with diabetes was of low quality.

Authors' conclusions: A steroid load of dexamethasone does not increase the risk for postoperative infections in the general surgical population. However, only low quality evidence suggests that dexamethasone does not increase the risk of delayed wound healing. Participants with an increased risk for delayed wound healing, e.g. participants with diabetes or on immunosuppressive drugs, were not included in the randomised studies reporting on delayed wound healing included in this meta-analysis. Our findings should therefore 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. Concluding, dexamethasone still holds an important place in the treatment of postoperative nausea and vomiting or as adjuvant in pain treatment and is not associated with an increased risk of postoperative wound infections. Whether this influences wound healing in a clinically relevant way has to be established.

Background

Description of the condition

Dexamethasone has several indications and is frequently administered in the perioperative period. Firstly, 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 multimodal PONV prophylaxis, in order to achieve a PONV-free hospital (Kranke 2014). This would substantially increase the number of people exposed to dexamethasone in the perioperative period. Secondly, 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). Thirdly, 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 considering general (multimodal) prophylaxis using dexamethasone, there is a need for a comprehensive evaluation of the associated potential adverse effects (Bartlett 2013). This review therefore focused on the side effects of incidental dexamethasone application at a low dose in the perioperative period. Side effects are defined as postoperative systemic or wound infections, delayed wound healing or hyperglycaemia.

Description of the intervention

Dexamethasone is mostly administered for the prophylaxis of PONV and is effective as a single dose (4 mg to 10 mg) given intravenously during surgery (De Oliveira 2013). It has also 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 also the recommended dose for PONV prophylaxis (Gan 2014). Thus, the dose given intravenously during surgery for the above-mentioned reason ranges between 4 mg and 20 mg. After administration of the drug, the concentration of dexamethasone rises quickly and will peak 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 has many side effects, such as adrenal insufficiency, hyperglycaemia and even development of diabetes mellitus (Liu 2014). The anti-inflammatory and immunosuppressive properties, e.g. inhibition of pro-inflammatory cytokines, reduced ability of leucocytes to enter sites of infection

or tissue injury and inhibitory effects on T and B cells, have been suggested to have a negative effect on wound healing and might increase the risk of infection in 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 an increased risk of wound infections, both in patients 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 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 multimodal pain treatment (Dahl 2014; Polderman 2015b), the potential adverse effects of a single low dose of dexamethasone have only briefly been mentioned in previous meta-analyses (De Oliveira 2013; Waldron 2013). Due to the 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 with any of the indications mentioned above in order to guide clinical decision-making with regard to the risk-benefit ratio, both in patients 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. We included a planned subgroup analysis for patients with and without diabetes.

Methods

Criteria for considering studies for this review

Types of studies

We searched for randomised controlled trials (RCTs), irrespective of blinding status. There were no restrictions on publication date or language. We did not include quasi-randomised, 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 definition of the respective authors) undergoing surgery, both in-patient and day-case surgery, under general or regional anaesthesia.

We excluded studies with paediatric participants (according to the definition of the respective 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 results of the adult subgroup had to be reported separately.

Types of interventions

We considered RCTs comparing intravenous dexamethasone given during surgery to a control group, which could be no treatment, placebo or another antiemetic or analgesic drug. However, the drug in the control group must not have had any glucocorticosteroid properties. We excluded studies with 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 a maximum dose and included studies with repeated doses of dexamethasone up 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 (Carlisle 2006; 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 the assessment of postoperative infections or delayed wound healing or 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: The time of follow-up for this outcome measure should be 30 days or more. We used the authors' definition of postoperative systemic or wound infection. We measured the outcome dichotomous. We calculated the risk difference (RD).

Delayed wound healing: The time of follow-up for this outcome measure should be 30 days or more. We measured the proportion of wounds not healed within 30 days. We measured the outcome dichotomous and calculated the RD.

Glycaemic response within 24 hours, defined 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. We calculated the mean differences (MD) of the change from baseline.

Secondary outcomes

The length of hospital stay, measured in days on a continuous scale. We calculated the mean difference (MD).

Re-admission or unplanned hospital admission. We assessed this as a dichotomous outcome and calculated the RD.

C-reactive protein (CRP), measured in the first 24 hours perioperatively, measured on a continuous scale. We calculated the MD.

30-day all-cause mortality. We assessed this as a dichotomous outcome and calculated the RD.

Search methods for identification of studies

We searched for RCTs in surgical participants, receiving dexamethasone as an intervention, with a sufficient follow-up period (30 days or more) for adverse side effects. When it is stated in the results section that no adverse effects were found, but the 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 the details of the assessment of adverse side effects. We only considered studies addressing at least one of our primary outcomes with sufficient duration of follow-up for inclusion in this meta-analysis; however, as stated above, we documented all studies excluded based on lack of outcome data. We placed no restrictions on the time period covered by the search. We excluded studies published by Yoshitaka Fuji because of the suggested invalidity of the results (Carlisle 2012). We did not apply any full-text language restrictions. We translated papers when written in another language than English.

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies as outlined in Chapter 6.4 of the Cochrane Handbook of Systematic reviews of

Interventions (Higgins 2011). We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed interface) (1946 to Febuary 8th 2017), Embase (1947 to Febuary 8th 2017) and the Web of Science. The search strategy can be found in appendix 1, 2, and 3 of the online version of the protocol (Polderman 2015a)

We searched for ongoing and unpublished studies on the following web sites on February 28th 2017:

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

The search strategy was developed in consultation with the Information Specialist.

Searching other resources

We hand searched the reference lists of the original included articles to retrieve additional relevant studies. In addition, we hand searched the 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 used a data extraction form to extract the data from the relevant trials. We used the GRADE system to assess the methodological quality of the trials, to assess the quality of the body of evidence associated with specific outcomes (sensitivity analysis of) postoperative systemic or wound infection, (sensitivity analysis of) 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, readmission, length of hospital stay, CRP and mortality) in our review and to construct a 'Summary of findings' table using the GRADEpro software (Guyatt 2008). We constructed one summery of findings table for the comparison dexamethasone versus control, reporting on postoperative systemic or wound infection, the sensitivity analysis of the postoperative systemic or wound infection, delayed wound healing and glycaemic control in all participants patients (change from baseline to 2 to 24 hours) and in participants with diabetes (change from baseline to 10 to 24 hours). We included a sensitivity analysis in our summary of findings table, as this gives a better illustration of the clinical picture and is our main finding of the review. 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), the directness of the evidence, heterogeneity of the data, precision of effect

estimates and risk of publication bias. We resolved differences of opinion by discussion. When no agreement was found, a third author should make a decision, but this was not necessary during the review process. We used the Review Manager statistical package provided by Cochrane to analyse the data (RevMan 5.3).

Selection of studies

After merging the search results using EndNote software, we removed all duplicate records of the same report (Higgins 2011). Two authors (JP and VFR) independently screened the reports for eligibility based on title and abstract. When there was a difference in opinion, this was resolved by discussion between the two authors (JP and VFR). When necessary, we consulted a third author (JH). Subsequently, two 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 get the relevant information. We documented the studies excluded based on lack of outcome data.

Data extraction and management

Two authors (JP and VFR) independently extracted data from the included studies. We recorded all relevant data on the data extraction form, developed for the purpose of this review (see online version of protocol, appendix 4 Polderman 2015a), and 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 the participants (demographic characteristics, type and length of surgery); details of the type of intervention (dose, timing, additional medication); details of relevant outcomes (definition and time of measurement); details of relevant results.

Assessment of risk of bias in included studies

Two authors (JP and VFR) independently assessed the risk of bias using the following Cochrane 'Risk of bias' domains. This is written out in full in the online version of the protocol (Polderman 2015a)

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). We used the RD to summarize study effects. This provides an unbiased estimate of the treatment effect and has been shown to be particularly appropriate in examining zero event data. Furthermore, we carried out a sensitivity analysis excluding all trials with zero events to be able to estimate the effect of these trials. When the effect of the zero event trials was small, we calculated the odds ratio (OR) after exclusion of the

zero event trials. This was done to assess the effect on postoperative infections and on delayed wound healing.

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 are often not normally distributed and frequently reported as median with interquartile range. We converted these data to mean values with standard deviations in order to be able to pool the data (Hozo 2005).

Regarding the secondary outcomes, we calculated the MD with 95% CIs for length of stay and CRP between the dexamethasone and control group. We calculate the RDs for the number of unplanned admissions and 30-day all-cause mortality.

Unit of analysis issues

For a dichotomous outcome, we documented the total number of patients and the number of patients who experienced the outcome for each group. 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 patients in each group. For the other continuous outcomes we used the mean, standard deviation and number of patients in each group.

We did not extract and included data in our meta-analysis that were only 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.

Dealing with missing data

We attempted to retrieve relevant data by contacting the corresponding author of all studies with missing data for the outcome of adverse side effects. Furthermore, when more outcomes were reported as a composite endpoint, we contacted the investigators for 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 with a p-value < 0.05 and an I^2 statistic value $> 60\%$ as cut-off for statistical heterogeneity. When heterogeneity was identified, we explored possible causes. When we could not explain the heterogeneity, we proceeded with meta-

analysis using a random-effects model. However, when there was 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) are: selection bias, poor methodological quality leading to inflated effects in smaller studies, true heterogeneity, artefactual and chance.

Data synthesis
We used the Review Manager software to perform the analysis (RevMan 5.3). 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 in order 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. Furthermore, we included a subgroup analysis for the following outcomes: postoperative risk of systemic or wound infection, delayed wound healing and glycaemic control, excluding studies with a high risk of bias.

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

Sensitivity analysis
Furthermore, we carried out a sensitivity analysis for a single dose versus multiple doses of dexamethasone, to estimate whether the effect was comparable.

Results

Description of studies

See Summary of findings table (figure 1).

Dexamethasone compared to Control in surgical patients

Bibliography: Polderman JAW, Farhang-Razi V, Van Dieren S, Kranke P, DeVries JH, Hollmann MW, Preckel B, Hermanides J. Adverse side effects of dexamethasone in surgical patients. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Dexamethasone
Postoperative systemic or wound infection follow up: 30 days	3339 (23 RCTs)	⨁⨁⨁◯ MODERATE a	**RD 0.00** (-0.01 to 0.01)	60 per 1.000	**60 fewer per 1.000** (61 fewer to 59 fewer)
Sensitivity analysis postoperative wound or systemic infection follow up: 30 days	2535 (14 RCTs)	⨁⨁⨁⨁ HIGH	**OR 0.94** (0.65 to 1.37)	80 per 1.000	**4 fewer per 1.000** (27 fewer to 27 more)
Delayed wound healing follow up: 30 days	1072 (8 RCTs)	⨁⨁◯◯ LOW [a,b]	**RD 0.00** (-0.01 to 0.01)	9 per 1.000	**9 fewer per 1.000** (10 fewer to 9 fewer)
Glycaemic response - change from baseline all participants assessed with: mg/dl follow up: range 2 hours to 24 hours	930 (10 RCTs)	⨁⨁⨁◯ MODERATE c	-	The mean glycaemic response - change from baseline all participants was **0**	MD **16.47 higher** (9.52 higher to 23.42 higher)
Glycemic response - Change from baseline 10 to 24 hours postoperatively in patients with diabetes assessed with: mg/dl follow up: range 10 hours to 24 hours	74 (2 RCTs)	⨁⨁◯◯ LOW [c,d]	-	The mean glycemic response - Change from baseline 10 to 24 hours postoperatively in patients with diabetes was **0**	MD **31.66 higher** (14.54 higher to 48.78 higher)

*__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; **OR:** Odds ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small number of events
b. Three studies at high risk for selection, performance and detection bias
c. Wide confidence intervals
d. Small sample size

Figure 1. Summary of finding table.

Results of the search

We screened 5287 articles on title and abstract, 398 were identified for full text screening, of which 33 articles were included. 270 studies had the appropriate study design, however, their follow up was only 24 to 48 hours, and these studies were therefore subsequently excluded (Figure 2).

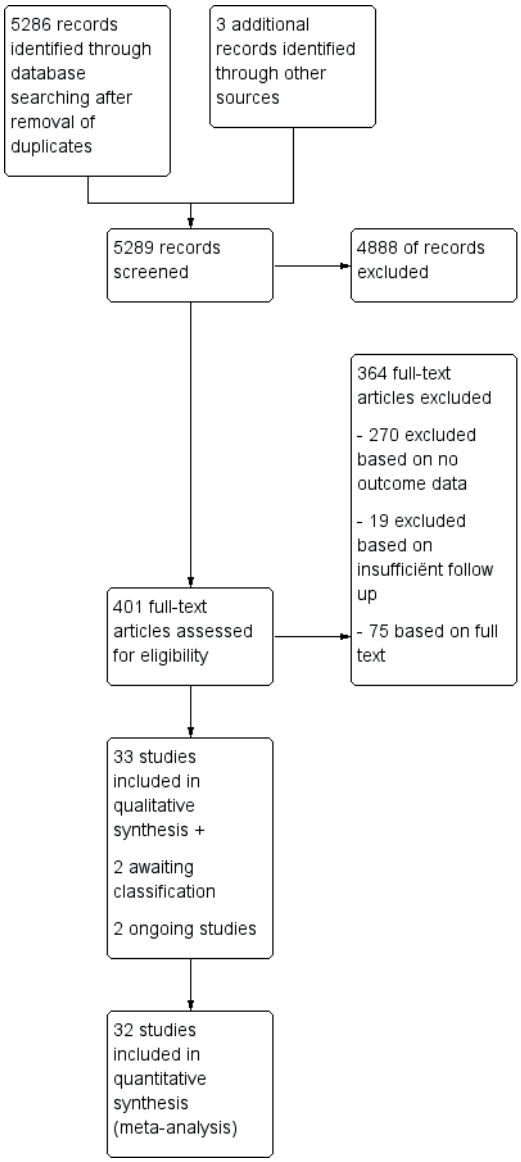

Figure 2. Flow diagram of systematic review.

Included studies

We included 33 RCTs of which 23 reported on postoperative (systemic or wound) infections, 9 reported on delayed wound healing and 11 reported on glycaemic control. In total, 1922 participants received dexamethasone, 1812 participants received a control intervention.

Setting

The RCTs were conducted in the following countries: Australia, Austria, Chile, China, Denmark, Ireland, Italy, Japan, Mexico, New Zealand, Norway, Romania, South Korea, Switzerland, Turkey, United States of America. An outline of the study characteristics is given below.

Population 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 (Kirdak 2008; Kurz 2015; Zargar-Shoshtari 2009)
- Craniotomies (Karacinar 2009)
- Different types of elective surgeries (Abdelmalak 2013a; Abdelmalak 2013b; Tien 2016; Wang 2009)
- Gastric bypass surgery (Nazar 2009)
- Hysterectomies (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)
- Lumbar discectomy (Nielsen 2015)
- Nissen fundoplication (Schietroma 2010)
- Thyroid surgery (Doksrod 2012; Feroci 2011; Schietroma 2013; Worni 2008; Zhou 2012)
- Total hip or knee arthroplasties (Backes 2013; Koh 2013)

Diabetes

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

Of the following 19 studies, participants with diabetes were eligible for inclusion in our meta-analysis (Abdelmalak 2013a; Abdelmalak 2013b; Backes 2013; Doksrod 2012; Feroci 2011; Kleif 2017; Koh 2013; Kurz 2015; Murphy 2011a; Nazar 2011; Nielsen 2015; Rafiq 2014; Schietroma 2013; Sanchez-Rodriguez 2010; Tien 2016; Wakasugi 2015; Worni 2008; Zargar-Shoshtari 2009; Zhou 2012).

Of those 19 studies, three excluded participants with poorly controlled diabetes. Backes 2013 excluded HbA1c > 7.5%, Murphy 2011a did not define poorly controlled diabetes, Sanchez-Rodriguez 2010 excluded HbA1c > 8%.

Four of the 19 studies excluded participants treated with insulin (Feroci 2011; Nazar 2011; Worni 2008; Zhou 2012)

Intervention and comparisons
Different doses of dexamethasone were used in the perioperative period. A low dose (4 to 5 mg) of dexamethasone was used in five of the included studies (Ionescu 2014; Karacinar 2009; Kawanishi 2014; Kurz 2015; Murphy 2014). Eight to 10 mg dexamethasone was used in 23 of the included studies (Abdelmalak 2013b; Backes 2013; Bisgaard 2003; Bjornholdt 2014; Cowie 2010; Feroci 2011; 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) Six groups studied a higher dose of 12 to 20 mg (Abdelmalak 2013a; Doksrod 2012; Choi 2013; Karacinar 2009; Murphy 2011a; Nielsen 2015).

Two studies used multiple doses of dexamethasone in their study design, however the total dose of dexamethasone did not exceed 20mg (Abdelmalak 2013a; Murphy 2011a).

Four studies were conducted with an active comparator in the control group: Ramosetron (Koh 2013), ondansetron (Rafiq 2014; Tien 2016), Topisetron (Zhou 2012). Two studies were conducted with an open label control group, which received a placebo (Ionescu 2014; Kawanishi 2014). Backes 2013 conducted the study in a blinded fashion, however, the control group did nor receive a placebo. All other studies were blinded and conducted with a placebo group (Abdelmalak 2013a; Abdelmalak 2013b; Bisgaard 2003; Bjornholdt 2014; Choi 2013; Cowie 2010; Doksrod 2012; Feroci 2011; Karacinar 2009; Kirdak 2008; Kleif 2017; Kurz 2015; Murphy 2011a; Murphy 2014; Nazar 2009; Nazar 2011; Nielsen 2015; Abdelmalak 2013b; Sanchez-Rodriguez 2010; Schietroma 2010; Schietroma 2013; Wakasugi 2015; Wang 2009; Worni 2008; Zargar-Shoshtari 2009).

Funding

Five studies (6 articles) received commercial funding (Abdelmalak 2013a; Abdelmalak 2013b; Backes 2013; Bjornholdt 2014; Kleif 2017; Kurz 2015). Seven trial groups received funds from research grants (Abukawa 2017; Bisgaard 2003; Doksrod 2012; 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). 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). None of the studies reported any conflicts of interest.

Outcomes

The definitions used for postoperative wound or systemic infection varied between the included studies. Five studies scored this according to the Center of Disease Control (CDC) criteria (Horan 2008) (Abdelmalak 2013a; Ionescu 2014; Kirdak 2008; Kurz 2015; Wakasugi 2015) 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 e.g. treatment with antibiotics (Backes 2013; Nielsen 2015; Zargar-Shoshtari 2009). Thirteen studies did not report the definition used for scoring a postoperative systemic or wound infection (Abukawa 2017; Bisgaard 2003; Bjornholdt 2014; Choi 2013; Doksrod 2012; Feroci 2011; Kawanishi 2014; Rafiq 2014; Sanchez-Rodriguez 2010; Schietroma 2010; Schietroma 2013; Worni 2008; Zhou 2012).

Delayed wound healing was reported in nine studies (Bjornholdt 2014; Choi 2013; Doksrod 2012; Feroci 2011; Koh 2013; Kurz 2015; Rafiq 2014; Wakasugi 2015; Worni 2008), namely assessed and reported by a surgeon performing the follow up, although no definition for delayed wound healing was stated in the respective studies. 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).

Fourteen studies reported on glucose values in the perioperative period. However, there was variability in the time points at which glucose levels were measured. Therefore, we chose to perform 3 subgroup analyses for the outcome glycaemic control; change from baseline 2 to 12 hours postoperative, change from baseline 24 hours postoperative and 10 to 24 hours postoperative in participants with diabetes. Two studies reported change from baseline values (Abdelmalak 2013b; Tien 2016). 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. Seven studies did not report the change from baseline (Cowie 2010; Doksrod 2012; Murphy 2011a; Murphy 2014; Nazar 2009; Wang 2009; Zhang 2016). We therefore calculated for these studies the change from baseline from the available data. Eight studies were included in the meta-analysis for change from baseline within 12 hours after dexamethasone administration (Abdelmalak 2013b; Doksrod 2012;Karacinar 2009; Murphy 2011a; Murphy 2014; Nazar 2009; Tien 2016; Wang 2009); as were four studies for the analysis of change from baseline at 24 hours postoperatively (Cowie 2010; 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).

The length of hospital stay was assessed in days. As this parameter was frequently reported as median with corresponding confidence interval, we transformed this data to mean (SD) in order to include the study in the meta-analysis (Bisgaard 2003; Murphy 2011a).

The frequency of readmission was evaluated in four studies (Ionescu 2014; Kirdak 2008; Sanchez-Rodriguez 2010; Zargar-Shoshtari 2009).

CRP was assessed as CRP level at 24 hours after surgery. (Abdelmalak 2013a; Kirdak 2008; Zargar-Shoshtari 2009)

Mortality was defined as all-cause mortality at 30 days. Five studies reported this outcome (Abdelmalak 2013a; Feroci 2011; Kirdak 2008; Kurz 2015; Rafiq 2014).

Excluded studies

We excluded 19 studies based on insufficient length of follow up, mostly between two and seven days. In three studies, the participants received dexamethasone based on a clinical decision (Pasternak 2004; Sethi 2016; Snall 2014). The studies were thus not randomised and were therefore not included.

Awaiting classification

Two studies are awaiting classification (Ko-Iam 2015; Simogai 2016). The full text of these articles could not be retrieved.

Ongoing studies

Two ongoing studies were identified, which will contribute to the body of evidence when they are finished (Kitcharanant 2016; Sidhu 2017).

Risk of bias in included studies

Figure 3 and Figure 4 show the overall risk of bias and the risk of bias for each study separately. The level of evidence was downgraded for studies we judged to be a high risk of bias.

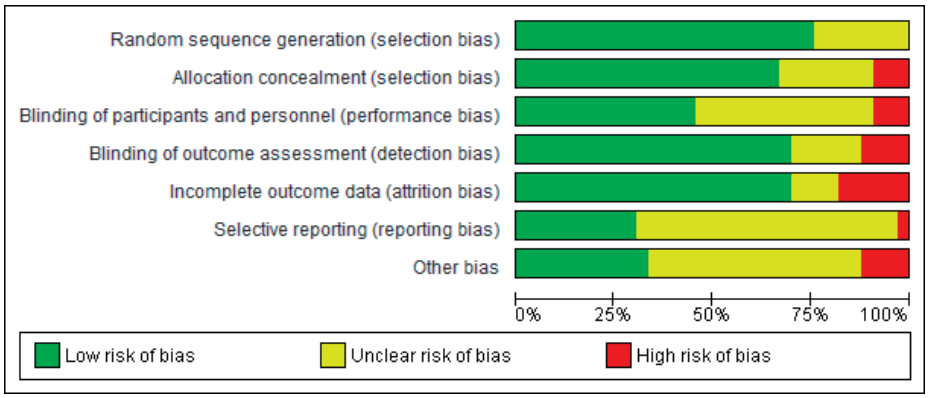

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Random sequence generation

Twenty-five of the 33 studies used a computer-generated list for randomization. A few studies failed to report on the randomisation process; therefore risk of bias was unclear. However, overall we judged these studies to be of high risk of bias and downgraded their level of evidence (Abukawa 2017; Karacinar 2009; Wang 2009; Zhang 2016).

Allocation (selection bias)

Overall, selection bias was low. Twenty-two studies had adequate allocation concealment, mostly with sequentially numbered opaque sealed envelopes. Four studies did not describe the randomisation and allocation process other than that the study was a randomised study (Abukawa 2017; Karacinar 2009; Wang 2009; Zhang 2016). We judged these studies to have an unclear risk of selection bias.

Blinding (performance bias and detection bias)

Fifteen studies clearly stated the blinding process of patients and personnel, with a low risk of performance bias. All placebo-controlled studies used normal saline in an identical syringe as placebo. In 23 studies, the outcome assessor was adequately blinded to avoid detection bias. Of the 24 studies reporting on postoperative infections, three did not report if the outcome assessor was blinded and we judged them to have an unclear risk of detection bias (Abukawa 2017; Doksrod 2012; Sanchez-Rodriguez 2010).

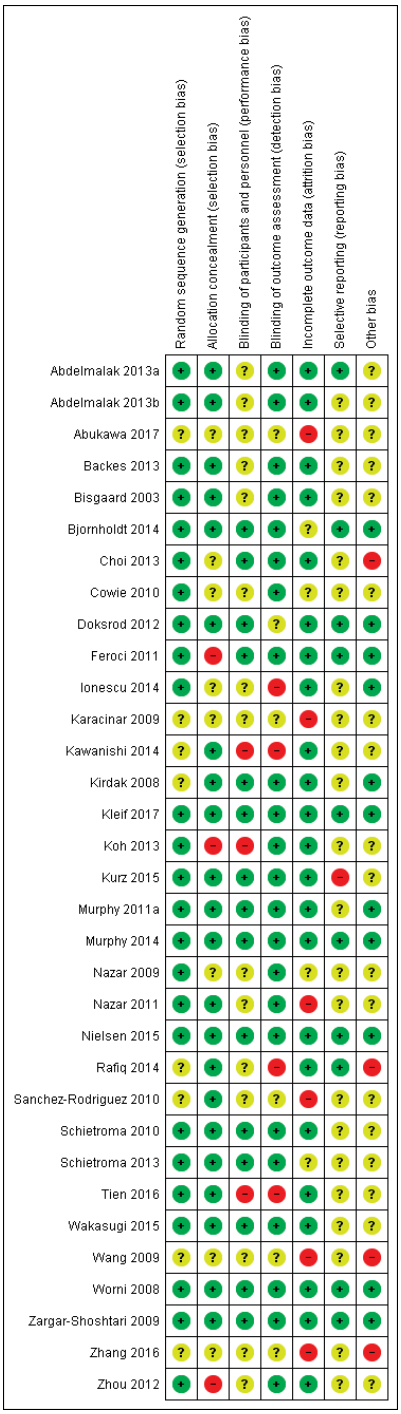

Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

We judged three studies to have a high risk of detection bias as it was stated that the outcome assessors in these studies were not blinded (Ionescu 2014; Kawanishi 2014; Rafiq 2014). Six of the eight studies assessing delayed wound healing had low risk of detection bias.

Incomplete outcome data (attrition bias)
Six studies reported no information about drop-outs or withdrawals during the study (and were therefore judged to have a high risk of attrition bias Abukawa 2017; Karacinar 2009; Nazar 2011; Sanchez-Rodriguez 2010; Wang 2009; Zhang 2016) . We judged four studies to have an unclear risk of attrition bias; it either appeared that no drop-outs occurred (Nazar 2009; Cowie 2010), or more drop-outs occurred in the placebo group (Bjornholdt 2014), or the number of drop-outs was provided, but without reasons (Schietroma 2013). The remaining studies had a low risk of attrition bias.

Selective reporting (reporting bias)
Twenty-one studies had an unclear risk of reporting bias, as the study protocol was not published or registered in a trial registry. Abdelmalak 2013b performed a subgroup analysis of the original data of 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 be of unclear risk of reporting bias. We identified Kurz 2015 as a 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.

Other potential sources of bias
The funnel plot was created for our primary outcome: postoperative wound or systemic infection. This plot showed little asymmetry, indicating a low risk of publication bias (figure 5).

Effects of interventions
All included studies can be found in the Summary of findings table (figure 1). The assessment of the quality of the evidence is also expressed in this table.

Primary outcome 1: Postoperative wound or systemic infection

Figure 6 and figure 7 display the effect of dexamethasone on postoperative wound or systemic infection.

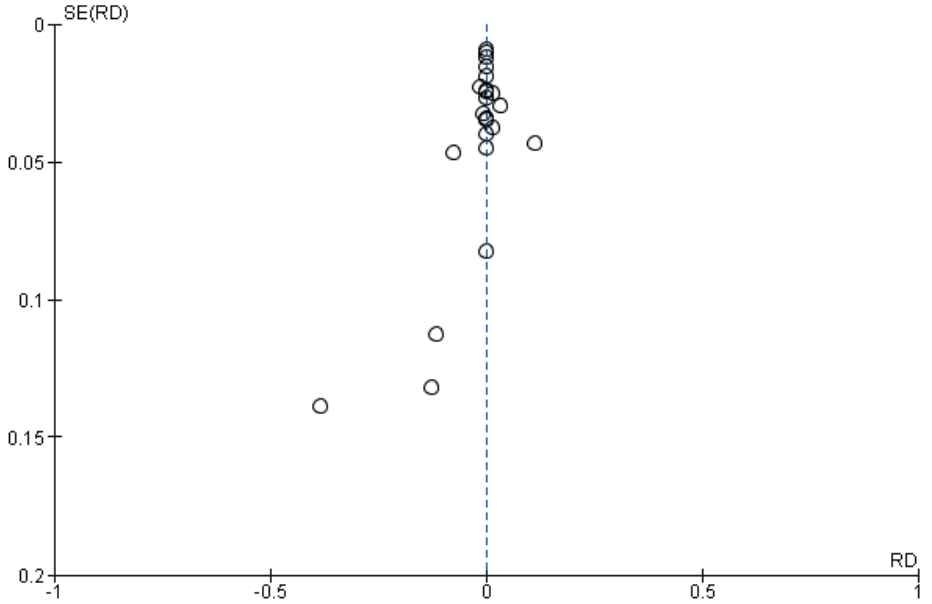

Figure 5. Funnel plot of comparison 1: dexamethasone versus control, outcome 1.1 Postoperative systemic or wound infection.

Study or Subgroup	Dexamethasone Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Abdelmalak 2013a	21	193	14	188	2.3%	0.03 [-0.02, 0.09]
Abukawa 2017	0	15	1	8	0.1%	-0.13 [-0.38, 0.13]
Backes 2013	0	42	0	37	3.3%	0.00 [-0.05, 0.05]
Bisgaard 2003	1	40	1	40	1.7%	0.00 [-0.07, 0.07]
Bjornholdt 2014	0	26	0	22	1.3%	0.00 [-0.08, 0.08]
Choi 2013	0	40	0	40	3.5%	0.00 [-0.05, 0.05]
Doksrod 2012	0	40	3	40	0.9%	-0.07 [-0.17, 0.02]
Feroci 2011	0	51	0	51	5.5%	0.00 [-0.04, 0.04]
Ionescu 2014	0	22	0	20	1.0%	0.00 [-0.09, 0.09]
Kawanishi 2014	0	10	0	12	0.3%	0.00 [-0.16, 0.16]
Kirdak 2008	0	14	5	13	0.1%	-0.38 [-0.66, -0.11]
Kleif 2017	3	59	2	57	1.4%	0.02 [-0.06, 0.09]
Koh 2013	1	135	1	134	18.5%	-0.00 [-0.02, 0.02]
Kurz 2015	50	283	50	272	1.9%	-0.01 [-0.07, 0.06]
Nielsen 2015	7	62	0	50	1.1%	0.11 [0.03, 0.20]
Rafiq 2014	1	77	2	74	3.9%	-0.01 [-0.06, 0.03]
Sanchez-Rodriguez 2010	0	105	0	105	22.9%	0.00 [-0.02, 0.02]
Schietroma 2010	1	41	1	41	1.7%	0.00 [-0.07, 0.07]
Schietroma 2013	2	163	2	165	13.8%	0.00 [-0.02, 0.02]
Wakasugi 2015	7	136	5	134	3.2%	0.01 [-0.03, 0.06]
Worni 2008	0	37	0	35	2.8%	0.00 [-0.05, 0.05]
Zargar-Shoshtari 2009	6	29	10	31	0.2%	-0.12 [-0.34, 0.11]
Zhou 2012	0	100	0	50	8.5%	0.00 [-0.03, 0.03]
Total (95% CI)		**1720**		**1619**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	100		97			

Heterogeneity: Tau² = 0.00; Chi² = 21.39, df = 22 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)

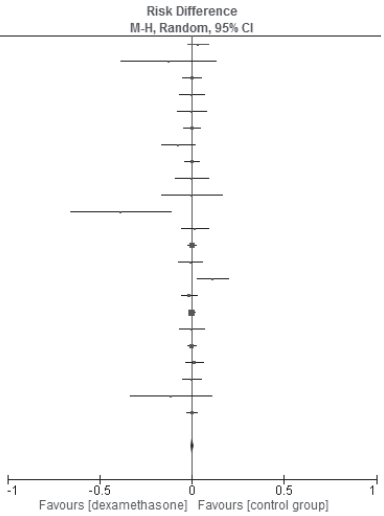

Figure 6. Forest plot comparison 1: dexamethasone versus control, outcome 1.1 Postoperative systemic or wound infection.

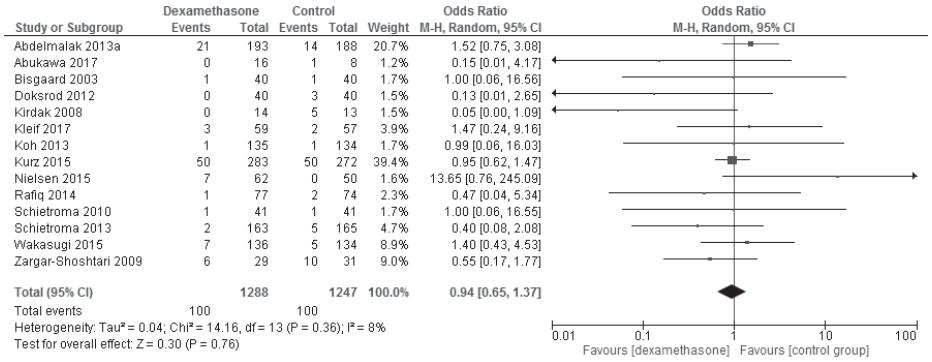

Figure 7. Forest plot comparison 1: dexamethasone versus control, outcome 1.2 Sensitivity analysis on postoperative systemic or wound infection.

Two studies reported on postoperative wound or systemic infections, but without sufficient length of follow up, therefore these studies were not included in the quantitative analysis of postoperative infections (Murphy 2011a; Zhang 2016).

We pooled the results of 23 studies (Abdelmalak 2013a; Abukawa 2017; Backes 2013; Bisgaard 2003; Bjornholdt 2014; Choi 2013; Doksrod 2012; Feroci 2011; Ionescu 2014; Kawanishi 2014;Kirdak 2008; Kleif 2017; Koh 2013; Kurz 2015; Nielsen 2015; Rafiq 2014;Sanchez-Rodriguez 2010; Schietroma 2010; Schietroma 2013; Wakasugi 2015; Worni 2008; Zargar-Shoshtari 2009; Zhou 2012) to estimate the effect of dexamethasone on postoperative wound or systemic infection rates. These studies included 3339 participants in total, 1720 in the intervention group and 1619 in the control group. There was no between group difference in the rate of postoperative wound or systemic infections (RD 0.00 95% CI -0.01 to 0.01; 3339 participants; 23 studies; I^2= 0%). A random-effects model was used, as there was significant variety in the definitions used for postoperative wound and systemic infections.

Overall, the risk of bias was low. The quality of evidence was downgraded 1 level to moderate due to the small number of events.

We performed a sensitivity analysis, excluding studies with zero events, which yielded similar results. As planned, we subsequently calculated the OR. Data of 14 studies were pooled, including 2535 participants (OR 0.94, 95% CI 0.65 to 1.34; I^2= 8%). The overall risk of bias was low and we scored the overall quality of evidence as high.

The subgroup analysis for the different dosages (4 to 5mg, 8 to 10mg and 12 to 20mg) of dexamethasone did not yield different results (data not shown).

Primary outcome 2: Delayed wound healing

Figure 8 and figure 9 display the effect of dexamethasone on delayed wound healing.

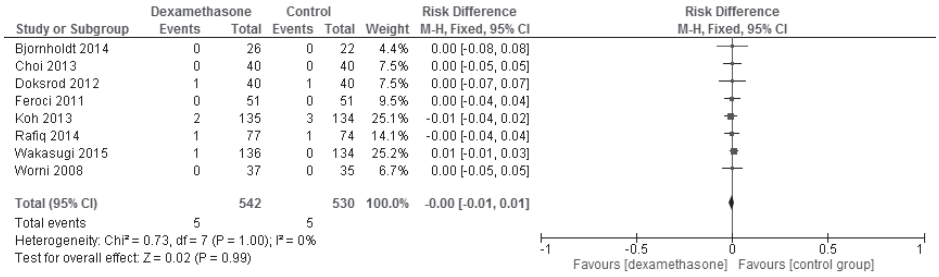

Figure 8. Forest plot of comparison 1: dexamethasone versus control, outcome 2.1 Delayed wound healing.

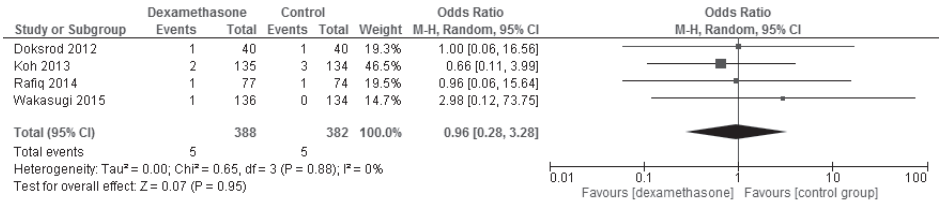

Figure 9. Forest plot of comparison 1: dexamethasone versus control, outcome 2.2 Sensitivity analysis on delayed wound healing.

One study assessed delayed wound healing with 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), pooling 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 of the groups, therefore, we primarily calculated the RD. Dexamethasone did not increase the incidence of delayed wound healing. (RD 0.00, 95% CI -0.01 to 0.01, 1072 participants; 8 studies; I^2= 0%). A sensitivity analysis was performed excluding zero event studies: 770 participants (OR 0.96, 95% CI 0.26 to 3.26; 770 participants; 4 studies; I^2= 0%). We scored this outcome as having a high risk of bias for both the primary analysis and the sensitivity analysis. Three studies (Feroci 2011; Koh 2013; Rafiq 2014) had a high risk of bias in the selection, performance or detection domains. Subsequently, the quality of evidence was downgraded 2 levels; one level for high risk of bias and one level for imprecision (low number of events).

The subgroup analysis for the different dosages (4 to 5mg, 8 to 10mg and 12 to 20mg) of dexamethasone did not change the results (data not shown)

Primary outcome 3: Glycaemic response

We analysed glycaemic response in three subgroups (figure 10). Glucose values are given in mg dl^{-1}. Conversion to mmol l^{-1}: divide by 18.

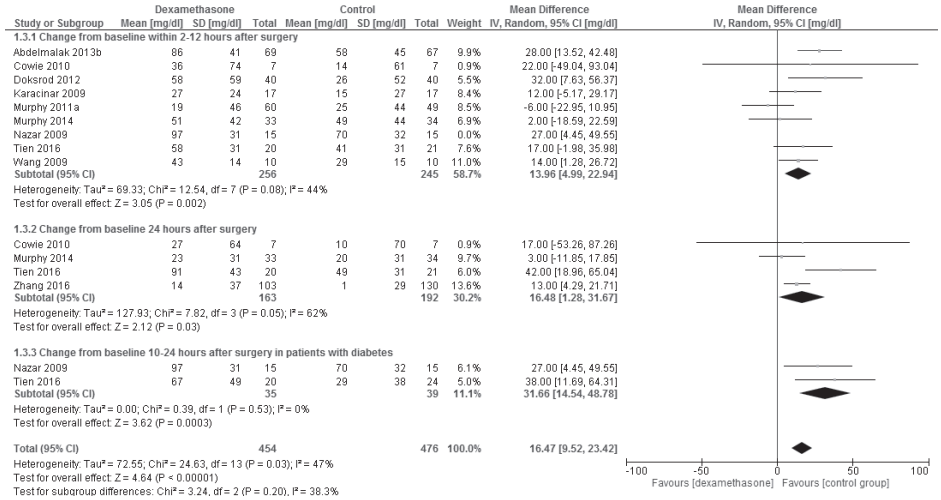

Figure 10. Forest plot comparison 1: dexamethasone versus control, outcome 3.0 Glycaemic control.

Four studies could not be included 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. In the study by Backes 2013, glucose values were reported for patients with and without diabetes receiving dexamethasone, however, no glucose values were reported for the control group. Again, we contacted the corresponding author but did not receive a response. Nazar 2011 only showed glucose values in a graph. The corresponding author was contacted, but we were unable to retrieve these results. One study reported glucose levels 18 hours postoperatively, which were outside the range of our prespecified outcome measures (not within 2 to 12 hours or 24 hours after dexamethasone administration) and was therefore not included in the meta-analysis (Choi 2013)

Overall change from baseline to maximum 24 hours for participants given dexamethasone was 16 mg dl^{-1} higher (95% CI 10 to 23 mg dl^{-1} 10 studies, 910 participants, $I^2 = 47\%$) than for participants not receiving dexamethasone. Quality of evidence was scored as moderate due to the large confidence intervals (imprecision).

Primary outcome 3a: Glycaemic response within 2 to 12 hours

Change from baseline was significantly higher in the dexamethasone group as compared to the control group. We used a random-effects model due to moderate heterogeneity. Eight studies were included for this outcome (MD 14% CI 5 to 23 ; 501 participants; I^2= 44%) (Abdelmalak 2013b; Cowie 2010; Doksrod 2012; Karacinar 2009; Murphy 2011a; Murphy 2014; Tien 2016; Wang 2009). We classified Wang 2009 as high risk of bias. Excluding this study from the analysis showed similar results (MD 14, 95% CI 3 to 25; 481 participants; 7 studies; I^2= 52%). The overall risk of bias was low, quality of evidence was moderate. The quality of evidence was downgraded for imprecision. Excluding studies with a 12 to 20mg dosage of dexamethasone showed similar results (18 mg dl^{-1}, 95% CI 11 to 26). Feroci 2011 was not included in the meta-analysis due to lack of baseline measurements. They found significant higher glucose values in the dexamethasone group compared to the control group at eight hours postoperatively.

Primary outcome 3b: Glycaemic response at 24 hours

Four studies (Cowie 2010; Murphy 2014; Tien 2016; Zhang 2016), including 355 participants, reported on this outcome. Change from baseline was significantly higher in the dexamethasone group as compared to the control group (MD 17, 95% CI 1 to 32; I^2= 62%). We classified Zhang 2016 as overall high risk of bias because no information was given in the report about randomization strategy, blinding and dropouts. This was the largest study for this outcome. When this study was excluded, the change from baseline was comparable in both groups (MD 20.6, 95% CI -10.9 to 52.0; 122 participants; 3 studies; I^2= 62%). The quality of evidence downgraded 3 levels to very low due to high risk of bias, significant heterogeneity and small sample size with large confidence intervals. One study (Murphy 2014) used a lower dosage (4 mg) of dexamethasone, excluding this study did not change the results (data not shown).

Choi 2013 found a 19 mg dl^{-1} increase in glucose 18 hours after surgery when dexamethasone was administered, compared to 4 mg dl^{-1} in the control group. However, no statistical analysis was performed on these data. Feroci 2011 found no difference in glucose values at 24 hours postoperatively between participants receiving dexamethasone or normal saline. Backes 2013 found a reduction in glucose (5.0 mg dl^{-1}) 24 hours after surgery in participants without diabetes receiving dexamethasone.

Primary outcome 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 in participants with diabetes (Backes 2013; Nazar 2009; Nazar 2011; Tien 2016). Nazar 2011 only depicted glucose values in a graph and this study was not included in the quantitative analysis. However, in participants with diabetes receiving dexamethasone, they found a

maximum difference in glucose of 34 mg dl^{-1} at 10 hours after dexamethasone administration. The graph showed a smaller maximum difference in glucose for participants with diabetes not receiving dexamethasone. Whether this difference was significant or not was not reported. Backes 2013 did not report glucose values for the control group and could therefore not be included in the quantitative analysis. However, they found that participants with diabetes receiving dexamethasone had a change from baseline of 4.8 mg dl^{-1} at 24 hours after the intervention.

Our meta-analysis showed that in participants with diabetes, the change from baseline was significantly greater in the dexamethasone group as compared to the control group (MD 31.7, 95% CI 14.5 to 48.8; I^2= 0%, 2 studies, 74 participants). The risk of bias for this outcome was low. However, we downgraded the quality of evidence by 2 levels to level "low" as there was a very small sample size with very large confidence intervals.

Secondary outcome 4: Length of hospital stay

Thirteen studies reported on the length of hospital stay. We did not include three 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 included 10 studies in the quantitative analysis (Backes 2013; Bisgaard 2003; Feroci 2011; Kirdak 2008; Kurz 2015; Murphy 2011a; Rafiq 2014; Sanchez-Rodriguez 2010; Wakasugi 2015; Worni 2008) with a total of 1654 participants reported on this outcome. Length of hospital stay did not differ between the two groups (MD -0.03, 95% CI -0.22 to 0.17; I^2= 81%). Excluding two studies (Rafiq 2014; Sanchez-Rodriguez 2010), with a high risk of bias did not change the results (MD 0.06, 95% CI -0.29 to 0.40; 1293 participants; 8 studies; I^2= 84%). For both analyses, a random-effects model was used due to high heterogeneity. We downgraded the quality of evidence 1 level to moderate due to significant heterogeneity.

Secondary outcome 5: Readmission

We pooled the data of 339 participants (Ionescu 2014; Kirdak 2008; Sanchez-Rodriguez 2010; Zargar-Shoshtari 2009). Use of dexamethasone was not associated with a higher risk of readmission (RR 1.18, 95% CI 0.43 to 3.25; I^2= 0%). The largest study contributing to this outcome had a high risk of bias (Sanchez-Rodriguez 2010). We scored the quality of evidence for this outcome as low (downgraded 2 levels) due to the low number of events and significant heterogeneïty.

Secondary outcome 6: C-reactive protein levels 1 day postoperatively

Six studies reported on CRP levels 1 day postoperatively (Abdelmalak 2013a; Bisgaard 2003; Kirdak 2008; Schietroma 2010; Schietroma 2013; Zargar-Shoshtari 2009). Three of

these studies only displayed CRP levels in a figure, without error bars (Bisgaard 2003; Schietroma 2010; Schietroma 2013). The corresponding authors were contacted to retrieve the original data, but we were unable to retrieve the original data. All figures showed lower CRP levels in the dexamethasone group on day one postoperatively.

The other three studies, with a total of 468 participants, all reported CRP levels at 1 day postoperatively (Abdelmalak 2013a; Kirdak 2008; Zargar-Shoshtari 2009). Pooling of the data showed a MD of -6.13 (95% CI -32.50 to 20.24; I^2= 87%) in favour of the dexamethasone group, but these differences were not statistically significant. We downgraded quality of evidence 3 levels to very low; there was significant heterogeneity, small sample size, large confidence intervals and various types of surgery in the small sample size.

Secondary outcome 7: Mortality

Five studies (Abdelmalak 2013a; Feroci 2011; Kirdak 2008; Kurz 2015; Rafiq 2014), including 1216 participants reported on 30-day mortality scores. Perioperative dexamethasone was not associated with a higher 30-day mortality (RR 0.62, 95% CI 0.21 to 1.82; I^2= 0%). Due to the small number of events together with a small sample size, we downgraded the level of evidence by 1 level to moderate (low number of events, and a small sample size with large confidence intervals).

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 infections, delayed wound healing and hyperglycaemia in surgical patients. We identified 23 RCTs which reported on postoperative systemic or wound infections, eight trials which reported on delayed wound healing and nine studies reporting on glycaemic response, to help us answer our questions. We found that an incidental steroid load of dexamethasone did not increase the risk of postoperative systemic or wound infections (moderate to high quality evidence), did not increase the risk of delayed wound healing (low quality evidence) but significantly increased glucose values in the first 12 hours after surgery (moderate quality evidence).

Overall completeness and applicability of evidence

Postoperative infections

We included studies with a wide spectrum of surgical interventions, which increases the applicability in everyday practice. The infection rates between the studies differed, ranging from 0% to 18%, reflecting the different surgical populations. No statistical heterogeneity was observed for this outcome; however, there was a large variety in definition of postoperative (wound or systemic) infection. The incidences of postoperative infections in the individual studies could either be too high or too low. However, the majority of the studies had a low risk of bias. In the perioperative period, dexamethasone (total dose up to 20 mg) can be used without increasing the risk of postoperative infections (moderate quality of evidence).

Delayed wound healing

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

Glycaemic response

Ten studies (Abdelmalak 2013b; Cowie 2010; Doksrod 2012; Karacinar 2009; Murphy 2011a; Murphy 2014; Nazar 2009;Tien 2016; Wang 2009; Zhang 2016) measured blood glucose values in the perioperative period while giving dexamethasone. Only one study (Doksrod 2012) adequately reported on the relation between blood glucose values and the incidence of postoperative complications. This meta-analysis showed that glucose was 16 mg dl^{-1} higher when participants had received dexamethasone as compared to participants not receiving dexamethasone. In a clinical setting we can therefore expect a mild increase in glucose values when administering dexamethasone. However, as shown above, this mild increase in glucose is probably not associated with an increased risk of postoperative infections.

For patients with diabetes, very limited evidence exists on the glycaemic response to dexamethasone. We could only identify two studies Nazar 2009; Tien 2016) reporting on this outcome (74 participants). This group is too small to draw definite conclusions.

However, data so far suggests 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 the evidence per outcome measure. The evidence of postoperative infections was scored as moderate quality. After excluding the studies with a high risk of bias, we scored the sensitivity analysis as high quality of evidence. For our outcome of delayed wound healing and the sensitivity analysis of delayed wound healing, the quality of evidence was downgraded to low quality. This was due to high risk of bias in the studies and limited events per study as opposed to what was expected. Glycaemic response in participants with diabetes was downgraded to low quality of evidence due to imprecision. For glycaemic response at 24 hours and postoperative CRP levels, the level of evidence was downgraded to very low quality of evidence due to imprecision, risk of bias and inconsistency. Although we do not question the estimated direction of the effect, we are less confident that we found a reliable effect size for these outcomes.

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 they are easily missed, especially in small studies. Pooling the data from small studies creates a much larger sample size. However, if the adverse effects did not occur in the small studies, pooling results of these studies could give a false low incidence of adverse effects. In this systematic review, due to the low incidence of delayed wound healing and readmissions, the effect of dexamethasone on these outcomes might be underestimated.

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

Furthermore, due to the large variety in surgical procedures, there is a large variety in 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 the 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, 270 trials were excluded due to insufficient follow-up for adverse events, which could have introduced selection bias.

Also, in four studies (Bisgaard 2003; Nazar 2011; Schietroma 2010; Schietroma 2013) glucose values and CRP were only depicted in a graph, not numerically. We tried to obtain these results from the corresponding author's, but these were not available. Therefore these studies were only reported descriptively.

Lastly, the studies awaiting classification (Ko-Iam 2015; Simogai 2016) could have a potential impact on the body of evidence and are thus a potential source of bias.

Agreements and disagreements with other studies or reviews

The objective of this review was to assess the effects of an incidental steroid load of dexamethasone on postoperative systemic or wound infections, number of wounds classified as delayed wound healing and blood glucose change in adult surgical patients as a primary outcome. Due to the multiple indications of dexamethasone, previous systematic reviews on the beneficial effects of dexamethasone were subjected to selective outcome reporting bias regarding the adverse effects. Waldron 2013 and De Oliveira 2011 did a systematic review on the effects of dexamethasone on postoperative pain and both assessed adverse effects as secondary outcome and found no increased risk of infection. Waldron 2013 also performed an analysis on delayed wound healing as secondary outcome and found no increased risk of delayed wound healing. De Oliveira 2011 was unable to perform an analysis on delayed wound healing, as only zero-event trials were included 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 on the safety of glucocorticosteroids in non-cardiac surgery. This meta-analysis included studies with dexamethasone, methylprednisolone or hydrocortisone. Toner 2017 assessed the effect on incidence of 'any infection' as primary outcome, glucose and length of hospital stay were assessed as secondary outcomes. Similar to our study, they found no increased risk of infection (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^{-1}, 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).

As the incidence of postoperative infections is low and easily missed in small studies, it could be helpful to review retrospective evidence on this topic. Assante 2015 identified five large retrospective studies, ranging from 235 to 3449 participants, assessing the effect of dexamethasone on postoperative infections. Four studies found no increased risk of postoperative infections in the dexamethasone group (Bolac 2013; Corcoran 2010; Eberhart 2011; Gali 2012). One study found an increased risk of postoperative infections, however, they excluded specific types of infections from the analysis (Percival 2010). In summary, the available evidence of larger studies suggests no harmful effect of an incidental steroid load of dexamethasone with respect to the risk of postoperative infections.

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 moderate to good quality evidence 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 is probably not clinically relevant. One has to keep in mind that patients with higher risk of postoperative infections and delayed wound healing, e.g. patients with diabetes, were probably not included in most of the included trials. Furthermore, only low quality evidence suggests that dexamethasone does not delay wound healing. 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 address the impact of dexamethasone on surgical site infection 30 days after surgery, with stratification for diabetes status. Patients undergoing surgery under general anaesthesia are randomised to receive either 8 mg of dexamethasone or placebo in the perioperative period. They aim is to include 8880 adults. As of 24th March 2017, 28 sites were recruiting and 1144 participants had been included.

Authors' conclusions

Implications for practice

Dexamethasone does not increase the risk for postoperative infections in the general surgical population. However, only low quality evidence suggests that dexamethasone does not increase the risk of wound infections. Participants with an increased risk for delayed wound healing, e.g. participants with diabetes or on immunosuppressive drugs, were not included in the randomised studies reporting on delayed wound healing in-

cluded in this meta-analysis, and our findings should therefore be extrapolated to the clinical setting with caution. Furthermore, one has to keep in mind that dexamethasone induces a mild increase in glucose, which is probably more pronounced in patients with diabetes. Also, the studies awaiting classification may alter the results once assessed (Ko-Iam 2015; Simogai 2016) Based on the available evidence so far, dexamethasone still holds an important place in the treatment of PONV or as adjuvant in pain treatment and is not associated with an increased risk of postoperative wound infections. However, whether or not an incidental steroid load of dexamethasone influences wound healing has to be established.

Implications for research

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

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