Original Article

A 20 mg dose of dexamethasone does not reduce the proportion of joint replacement patients needing rescue analgesia: a matched cohort study

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Background: Consistent pain control after total joint replacement (TJR) has not yet been reached in all patients managed with a multimodal analgesia regime. Questions remain on dosage and timing of analgesics. Glucocorticoids such as dexamethasone are considered most powerful in reducing the surgery-induced inflammatory response with most pain studies using a 6–12 mg dose. Reviews agree that additional glucocorticoids may provide more analgesia, but a dose-finding analysis is limited. The primary aim of this study was to determine if a high, single preoperative dose of dexamethasone resulted in a reduced need for rescue analgesics during the first 24 hours after TJR when compared to a standard 8 mg dose of dexamethasone.

Methods: A cohort study in which 59 patients who received 20 mg dexamethasone intravenously just prior to incision were matched 1:1 to patients who received a standard 8 mg dose. Consecutive elective hip and knee replacement patients managed by one anaesthesiologist were included in the high dose group between June 2019 and March 2020. Patients were matched for arthroplasty type, gender, age, anaesthesia type and pre-operative pain. Patients with opioid use before surgery or with diabetes mellitus were excluded. Oxynorm rescues analgesics (number of times given and dosage) usage during hospitalization was retrieved from the electronic nursing files.

Results: There were no significant differences between groups in gender distribution, mean age and body mass index (BMI), in American Society of Anesthesiologists (ASA), type of arthroplasty, anaesthesia type and pre-operative pain score. In the 20 mg group 54 patients (91.5%) needed oxynorm during hospitalization versus 58 (98.3%) in the 8 mg group (P=0.09). High dose group patients received a median of 5 mg [interquartile range (IQR): 0] oxynorm versus 5 mg (IQR: 0) in the standard dose group (P=0.70).

Conclusions: In this matched cohort study there was no difference in the proportion of patients needing rescue analgesics during hospitalization between the group of patients who preoperatively received 20 mg dexamethasone and the group of patients who received 8 mg. Future blinded randomized controlled trials are needed to further investigate the effect of different glucocorticoids dosages on pain after joint replacement surgery.

Keywords: Arthroplasty; multimodal analgesia; dexamethasone; rescue analgesics

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Introduction

Optimizing pain management for patients after total joint replacement (TJR) surgery is an ongoing effort. Uncomfortable postoperative pain is detrimental to the patients recovery and may cause anxiety, sleep disturbance, delayed mobilisation, prolonged length of hospital stay and increased opioid use (1,2). Postoperative pain control following a TJR procedure has improved considerably with the introduction of multi-modal analgesic protocols (3). However, a predictable and consistent amount of pain after TJR has not yet been fully achieved.

Corticosteroids (dexamethasone, methylprednisolone) play an important role within the multi-modal analgesic approach (4). Systematic reviews on this topic show positive effects on length of hospital stay, on postoperative pain, on opioid consumption and on postoperative nausea and vomiting but also that the quality of evidence is moderate to low (5-7). Various placebo controlled randomized trials have demonstrated the efficacy of corticosteroids in controlling postoperative pain, with significantly less pain during the early post-operative phase after TJR if dexamethasone is used (7). However, timing of administration of these corticosteroid varies widely, ranging from a single dose given one week before TJR surgery, a single intravenous (IV) injection immediately before surgery to two doses (one immediately before surgery and one 24 hours later) (8-10). Besides timing, the optimal dose of corticosteroids for postoperative pain control is still unknown, with dexamethasone dosing varying from 8 mg up to 40 mg preoperative (5,11). A meta-analysis by Hannon *et al.* showed strong evidence for intravenous dexamethasone but insufficient evidence on optimal dose or number of doses (12). Of their 16 included studies using dexamethasone the low dose was 0.1 and 0.2 mg/kg for high dose, ranging in clinical practice from 6–10 mg (low dose) to 12–20 mg/kg (high dose). Only two included studies compared the effects of different doses of dexamethasone, limiting their ability to draw any conclusions regarding the optimal dose, urging them to call for further research on the safest and most efficacious dose and number of doses.

Therefore the primary aim of this study was to determine if a higher (20 mg compared to 8 mg), single preoperative dose of dexamethasone results in a reduced need for rescue analgesics during the first 24 hours after joint replacement surgery. For the reporting of this study, we adhered to the STROBE reporting checklist (available at https://aoj.amegroups.com/article/view/10.21037/aoj-22-34/rc) (13).

Highlight box

Key findings

- A single, peroperative dose of 20 mg dexamethasone did not reduce the use of rescue analgesics in the first 24 hours after hip or knee replacement surgery compared to 8 mg dexamethasone.

What is known and what is new?

- Glucocorticoids are considered most powerful in reducing the surgery-induced inflammatory response with most pain studies using a 6–12 mg dose. Additional glucocorticoids may provide more analgesia, but a dose-finding analysis is limited.
- A single peroperative dose 20 mg dexamethasone appears not to be superior in reducing the need for postoperative rescue analgesics compared to an 8 mg dose.

What is the implication, and what should change now?

- Future blinded randomized controlled trials are needed to further investigate the effect of different glucocorticoids dosages on pain after joint replacement surgery.

Methods

Study design

We conducted a matched cohort study. The Regional Medical Ethical Review Board (Medisch Ethische Commissie Máxima Medisch Centrum) approved the study (No. N20.119) and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All consecutive patients without diabetes, planned for an elective TJR procedure between June 2019 and March 2020 and who were managed by the anaesthesiologist involved in this study (KV) were given a 20 mg dose [high dose group (HDG)]. This dose was administered intravenously just prior to incision. After the HDG group was completed, each HDG patient was matched with a patient who received a standard 8 mg dose [standard dose group (SDG)] in the same hospital. SDG patients were operated between December 2015 and March 2020. Patients and observers were not blinded for the administered dose of dexamethasone. For matching, the following items were used: type of arthroplasty [primary total hip arthroplasty (THA) or total knee arthroplasty (TKA)], gender, age (±10 years), type of anaesthesia (general or spinal) and level of pre-operative pain during activity (±1 point on pain Numeric Rating Scale). Patients with opioid use before surgery were

excluded. Besides the difference in dexamethasone dose, all patients were managed with our standard perioperative multimodal analgesia protocol for joint replacement surgery: paracetamol (1,000 mg, 4 times per day for 7 days, followed by 1,000 mg 3 times per day as needed, for another 7 days), celebrex (200 mg 2 times per day for 7 days, followed by 200 mg 2 times per day as needed, for another 7 days), oxycontin (5 or 10 mg 2 times per day for 3 days) and oxynorm (5 mg as needed 4 times per day for 4 days). Additionally, pantoprazole (40 mg once per day for 14 days) and movicolon (once per day for 4 days) are given. Local Infiltration Analgesia [LIA, 150 mL ropivacaine 0.2% with epinephrine (10 mg mL)] was perioperative administered in case of total knee replacement but not with total hip replacement. No adductor canal or femoral nerve blocks were used. We included patients who had either general or spinal anaesthesia during TJR surgery.

Per protocol, the aim is to postoperatively control the NRS pain to <4. If patients experience uncomfortable pain with a NRS score >3 after surgery, opioids are given if the Ramsay sedation score is <4, breathing frequency is >10/minute and the systolic blood pressure is >100 mmHg (14). Pain is reassessed after 60 minutes. In case the NRS score is still ≥4 and there are no side effects, a second 5 mg dose of oxynorm can be given with a maximum of 10 mg within 6 hours. Patients were not informed about this postoperative pain protocol but daily three rounds of scoring pain levels is standard care on our orthopedic ward. Of course, patient who experienced high pain levels between pain scoring rounds were able to contact a nurse for further pain management.

For all patients the following data was collected: (I) involved joint and type of anaesthesia (general or spinal); (II) use of rescue analgesics (number and total dosage) during hospitalization; (III) Numeric Rating Scale (NRS) scores for knee or hip pain, routinely collected three times per day (8 am, 3 pm and 10 pm) during hospital admission; (IV) all complications and readmissions within 90 days. Primary outcome of the study was the proportion of patients who needed oxynorm after TJR during their stay at the nursing ward. Secondary outcomes were rescue analgesia on the post-anesthesia care unit (general anesthesia patients only), length of stay (LOS, measured from time admitted in hospital to discharge time) and complications (number and severity).

Statistical analysis

For sample size calculation we used an online tool (powerandsamplesize.com) comparing two proportions (two independent samples, two sided equality). The study was powered to detect a reduction of 25% (from 80% to 55%) in the proportion of patients needing rescue analgesics after the arthroplasty procedure (β=0.8, α=0.05). This resulted in 52 patients per group.

Descriptive statistics were used to present patient demographics and surgery details. Data was checked for distribution and outcomes with normally distributed data were tested with a 2-sided Student *t*-test, non-parametric data with a Mann-Whitney U test Binominal outcomes were tested with the Chi-Square test. All analysis was performed using SPSS (IBM SPSS statistics version 25) with P<0.05 considered statistically significant.

Results

A total of 59 patients who received a single preoperative dose of 20 mg dexamethasone (HDG, n=59) were matched to 59 patients who received a standard dose of 8 mg dexamethasone (SDG, n=59) (*Table 1*). On the nursing ward 54 patients (91.5%) from the HDG needed oxynorm versus 58 (98.3%) in the SDG (Chi square test: P=0.09, odds ratio 0.19 with 95% confidence interval: 0.21–1.65). HDG patients received a median of 5 mg [interquartile range (IQR): 0] oxynorm, SDG patients received a median of 5 mg (IQR: 0) oxynorm (P=0.70). See *Table 2* and *Table 3* for all outcomes.

Discussion

We found that on the nursing ward a high number of patients received rescue analgesics, both in the HDG and the SDG. This questions the efficacy of our multimodal analgesic protocol. Compared to the multimodal analgesic protocol presented in the study by Kardash *et al.*, ours does without morphine which might explain the higher need for rescue analgesics (15). The multimodal analgesic protocol in the study by Lunn *et al.* combined gabapentin, acetaminophen and celecoxib with LIA (11). In the first postoperative 24 hours, their median cumulative use of rescue analgesics was 20 mg of oxycodone, quite a bit more than the median 5 mg oxycodone which our HDG patients received during their postoperative stay in hospital.

Key findings

This study investigated the effect of a high (20 mg)

Table 1 Patient demographics

Demographics	20 mg group (n=59)	8 mg group (n=59)	P
Male/female	30/29	30/29	1.0*
Age (years), mean (SD)	65.7 (7.5)	66.3 (7.0)	0.63**
BMI (kg/m^2), mean (SD)	28.7 (4.5)	27.1 (3.6)	0.18**
ASA, n (%)			
1	7 (12%)	9 (15%)	
2	45 (76%)	43 (73%)	
3	7 (12%)	7 (12%)	
THA/TKA	20/39	20/39	1.0
Anesthesia, n (%)			
General	29 (49%)	29 (49%)	
Spinal	30 (51%)	30 (51%)	
Preoperative NRS joint pain score during activity, mean (SD)	72.4 (17.5)	72.9 (16.9)	0.87**

*, Chi-Square test; **, two-sided independent samples *t*-test. SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; THA, total hip arthroplasty; TKA, total knee arthroplasty; NRS, Numeric Rating Scale.

Table 2 Results comparing low dose dexamethasone group versus high dose dexamethasone group

Outcome	20 mg group (n=59)	8 mg group (n=59)	P
Patients who received oxynorm, nursing ward	91.5%	98.3%	0.09**
Oxycodone use on nursing ward (mg), median (IQR)	5 (0)	5 (0)	0.07¥
Patients who received antiemetic medication, nursing ward	0%	3.3%	0.15**
Patients who received sufentanil or piritramide, recovery ward*	80.0%	92.9%	0.69**
Sufentanil use on recovery ward (µg), median (IQR)	0 (2.5)	0 (5.0)	0.000¥
Piritramide use on recovery ward (mg), median (IQR)	0 (2.5)	0 (0)	0.53¥
NRS pain 0–24 hours postoperative, mean (SD)	2.2 (1.0)	2.4 (1.1)	0.30T
Length of stay (hours), mean (SD)	36.5 (32.5)	37.5 (15.7)	0.84T
Postoperative complications <30 days	3.4%	5.0%	0.40**

*, general anesthesia patients only; **, Chi-Square test; T, independent *t*-test; ¥, Mann-Whitney U test. IQR, interquartile range; NRS, Numeric Rating Scale; SD, standard deviation.

Table 3 Overview of complications <90 days postoperative

Group	Complications
20 mg group (n=59)	Manipulation under anesthesia after total knee replacement (n=1)
	DVT suspected, resolved (n=1)
8 mg group (n=59)	Manipulation under anesthesia after total knee replacement (n=1)
	Postoperative skin defect (n=1)
	Persistent pain (n=1)

DVT, deep vein thrombosis.

perioperative dose of dexamethasone versus a standard (8 mg) dose. There was no difference between the HDG and the SDG regarding the number of patients needing rescue analgesics. Also, given doses of rescue analgesics did not differ between both groups. There were no differences in any of the secondary outcomes. Our results do not demonstrate any beneficial effect of a higher (20 mg) dose of dexamethasone compared to a standard 8 mg dose.

Strengths and limitations

This study has several limitations. First of all it is a non-randomized design, possibly introducing bias. Moreover, the number of included patients is limited. However, the absolute differences between the groups were small, which makes a type 2 error due to limited number of patients less likely. Strong points are that we were able to include a group of patients matched on an extensive number of details and the observational character extends the clinical validity of our results.

Comparison with similar researches

Quite a number of systematic reviews elaborate on positive effects of dexamethasone with regards to pain, LOS and post operative nausea and vomiting (5,6,16,17). The included studies almost exclusively use a dose of 5 to 10 mg corticosteroids, comparable to our standard dose of 8 mg. Four studies used a higher dose. In a randomized controlled with 50 THA patients, Kardash *et al.* tested 40 mg dexamethasone against placebo and found a prolonged suppressive effect on the inflammatory response and a significant decrease of pain on mobilisation in the first 24 postoperative hours (15). Their reported mean NRS pain scores at rest during the first 24 hours for patients who received dexamethasone were comparable to the pain scores found in our study. Lunn *et al.* used methylprednisolone (equivalent to 25 mg dexamethasone) versus placebo (11). Their reported median pain scores on a NRS at rest with methylprednisolone ranged from 1.5 to 2 points during the first 24 hours, only slightly lower than the mean 2.2 (HDG) and 2.4 (SDG) found in our study. These differences are minimal and clinically not relevant. Nielsen *et al.* found improved analgesic and functional outcomes when using 1 mg·kg dexamethasone compared to 0.3 mg·kg a in a double blind randomized controlled trial (18). In contrast to our study, only high pain responders undergoing total knee replacement were included. Gasbjerg *et al.* found in a double blind randomized controlled trial reduced pain and morphine consumption 48 hours after total knee replacement with a second 24 mg dose of dexamethasone compared to placebo and to a single 24 mg dose (19).

Explanations of findings

Although intuitively a higher dose of analgesics implies increased postoperative pain reduction, the potential hazards of administering higher doses of corticosteroids should be taken into account. Corticosteroids have an immunosuppressive action, raising concern that postoperative wound infections are more likely with higher doses (20). In our study we did not observe postoperative wound infection in either group. Furthermore, corticosteroids can deregulate the glucose balance, with a measurable raise of postoperative blood glucose that is however without clinical significance in regard to postoperative complications (20). Since diabetes mellitus is a common co-morbidity of arthroplasty patients, this should be taken into consideration (21).

Implications and actions needed

Randomized controlled trials, preferably blinded, are needed to further investigate the effect of different dosages of glucocorticoids on postoperative pain in TJR.

Conclusions

In conclusion, we did not find better postoperative pain control in our patients who preoperatively received 20 mg dexamethasone compared to our arthroplasty patients who received 8 mg dexamethasone.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://aoj.amegroups.com/article/view/10.21037/aoj-22-34/rc

Data Sharing Statement: Available at https://aoj.amegroups.

com/article/view/10.21037/aoj-22-34/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Regional Medical Ethical Review Board (Medisch Ethische Commissie Máxima Medisch Centrum) approved the study (No. N20.119) and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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