

CLINICAL INVESTIGATION

Safety aspects of preoperative high-dose glucocorticoid in primary total knee replacement

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Abstract

Background: Preoperative single high-dose glucocorticoid may have early outcome benefits in total hip arthroplasty (THA) and knee arthroplasty (TKA), but long-term safety aspects have not been evaluated.

Methods: From October 2013, the departments reporting to the prospective Lundbeck Foundation Database for Fast-track Hip and Knee Replacement introduced preoperative methylprednisolone (MP) 125 mg as part of a multimodal analgesic protocol in TKA. We analysed the risk of length of hospital stay (LOS) >4 days, 30 and 90 day readmissions in patients with MP vs patients having TKA before the use of MP and adjusted for comorbidity and place of surgery. An unadjusted comparison was specifically done to evaluate deep prosthetic infections.

Results: Of a total of 3927 TKA procedures, 1442 received MP. Median LOS was 2 days in both groups, but the fraction with LOS >4 days was 6.0% vs 11.5% ($P < 0.001$) in patients with MP vs those without, and with a reduced risk of LOS >4 days in adjusted analysis [odds ratio (OR) 0.51; confidence interval (CI) 0.39–0.68; $P < 0.001$]. Readmission rates were 5.6% (CI 4.5–6.9) vs 4.4% ($P = 0.095$) and 7.8% vs 7.3% ($P = 0.53$) at 30 and 90 days with and without MP, respectively. Adjusted analysis did not identify MP to be associated with 30 day (OR 1.18; CI 0.89–1.56; $P = 0.25$) or 90 day (OR 1.12; CI 0.86–1.46; $P = 0.39$) readmissions. The incidence of deep infections requiring surgical intervention was 0.8% vs 0.7% with MP vs without, respectively ($P = 0.78$).

Conclusions: In this detailed prospective cohort study, preoperative high-dose glucocorticoid administration was not associated with LOS >4 days, readmissions or infectious complications in TKA patients without contraindications. Clinical trial registration: NCT01515670.

Key words: glucocorticoids; arthroplasty; replacement; knee; patient safety; orthopaedics

Despite an improved understanding of pain mechanisms and development of procedure-specific analgesic techniques, sufficient pain management after TKA remains a major clinical

challenge.^{1 2} In this context, preoperative use of high-dose glucocorticoids may be of value and in higher doses than used routinely for postoperative nausea and vomiting (PONV)

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Editor's key points

- Glucocorticoids can improve some indices of recovery after surgery but there is ongoing uncertainty about increased infection risk.
- Registries offer excellent opportunities to monitor safety in healthcare.
- This analysis demonstrates success with an enhanced recovery pathway that includes high-dose methylprednisolone for knee arthroplasty, and no evidence of increased infectious complications.

prophylaxis.³⁻⁵ Thus, some recent studies in major joint arthroplasty have found significant benefits on pain, even when combined with basic evidence-based multimodal analgesia.⁶⁻⁹ In addition, preoperative administration of such 'high dose' glucocorticoids in other major procedures is promising to enhance recovery by reducing the surgery induced inflammatory response.¹⁰⁻¹² However, despite these early promising effects, clinicians have been reluctant to use high doses of preoperative glucocorticoids because of a relevant concern about side-effects on wound healing and risk of infections, although existing data from other procedures have not demonstrated any safety issues to date.^{4 6-9 13-15} Furthermore, because of their effect on gene transcription, glucocorticoids have numerous potential systemic side-effects, including neuropsychiatric and cardiovascular problems, disturbances in glucose balance and increased risk of gastric ulcers, especially when combined with non-steroidal anti-inflammatory drugs.^{16 17} Although most side-effects of steroids occur with long-term treatment, a study in patients with multiple sclerosis receiving pulse therapy for attacks found that patient-reported adverse effects occurred on the second day in >50% of patients,¹⁸ and the onset of neuropsychiatric symptoms may also occur after as little as five days of treatment with 40 mg of prednisone.¹⁹ However, in this context, the effect of a single high-dose glucocorticoid in surgical patients is unknown.¹³

Based on the documented positive analgesic effect and early positive outcome results of high-dose glucocorticoids in major joint arthroplasty,⁶⁻⁸ several centres from the Lundbeck Foundation collaboration for Fast-track Hip and Knee arthroplasty decided to introduce routine use of high-dose glucocorticoid in TKA beginning in October 2013. At the same time, a study protocol was designed in order to provide one year safety data regarding prosthetic infections in a large prospective cohort compared with the previous prospective cohort that did not receive preoperative glucocorticoid. However, in order to provide data about other potential glucocorticoid-related safety issues in the early 90 day postoperative phase, a separate analysis on associations with prolonged length of hospital stay (LOS) and 90 day readmissions was also planned.

Methods

This study was based on the ongoing prospective study registry on patient characteristics administered by the Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaboration (www.fthk.dk),²⁰ which is registered on ClinicalTrials.gov (NCT01515670). Parts of the study cohort have been reported previously in different works focusing on preoperative risk factors and postoperative morbidity.^{21 22} Prior to

the surgical procedure, all patients having THA and TKA in the participating departments complete a questionnaire on comorbidity and other demographic information, which is subsequently merged with the Danish National Database on Reimbursed Prescriptions for additional information on dispensed drugs before and after surgery.²³ Follow-up on LOS (defined as nights spent in hospital), 90 day readmissions requiring overnight stay in hospital and mortality is acquired through the Danish National Patient Registry (DNPR). As reporting to the DNPR is required to receive reimbursement from the Danish government, complete follow-up is assured.²⁴ Finally, any case of LOS >4 days, readmissions or mortality is followed by the review of discharge papers and, if necessary, the complete medical records, in order to determine the type of morbidity. These are then divided into 'medical' and 'surgical' complications based on previous works²² (Table 1). From October 2013 to October 2015, the centres at different time periods decided to use methylprednisolone (MP) 125 mg preoperatively. Information on whether each patient had received MP as well as reasons for not giving it were prospectively reported in all elective TKA patients. The initial contraindications for MP were standardized and included: allergy to glucocorticoids; preoperative systemic glucocorticoid treatment; insulin-dependent diabetes mellitus (IDDM); and active gastric ulcer. At the same time, a study protocol for providing one year safety data specifically on prosthetic infections was designed and registered at ClinicalTrials.gov (NCT02019511). No other major changes to the implemented fast-track protocols were reported during the study period. In this separate analysis on postoperative morbidity, resulting in a LOS >4 days or readmissions/mortality within 90 days of surgery, consecutive data were included from January 2012 to October 2014, and only in those centres who had initiated high-dose glucocorticoids within this time period. Patients reported to have IDDM prescriptions for insulin or systemic glucocorticoids within 90 days pre- or postoperatively were excluded from the control group, which had all had surgery between January 2012 and to the start of using MP.

Ethics

No approval from the National Ethics Committee was necessary as this was a non-interventional observational study. Permission to store and review patient data was given by the Danish National Board of Health (j.nr:3-3013-56/1/HKR) and Danish Data Protection Agency (j.nr:20047-58-0015).

Statistics

Continuous data were evaluated for normality distribution using the Kolomogorov-Smirnov test. Non-parametric data are reported as medians with inter-quartile range (IQR) and categorical data are reported as proportions. Unadjusted analysis was done using χ^2 test or Fisher's exact test as appropriate. For adjusted analysis, we used the SPSS Generalized Linear Mixed Models to perform multiple logistic regression adjusting for the following preoperative patient characteristics: age group, BMI group, smoking, alcohol use >24 g day⁻¹, use of walking aids, living alone or in an institution, preoperative anaemia, pharmacologically treated cardiac disease, pharmacologically treated pulmonary disease, pharmacologically treated psychiatric disorder, use of anticoagulants, and non-insulin-dependent diabetes mellitus (NIDDM). Finally, place of surgery was included as a random effect. Cases with missing data were excluded from the logistic regression model. Model fit was evaluated using the

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