Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial

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Background. Total knee arthroplasty (TKA) is associated with severe pain and inflammation despite an extensive multimodal analgesic approach, but the effect of high-dose glucocorticoid administration has not been studied.

Methods. Forty-eight patients undergoing unilateral TKA were included in a randomized, double-blind, placebo-controlled trial receiving preoperative methylprednisolone (MP) 125 mg i.v. or saline. All surgery was performed under lumbar spinal anaesthesia and patients received a standardized, multimodal analgesic regime. The primary endpoint was pain during walking 24 h after surgery, and secondary endpoints were pain at rest, pain upon hip flexion, and pain upon knee flexion. Pain assessments were performed repeatedly for the first 48 h after surgery, in a questionnaire from days 2 to 10, and at follow-up on days 21 and 30. Tertiary endpoints were postoperative nausea and vomiting (PONV), plasma C-reactive protein (CRP) concentrations, fatigue, sleep quality, and rescue analgesic and antiemetic requirements.

Results. Pain during walking was significantly lower in the MP group up to 32 h after operation. Overall pain and cumulative pain scores (2–48 h) were lower for all pain assessments (P<0.04). Consumption of rescue oxycodone was lower from 0 to 24 h (P=0.02) and PONV, consumption of ondansetron reduced (P<0.05), and CRP concentrations were lower at 24 h (P<0.000001). Fatigue throughout the day of surgery was lower (P=0.02), but sleep quality was worse on the first night (P=0.002). No side-effects or complications were observed in other respects.

Conclusions. MP 125 mg before surgery improves analgesia and immediate recovery after TKA, even when combined with a multimodal analgesic regime. These findings call for further studies on safety aspects. Registered with ClinicalTrials.gov under the US National Library of Medicine (registration number: NCT00968578).

Keywords: arthroplasty, replacement, knee; glucocorticoids; methylprednisolone; pain, postoperative

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The surgical stress response includes inflammatory components1 and may be of importance for postoperative pain and recovery.2 Total knee arthroplasty (TKA) is associated with a considerable increase in C-reactive protein (CRP)3 and severe pain, despite an extensive multimodal analgesic approach.4 To our knowledge, the effect of high-dose glucocorticoid administration in TKA has not been studied.

Glucocorticoids have proven to relieve pain in a number of minor procedures.5 Most studies have evaluated the effect of low-dose glucocorticoid, where dexamethasone 4–8 mg represents a well-documented recommendation for postoperative nausea and vomiting (PONV) prophylaxis.6 7 Promising results regarding an analgesic effect of a single, high-dose of glucocorticoid have been shown in total hip arthroplasty8 and other procedures.9–13 Furthermore, glucocorticoids have also proven to reduce fatigue13–15 and the systemic inflammatory response after surgery.8 14 16 However, pain and the inflammatory response after TKA are pronounced compared to minor procedures.
Effect of glucocorticoid in knee replacement

with previous studies in other procedures, and procedure-specific pain studies are needed.

Therefore, the aim of the present study was to evaluate the effect of a single high-dose of methylprednisolone (MP), 125 mg i.v. on acute postoperative pain and recovery after TKA: this dose has previously been shown to be promising in clinical studies involving other surgical procedures. The primary endpoint was pain during walking 24 h after surgery; secondary endpoints were: pain at rest (supine), pain upon flexion of the hip, and pain upon knee flexion. We also evaluated the effect on PONV, CRP response, knee joint swelling, fatigue, sleep quality, and rescue analgesic-and antiemetic requirements. We hypothesized that a single, high-dose of MP would improve acute, postoperative analgesia during walking after unilateral, primary TKA.

Methods

Patients and design

Before patient enrolment, the trial was approved by the local ethics committee (reg. no. H-C-2008-134) and the Danish data protection agency, and was registered with Clinical-Trials.gov (reg. no. NCT00968578). The study was carried out in accordance with the principles of the Helsinki Declaration, and we followed the CONSORT recommendations for reporting randomized, controlled, clinical trials.

From August to November 2009, all patients undergoing elective, unilateral, primary TKA by one of the three orthopaedic surgeons at Hvidovre University Hospital, Copenhagen, Denmark, were consecutively screened for inclusion in the study. Patients had to be able to speak and understand Danish and to provide informed oral and written consent. Exclusion criteria were alcohol and medical abuse, allergies to MP, age <18 yr, daily use of glucocorticoids or strong opioids (morphine, fentanyl, hydromorphone, ketobemidone, methadone, nicomorphine, oxycodone, or meperidine), fertile women, history of severe heart disease (NYHA >2), renal failure (increased s-creatinine), active peptic ulcer disease, diabetic neuropathy, rheumatoid arthritis, and neurologic or psychiatric diseases potentially influencing pain perception.

The trial was performed as a single-centre, prospective, single-dose, randomized, double-blind, placebo-controlled study. Forty-eight included patients were randomly assigned to two groups of 24. A random allocation sequence concealed in 48 consecutively numbered, opaque, sealed envelopes determining active treatment or placebo was computer-generated by a project nurse not otherwise involved in the trial. The envelopes were opened consecutively on the morning of surgery, and trial drug was prepared by a senior anaesthetist not otherwise involved with the collection of patient data. The active treatment group received a single dose of MP, 125 mg (2 ml) i.v. (Solu-Medrol®; Pfizer, Ballerup, Denmark). The placebo group received a single dose of isotonic saline (2 ml) i.v. Both solutions were transparent and identical in appearance, so masking of syringes was not performed. The test solution was administered just before performing spinal anaesthesia. Trial participants, care providers, and data collectors were all blinded to the allocation. All participant enrolment and data collection was performed by one of the two investigators and all surgery by one of the three surgeons specialized in arthroplasty. To minimize potential differences in the surgical procedure, the surgeons agreed on similar technique before the study. Likewise, instructions on assessment of pain and recovery were similar.

Surgery, anaesthesia, and postoperative analgesia

Standard procedures for surgery, anaesthesia, and analgesia were followed. About 1–2 h before surgery, patients received oral gabapentin 600 mg, slow-release acetaminophen 2 g, and celecoxib 400 mg. All surgery was performed under lumbar spinal anaesthesia with 10 mg hyperbaric bupivacaine (0.5%). Additional sedation with propofol (1–5 mg kg⁻¹ h⁻¹) was administered as required. Cefuroxime 1.5 g for infectious prophylaxis and tranexamic acid 1 g for control of haemostasis were administered i.v. Low molecular weight heparin (4500 U) for thromboprophylaxis was administered after operation once daily until discharge. Intraoperative fluid therapy was standardized and consisted of 0.9% saline 5 ml kg⁻¹ h⁻¹ and colloid (Voluven®; Fresenius Kabi AB, Uppsala, Sweden) 7.5 ml kg⁻¹ h⁻¹. TKA was performed with insertion of tricompartmental prostheses, using a standard medial parapatellar approach, in a bloodless field obtained by the use of a femoral tourniquet (100 mm Hg above systolic arterial pressure) from incision until prosthesis implantation. Prostheses were cemented AGC-prostheses (Biomet-Merck, Warsaw, IN, USA), cemented LPS Flex-prostheses (Zimmer, Warsaw, IN, USA), or un-cemented PFC Sigma RP duo-fix-prostheses (Johnson & Johnson, Warsaw, IN, USA). Drains were not used. Local infiltration analgesia was performed intraoperatively with 150 ml ropivacaine 0.2% with epinephrine (10 μg ml⁻¹) injected by a systematic technique ensuring uniform delivery of local anaesthetic to all tissues incised and instrumented during the operation. At the end of surgery, a compression bandage from toes to the mid-thigh and a cooling device (Cryo/Cuff; Aircast Europe GmbH, Hüsselby, Sweden) were applied. All operations were finished between 9.15 a.m. and 12.15 a.m. Rescue analgesics consisted of sufentanil 5 μg i.v. in the post-anaesthesia care unit (PACU) and thereafter of oral oxycodone 5 mg. PONV was treated with ondansetron 4 mg and sleep disturbances were with zolpidem 5 mg. Patients followed a routine, well-defined, fast-track rehabilitation regime. They received oral celecoxib 200 mg and slow-release acetaminophen 2 g twice daily (7 a.m. and 10 p.m.) and gabapentin 300 mg (7 a.m.) and 600 mg (10 p.m.) from the evening of surgery up to and including the sixth postoperative day. Thereafter, the patient’s general practitioner handled pain management. All patients were discharged to their homes according to functional discharge criteria.
Study parameters

Assessment of the primary endpoint: pain from the operated knee during walking (5 m) with a walking frame 24 h after surgery was done using a 100 mm visual analogue scale (VAS; 0, no pain, and 100, worst pain imaginable). Likewise assessment of the secondary endpoints, pain at rest (supine), upon 45° flexion of the hip with straight leg, and upon 45° knee flexion, was done with a 100 mm VAS. Pain was evaluated at 2, 4, 6, 24, 28, 32, and 48 h after operation, preceding at least 30 min rest in the bed before testing. Recording occurred in the following order at each time point: at rest (supine), upon 45° flexion of the hip with straight leg, upon 45° knee flexion, and during walking. Cumulated consumption of oxycodeone (mg) and total amount of sufentanil (µg) were recorded. Nausea was assessed using a four-point numeric rating scale (NRS; 0, none; 1, slight; 2, moderate; 3, severe) and vomiting by number of episodes (since last recording) at the same time points as above. Furthermore, cumulated consumption of ondansetron (mg) was registered. Systemic inflammation was measured by CRP in venous blood before operation, 4, and 24 h after surgical incision. Knee circumference (local inflammation) was measured 1 cm proximal to the upper border of the patella before operation, and on the second postoperative morning at 8 a.m., and on day 21. Each measurement was performed twice, and the smallest value was registered. A pilot study in 10 patients preceding the trial showed a median difference in circumference on 2 mm (range 1–4 mm) between the two investigators.

Fatigue was assessed using a 10-point NRS (1, fit; 10, fatigued) and sleep quality using a 100 mm VAS (0, best conceivable sleep, and 100, worst conceivable sleep) on the first and second postoperative morning at 8 a.m. Regarding fatigue, we asked for the average level throughout the previous day and night to be scored. Consumption of zolpidem 5 mg the previous night (yes/no) was recorded. Haemoglobin concentrations were measured before operation and on the first postoperative morning. Time spent in the PACU and length of stay (LOS) in hospital were registered, the latter measured as nights spent in hospital.

Before operation, and in a questionnaire from days 2 to 10 (self-reported registrations just before going to bed in the evening) and also at follow-up examination on day 21, and in a telephone interview on day 30 average pain throughout the day during walking (from chair to door) and at rest was recorded. Furthermore, average level of nausea and incidence of vomiting throughout the day, sleep quality at night and fatigue throughout the day, daily consumption of analgesics (type and dose), sleeping medicine (yes or no), and antiemetics (yes or no) were recorded.

Side-effects and complications were registered during hospitalization, at follow-up examination on day 21, and in a telephone interview on day 30 after surgery.

Statistical analysis

Estimated sample size for the primary effect variable was calculated based on the results from a previous pain study in TKA at our institution, where average pain during walking the first postoperative day was 54 mm with a standard deviation (SD) of 25 mm. A reduction of 50% in VAS in the MP group compared with the placebo group was considered clinically relevant. With a type-2 error of 10% at a two-sided 5% significance level, we estimated that 36 patients had to be included. A 10% exclusion rate was expected, and we decided to include 48 (2×24) patients.

Continuous numeric data were assessed for normal distribution with the Kolmogorov–Smirnov test. They are presented as median with inter-quartile range (IQR) or as mean with SD, and tests for significant differences between the groups were done with the Mann–Whitney rank-sum test and the unpaired t-test when appropriate. Categorical data are presented as count, and tests for significant differences between the groups were done with Fisher’s exact test or χ² test when appropriate. Continuous data with repeated measures were analysed with repeated measurement regression with random intercepts and first-order autocorrelation (ANOVA), and presented as time-specific t-tests and an overall Wald χ² test for differences in means between the groups. In addition, composite pain scores were calculated by adding up individual pain scores. Categorical data were corrected with a factor equivalent to the number of time points investigated (post hoc Bonferroni’s correction). Endpoints for the first 48 postoperative hours and endpoints thereafter (days 3–30) were analysed separately, since our hypothesis was based on the acute postoperative course. Data analyses were conducted using SPSS for windows, version 12.0 (SPSS Inc., Chicago, IL, USA) and R for windows, version 2.11.1 (R Foundation for Statistical Computing, Vienna, Austria). P<0.05 was considered statistically significant.

Results

Seventy-three patients were assessed for eligibility in the trial. Forty-eight were included, and randomized patients all received their allocated intervention, completed the trial, and were analysed according to the ‘intention-to-treat’ principle (Fig.1). Seven patients failed to walk 5 m at least at one time point after operation, mainly due to the prolonged effect of the spinal anaesthesia (4 h after operation) and in three patients because of pain (all in the placebo group). Baseline pre- and perioperative patient characteristics were similar in both groups (Table 1).

Pain and rescue analgesic requirement

Overall pain in the first 48 h was lower in the MP group compared with the placebo group for all four pain assessments: during walking (P=0.000007), at rest (P=0.003), upon 45° flexion of the hip with straight leg (P=0.04), and upon 45° knee flexion (P=0.02) (Fig. 2A–D). Time-specific pain scores...
were lower during walking at 4 h \((P=0.004)\), 6 h \((P=0.000007)\), 24 h \((P=0.000007)\), 28 h \((P=0.01)\), and 32 h \((P=0.0005)\); at rest at 4 h \((P=0.02)\), 6 h \((P=0.007)\), 24 h \((P=0.00002)\), and 28 h \((P=0.002)\); upon 45° flexion of the hip with straight leg at 6 h \((P=0.005)\), 24 h \((P=0.009)\), and 28 h \((P=0.002)\); and upon 45° knee flexion at 4 h \((P=0.03)\), 6 h \((P=0.006)\), 24 h \((P=0.0004)\), 28 h \((P=0.002)\), and 32 h \((P=0.02)\) (Fig. 2A–D). Composite pain (added up pain scores) from 2 to 48 h was lower during walking \((P=0.0002)\), at rest \((P=0.02)\), upon 45° flexion of the hip with straight leg \((P=0.02)\), and upon 45° knee flexion \((P=0.001)\) (Fig. 3A).

No significant differences between the groups in pain throughout the day during walking (from the chair to door) and at rest from the second to the 10th postoperative day, and on days 21 and 30 were observed. No differences in composite pain scores from days 3 to 30 for neither pain during walking nor pain at rest were observed. The number of patients reporting severe pain (VAS 60–100 mm) at rest and during walking on days 10, 21, and 30 did not differ between the groups. On day 30, two patients in the MP group and one patient in the placebo group reported severe pain at rest (median 30, IQR 10–39 vs median 20, IQR 10–44) and four patients in each group during walking (median 32.5, IQR 21–49 vs median 35, IQR 21–50).

Two patients in the MP group compared with 10 patients in the placebo group required sufentanil i.v. in the PACU \((P=0.02)\). Cumulative consumption of oxycodone was significantly lower in the MP group compared with the placebo group from 0 to 24 h \((P=0.02)\) (Fig. 3B). Oxycodone requirement did not differ between the groups during the remaining study period.

**PONV and antiemetic requirement**

The incidence of PONV was overall low. The number of patients with nausea was significantly lower in the MP vs in the placebo group at 24 h, being 0 vs 8 (4 slight, 3 moderate, 1 severe) \((P=0.01)\). At 48 h, the number was 0 vs 5 (all slight) \((P=0.10)\). Combined nausea score and amount of ondansetron were significantly lower at 0–24 and 24–48 h after surgery, and the number of patients requiring ondansetron was significantly lower at 0–24 h after surgery (Table 2). Significantly fewer patients reported nausea at any time from the second to 30th day after surgery in the MP group compared with the placebo group (8 vs 15, \(P=0.04\)). There was no significant difference in combined nausea score, and no episodes of vomiting were registered in any of the groups from the second to 30th day after surgery.

**Systemic and local inflammation**

The CRP response 24 h after surgical incision was significantly lower in the MP group compared with the placebo group, with
no change in any of the groups at 4 h after surgical incision (Fig. 4). No difference in knee swelling was found between the groups at 48 h or 21 days after surgery (P > 0.60).

**Fatigue and sleep quality**

Fatigue throughout the day of operation was significantly lower in the MP group compared with the placebo group (P = 0.02), but no difference was found during the rest of the study period. No difference in change in haemoglobin (concentration first postoperative morning minus concentration before surgery) was found between the MP group and the placebo group, mean –1.6 mmol litre⁻¹ (sd 0.5) vs mean –1.3 mmol litre⁻¹ (sd 0.6), P = 0.15.

Sleep quality was significantly lower on the first postoperative night in the MP group compared with the placebo group (P = 0.002), whereas no difference was found during the rest of the study period. There was no significant difference in consumption of hypnotic drugs for night sedation between the MP and placebo groups throughout the study period (P > 0.56).

**LOS, side-effects, and complications**

No significant difference was observed in time spent in the PACU or in LOS, the latter being median 2 days (IQR 2–3) in both groups.

No apparent serious side-effects or complications during hospitalization or at follow-up examination at 21 or 30 days after surgery were observed. Especially, no wound or deep infections occurred, and no patients were readmitted in the study period.

**Discussion**

This randomized, double-blind, placebo-controlled trial demonstrates that MP 125 mg i.v. before elective, unilateral, primary TKA significantly improves analgesia during walking the first 32 h after surgery, even when combined with our standardized, extensive, multimodal analgesic regime. Pain at rest (supine), upon flexion of the hip, and upon knee flexion was reduced in the same period, and overall pain and composite pain scores (from 2 to 48 h) were significantly lower for all four pain assessments. Significantly fewer patients required rescue sufentanil in the PACU, and oxycodone requirement was significantly lower in the first 24 h after surgery. Furthermore, plasma CRP concentrations were reduced at 24 h, PONV was reduced during the first 48 h, and fatigue was reduced throughout the day of operation, whereas sleep quality was worse on the first postoperative night.

In both groups, pain peaked at 24 h after surgery. The lack of significant differences between the groups at some time points for pain at rest, upon flexion of the hip, and upon knee flexion may partly reflect the multimodal analgesia regime resulting in lower pain scores. However, overall pain and composite pain scores (from 2 to 48 h) were significantly lower in the MP group for all pain assessments.

Our study does not contribute to a more detailed explanation of the analgesic benefit observed. However, suppressing the inflammatory response (CRP) may be a possible explanation, since inflammatory mediators are also involved in nociceptive processing.25 We did see a significant reduction in CRP, but no reduction in local inflammation (knee swelling). The observed lower fatigue level in the MP group may also be explained by the reduced inflammatory response,14 and also pain levels after surgery may be related to the self-perceived fatigue.26 A pharmacologically induced psychological effect resulting in change in mood rather than an anti-inflammatory effect may be another possible explanation. Insomnia observed during the first postoperative night has previously been reported to be associated with the use of glucocorticoid.10,27 Regarding PONV, our result is concordant with the extensive literature supporting the efficacy of glucocorticoids as a prophylactic agent.6,7 Nausea continued after discharge in some patients and has been related to the continuous use of opioids.
A sustained analgesic effect of a single high dose of MP has previously been demonstrated in other procedures, but was not found in our study. Thus, after TKA, a more prolonged administration of glucocorticoid may be warranted, but then safety aspects may be more fully evaluated.

Studies mainly in patients undergoing minor surgery have demonstrated a moderate, but inconsistent analgesic effect and reduced opioid requirement using lower antiemetic doses of glucocorticoids (dexamethasone 8–10 mg). A dose-finding study indicated that higher doses (15 mg dexamethasone) may be superior in reducing postoperative opioid requirements compared with lower doses (5 mg dexamethasone), a finding which has been supported by others. 0.75 mg dexamethasone is equivalent to 4 mg MP and 5 mg prednisolone. Few studies have evaluated the effect of higher pharmacological doses of glucocorticoids for pain relief in major surgery, and even fewer in orthopaedic surgery. Kardash and colleagues demonstrated a significant reduction in pain with movement (standing) after total hip arthroplasty, but no difference in pain at rest (using a dose of 40 mg dexamethasone). Unfortunately, pain assessment with movement was only available 24 h after surgery.

Romundstad and colleagues found reduced pain intensity at rest 24 h after surgery and reduced opioid requirements up to 72 h after surgery in patients undergoing a variety of orthopaedic surgical procedures (using 125 mg MP). Despite the fact that patients in these studies were undergoing heterogeneous surgical procedures, their findings are supported by our study. Recently, in patients undergoing hallux valgus surgery, oxycodone consumption for 3 days after surgery...
and pain at rest and on movement the first day were all reduced in patients receiving 9 + 9 mg dexamethasone. The question remains as to whether a relatively short-lived improvement in analgesia observed in our study can justify

Table 2 Nausea, vomiting, and consumption of ondansetron up to 30 days after surgery. Data are expressed as median (IQR) or count where appropriate. Combined nausea scores were calculated by adding nausea scores (0–3) from the assessments in the periods: 0–24 h (2, 4, 6, and 24 h); 24–48 h (28, 32, and 48 h); and days 2–30 (daily days 2–10, 21, and 30). Owing to the low prevalence of nausea and vomiting (massive zero effect), ANOVA for repeated measurement was not useful. Tests for significant differences between the groups were consequently done with the Mann–Whitney rank-sum test (continuous data) and Fisher’s exact test (categorical data), both with post hoc Bonferroni’s correction. n, number of patients; MP, methylprednisolone.

<table>
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<tr>
<th>Variable</th>
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<th>Placebo (n = 24)</th>
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<tbody>
<tr>
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<td></td>
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<tr>
<td>0–24 h</td>
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<td>Days 2–30</td>
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Fig 3 (a) Composite pain (added up pain scores) 2–48 h after total knee arthroplasty for pain during walking (5 m), at rest (supine), upon 45° flexion of the hip with straight leg, and upon 45° knee flexion, and (b) cumulative consumption of oxycodone (mg) 0–24 and 24–48 h after total knee arthroplasty. Horizontal lines indicate medians, boxes indicate IQRs, and whiskers indicate 5–95th percentiles. Tests for significant differences between the groups were done with the Mann–Whitney rank-sum test for each one of the four composite pain scores, and with repeated measurement regression with random intercepts and first-order auto-correlation (ANOVA) for cumulative consumption of oxycodone. +P<0.05; ++P<0.01.

Fig 4 Plasma CRP concentrations 4 and 24 h after total knee arthroplasty. Horizontal lines indicate medians, boxes indicate IQRs, and whiskers indicate 5–95th percentiles. Tests for significant differences between the groups were performed with repeated measurement regression with random intercepts and first-order auto-correlation (ANOVA). +P<0.000001.
the administration of a large dose of glucocorticoid. However, TKA is associated with considerable acute pain, despite an extensive, multimodal analgesic approach.1–3 Secondly, previous reviews have not shown that a single high dose of glucocorticoid is associated with severe complications such as wound or deep infections, or gastrointestinal bleeding.32–34 However, there is clearly a lack of sufficiently powered, safety studies with long-term follow-up to address the occurrence of rare, but potentially detrimental adverse effects. Such studies are ideally required before a final recommendation can be made.

We feel that the strength of this trial primarily arises from the detailed assessment of pain, and a standardized surgical, anaesthetic, and multimodal analgesic regime. Protocol violations were rare, and the use of only two data collectors may have minimized the risk of performance bias. However, there are some limitations regarding the interpretation of the findings from this study: our study may have been insufficiently powered to demonstrate a true difference at more time points for secondary endpoints with lower pain scores. Furthermore, it was not powered to evaluate sub-acute outcomes or safety, and pain management was not standardized from day 6 after surgery.

In conclusion, a single, preoperative dose of MP 125 mg i.v. before TKA led to further improvement of postoperative analgesia and immediate recovery even when combined with an extensive, multimodal oral and local infiltration analgesic regime. These findings call for further studies on safety aspects.

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Conflict of interest
None declared.

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