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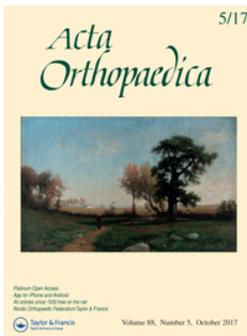
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A randomized, double-blind, placebo-controlled trial of 61 patients

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Background and purpose — Patients undergoing total knee arthroplasty (TKA) face challenges related to postoperative reduction in knee-extension strength. We evaluated whether inhibition of the inflammatory response by a single preoperative dose of methylprednisolone (MP) reduces the pronounced loss of knee-extension strength at discharge after fast-track TKA.

Patients and methods — 70 patients undergoing elective unilateral TKA were randomized (1:1) to preoperative intravenous (IV) MP 125 mg (group MP) or isotonic saline IV (group C). All procedures were performed under spinal anesthesia without tourniquet, and with a standardized multimodal analgesic regime. The primary outcome was change in knee-extension strength from baseline to 48 hours postoperatively. Secondary outcomes were knee joint circumference, functional performance using the Timed Up and Go (TUG) test, pain during the aforementioned tests, rescue analgesic requirements, and plasma C-reactive protein (CRP) changes.

Results — 61 patients completed the follow-up. The loss in quadriceps muscle strength was similar between groups; group MP 1.04 (0.22–1.91) Nm/kg (–89%) vs. group C 1.02 (0.22–1.57) Nm/kg (–88%). Also between-group differences were similar for knee circumference, TUG test, and pain scores. MP reduced the inflammatory response (CRP) at 24 hours postoperatively; group MP 33 (IQR 21–50) mg/L vs. group C 72 (IQR 58–92) mg/L (p < 0.001), and 48 hours postoperatively; group MP 83 (IQR 56–125) mg/L vs. group C 192 (IQR 147–265) mg/L (p < 0.001), respectively.

Interpretation — Preoperative systemic administration of MP 125 mg did not reduce the pronounced loss of knee-extension strength or other functional outcomes at discharge after fast-track TKA despite a reduced systemic inflammatory response.

Patients undergoing total knee arthroplasty (TKA) face challenges related to postoperative pain and decreased functional performance, the latter related to the reduction in knee-extension strength. Thus, the profound reduction by about 80% in early postoperative in knee-extension strength after TKA is well known (Holm et al. 2010, Mizner et al. 2005b) and limited strength may contribute to delayed early mobilization and hospital discharge, as well as risk of falling (de Zwart et al. 2015). The mechanisms underlying the inhibition of the quadriceps muscle after TKA have not been completely clarified, but include pain, swelling (Holm et al. 2010), and arthrogenic muscle inhibition (Mizner et al. 2005b, Rice and McNair 2010, Rice et al. 2014). Avoidance of tourniquet use does not prevent early loss of knee-extension strength (Harsten et al. 2015). However, the effect of modulating the inflammatory response has not been studied before.

Glucocorticoids are known to reduce the systemic inflammatory response after surgery (Smith et al. 2006, Jules-Elysee et al. 2012, Jorgensen and Kehlet 2013, Kardash et al. 2008), and have well-documented anti-inflammatory effects in general (Rhen and Cidlowski 2005) as well as improving pain control and early fatigue in total arthroplasty settings (Lunn et al. 2011, Backes et al. 2013, Rytter et al. 2017). Furthermore, the literature suggests that higher doses of glucocorticoids improve pain control and recovery compared with lower doses for postoperative nausea and vomiting (PONV) prophylaxis (De Oliveira et al. 2011). Since regain of muscle strength is important, further studies of the involved pathogenic mechanisms are required (Kehlet 2013).

To our knowledge, the effect of high-dose glucocorticoid administration on knee-extension strength after TKA has not been studied. Consequently, the purpose of our study was to evaluate whether inhibition of the inflammatory response by

a single preoperative high dose of methylprednisolone (MP) (Lunn et al. 2011) reduced the loss of knee-extension strength at discharge after fast-track TKA.

Patients and methods

The study was performed as a single-center, randomized, placebo-controlled superiority trial with 2 parallel groups, and blinding of the participants, intervention deliverers, and outcome assessors. Functional outcomes were assessed preoperatively (baseline) and 48 hours after surgery. Blood samples were collected at baseline, and 2, 6, 24 and 48 hours postoperatively.

Participants

From February 2015 to April 2016, 163 patients undergoing elective, unilateral, primary TKA at Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, were consecutively assessed for eligibility. The inclusion criteria were: ability to speak and understand Danish, and to provide informed oral and written consent. The exclusion criteria were; age < 55 and > 80 years, general anesthesia, allergy to glucocorticoids, daily use of systemic glucocorticoids, local or systemic infection, insulin-dependent diabetes mellitus, treatment of peptic ulcer within 30 days from inclusion, cancer, autoimmune disease including rheumatoid arthritis, fertile women. Patients were enrolled at their pre-surgical hospital visit several days prior to their TKA. Randomization was performed after the baseline assessment. Screening for eligibility, enrolment, and allocation of patients was carried out by the principal investigator.

Randomization, trial intervention, and blinding

70 included patients were randomly allocated to 2 groups of 35 (Figure 1). A research assistant not otherwise involved in the trial performed a computer-generated random allocation sequence (1:1 allocation rate) concealed in 70 consecutively numbered, opaque, sealed envelopes determining active treatment or placebo. On the morning of surgery the envelopes were opened consecutively, and the trial drug was prepared by 2 anesthetist nurses not otherwise involved in the collection of trial data. The patients received either a single dose of MP, 125 mg (2 mL) IV (Solu-Medrol®; Pfizer, Ballerup, Denmark) (group MP) or a single dose of isotonic saline (2 mL) IV (group C). Even though both solutions were transparent and identical in appearance, the syringes were masked. The principal investigator administered the test solution immediately after spinal anesthesia. Trial participants, care providers, data collectors, and investigators were all blinded to the allocation. The blinded randomization list was dispatched to the primary investigator only after study termination, enabling blinded analyses. After all statistical analyses had been carried out the list was un-blinded with respect to intervention type.

Anesthesia and surgery

Standard procedures for anesthesia, surgery, and analgesia were followed. Patients received oral paracetamol 1 g and naproxen 500 mg about 1 hour prior to surgery. Surgery was performed under lumbar spinal anesthesia with 7.5–12.5 mg hyperbaric bupivacaine (5 mg/mL, 0.5%) and sedation with propofol (1–5 mg/kg/h) was administered as required. Immediately after spinal anesthesia cefuroxime 1.5 g and tranexamic acid 1 g were administered IV. Intraoperative fluid therapy was standardized and consisted of 0.9% saline 12 mL/kg/h during the first hour of surgery, followed by 6 mL/kg/h if the surgery was prolonged beyond 1 hour.

TKA was performed without the use of a tourniquet or drains, and with insertion of tricompartmental prostheses (Sigma Total Knee System, DePuy Synthes) via a standard medial parapatellar approach. Intraoperatively, local infiltration of analgesia was performed with 150 mL ropivacaine 0.2% injected by a systematic technique ensuring uniform delivery of local anesthetic to all tissues incised and instrumented during the surgery. All procedures were performed by 3 experienced surgeons specialized in knee arthroplasty surgery. Duration of surgery (minutes) was registered beginning with the first incision and ending at the last suture. Ice packings or mechanical calf compression devices were not used. Thrombo-embolic prophylaxis was started 6–8 hours after surgery with rivaroxaban 10 mg/day.

Patients followed a routine, well-defined, fast-track rehabilitation regime (Jorgensen and Kehlet 2013) receiving oral paracetamol 1 g 4 times daily and naproxen 500 mg twice daily from the day of surgery. Rescue analgesia on request consisted of opioids (not PCA) if pain exceeded numeric rating scale (0–10) at 3 during rest or 5 during active movement. All patients received zolpidem 10 mg at night time and postoperative nausea and vomiting (PONV) was treated with ondansetron 4 mg.

Outcome measures

The primary outcome was the change in knee-extension strength (Nm/kg body mass) from baseline to discharge. Secondary outcomes measures included knee joint circumference, Timed Up and Go (TUG) test, plasma CRP, and pain assessment during the functional tests using visual analogue scale (VAS).

Knee-extension strength

After warm-up and instruction in the procedure, maximal isometric knee-extension force was measured using a Good Strength adjustable chair (Metitur Ltd, Jyväskylä, Finland) using the inherent Metitur software. The chair was adjusted for each patient using the same settings pre- and postoperatively ensuring an identical individualized setup; hip angle of 90° and knee angle of 60° (0° = full extension). The force transducer was attached with its center 5 cm proximal to the lateral malleolus to measure knee-extension force. Patients were instructed to extend "as forcefully as possible with a gradual increase in

force", and strong verbal encouragement was provided during contractions. They performed 1 practice trial followed by 5 contractions separated by 60-second breaks, and the highest value was used as result. Knee-extension strength was expressed at the maximal voluntary torque per kilo of body mass using the external lever-arm length and body mass of each patient. Changes of knee-extension strength were quantified as absolute (Nm/kg body mass, primary outcome) and relative (%) from preoperative values.

Knee circumference

The knee circumference was measured 1 cm proximal to the proximal pole of patella using the same tape measure in all patients (Holm et al. 2010) and with the patient relaxed in supine position. 2 measurements were performed using the highest value as result. Intra-tester reliability has been reported to be high, with an intra-class correlation coefficient (ICC2,1) of 0.98 (Jakobsen et al. 2010). Knee circumference measurements were performed before testing of knee-extension strength and performance of TUG test to avoid potential test-induced supplementary swelling. Changes in knee joint circumference were quantified as absolute (centimeters) and relative (%) from preoperative values.

Functional performance

The TUG test was used to measure the time (in seconds) it took the patients to rise from a chair (chair seat height 0.45 m), walk 3m to a line drawn on the floor, and return to the chair as quickly and safely as possible. Time was measured from the seated position with the back against the backrest with a stopwatch started on the command "ready–go" and stopped when the seated position was regained. Patients performed 3 timed trials without prior practice trial (Kristensen et al. 2010). The lowest value was used as result. No personal assistance was allowed, but verbal guidance was provided, if necessary. No walking aid was used at preoperative testing, and 2 elbow crutches were used postoperatively.

Knee pain, VAS

Knee pain was quantified using VAS during each active assessment. Patients rated pain in and around the operated knee immediately after all measurements using a VAS ruler on a scale from 0 to 100 mm, with 0 representing no pain and 100 representing the worst pain imaginable. We quantified changes in pain as absolute (millimeters).

A single experienced physiotherapist supervised and recorded all measurements. Preoperative testing was performed 7–10 days prior to surgery. After preoperative measures were recorded, preoperative results were not accessible until after postoperative measurements had been recorded, in an attempt to avoid recall bias.

Paraclinical markers

Blood was drawn at baseline, 2 hours, 6 hours, 24 hours and 48 hours postoperatively for plasma C-reactive protein (CRP) measurements.

Sample size

The sample size was calculated and estimated for the primary outcome assuming a minimal relevant group difference in knee extension strength loss of 40% from baseline to 48 hours postoperatively (40% less loss with MP), corresponding to 0.32 Nm/kg body weight. The magnitude of this between-group difference is larger than that considered the minimal clinically important difference, as the average knee-extension strength loss at discharge is about 80% (Holm et al. 2010, Mizner et al. 2005b). In the case of promising results with the use of MP in our study, we considered it necessary to verify this in at least 1 (phase-3-like) confirmatory trial (Christensen and Langberg 2012). We assumed a 5% significance level, a power of 80%, and a common standard deviation (SD) of 0.39 Nm/kg body-weight (Holm et al. 2010). These calculations resulted in a sample size of 52 patients and allowing for 25% drop-outs, 70 patients were included in the trial.

Statistics

Before analyses, all data were validated by double entry, and evaluated for normal distribution by histograms and Q–Q plots, and by the Kolmogorov–Smirnov test. All continuous variables were compared between allocation groups using independent-sample t-tests for normally distributed data or the Mann–Whitney U-test for variables not following normal distribution. Continuous variables are presented as mean (range) or median with interquartile range (IQR) as appropriate, and categorical variables as number and frequencies (%), respectively. Primary analysis was performed on the per-protocol population, and not on the intention-to-treat population as stated in the protocol as the excluded patients (due to conversion to general anesthesia) did not perform postoperative functional testing. The planned multiple imputations on dropouts for functional outcomes (2 patients) were not performed after consultation with a statistician.

Statistical analyses were carried out in SPSS version 22.0 (IBM Corp., Troy, NY, USA). A 2-sided p-value < 0.05 was considered statistically significant.

Ethics, registration, funding and potential conflicts of interest

The trial was conducted according to the International Conference on Harmonization guidelines for Good Clinical Practice (GCP) and the principles of the Helsinki Declaration. Before patient enrolment, the trial was approved by the Ethics Committee for the Capital Region of Denmark (H-6-2014-101), the Danish Data Protection Agency, the Danish Health and Medicine Authority (EudraCT 2014-003395-23), and was registered on ClinicalTrials.gov under the U.S. National Library of Medicine (NCT02319343, https://clinicaltrials.gov/ct2/show/NCT02319343). The study was monitored by the GCP
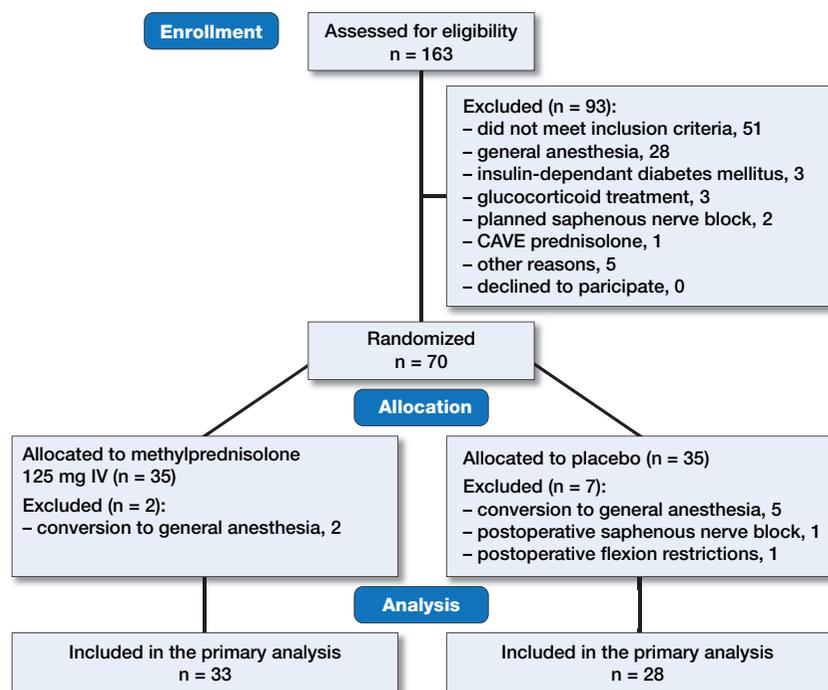
CONSORT flow diagram for screening, inclusion, and exclusion of trial participants.

unit of Copenhagen University Hospital, Copenhagen, Denmark. Oral and written informed consent was obtained from all patients before participation and the CONSORT recommendations for reporting randomized, controlled, clinical trials were followed (Moher et al. 2010).

No benefits in any form have been received from a commercial party related directly or indirectly to the subject of this article. No competing interests declared.

Results

Participants

163 patients were assessed for eligibility. Of these, 93 were not eligible or did not consent, leaving 70 patients for randomization (Figure 1). 9 patients were excluded following randomization; 5 before receiving the trial drug due to planned conversion to general anesthesia, and 2 after receiving the trial drug but changed to general anesthesia due to insufficient spinal anesthesia. 2 patients (group C) dropped out prior to postoperative testing; 1 received a saphenous nerve block in the ward because of severe pain, and 1 was subject to postoperative flexion restrictions due to risk of joint capsule rupture. Consequently, 33 (group MP) and 28 (group C) patients were available for analysis of the primary outcome using the non-missing scores only. Baseline characteristics were comparable between allocation groups (Table 1). Likewise, there were no between-group differences in intraoperative data including

spinal local anesthetic dose, propofol sedation, duration of surgery, and fluid administration (Table 2). No patient received blood components during or after surgery.

Outcomes

Results from the functional outcomes are listed in Table 3. For the primary outcome, we found similar loss of quadriceps muscle strength between the 2 groups. These results correspond to a relative reduction in quadriceps muscle strength of 89% in group MP and 88% in group C. We found similar knee circumference between the 2 groups. The increase in knee circumference was 8% in group MP and 9% in group C, respectively. Both groups showed a similar reduced functional performance using TUG testing comparing preoperative and postoperative measures.

Pre- and postoperative pain scores (VAS) were similar in the 2 groups during knee-extension testing and TUG test.

CRP levels were statistically significantly reduced at 24 hours postoperatively in group MP compared with group C; median 33 mg/L versus 72 mg/L, and respectively, 83 mg/L versus 192 mg/L 48 hours after surgery ($p < 0.001$). There was no correlation between the inflammatory response (CRP) and quadriceps muscle strength decline in either group MP ($r = -0.20$; $p = 0.3$) or group C ($r = 0.03$; $p = 0.9$).

At the postoperative assessment, 2 patients (1 in each group) declined to perform the TUG because of fatigue and nausea. Median length of stay (LOS) in both groups was 2 (IQR 2–2) days.

There were no wound complications, deep infections, or clinically apparent VTE in either group during the study period.

Table 1. Baseline characteristics by allocation group. Values for continuous variables are mean (range) and number for categorical variables

Variables	Group MP (n = 33)	Group C (n = 28)
Age	65 (55–79)	69 (56–80)
Sex (F/M)	20/13	13/15
BMI	32 (21–48)	30 (22–43)
ASA, n (%)		
I	10 (30)	4 (14)
II	23 (70)	21 (75)
III	–	3 (11)
Side of surgery (L/R)	19/14	17/11
Oxford Knee Score	36 (23–49) [a]	34 (19–50)
Range of motion	106 (75–134)	108 (64–131)
Preoperative VAS score	4.3 (0–61)	1.9 (0–32)

[a] n = 31.
VAS: visual analog scale

Table 2. Intraoperative characteristics. Values are mean (range)

Variables	Group MP (n = 33)	Group C (n = 28)	p-value [a]
Duration of surgery (min)	57 (41–110)	60 (39–121)	0.5
Spinal bupivacaine dose (mg)	11.7 (10–14)	11.3 (9.5–12.5)	0.1
Intraoperative propofol sedation (mg)	215 (0–780)	209 (0–900)	0.9
Crystalloids (L)	1.02 (0.55–1.50)	1.01 (0.65–2.00)	0.9
HES (hydroxyethyl starch)	0	0	–
Packed erythrocytes	0	0	–
Blood loss (mL)	117 (25–750)	126 (0–300)	0.8

[a] independent-sample t-test (MP versus C)

Table 3. Primary and secondary study outcomes

	Group MP (n = 33)	Group C (n = 28)	p-value [a]
Knee-extension strength (Nm/kg body weight), mean (range)			
Baseline	1.15 (0.33–2.0)	1.17 (0.33–1.9)	
Discharge	0.10 (0.01–0.28)	0.14 (0.01–0.66)	
Mean change [b]	1.04 (0.22–1.9)	1.02 (0.22–1.6)	0.8
Mean change in % [b]	–89	–88	
Pain during knee-extension strength test ,VAS (mm), median (IQR)			
Baseline	0 (0–13)	1 (0–16)	
Discharge	30 (11–54)	26 (14–51)	
Mean change [b]	21 (10–47)	23 (8–42)	0.7
Knee circumference (cm), mean (range)			
Baseline)	45 (36–57)	43 (36–50)	
Discharge	48 (41–62)	47 (41–54)	
Mean change [b]	3.6 (–1.5 to 6.5)	3.8 (0.8–7.2)	0.7
Mean change in % [b]	8	9	
TUG test (s), mean (range)			
Baseline	8.5 (5.0–13) [c]	8.1 (5.0–11) [d]	
Discharge	24 (9.9–49) [c]	25 (5.6–63) [d]	
Mean change [b]	16 (2.9–40) [c]	17 (0.6–53) [d]	0.8
Mean change in % [b]	183	196	
Pain during TUG test, VAS (mm), median (IQR)			
Baseline	4 (0–13) [c]	4 (0–21) [d]	
Discharge	6 (0–29) [c]	10 (6–29) [d]	
Mean change [b]	0 (–7 to 29) [c]	8 (1–14) [d]	0.1
CRP (mg/L), median (IQR)			
Baseline	2 (1–6)	2 (1–7)	0.7
2 h postoperatively	2 (1–6)	2 (1–6)	0.9
6 h postoperatively	2 (2–6)	3 (1–7)	0.7
24 h postoperatively	33 (21–50)	72 (57–92)	< 0.001
48 h postoperatively	83 (56–125)	192 (147–258)	< 0.001
Rescue morphine equivalents (mg), median (IQR)			
baseline to 48 h postoperatively	70 (51–84) [c]	75 (55–94)	0.5

Nm = Newton meter; IQR = interquartile range
[a] independent-sample t-test or Mann–Whitney U-test (MP versus C)
[b] from baseline to discharge
[c] n = 32
[d] n = 27

Discussion

Our hypothesis was that administration of a single preoperative intravenous dose of MP 125 mg with the associated reduction of the inflammatory response (Lunn et al. 2011) would reduce the early postoperative loss of knee-extension strength at discharge after TKA. However, this was not the case as both groups experienced the well-known large decrease in knee-extension strength (group MP –89% versus group C –88%) (Holm et al. 2010, Mizner et al. 2005b).

Also, we found similar changes in knee circumference between the 2 groups consistent with the findings in a study with a similar setup (Lunn et al. 2011). However, our results do not match the findings in a randomized controlled trial (RCT) on unicompartmental knee replacement—a procedure causing a substantially smaller surgical trauma, where Rytter et al. (2017) found a decrease in knee swelling in the MP group on the first postoperative day compared with baseline. The different findings might be related to the amount of hemarthrosis postoperatively due to different levels of trauma. Theoretically, the use of drains might reduce the intra-articular swelling (and thereby knee-extension strength), but drains have not been shown to be beneficial in TKA (Parker et al. 2004, Husted et al. 2014).

We examined knee swelling from baseline to 48 hours postoperatively where the possible positive impact of MP may be diminished (Harsten et al. 2015), as the half-life of MP is only 18–26 hours. Overall, the specific role of intra-articular fluid accumulation on knee-extension strength may be important, but not known after TKA.

We also found that MP did not improve the TUG test, probably reflecting the similar loss of knee-extension strength in the 2 groups.

Finally, there was no effect of MP on pain during the functional tests 48 hours postoperatively, which is not unexpected, since the analgesic effect of MP lasts for only about 32 hours (Lunn et al. 2011). Moreover, the 2 groups had similar rescue analgesic consumption within the first 48 hours after surgery. A difference could perhaps be found looking at the opioid consumption in the first 24 hours postoperatively (Lunn et al. 2011), but this was not an outcome in this study.

Early mobilization is crucial for gaining the maximum benefits from TKA (Labraca et al. 2011), and is considered a cornerstone in the fast-track setup improving functional performance. Preoperative quadriceps strength has been found to be a strong predictor of functional performance 6–12 months postoperatively (Mizner et al. 2005a); limited quadriceps function in general may also be a risk factor for falling (de Zwart et al. 2015). In addition, loss of quadriceps function is important for postoperative rehabilitation, again arguing for evaluation of the pathogenesis. The mechanisms for the pronounced reduction in knee-extension strength after

TKA are probably multi-fold and include an inhibitory arthrogenic reflex mechanism (Rice and McNair 2010), pain, and swelling (Holm et al. 2010). The arthrogenic inhibitory reflex mechanism may include peripheral mechanisms from the joint, but also modifying mechanisms at a higher central nervous system level where the neuro-inflammatory response to injury may contribute. A previous study showed the presence of inflammatory markers in the cerebrospinal fluid after surgery possibly causing an alteration in central signaling (Buvanendran et al. 2006) but a study by Rice et al. (2014) found no evidence for a central neurological effect on quadriceps inhibition, suggesting a more local effect.

It has also been discussed whether the early loss of knee-extension strength is related to use of intra-operative tourniquet, but no support for this hypothesis was demonstrated in a recent RCT (Harsten et al. 2015) and a tourniquet was not used in our study. Other surgical approaches might reduce inflammation such as minimal invasive surgery, but have not been studied in detail.

A previous study in bilateral TKA found a sustained suppression of the inflammatory marker interleukin-6 (IL-6) by administering three 100 mg doses of hydrocortisone over 24 hours perioperatively (Jules-Elysee et al. 2012), while the same investigators showed that fewer doses of glucocorticoid were unable to suppress IL-6 in a durable fashion (Jules-Elysee et al. 2011). Thus, despite our negative findings, further procedure-specific dose–response studies and potential second dosing of glucocorticoid to prolong analgesia (Backes et al. 2013) would be of interest.

The strengths of our trial include the high degree of standardized anesthetic, surgical, and multimodal analgesic regime. All patients received spinal anesthesia using bupivacaine only, thus avoiding intrathecal opioids. The same surgical incision technique was used and local infiltration analgesia was administered in all patients. Furthermore, the patients received similar standardized training by physiotherapists in the ward. Finally, the use of only 2 data collectors may have minimized the risk of performance bias. Limitations include a short follow-up period, and lack of power to evaluate pain scores and opioid consumption. Moreover, there are no previous studies to support the power calculation when using glucocorticoids. The minimal clinically important difference (MCID) is not known for knee-extension strength, but would probably be estimated to ~15% (15% reduced loss in knee-extension strength in the intervention group compared with the placebo group). This difference (with equal mean and SD) would call for a much bigger study population than included in our study. So before setting up a bigger and potentially conclusive RCT than the present study, we decided to do a detailed physiological and exploratory RCT. We therefore defined a greater effect size than MCID to determine the tentative effect.

In summary, the well-described pronounced early (48 h) reduction in knee-extension strength after TKA was not modified by using a single high-dose of MP, although the systemic inflammatory response was reduced. Furthermore, MP did not improve functional performance in terms of TUG, knee circumference, pain scores during testing and opioid consumption. Further studies are required to identify the pathogenic mechanisms to loss of knee-extension strength after TKA in order to enhance early postoperative recovery.

Backes J R, Bentley J C, Politi J R, Chambers B T. Dexamethasone reduces length of hospitalization and improves postoperative pain and nausea after total joint arthroplasty: A prospective, randomized controlled trial. J Arthroplasty 2013; 28 (8 Suppl): 11-17.

Buvanendran A, Kroin J S, Berger R A, Hallab N J, Saha C, Negrescu C, Moric M, Caicedo M S, Tuman K J. Upregulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. Anesthesiology 2006; 104 (3): 403-10.

Christensen R, Langberg H. Statistical principles for prospective study protocols: Design, analysis, and reporting. Int J Sports Phys Ther 2012; 7 (5): 504-11.

De Oliveira G S, Jr., Almeida M D, Benzon H T, McCarthy R J. Perioperative single dose systemic dexamethasone for postoperative pain: A meta-analysis of randomized controlled trials. Anesthesiology 2011; 115 (3): 575-88.

de Zwart A H, van der Esch M, Pijnappels M A, Hoozemans M J, van der Leeden M, Roorda L D, Dekker J, Lems W F, van Dieen J H. Falls associated with muscle strength in patients with knee osteoarthritis and self-reported knee instability. J Rheumatol 2015; 42 (7): 1218-23.

Harsten A, Bandholm T, Kehlet H, Toksvig-Larsen S. Tourniquet versus no tourniquet on knee-extension strength early after fast-track total knee arthroplasty: A randomized controlled trial. Knee 2015; 22 (2): 126-30.

Holm B, Kristensen M T, Bencke J, Husted H, Kehlet H, Bandholm T. Loss of knee-extension strength is related to knee swelling after total knee arthroplasty. Arch Phys Med Rehabil 2010; 91 (11): 1770-6.

Husted H, Gromov K, Malchau H, Freiberg A, Gebuhr P, Troelsen A. Traditions and myths in hip and knee arthroplasty. Acta Orthop 2014; 85 (6): 548-55.

Jakobsen T L, Christensen M, Christensen S S, Olsen M, Bandholm T. Reliability of knee joint range of motion and circumference measurements after total knee arthroplasty: Does tester experience matter? Physiother Res Int 2010; 15 (3): 126-34.

Jorgensen C C, Kehlet H. Role of patient characteristics for fast-track hip and knee arthroplasty. Br J Anaesth 2013; 110 (6): 972-80.

Jules-Elysee K M, Lipnitsky J Y, Patel N, Anastasian G, Wilfred S E, Urban M K, Sculco T P. Use of low-dose steroids in decreasing cytokine release during bilateral total knee replacement. Reg Anesth Pain Med 2011; 36 (1): 36-40.

Jules-Elysee K M, Wilfred S E, Memtsoudis S G, Kim D H, YaDeau J T, Urban M K, Lichardi M L, McLawhorn A S, Sculco T P. Steroid modulation of cytokine release and desmosine levels in bilateral total knee replacement: A prospective, double-blind, randomized controlled trial. J Bone Joint Surg Am 2012; 94 (23): 2120-7.

Kardash K J, Sarrazin F, Tessler M J, Velly A M. Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. Anesth Analg 2008; 106 (4): 1253-7.

Kehlet H. Fast-track hip and knee arthroplasty. Lancet 2013; 381 (9878): 1600-2.

Kristensen M T, Ekdahl C, Kehlet H, Bandholm T. How many trials are needed to achieve performance stability of the Timed Up & Go test in patients with hip fracture? Arch Phys Med Rehabil 2010; 91 (6): 885-9.

Labraca N S, Castro-Sanchez A M, Mataran-Penarrocha G A, Arroyo-Morales M, Sanchez-Joya Mdel M, Moreno-Lorenzo C. Benefits of starting rehabilitation within 24 hours of primary total knee arthroplasty: Randomized clinical trial. Clin Rehabil 2011; 25 (6): 557-66.

Lunn T H, Kristensen B B, Andersen L O, Husted H, Otte K S, Gaarn-Larsen L, Kehlet H. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: A randomized, placebo-controlled trial. Br J Anaesth 2011; 106 (2): 230-8.

Mizner R L, Petterson S C, Stevens J E, Axe M J, Snyder-Mackler L. Preoperative quadriceps strength predicts functional ability one year after total knee arthroplasty. J Rheumatol 2005a; 32 (8): 1533-9.

Mizner R L, Petterson S C, Stevens J E, Vandenborne K, Snyder-Mackler L. Early quadriceps strength loss after total knee arthroplasty: The contributions of muscle atrophy and failure of voluntary muscle activation. J Bone Joint Surg Am 2005b; 87 (5): 1047-53.

Moher D, Hopewell S, Schulz K F, Montori V, Gotzsche P C, Devereaux P J, Elbourne D, Egger M, Altman D G. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340: c869.

Parker M J, Roberts C P, Hay D. Closed suction drainage for hip and knee arthroplasty: A meta-analysis. J Bone Joint Surg Am 2004; 86-A (6): 1146-52.

Rhen T, Cidlowski J A. Antiinflammatory action of glucocorticoids: New mechanisms for old drugs. N Engl J Med 2005; 353 (16): 1711-23.

Rice D A, McNair P J. Quadriceps arthrogenic muscle inhibition: Neural mechanisms and treatment perspectives. Semin Arthritis Rheum 2010; 40(3): 250-66.

Rice D A, McNair P J, Lewis G N, Dalbeth N. Quadriceps arthrogenic muscle inhibition: The effects of experimental knee joint effusion on motor cortex excitability. Arthritis Res Ther 2014; 16 (6): 502.

Rytter S, Stilling M, Munk S, Hansen T B. Methylprednisolone reduces pain and decreases knee swelling in the first 24 h after fast-track unicompartmental knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2017; 25 (1): 284-90.

Smith C, Erasmus P J, Myburgh K H. Endocrine and immune effects of dexamethasone in unilateral total knee replacement. J Int Med Res 2006; 34 (6): 603-11.