

Infection Safety of Dexamethasone in Total Hip and Total Knee Arthroplasty: a Study of 18 872 Operations

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Abstract

Purpose: Dexamethasone has been shown to prevent postoperative nausea and vomiting (PONV) and seems to reduce postoperative pain. Both factors, which can extend the hospital stay, delay rehabilitation, and impact patient satisfaction. Because of the immunosuppressive and glucose-raising effects of dexamethasone, there has been concern of its safety in arthroplasty surgery. The purpose of our study was to examine infection safety of dexamethasone in arthroplasty surgery with enough large study material to reliably detect a possible, even small, difference in infection incidence.

Methods: A total of 18 872 consecutive primary and revision hip and knee arthroplasties were analyzed with data gathered from clinical information databases and a surgical site infection surveillance database with prospective data collection. Also emergency operations due to fractures were included except for hip hemiarthroplasties.

Results: During the follow-up, 189 (1.0%) PJIs occurred: 0.8% after primary arthroplasty and 1.9% after revision arthroplasty. Dexamethasone was used in 2922 (15.5%) operations. The PJI rate in the dexamethasone group was 1.1% (31/2 922) and in the non-dexamethasone group 1.0% (161/15 950), with no significant difference in the risk of PJI between the two groups (OR 1.052, 95% CI 0.715–1.548, P=0.773).

Conclusions: In our study material, the use of a single 5-10 mg dose of dexamethasone did not increase the incidence of postoperative PJI. Dexamethasone may be safely used to prevent PONV and as part of multimodal analgesia on patients undergoing arthroplasty operation.

Keywords: prosthetic joint infection, infection, corticosteroid, risk factor, PONV, postoperative nausea

Introduction

Total joint arthroplasty (TJA), when successful, improves patients' physical ability, reduces pain, and increases quality of life. The annual volumes of total hip arthroplasty (THA) and total knee arthroplasty (TKA) have increased dramatically since the 1990s. In the US alone, the annual volume of THA had increased fourfold to 280 000 by the year 2009 [1] and TKA tripled to 630 000 by 2012 [2]. The trends are expected to steepen even more in the near future [2]. Postoperative nausea and pain inflicts a remarkable challenge in patients' early recovery and rehabilitation from the operation. It can extend the hospital stay, delay rehabilitation, and have an impact on patient satisfaction [3].

Dexamethasone is a glucocorticoid that has been shown to prevent postoperative nausea and vomiting (PONV) [4]. The exact mechanisms by which dexamethasone prevents PONV are not clear. An anti-inflammatory effect, inhibition of serotonin expression, and direct central action at the solitary tract nucleus have been proposed [5]. Dexamethasone also seems to reduce postoperative pain and opioid consumption [6,7-], which may also lead to less PONV [8].

In surgical settings, dexamethasone is usually given as a single intravenous dose before or after the induction of anesthesia. An effective dose to reduce PONV in adults is 4–5 mg IV; higher doses (i.e., 8–10 mg IV) seem to have no additional clinical effect in the reduction of PONV [9]. However, higher doses (> 0.1mg/kg) may be warranted in situations where dexamethasone is used as part of multimodal analgesia [7], but dose-response to the opioid-sparing effect has not been fully established [6].

Glucocorticoids have effects that arouse concern in total joint surgery: a suppressive effect on immune system and an increase in blood glucose level. Immunosuppression and high blood glucose levels are both known risk factors for prosthetic joint infection (PJI) [10]. The dose and duration of glucocorticoid therapy correlates to the depth of immunosuppression [11,12]. The effect of a perioperative single dose of dexamethasone in the incidence of surgical site infections has been studied [6], but more data is needed in joint replacement surgery to prove that dexamethasone is infection safe.

The beneficial influence of perioperative dexamethasone use on PONV has also been shown in studies concerning joint replacement surgery [13-16]. However, the sample sizes of these studies have been too small (120, 269, 110 and 108 patients, respectively) and the follow-up time too short in three out of the four studies (six months, one year, two weeks and three days, respectively) to prove infection safety. Three recent systematic reviews analyzed the efficacy and infection safety of dexamethasone (with study material from 655, 297, and 361 patients, respectively) [17-19], but were also too small to prove the difference in the incidence of PJI with the follow-up times too short to catch PJIs reliably. A retrospective study of 6294 patients (557 with and 5737 without dexamethasone, the largest so far concerning infection

safety of dexamethasone in joint replacement surgery) did not show any significant increase in the number of PJI in the group given dexamethasone [20]. However, because PJI is a rare outcome, the study had limited power to show the difference between groups.

PJI is still one of the most severe complications after total hip or knee surgery, leading to revision operations and long antibiotic therapies, causing a burden on the patient and healthcare systems [21]. Because of this, the perioperative factors that may affect the incidence of PJI must be studied carefully. The aim of this study was to examine the infection safety of perioperative dexamethasone therapy used in TKA and THA surgery with a large study material and long enough follow-up time.

Materials and methods

The study consisted of a total of 18 872 THA or TKA operations, including all consecutive primary and revision hip and knee arthroplasties, performed on 14 792 patients between January 2008 and November 2016. Emergency operations due to fractures were also included except for hip hemiarthroplasties. All the operations were done in The Hospital District of Helsinki and Uusimaa (HUS), Peijas Hospital.

Data collection and endpoints

The data of operations performed were collected from two clinical information systems. The Anesthesia Information Management System is used for collecting perioperative data and guiding the treatment of patients. Among other things, it contains information from operation day, the operation code, use of peri- and intraoperative medications, height and weight of the patient, type of anesthesia used, and blood loss. The Surgery Management System contains information about operation codes, operation duration, medical priority, surgeon, American Society of Anesthesiologists (ASA) physical status classification, wound classification, and diagnosis. Our current Surgery Management System has been used since December 2009, and the information provided by it was collected from then onwards.

The data of postoperative infections were recorded in the postoperative surgical site infection surveillance database. The database contains information about infection date, infection type, and cultured bacteria. The infection surveillance has been performed with active prospective surveillance with in-patient and post-discharge surveillance [22]. Case-finding relies on the active cooperation of infectious disease specialists and orthopedic surgeons in diagnosing and treating the PJIs. Most cases have been examined by one infectious disease specialist (Huotari K.) with a special interest in PJIs. In addition, a systematic review of microbiology reports was performed at least weekly. All patients suffering any symptoms

of postoperative infection are advised to contact the operating hospital. During most of the study period, a post-discharge questionnaire was also given to all patients having had operations.

In prospective surveillance from January 2008 to November 2016, Centers for Disease Control and Prevention (CDC) definitions for PJI from 1992 [23] were used according to national guidelines. Only postoperative PJIs were recorded, hematogenous PJIs were excluded. The 192 postoperative PJIs, which were detected in the surveillance, were retrospectively evaluated in order to validate, whether the cases fulfilled the PJI definition of Musculoskeletal Infection Society (MSIS) definition modified in the International Consensus Meeting [24]. A total of 189 cases fulfilled this definition. PJI was defined as two positive periprosthetic cultures with phenotypically identical organisms, or a sinus tract communicating with the joint, or having three of the following minor criteria: elevated serum C-reactive protein and erythrocyte sedimentation rate, elevated synovial fluid white blood cell count or ++change on leukocyte esterase test strip, elevated synovial fluid polymorphonuclear neutrophil percentage, positive histological analysis of periprosthetic tissue, or a single positive culture. The occurrence of postoperative PJI fulfilling the International Consensus Meeting definition was the main endpoint for the study.

During the study period, both orthopedic surgeons and anesthesiologists independently prescribed perioperative dexamethasone to patients according to individual risk for PONV or as part of multimodal analgesia.

For all 18 872 operations, information of the use of dexamethasone and infection outcome was documented. Information from the ASA classification, wound classification, medical priority, and simultaneous periprosthetic fracture operations was missing from 4 047 operations (21.4%), mainly because our current Surgery Management System has been in use only since December 2009. Information about BMI and blood loss was missing for 398 operations and 65 operations, respectively, and information about preoperative antibiotics was missing from 3871 (20.5%) operations. All operations were included in the analysis to the extent that information was available. The mean follow-up time to the point the data was collected was 4.9 (range: 1.0–9.7) years.

Statistics

Univariable analyses were calculated with the chi-squared test or Fisher's exact test, as appropriate, for categorical variables and the Mann–Whitney U test for continuous variables. The potential risk factors for PJI with P-value below 0.2 in univariable analysis together with some basic demographics (gender and age) were selected into the multivariable analysis. The multivariable analysis was performed on the material with complete data available using the logistic regression with forward selection process. P-value of less than 0.05 was considered statistically significant. The analyses were calculated with SPSS for Windows, version 23.0.

In this study, the size of dexamethasone and non-dexamethasone groups were 2922 and 15 950 operations, respectively, and the power of the study is sufficient to differentiate at least a 0.67% change in the occurrence of PJI (the change from 1% to 1.67% with the power of 80.4% and the level of significance of 5%).

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Results

During the follow-up time occurred 189 PJIs (1.0% of 18 872 operations, 0.8% after primary arthroplasty and 1.9% after revision arthroplasty). In the dexamethasone group, the PJI rate was 1.0% (30/2922), and in the non-dexamethasone group, it was 1.0% (159/15 950). There was no significant difference in the risk of PJI between the two groups (OR 1.052, 95% CI 0.715–1.548, $P=0.773$).

Intra- or perioperative corticosteroids were given in 3352 (17.8%) operations. Dexamethasone was given in 2922 (15.5%) operations to prevent PONV and/or to reduce postoperative pain. The initial dexamethasone dose given was primarily 10 mg or 5 mg (75.3% and 24.5%, respectively, mean 8.8 mg \pm SD 2.7mg). An additional dose of dexamethasone was given in 23 operations.

In 430 (2.3%) operations, corticosteroids other than dexamethasone were given for indication other than PONV (hydrocortisone [94.0%], methylprednisolone [3.5%], and prednisolone/prednisone [2.6%]): in this group, the infection rate was 1.4% (6/430) (OR 1.403, 95% CI 0.617–3.189 when comparing to the group not given corticosteroids, $P=0.455$).

There were no differences in demographics between dexamethasone and non-dexamethasone groups (Table 1).

Potential factors predisposing to PJI by univariable analysis are presented in Table 2. In multivariable analysis, the independent risk factors were male gender, knee arthroplasty, revision operation, BMI equal to or higher than 30, and ASA classification of 3–4 (Table 3).

Of the 189 PJI occurrences, 56.3% were in males and 65.6% involved the knee joint. Only one patient was involved with two PJIs, one within dexamethasone group and one within non-dexamethasone group. The median time from the index operation to the infection was 16.0 (Q1–Q3 13.0–23.0) days. In dexamethasone and non-dexamethasone group the three

most commonly cultured bacteria in PJI did not differ: *Staphylococcus aureus* (40.0% and 45.0%, respectively, the former number including one methicillin-resistant *Staphylococcus aureus* (MRSA)), *Staphylococcus epidermidis* (14.3% and 10.7%, respectively), and other coagulase-negative staphylococci (11.4% and 11.8%, respectively). In dexamethasone group, four (13.3%) were polymicrobial infections comparing to 14 (8.8%) in non-dexamethasone group (p=0.495).

Discussion

The main objective of the study was to examine infection safety of dexamethasone use in THA and TKA operations. Based on the large study material (18 872 operations) and long follow-up time (mean 4.9 years), the use of 5–10 mg of dexamethasone did not increase the incidence of postoperative PJI.

Our study is the largest single center study so far that has examined the infection safety of dexamethasone on TJA patients. We tried to diminish the possibility for errors caused by chance by collecting extensive material from 18 872 operations. Previous studies have been limited by sample size, lacking the power to show a difference in the incidence of PJI between the two groups [13-20], and there is wide heterogeneity in how the complications have been reported [17-19]. Also the follow-up time of the studies has been too short to find a PJI [13,15-19]. The largest of the previous studies (sample size of 6294 patients) showed no statistically significant difference in the incidence of PJI between groups, but it also lacked the power to prove dexamethasone infection safe [20].

Our data of 18 872 operations also included revision arthroplasty, compared to the recent study by Richardson et al. of 6294 primary total hip and knee arthroplasty operations [20]. The PJI rate of 0.8% after 15 789 primary arthroplasty operations in our study was significantly lower than the 1.2% of the study by Richardson et al. [20]. The criterion for PJI differed in these two studies: in the recent study [20], the diagnosis of PJI was made retrospectively based on the need for a return to the operating room because of infection, whereas in the current study, MSIS definition modified in the International Consensus Meeting for PJI [24] was used leaving the treatment protocol open.

In our data, the use of single-dose dexamethasone was not a significant risk factor for PJI, nor was there any relation to the dose used (5–10 mg). In the current study, the dose was 10 mg in three out of four operations and 5 mg in the one out of four. The recent study by Richardson et al. [20] was made with an intravenous dexamethasone dose of 4–10 mg. In the review articles [17-19], the dexamethasone dose was no less than 7.5 mg IV, and doses even as high as 40 mg IV were used. In two of the recent studies two 10 mg IV doses of dexamethasone were used (15,16). The doses given were higher than the 4–5 mg effective dose to reduce PONV. Higher doses seem to have no additional clinical effect on PONV [9], but may help to reduce pain [7]. In the current study, an additional dose of dexamethasone was given in only 23 operations.

According to our data, male gender, knee joint operation, revision operation, BMI equal to or more than 30 and ASA classification of 3 or 4 were well known risk factors predisposing the patient to PJI, as shown in previous studies, which our material supports [13].

The distribution of causative bacteria between the two groups was uniform and are in line with earlier studies [20,25]. One exception was that only one (0.5%) methicillin-resistant *Staphylococcus aureus* (MRSA) was cultured in our study compared to 11% in the previous study [20]. The use of dexamethasone does not seem to increase the incidence of low virulent bacteria, nor was there a significant difference in polymicrobial infections.

The clinical databases cause limitations to the study, and the analyses can be done only with the information available. For example, not all comorbidities or home medications (per oral glucocorticoids) were able to be analyzed.

The strength of our study is the large study material collected from a single center where indications to operate and surgical protocols have remained basically the same during the study period. All infections have been diagnosed and treated by the same single center that operated on the joints in the first place, and the infections have been captured reliably.

Conclusions

There has been concern about the infection safety of dexamethasone in THA and TKA patients. In our large data, the use of single 5–10 mg dose of dexamethasone had no impact on the incidence of PJI. Dexamethasone may be safely used to prevent PONV and as part of multimodal analgesia in patients undergoing arthroplasty operation.

Table 1. Demographics of the patients treated with and without perioperative dexamethasone (DXM)

	DXM		Non DXM	
	n=2 922		n=15 950	
	n	%	n	%
Age (median, Q1–Q3, years)	67.0	(59.0–74.0)	68.0	(60.0–75.0)
Gender (male)	752	25.7	5 933	37.2
BMI equal to or more than 30	1 022	35.6	5 445	34.9
Operated joint (knee)	1 401	47.9	8 093	50.7
Operation type (primary)	2 383	81.6	13 406	84.1
Anesthesia type (spinal)	2 545	88.6	13 887	89.0
ASA classification (3–4)*	1 310	54.5	6 855	55.1

* Data available from 14 825 operations

Table 2. Potential factors from the univariable analysis affecting the incidence of PJI

Risk factor	PJI (n=189)		No PJI (n=18 679)		P-value	OR	95% CI
	n	%	n	%			
Age (median, Q1–Q3, years)	67.0	(60.0–76.0)	67.0	(60.0–75.0)	0.360	1.008	0.995–1.022
Gender (male)	107	56.6	6 578	35.2	<0.001	2.403	1.798–3.205
Operated joint (knee)	124	65.6	9 370	50.2	<0.001	1.896	1.403–2.563
Operation type (revision)	60	31.7	3 023	16.2	<0.001	2.409	1.769–3.281
Anesthesia type (general)	23	12.2	1 306	7.0	0.009	1.845	1.188–2.865
Anesthesia changed	8	4.2	1 179	6.3	0.293	0.656	0.322–1.335
Given dexamethasone (any dose)	30	15.9	2 892	15.5	0.849	1.030	0.696–1.525
Given dexamethasone (4–5 mg)	7	3.7	693	3.7	1.000	0.998	0.468–2.132
Given dexamethasone (6–10 mg)	23	12.2	2 192	11.7	0.832	1.042	0.672–1.616
Given dexamethasone (over 10 mg)	0	0.0	7	0.0	1.000	0.990	0.989–0.991
Additional dose of dexamethasone	0	0.0	23	0.1	1.000	0.990	0.989–0.991
Given any type of corticosteroid	36	19.0	3 316	17.7	0.639	1.090	0.757–1.571
Use of local infiltrative analgesia	33	17.5	4 485	24.0	0.042	0.670	0.459–0.976
Blood loss (mean, \pm SD, ml)	100.3	(\pm 108.6)	82.5	(\pm 98.0)	0.006	1.002	1.000–1.003
Medical priority (emergency)*	19	12.5	777	5.3	0.001	2.557	1.572–4.157
BMI equal to or more than 30	78	41.9	6 389	34.9	0.052	1.345	1.004–1.803
ASA classification (3–4)*	109	71.7	8 056	54.9	<0.001	2.085	1.463–2.972
Wound classification (clean)*	150	98.7	14 401	98.1	1.000	1.417	0.349–5.746
Simultaneous fracture operation*	3	2.0	87	0.6	0.065	3.378	1.057–10.799
Given preoperative antibiotics**	156	100.0	14 845	100.0			

OR: Odds Ratio, CI: confidence interval.

* Data available from 14 825 operations

** Data available from 15 001 operations

Table 3. Independent risk factors from the multivariable analysis predisposing patients to PJI when analyzing the 14 825 operations with complete data

Risk factor	P-value	OR	95% CI
Gender (male)	<0.001	2.075	1.499–2.873
Operated joint (knee)	<0.001	2.262	1.503–3.342
Operation type (revision)	<0.001	2.179	1.503–3.160
BMI equal to or more than 30	0.025	1.471	1.049–2.061
ASA classification (3–4)	0.001	1.852	1.287–2.663

OR: Odds Ratio, CI: confidence interval.

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Conflict of Interest

Authors Markku Vuorinen, Riku Palanne, Tatu Mäkinen, Jarkko Leskinen, Heini Huhtala and Kaisa Huotari declare that they have no conflicts of interest.

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