



Low-dose dexamethasone during arthroplasty: what do we know about the risks?

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- Dexamethasone is commonly applied during arthroplasty to control post-operative nausea and vomiting (PONV). However, conflicting views of orthopaedic surgeons and anaesthesiologists regarding the use of dexamethasone raise questions about risks of impaired wound healing and surgical site infections (SSI).
- The aim of this systematic review is to determine the level of evidence for the safety of a peri-operative single low dose of dexamethasone in hip and knee arthroplasty.
- We systematically reviewed literature in PubMed, EMBASE and Cochrane databases and cited references in articles found in the initial search from 1980 to 2013 based on predefined inclusion criteria. The review was completed with a 'pro' and 'con' discussion.
- After identifying 11 studies out of 104, only eight studies met the inclusion criteria. In total, 1335 patients were studied without any incidence of SSI. Causes of SSI are multifactorial. Therefore, 27205 patients would be required (power = 90%, alpha = 0.05) to provide substantiated conclusions on safety of a single low dose of dexamethasone.
- Positively, many studies demonstrated showed convincing effects of low-dose dexamethasone on prevention of PONV and dose-dependent effects on post-operative pain and quality of recovery. Dexamethasone induces hyperglycaemia, but none of the studies demonstrated a concomitant SSI.
- Conversely, animal studies showed that high dose dexamethasone inhibits wound healing.
- A team approach of anaesthesiologists and orthopaedic surgeons is mandatory in order to balance the risk-benefit ratio of peri-operatively applied steroids for individual arthroplasty patients.
- We did not find evidence that a single low dose of dexamethasone contributes to SSI or wound healing impairment from the current studies.

Keywords: arthroplasty; hip; knee; post-operative nausea and vomiting; PONV; surgical site infections; SSI

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Introduction

In the last decade, many improvements in the peri-operative management of patients undergoing arthroplasty have facilitated the initiation of fast-track surgery, shortening the length of hospital stay up to 60%.¹ A substantial part of the shortened hospital stay is related to improved peri-operative pain management and prevention of post-operative nausea and vomiting (PONV), resulting in faster mobilisation and discharge of patients. Meanwhile, many peri-operative strategies in preventing surgical site infections (SSI) after arthroplasty have been taken. Currently, conflicting views among orthopaedic surgeons and anaesthesiologists raise doubts on the use of dexamethasone during joint arthroplasty surgery.

For prevention of PONV, a single dose of dexamethasone is often used peri-operatively as it has been proven to be effective in PONV reduction.^{2,3} Its effectiveness and safety has been shown in a Cochrane review of 10 000s of patients undergoing all kinds of surgeries.⁴ In addition, dexamethasone has been shown to decrease post-operative pain and opioid consumption up to 24 hours in doses above 0.1 mg/kg in a recent meta-analysis.⁵

However, administration of an immunosuppressive drug like dexamethasone to patients undergoing joint arthroplasty surgery seems to conflict with the strict rules and strategies to prevent SSI. Therefore, the question

remains regarding whether the benefits of dexamethasone outweigh its potential risks.

We set out to determine whether there is sufficient evidence to consider a single dose of peri-operative corticosteroids as safe in joint arthroplasty surgery. In the end, we will complete the systematic review with a discussion of the results obtained either from an anaesthesiological ('pro' dexamethasone) or orthopaedic ('con' dexamethasone) point of view.

Search strategy and criteria

This review was performed by a search of the literature on the basis of predefined inclusion criteria according to the PRISMA guidelines.⁶

Inclusion of studies

In a primary search all original randomised controlled trials (RCTs) comparing peri-operative administration of a single dose of glucocorticosteroids intravenously to non-glucocorticosteroids or placebo in adult patients undergoing hip or knee arthroplasty.

In addition, we identified the present literature on the theoretical increased risk of infection and wound healing disturbances following the use of glucocorticosteroids (dexamethasone). In this search, we also included retrospective comparative studies, cohort studies, explanatory studies and meta-analyses performed in post-operative patients beyond arthroplasty surgery.

Search strategy

The search was limited to studies published in the PubMed/MEDLINE, EMBASE and Cochrane databases, and cited references in articles found in the initial search written in English, German and Dutch in the period between 1980 and August 2013 using the following medical subject heading (MESH) terms: glucocorticosteroids, arthroplasty, joint replacement, prosthesis, PONV, critical pathway, fast track, hip, knee and surgical wound infection. Two reviewers analysed independently the abstracts obtained from the literature search to identify relevant articles for full text assessment and selection when meeting the inclusion criteria. Disagreement was resolved by group discussion, with arbitration by a third author where differences remained. Studies were not blinded for author, affiliation and source.^{2,3} References of collected publications were manually checked for additional publications potentially meeting the inclusion criteria and not found by the electronic search.

Results

Out of 104 studies, we identified 11 studies that were examined in detail, in which the peri-operative use of glucocorticosteroids in hip or knee arthroplasty was

studied.^{2,7,8-19} Of these 11 studies, eight studies were RCTs that met our inclusion criteria.^{7,20,11-15,17} A flow diagram of the literature search is shown in Fig. 1.

Excluded studies

Several studies did not meet our inclusion criteria of a prospective comparison between dexamethasone *versus* placebo or other agents.^{7-10,16,18} We excluded studies employing patients other than those specifically undergoing hip or knee arthroplasty.² The study by Clarke et al was excluded because randomisation was done for the use of gabapentin and not for glucocorticosteroids.²¹ The study by Hartrick et al was also excluded on the grounds of the retrospective matched case-control study design.¹⁰ Further, the study by Skinner and Shintani was excluded, considering a retrospective comparison of a newly introduced pain protocol including dexamethasone *versus* regular treatment.¹⁸ The study by Smith, Erasmus and Myburgh was listed under excluded studies because dexamethasone was administered epidurally.¹⁹ Also, the study by Apfel et al was excluded based on study design, and the lack of any report on wound infections.² Finally, we excluded all publications by Fujii and Nakayama⁹ because of retraction due to the suspected fabrication of data.

Included studies

Tables 1 and 2 display the characteristics of the included studies.

Bergeron et al²⁰ and Kardash et al¹² both performed a different analysis in the same group of patients, comparing dexamethasone with saline in patients undergoing primary total hip arthroplasty in a RCT. Therefore, we assessed their results as one study. Bergeron et al recorded complications in wound healing, osteonecrosis and SSI for each patient after six weeks and one year. The follow-up evaluation in the study of Kardash et al was carried out only 48 hours post-operatively, and a chart review after one month. Both authors found no increase in wound complications or infections. Mathiesen et al investigated the analgesic effect of dexamethasone and pregabalin in 120 hip arthroplasty patients in a RCT.¹⁵ Patients were followed during the first 24 hours post-operatively, without signs of wound infections. Rasmussen et al reported a preliminary study in which they examined the analgesic effect of a multimodal regime including dexamethasone in 42 hip arthroplasty patients.¹⁷ The duration of follow-up was 24 hours and wound healing complications or infections were not mentioned. Backes et al reported one superficial stich abscess in the dexamethasone group that was not considered to be a SSI.⁷

In eight studies, 1335 patients were investigated with 472 patients being included, 240 receiving dexamethasone and 228 receiving placebo. The reported incidence

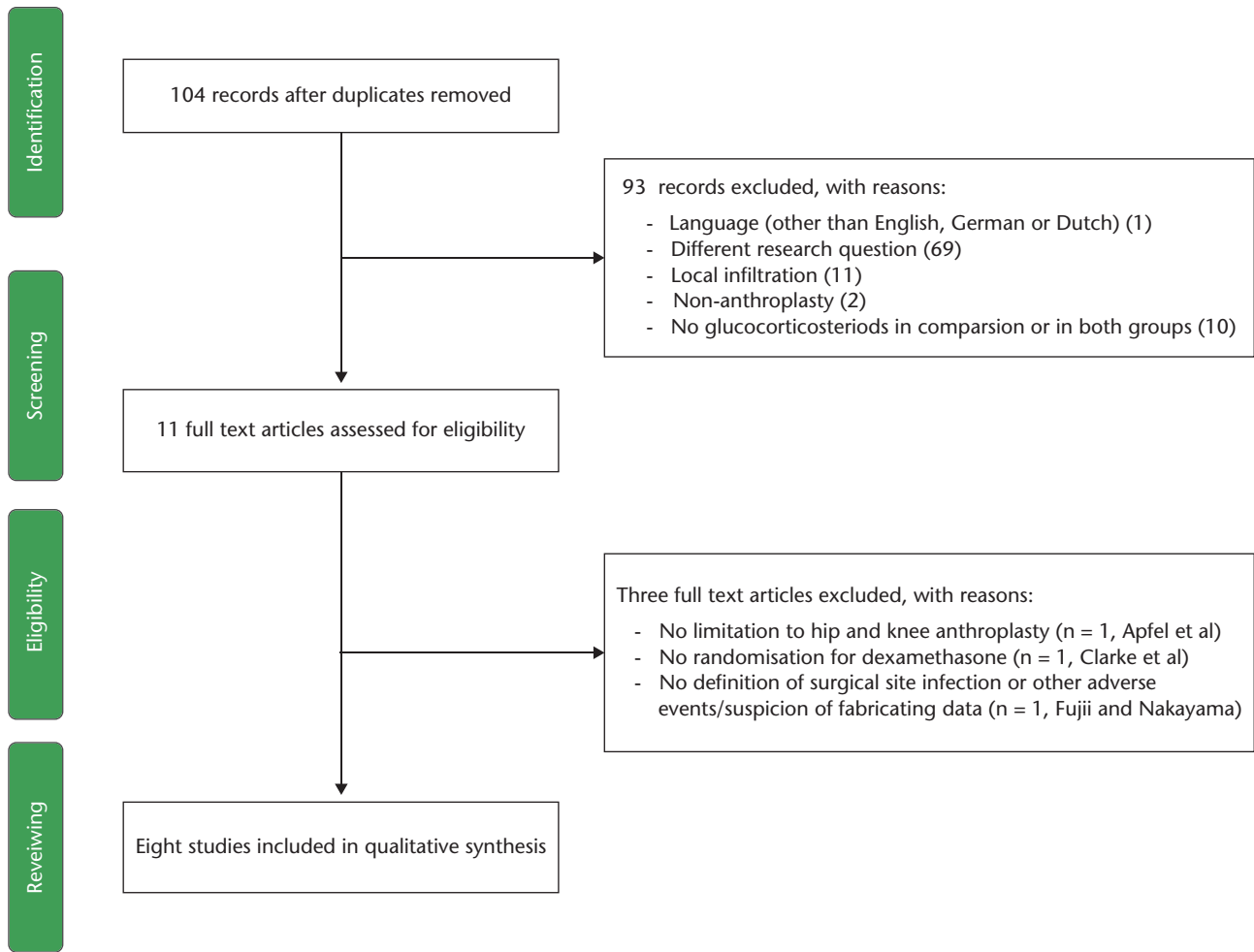


Fig. 1 Flow diagram of the literature search.

Table 1. Study design and primary outcome of included studies

Lead author	Date	Study design	Level of evidence	Primary outcome	Parameter
Bergeron*	2009	RCT	I	Functional outcome	Harris hip score
Kardash*	2008	RCT	I	Dynamic pain	Numeric rating scale
Mathiesen	2008	RCT	I	Analgesic effect of pregabalin and dexamethasone	Morphine consumption in mg
Rasmussen*	2010	RCT	I	Analgesic effect of combination therapy	Morphine consumption in mg
Lunn	2011	RCT	I	Dynamic pain at 24 h	VAS
Jules-Elysee	2012	RCT	I	IL-6 levels	Measured IL-6 levels
Lunn	2013	RCT	I	Time to meet discharge criteria	Time
Backes	2013	RCT	I	Length of stay and pain	Length of stay and VAS†

*The same group of patients was observed in two different studies.

†RCT, randomised controlled trial; VAS, visual analogue scale.

of surgical site infections was 0.0% for both the dexamethasone group and the control group.

Discussion

None of the eight included studies (1335 patients) convincingly demonstrated any increase in risk of SSI after a single dose of dexamethasone during total hip or knee

arthroplasty (Table 2). The main limitation of this systematic review is the fact that the included studies were not specifically designed to investigate the risk of SSI after a single dose of dexamethasone, and lacked an adequate follow-up and sample size in this respect. The primary outcome of the included studies varied from functional outcome,²⁰ post-operative analgesia or morphine consumption^{13,15,17} and length of stay (Table 1). The

Table 2. Characteristics of the included studies

Lead author	Date	Number of patients included	Selected from n patients	Dose iv dexamethasone / hydrocortisone	Comparison groups	Number of groups	Follow-up duration	Reported wound healing and infection
Bergeron*	2009	50	67	40 mg	<ul style="list-style-type: none"> • Saline • Dexamethasone 	n = 25 n = 25	Questionnaire at 6 weeks and one year	Did not increase wound complications and deep infections
Kardash*	2008	50	67	40 mg	<ul style="list-style-type: none"> • Saline • Dexamethasone 	n = 25 n = 25	48 h and record review at one month	No wound complications or infections in both groups
Mathiesen	2008	120	514	8 mg	<ul style="list-style-type: none"> • Placebo/placebo • Pregabalin/ placebo • Pregabalin/dexa 	n = 40 n = 40 n = 40	24 h	Not investigated/ reported
Rasmussen	2010	42	284	8 mg	<ul style="list-style-type: none"> • Paracetamol + ketorolac + placebo • Gabapentin + dexamethasone + ketamine + paracetamol + ketorolac 	n = 18 n = 24	24 h	Not investigated/ reported
Lunn	2011	48	73	125 mg	<ul style="list-style-type: none"> • Methylprednisolone • Placebo 	n = 24 n = 24	48 h and 21 days	No wound complications or infections in both groups
Jules-Elysee	2012	34	86	100 mg	<ul style="list-style-type: none"> • Hydrocortisone 3 doses every 8 h • Placebo 	n = 17 n = 17	48 h, three and six months by phone or mail	No wound complications or infections in both groups
Lunn	2013	48	100	125 mg	<ul style="list-style-type: none"> • Methylprednisolone • Placebo 	n = 24 n = 24	48 h and 30 days by phone	No wound complications or infections in both groups
Backes	2013	130	211	10 mg	<ul style="list-style-type: none"> • Placebo • Dexamethasone intra-operative • Dexamethasone intra-operative and 24 h post-operative 	n = 40 n = 46 n = 44	Up to 24 weeks	One superficial infection without elevated WBC count

*The same group of patients was studied in two different studies. h, hours; WBC, white blood cell.

duration of clinical follow-up (i.e. not by telephone or questionnaire), is far too short for a good evaluation of wound healing in most studies (Table 2). However, the included studies are currently the only available RCTs in which the effect of a single low dose of dexamethasone is evaluated in adult hip and knee arthroplasty patients. It might be questionable to conduct a systematic review without truly sufficient studies with adequate outcome parameters and follow-up to evaluate the impact of dexamethasone on SSI. However, we believe that the potential consequences for arthroplasty patients and the common use of dexamethasone justifies this systematic review. With the currently available literature it cannot be concluded that peri-operative dexamethasone has no impact on SSI.

The incidence of SSI after knee arthroplasty is low, about 0.3% to 1% and its cause is multi-factorial.²² On the basis of this information we conducted a sample size analysis. To detect a clinically meaningful 30% increase in SSI with a power of 90% and an alpha of 0.05, a group size of 27 205 patients would be required to demonstrate an association between dexamethasone and SSI. Certainly,

such an extensive RCT is unlikely to be performed. However, in recent years, various data registry studies of SSI using national databases have been conducted.^{22,23} Unfortunately, in this database the medication given peri-operatively was not registered in detail. However, considering the present and future absence of convincing data, evidence has to be based on the available data and pathophysiological reasoning. Such evidence is always debatable because of possible bias. Therefore, we divided the discussion into a ‘pro’ part from the anaesthesiologists’ point of view and a ‘con’ part from the orthopaedic surgeons’ point of view.

Pro: dexamethasone, anaesthesiologic point of view

A single low dose of dexamethasone is often used during joint arthroplasty surgery for its strong beneficial effects on PONV. Dexamethasone is a long-acting anti-emetic that is administered routinely as a prophylactic single dose during surgery in patients at high risk of developing PONV.²⁴ Prevention of PONV improves patient

satisfaction, because from the perspective of patients, vomiting is frequently rated even worse than pain.² There are many advantages in using dexamethasone over other anti-emetics including cost, duration of action and tolerability, although its exact mechanism of action as an anti-emetic remains unclear. A cohort study employing an equivalent dose of methylprednisolone in patients undergoing total hip and knee surgery reported a statistically significant reduction in nausea and prevention of vomiting, supporting our notion that dexamethasone is most likely the most effective glucocorticoid used to prevent PONV.²⁵

In order to answer the question of whether a single low dose of dexamethasone should be used, we analysed the benefit-risk ratio. The number needed to treat (NNT) of a single low dose of dexamethasone to prevent PONV was 7.1 in a systematic review of 17 trials including 1946 patients.²⁶ On the other hand, no incidence of SSI was detected in 1335 patients in the eight studies we reviewed. Thus, the number needed to harm (NNH) should be more than 1335. The question raises whether the use of a low dose of dexamethasone has any clinical relevance in the risk of SSI.

Analgesic effects

A second important property of dexamethasone is its analgesic effect, which has been demonstrated in numerous studies.⁵ The analgesic mechanism is not linked to the slow-onset anti-inflammatory action of dexamethasone. Acting on membrane receptors, its analgesic effect occurs in seconds to minutes.²⁷ Glucocorticosteroids inhibit spontaneous discharge of the peripheral nerve terminals at the area of tissue injury and prevent pain transmission at the synapses of afferent nociceptive C-fibres in the dorsal horn that are responsible for central sensitisation. Pre-operative administration of dexamethasone appears to produce a more consistent analgesic effect compared with intra-operative administration. Opioid-sparing effects were demonstrated for intermediate and high doses, but not for low dose dexamethasone.

Quality of recovery

A single high dose of dexamethasone has been demonstrated to improve patient-perceived quality of recovery for total knee arthroplasty and other types of surgery.²² Improved recovery is probably a result of combined beneficial effects of steroids like limiting systemic inflammation, reduced C-reactive protein (CRP) and cortisol levels, and improved mental state and less post-operative fatigue, besides the well-known effects on post-operative pain and PONV.

Hyperglycaemia

Low doses of dexamethasone for preventing PONV may cause short-lasting hyperglycaemia even in non-diabetic

patients in the post-operative period.^{28,29} Hyperglycaemia has been demonstrated to be an independent risk factor of SSI following different types of surgery.²⁸ After analysing more than one million arthroplastic operations with respect to SSI, the identified patient-related risk factors were male sex, age, ethnicity and comorbidity burden including complicated diabetes.³⁰ However, diabetes without signs of permanent organ manifestations was not a risk factor. Thus, a peri-operatively increased glucose level does not seem to increase the risk of SSI in patients undergoing arthroplasty.

Retrospective case-control studies in gynaecologic surgery showed higher infection percentages than in arthroplasty surgery, but without any significant differences in SSI between the dexamethasone-treated and control groups.³¹

From the anaesthesiologist's point of view, a single low dose of dexamethasone is a long-acting potent anti-emetic with few side effects. Steroids have beneficial dose-dependent effects on pain relief and quality of recovery without any evidence of increased risks of SSI, even in patients with hyperglycaemia. However, in mutual consent dexamethasone should be avoided in high-risk patients and those with complicated diabetes.

Con: dexamethasone, orthopaedic point of view

A post-operative infection has the potential to be a devastating and costly adverse outcome in major orthopaedic joint reconstruction. This complication can lead at times to revision surgery, delayed wound healing, increased use of antibiotics and increased length of hospital stay, all of which have a significant impact on the patient's quality of life and the costs of healthcare. The impact of this complication can be reduced by focussing on preventive strategies that can successfully reduce the burden of peri-operative infection. Preventing infections should be a top priority and a unifying concern when preparing for major orthopaedic surgery. From this point of view, the use of dexamethasone is questionable.

Wound healing

There is evidence from animal studies that high dose dexamethasone inhibits wound healing. Durmus et al investigated the effect of a single dose (1 mg/kg) of dexamethasone on skin healing in rats, showing that collagenisation, epithelisation and fibroblast content were significantly lower in the dexamethasone group compared to the control group (saline).³² Thus, a single high dose of dexamethasone had negative effects on wound healing in this animal model; however, the effects of low dose dexamethasone on wound healing have never been studied. Meisler et al demonstrated that dexamethasone abrogates the

fibrogenic effect of transforming growth factor-beta (TGF- β).³³ Other studies showed similar effects of corticosteroids on collagen synthesis.^{34,35} Smith, Erasmus and Myburgh demonstrated in a prospective comparative trial that a single dose of 16 mg dexamethasone, administered epidurally prior to surgery for total knee arthroplasty, inhibited a post-operative monocyte response for five days and limited the peak CRP.¹⁹ The most plausible explanation of this phenomenon is a dexamethasone-induced reduction in cell proliferation. Although this underpowered study did not show differences in clinical outcome, it did demonstrate an attenuated post-operative inflammation response after dexamethasone administration. A reduced inflammation response by the immunosuppressive effects of single low-dose dexamethasone may improve the post-operative catabolic state of the patient, but inducing immune suppression might be hazardous.

Since the incidence of SSI is fortunately so low in arthroplasty, we looked at other patient groups for an increase in SSI by a single low dose of dexamethasone. In a retrospective case-control study of non-emergency surgical patients, the risk of post-operative infections was associated with a low dose of dexamethasone compared to controls.¹⁶ Extrapolating these results of a three-time increased risk of SSI to the application of dexamethasone in arthroplasty surgery would be catastrophic to arthroplastic surgery and might have been unrevealed in the four reviewed studies, since these studies were tremendously underpowered for the detection of SSI induced by dexamethasone.

Therefore, administering a corticosteroid, well-known for its immunosuppressive effects, seems controversial.

In summary, based on current studies, the number of patients treated with a single low dose of dexamethasone or other corticosteroids during arthroplastic surgery is far too low to analyse the risk of SSI and wound healing disturbances. Furthermore, it is not likely that a prospective, double-blind randomised study conclusively answering this question will become available. Therefore, we are left with rather indirect evidence. However, all authors agree that on an individual basis there can be clear indications for or against the use of dexamethasone, e.g. healthy patients with a risk of developing PONV will clearly benefit peri-operatively from dexamethasone prophylaxis and risk of infection is very low, with or without dexamethasone. On the other hand, a patient with multi-morbidity and complicated diabetes and with a low risk of PONV according to the algorithm should most likely not be treated with dexamethasone. Moreover, this patient will have an elevated risk of SSI, which might be further increased by steroids. Because risks of SSI in most patients will be estimated between these two extreme examples, a team approach from the anaesthesiologist and the orthopaedic surgeon is mandatory to balance the risks and benefits of a

peri-operative low dose of dexamethasone on an individual basis in each patient.

Conclusion

From the currently available studies, we did not find evidence that a single low dose of dexamethasone contributes to SSI or wound-healing impairment. A team approach from anaesthesiologists and orthopaedic surgeons is mandatory to balance the risk–benefit ratio of peri-operatively applied steroids for individual arthroplasty patients.

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CONFLICT OF INTEREST

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