ORIGINAL ARTICLE

Effect of pre-operative methylprednisolone on orthostatic hypotension during early mobilization after total hip arthroplasty

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Background: Orthostatic hypotension (OH) and intolerance (OI) are common after total hip arthroplasty (THA) and may delay early mobilization. The pathology of OH and OI includes a dysregulated post-operative vasopressor response, by a hitherto unknown mechanism. We hypothesized that OI could be related to the inflammatory stress response which is inhibited by steroid administration. Consequently, this study evaluated the effect of a pre-operative high-dose methylprednisolone on OH and OI early after THA.
Methods: Randomized, double-blind, placebo-controlled study in 59 patients undergoing elective unilateral THA with spinal anesthesia and a standardized multimodal analgesic regime. Patients were allocated (1 : 1) to pre-operative intravenous (IV) methylprednisolone (MP) 125 mg or isotonic saline (C). OH, OI and cardiovascular responses to sitting and standing were evaluated using a standardized mobilization protocol pre-operatively, 6, and 24 h after surgery. Systolic and diastolic arterial pressure and heart rate were measured non-invasively (Nexfin®). The systemic inflammation was monitored by the C-reactive protein (CRP) response.
Results: At 6 h post-operatively, 11 (38%) versus 11 (37%) patients had OH in group MP and group C, respectively (RR 1.02 (0.60 to 1.75; $P = 1.00$)), whereas OI was present in 9 (31%) versus 13 (43%) patients (RR 0.76 (0.42 to 1.36; $P = 0.42$)), respectively. At 24 h post-operatively, the prevalence of OH and OI did not differ between groups, though CRP levels were significantly reduced in group MP ($P < 0.001$).
Conclusion: Pre-operative administration of 125 mg methylprednisolone IV did not reduce OH or OI compared with placebo despite a reduced inflammatory response.

Editorial Comment
Orthostatic hypotension (OH) and intolerance (OIH) are common after hip surgery, and may be associated with the surgical inflammatory response. In this trial, 125 mg of perioperative methylprednisolone failed to reduce post-operative OH and OIH. Effective strategies for reduction of orthostatic intolerance and hypotension still remain to be defined.

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Introduction

Early mobilization is essential for enhanced functional recovery after surgery to reduce post-operative morbidity.[1] Patients undergoing fast-track total hip arthroplasty (THA) should be mobilized on the day of surgery and are expected to participate in physiotherapy sessions in the early post-operative period.[2] However, early ambulation may be delayed due to failed orthostatic cardiovascular regulation resulting in post-operative orthostatic hypotension (OH). OH is defined as a decrease in systolic arterial pressure (SAP) > 20 mmHg or diastolic arterial pressure (DAP) > 10 mmHg, and orthostatic intolerance (OI) is characterized by dizziness, nausea, vomiting, visual disturbances, or syncope.[3,4] During mobilization 6 h after THA, the prevalence of OI and OH has been reported to be as high as 42% and 50%, respectively.[5] It has been demonstrated that an attenuated vasopressor response and a concomitant decrease in CO during post-ural changes after surgery contributes to OH.[5] Moreover, the few existing studies suggest that OH with a concomitant decrease in cerebral perfusion is the main mechanism for post-operative OI symptoms.[5–7] Consequently, strategies aiming to reduce the incidence of OH and OI are of increasing interest. Previously, pain management,[8] treatment with midodrine hydrochloride[9] and optimized fluid management with goal-directed fluid therapy[7] have not solved the problems.

It has been suggested that the impaired cardiovascular regulation early after surgery may be associated with the pronounced systemic inflammatory response.[8] In this context, increased post-inflammatory parasympathetic (vagal) activity, the so called "inflammatory reflex"[10] may potentially contribute to OI. As glucocorticoids are known to reduce the systemic inflammatory response after surgery[11–13] we hypothesize that they may reduce the incidence of OH and OI during early post-operative mobilization.

Therefore, we investigated the effect of a pre-operative high-dose glucocorticoid on the post-ural vasopressor response including OH and OI 6 and 24 h after THA.

Methods

The trial was approved by the Danish Health and Medicine Authority (EudraCT 2015-000102-19), the Ethics Committee for the Capital Region of Denmark (H-15007653, protocol approval July 2015), the Danish Data Protection Agency, and registered on ClinicalTrials.gov under the U.S. National Library of Medicine (NCT02445898). The study was conducted according to the principles of the Helsinki Declaration as well as the International Conference on Harmonization guidelines for Good Clinical Practice (GCP), and was monitored by the GCP unit of the Copenhagen University Hospital, Copenhagen, Denmark. Before participation oral and written informed consent was obtained from all patients and the CONSORT recommendations for reporting randomized, controlled, clinical trials were followed.[14] Other studies on glucose homeostasis (NCT02332603), immune signalling (NCT02542592) and cardiovascular regulation after surgery (NCT02445898) were embedded in present study.

Inclusion criteria were; age 55–80 years, ability to speak and understand Danish as well as informed oral and written consent. Exclusion criteria were; general anesthesia, cancer, insulin-dependent diabetes mellitus, atrial fibrillation, local or systemic infection, treatment of peptic ulcer within 30 days from inclusion, autoimmune disease including rheumatoid arthritis, daily use of systemic glucocorticoids, alcohol use > 35 units per week, allergy toward glucocorticoids and fertile women. Patients using antihypertensive medication were accepted in the study but instructed to pause the medication from the day prior to surgery and 24 h post-operatively if found safe by the consulting anesthesiologist. Participants, surgeons, and outcome assessors were blinded to treatment allocation. Screening for eligibility, enrollment, and allocation of patients was carried out by the principal investigator, and randomization was performed after baseline assessments.

Randomization, trial intervention, and blinding

A research assistant not otherwise involved in the trial generated a random allocation sequence (1 : 1 allocation rate, no block randomisation) by computer (retrieved from https://sealedenvelope.com) concealed in 64 consecutively numbered, opaque, sealed envelopes determining active treatment or placebo. On the morning of

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surgery, the envelopes were opened consecutively, and two nurse anesthetists not otherwise involved in the collection of patient data prepared the trial drug. Trial patients received either a single dose of MP 125 mg (2 ml) IV (Solu-Medrol®; Pfizer, Ballerup, Denmark) (group MP) corresponding to 24 mg dexamethasone, or a single dose of isotonic saline (2 ml) IV (group C). The syringes were carefully masked despite both being transparent in appearance. The trial solution was administered by one of two investigators just after induction of spinal anesthesia. Trial participants, care providers, data collectors, and investigators were all blinded to the allocation, and the randomization list was unblinded with respect to intervention type only after all statistical analyses had been carried out.

Anesthesia and surgery

Standard procedures for anesthesia, surgery, and analgesia were followed. The pre-operative fasting period was 6 h for solid foods and 2 h for clear liquids. In the ward before surgery, all patients received oral paracetamol 1 g, naproxen 500 mg, and gabapentin 600 mg. All surgery was performed under lumbar spinal anesthesia with 12.5–17.5 mg isobaric bupivacaine (5 mg/ml, 0.5%) and additional sedation with propofol (1–5 mg/kg/h) was administered as required. Immediately after spinal anesthesia Cefuroxime 1.5 g for infectious prophylaxis and tranexamic acid 1 g for control of hemostasis were administered IV. Intraoperative fluid therapy was standardized consisting of 0.9% saline 12 ml/kg/h the first hour of surgery, followed by 6 ml/kg/h if surgery was prolonged beyond 1 h. A forced-air warming devices (Bair Hugger®; Augustine Medical, Minneapolis, MN) was used for maintaining normothermia. Local infiltration analgesia was not used. Patients were allowed to drink freely in the post-anesthesia care unit (PACU) and in the ward. Patients followed a routine, well-defined, fast-track rehabilitation regime,[15] and received oral paracetamol 3 g, naproxen 500 mg, and 300 mg gabapentin on the remaining day of surgery, followed by paracetamol 4 g, naproxen 1 g, and gabapentin 900 mg daily during the hospital stay. Rescue analgesia opioids were administered on request if pain exceeded numeric rating scale (0–10) 3 during rest or 5 during active movement. All patients received zolpidem 10 mg at night time and PONV was treated with ondansetron 4 mg.

Orthostatic challenge

Mobilization following a standardized procedure was performed pre-operatively on the day of surgery, and was repeated 6 and 24 h post-operatively defined from the time of wound closure. Two dedicated investigators carried out the mobilization procedure which included patient supine rest (5 min), followed by sitting on the bed with feet resting on the floor (3 min), followed by standing (3 min) using a walker while encouraged verbally to shift body weight for prevention of venous pooling. The mobilization procedure was terminated with supine rest (5 min). The procedure was stopped prematurely during the sitting or standing position if patients experienced symptoms of OI (blurred vision, dizziness, nausea or vomiting, visual disturbances, or syncope) or if SAP decreased >30 mmHg compared to supine position. Continuous arterial pressures were measured by a finger cuff applied on the middle part of the third finger (Nexfin®, BMeye, Amsterdam, the Netherlands)[16] during the mobilization procedure. For each body position during each mobilization, procedure pain was graded using a numeric rating scale (0–10). Intravenous fluid administration was registered until 24 h post-operatively. Before the 6 h procedure, remaining motor blockade was ruled out using a modified Bromage scale.[17]

The primary outcome measure was prevalence of OH during mobilization in the sitting or standing position 6 h post-operatively. OI during mobilization 6 h post-operatively was the main secondary outcome. Other secondary outcome measures included OH and OI during mobilization 24 h post-operatively as well as blood pressure and heart rate (HR) responses during mobilization. Furthermore, plasma CRP and hemoglobin concentrations were measured pre-operatively and 2, 6, and 24 h post-operatively.

Orthostatic classification

Patients were classified as having OH when showing a decrease in SAP of > 20 mmHg or a

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decrease of > 10 mmHg in DAP during sitting or standing compared with supine rest.[3] Patients were classified as having OI if the mobilization procedure was terminated prematurely due to visual disturbances, dizziness, nausea, vomiting, or syncope.[3]

Data collection and analysis

Cardiovascular data collected during mobilization were stored electronically and analyzed offline using the Nexfin@PC 1.0 software package (BMeye, Amsterdam, The Netherlands). Each finger arterial pressure curve was visually inspected for artefacts before averaging, and such data were excluded. During the supine rest periods values were averaged over 5 min, and over the last 10 s for values representing the mobilization periods of sitting and standing, both in patients completing the mobilization procedure and patients terminating the procedure prematurely due to OI.

Sample-size calculation

The study was conducted as a superiority trial. On the basis of a previous evaluation of early mobilization after THA showing a 40% prevalence of OH 6 h post-operatively,[9] we calculated that 58 patients were needed to detect an absolute reduction in OH from 40% to 10% with a power (1-β) of 80% and a two-sided $\alpha = 0.05$. To account for dropouts, a total of 64 patients were included in the trial (Fig. 1).

Statistical analysis

All data were validated by double entry, and evaluated for normal distribution by Q-Q plots before analyses. There were no missing data regarding patient characteristics. Continuous variables are reported as mean (SD) or median (IQR) as appropriate and categorical variables are reported as number (%). Baseline marker values were compared using an independent sample *t*-test for continuous variables and the chi-square test for categorical variables. Fisher's exact test was used for calculating relative risk. CRP values were logarithmically transformed before analysis due to non-normal distribution.

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

Results

Participants

In the period from September 2015 to December 2016, a total of 190 patients undergoing elective THA were assessed for eligibility in a single-center, randomized, placebo-controlled trial with two parallel groups. Of these, a total of 126 were not eligible or did not consent to participate in the study leaving 64 patients for randomization. The flow of patients from screening to analysis of data is shown in Fig. 1. Five patients were excluded following randomization; three before receiving the trial drug due to planned conversion to general anesthesia, and two after receiving trial drug because of general anesthesia due to insufficient spinal anesthesia. Consequently, 29 (group MP) and 30 (group C) patients were available for analysis of the primary outcome using the non-missing scores only.

Baseline outcomes, pain, opioid consumption and hemoglobin concentrations

Baseline characteristics were comparable between allocation groups (Table 1). Likewise, there were no between-group differences in intraoperative data except duration of surgery, $P = 0.04$ (Table 2).

Pain scores during post-operative mobilization did not differ between allocation groups and their median (interquartile range) were 3 (2–5), 3 (2–5), and 3 (2–6) at 6 h and 2 (1–2), 2 (2–4), and 2 (1–4) at 24 h during supine, sitting, and standing positions, respectively. However, group MP showed a significant reduced cumulated rescue opioid consumption from 0 to 6 h post-operatively compared to group C, $P = 0.02$ (Table 2). At 6–24 h post-operatively no difference in opioid consumption between allocation groups was observed, $P = 0.22$. In group MP, three patients received supplementary 1000 ml intravenous isotonic saline post-operatively

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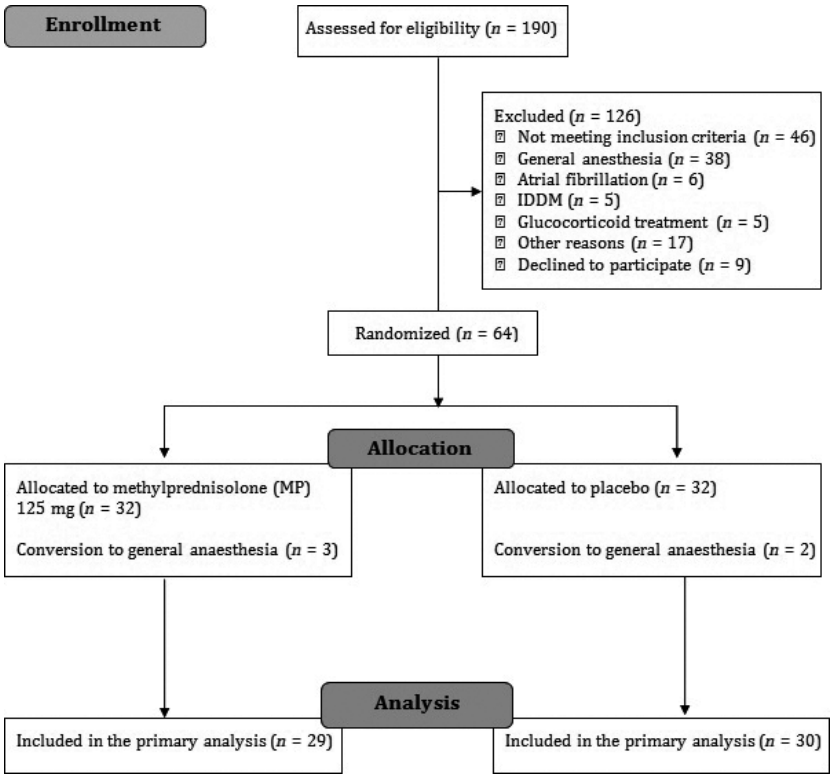

Fig. 1. CONSORT flow diagram for screening, inclusion, and exclusion of trial participants. IDDM, insulin-dependent diabetes mellitus.

compared to four patients in group C ($P = 0.77$). The CRP response was significantly reduced 24 h post-operatively in group MP compared to group C (median, IQR); 32.0 (20.0–45.0) mg/l versus 67.5 (50.8–82.8) mg/l, $P < 0.001$ (Table 2). Plasma hemoglobin concentrations did not differ between groups at any sampling time point (Table 2). No patients received blood transfusion during or after surgery.

Table 1 Patient demographics, baseline characteristics, and intraoperative characteristics by allocation group.

Variables	Group MP (n = 29)	Group C (n = 30)
Age, mean (SD), year	67.4 (5.4)	67.2 (6.7)
Female sex, no. (%)	17 (59)	12 (40)
BMI, mean (SD), kg m^{-2}	26.9 (4.1)	27.5 (4.3)
ASA physical status classification, no. (%)		
I	6 (21)	6 (20)
II	22 (76)	24 (80)
III	1 (3)	0 (0)
Hemoglobin baseline, mean (SD), g/dl	8.7 (0.7)	8.7 (0.6)
C-reactive protein, median (IQR), mg/l	1.0 (1.0–3.0)	2.5 (1.0–4.0)

Values are reported as mean (SD) or median (IQR) for continuous variables and as number (%) for categorical variables. ASA, American Society of Anesthesiologists; BMI, body mass index.

Outcomes; orthostatic challenge

The main outcome OH during mobilization 6 h post-operatively was present in 11 patients (38%; 95% CI 21–55%) in group MP compared to 11 patients (37%; 95% CI 20–53%) in group C ($P = 1.00$, Table 3). At 6 h post-operatively, 9 patients (31%; 95% CI 14–48%) in group MP versus 13 patients (43%; 95% CI 27–63%) in group C terminated the mobilization procedure due to OI ($P = 0.42$). Furthermore, 15 (68%) of the OI patients had concomitant OH. Two patients (one in each allocation group) were not able to proceed from supine position at the 6 h mobilization procedure due to fatigue, nausea and vomiting (Fig. 2A). At 24 h post-

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Table 2 Intra- and post-operative data.

	Group MP (n = 29)	Group C (n = 30)	*P*-value
Duration of surgery, min	60 (18)	51 (14)	**0.04**
Spinal bupivacaine dose, mg	15.1 (1.0)	14.8 (1.2)	0.33
Intraoperative propofol sedation, no. (%)	22 (76)	24 (80)	0.17
Crystalloids, ml	960 (281)	868 (200)	0.16
Colloids	0	0	–
Packed erythrocytes	0	0	–
Blood loss, ml	290 (200–375)	200 (150–300)	0.10
PACU and ward, 0–24 h			
Crystalloids, no. (%)	3 (10)	4 (13)	0.77
Rescue opioids 0–6 h, mg	4.3 (4.2)	7.3 (5.6)	**0.02**
Rescue opioids 6–24 h, mg	11.1 (12.1)	15.4 (14.3)	0.22
Hemoglobin concentration			
2 h after surgery, g/dl	8.1 (0.7)	8.0 (0.5)	0.74
6 h after surgery, g/dl	7.9 (0.8)	7.7 (0.7)	0.33
24 h after surgery, g/dl	7.1 (0.7)	7.2 (0.7)	0.36
C-reactive protein concentration			
2 h after surgery, mg/l	1.0 (1.0–2.0)	2.0 (1.0–4.0)	**0.04**
6 h after surgery, mg/l	3.0 (2.0–4.0)	4.5 (2.0–6.0)	0.13
24 h after surgery, mg/l	32.0 (20.0–45.0)	67.5 (50.8–82.8)	**<0.001**

Values are reported as mean (SD) or median (IQR) for continuous variables and as number (%) for categorical variables. *P*-values refer to analyses between groups (MP and C) using an independent sample *t*-test for continuous data and a χ test for categorical data. PACU, post-anesthesia care unit. Bold values represent statistical significant difference between groups.

Table 3 Primary and secondary outcomes.

	Group MP (n = 29)	Group C (n = 30)	RR (95% CI)	*P*-value
Primary outcome, no/total no. (%)				
OH at 6 h after surgery	11/29 (38%)	11/30 (37%)	1.02 (0.60–1.75)	1.00
Secondary outcomes, no/total no (%)				
OI at 6 h after surgery	9/29 (31%)	13/30 (43%)	0.76 (0.42–1.36)	0.42
OH at 24 h after surgery	2/28 (7%)	5/30 (17%)	0.56 (0.17–1.86)	0.43
OI at 24 h after surgery	1/28 (4%)	5/30 (17%)	0.32 (0.05–1.96)	0.20

OH, orthostatic hypotension; OI, orthostatic intolerance; RR, relative risk.

operatively, there was no difference in the prevalence of OH or OI during mobilization between groups (Table 3); two patient had OH in group MP (7%; 95% CI 0–18%) compared to 5 patients in group C (17%; 95% CI 3–33%), $P = 0.43$, and one patient presented OI in group MP (4%; 95% CI 0–11%) compared to five patients in group C (17%; 95% CI 3–30%), $P = 0.20$. One patient in group MP dropped out before the 24 h assessment due to prosthesis dislocation not related to the trial mobilization procedure (Fig. 2B). No patients experienced OI pre-operatively, but one patient in group C was found to have OH.

Outcomes; hemodynamic response

Supine blood pressure and HR data at baseline assessment together with changes from supine to termination of the mobilization procedure were comparable between allocation groups (Table 4, presented for all three mobilization sessions; pre-operatively, 6 and 24 h after surgery). Changes in hemodynamic data between

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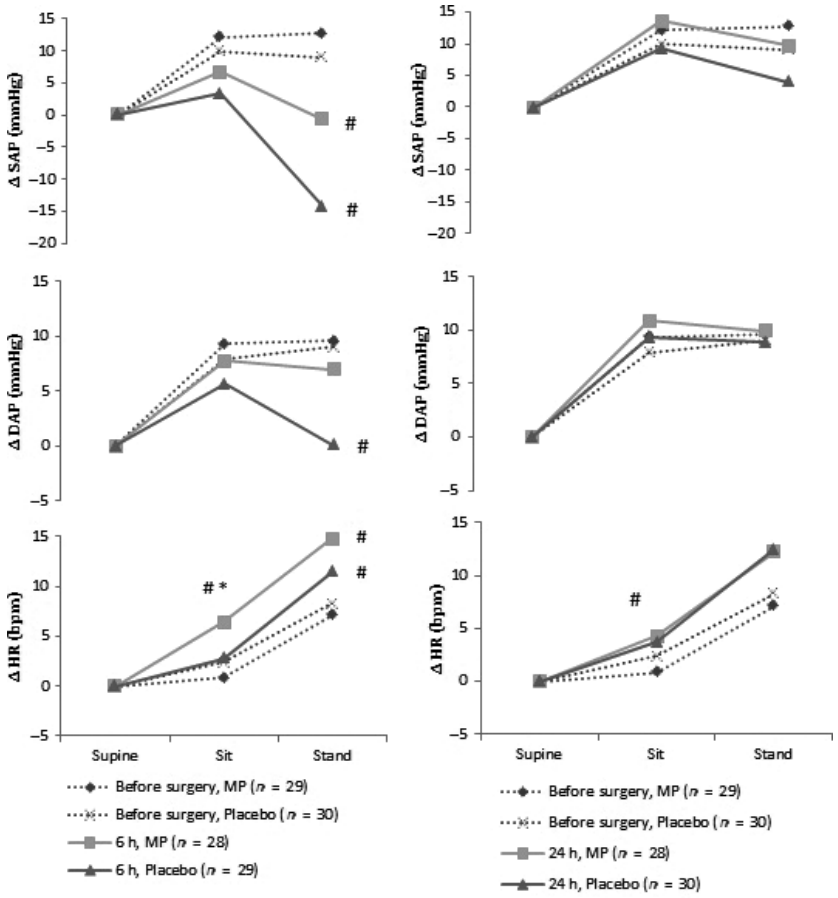

Fig. 2. Changes in arterial pressures and heart rate (HR) during a standardized mobilization procedure 6 and 24 h after surgery compared to before surgery, grouped by allocation. SAP, systolic arterial pressure; DAP, diastolic arterial pressure. * Different between groups (group MP versus group C). # Different from pre-operative evaluation.

allocation groups (group MP versus group C) are illustrated in Fig. 2. At 6 h post-operatively, the SAP decreased while DAP and HR increased in both group MP and group C during mobilization compared to pre-operative assessment ($P < 0.05$, Table 4). Furthermore, the HR response increased in group MP compared to group C during sitting ($P = 0.03$, Fig. 2A). At 24 h post-operatively, SAP, DAP and HR increased from supine during mobilization in both allocation groups ($P < 0.05$, Table 4), though not differing from pre-operative data. No difference in SAP, DAP, and HR changes between allocation groups was found (Fig. 2B).

Comparison of the hemodynamic responses during mobilization at 6 and 24 h post-operatively between orthostatic-intolerant (OI) and orthostatic-tolerant patients (OT, completing the mobilization procedure) regardless of allocation group is presented in Fig. 3. At 6 h post-operatively, both SAP and DAP showed a more pronounced decrease from supine to sitting and standing position ($P < 0.001$) in OI patients compared to OT patients, whereas the increase in HR did not differ between the two groups (Fig. 3A). At 24 h post-operatively, SAP and DAP decreased more from supine to standing position ($P = 0.002$ and $P = 0.02$) in OI patients compared to OT patients, whereas the increase in HR did not differ between the two groups (Fig. 3B). Furthermore, the changes in SAP, DAP and HR in the OI patients differed significantly from pre-operative assessment, both at 6 h and 24 h post-operatively (Fig. 3A and B). In contrast, the responses in OT patients at 6 h

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Table 4 Supine hemodynamics and changes from supine to termination (preterm or completion) of the mobilization procedure during sitting or standing pre-operatively, 6 and 24 h after surgery grouped by allocation.

	Supine		Sit		Stand	
Variables	Group MP (n = 29)	Group C (n = 30)	Group MP (n = 29)	Group C (n = 30)	Group MP (n = 29)	Group C (n = 30)
Before surgery						
SAP, mmHg	130 (122–138)	132 (125–139)	12 (7–17)‡	10 (5–15)‡	13 (6–19)‡	9 (3–15)†
DAP, mmHg	68 (65–72)	70 (67–73)	9 (6–12)‡	8 (5–10)‡	10 (7–12)‡	9 (6–12)‡
HR (beats/min)	68 (64–72)	71 (67–74)	1 (0–2)	2 (1–4)†	7 (5–9)‡	8 (6–11)‡
6 h after surgery	n = 29	n = 30	n = 28	n = 29	n = 28	n = 23
SAP, mmHg	112 (104–120)	109 (101–118)	7 (−2–15)	3 (−4–10)	−1 (−13–11) #	−14 (−25–4)† #
DAP, mmHg	59 (56–63)	58 (54–62)	8 (4–12))†	6 (2–9)†	7 (1–13)¥	0 (−5–5) #
HR (beats/min)	80 (75–84)	74 (70–79)	6 (4–12)‡ * #	3 (1–5)†*	15 (12–18)‡ #	11 (7–16)‡ #
24 h after surgery	n = 28	n = 30	n = 28	n = 30	n = 28	n = 30
SAP, mmHg	103 (97–110)	108 (100–116)	14 (9–19)‡	9 (4–15)†	10 (2–18)¥	4 (−4–12)
DAP, mmHg	55 (52–58)	56 (53–60)	11 (9–13)‡	9 (7–12)‡	10 (7–13)‡	9 (5–13)‡
HR (beats/min)	76 (73–80)	76 (72–80)	4 (3–6)‡ #	4 (2–5)‡	12 (9–16)‡	13 (9–16)‡

*In between group difference ($P < 0.05$). ¥Different from supine ($P < 0.05$). †Different from supine ($P < 0.01$). ‡Different from supine ($P < 0.001$). #Different from pre-operative evaluation: Group MP: HR 6 h sit ($P = 0.001$), SAP 6 h stand ($P = 0.013$), and HR 6 h stand ($P < 0.001$). Group C: SAP 6 h stand ($P < 0.001$), DIA 6 h stand ($P = 0.009$), and HR 6 h stand ($P = 0.001$). All values are presented as mean (95% CI). DAP, diastolic arterial pressure; HR, heart rate; SAP, systolic arterial pressure.

and 24 h post-operatively were comparable with the pre-operative data characterized by an increase in SAP, DAP, and HR during the mobilization procedure from supine to standing (Fig. 3A and B). We found no difference in post-operative fluid balance when comparing OH patients with OI patients (data not shown). Finally, we found no correlation between the development of OH or OI and levels of plasma CRP (data not shown).

Discussion

The main finding of this randomized, blinded, clinical trial was that administration of a single high-dose glucocorticoid versus placebo did not result in a significant reduction in the occurrence of OH 6 h post-operatively despite a reduced inflammatory response. Furthermore, we confirmed the high prevalence of OH (~40%) and OI during same-day ambulation after THA.[5,9] The optimal time point for mobilization after surgery is still not established, but early mobilization in a fast-track setup is important to reduce post-operative morbidity and hospital length of stay (LOS).[1] However, the occurrence of OH and OI during mobilization may lead to syncope, and subsequent falls may result in prosthesis dislocation or fracture.[18,19]

Strategies aiming to reduce the incidence of post-operative OH and OI have received little attention, but the pathophysiological mechanisms may include hypovolemia, post-operative anemia and opioid use. A RCT found no beneficial effect of perioperative goal-directed fluid therapy in reducing OI.[7] Neither did administration of the oral α1-adrenoreceptor agonist midodrine hydrochloride used for treatment of recurrent symptomatic OI and OH in patients with autonomic failure[20] prevent the problem, although a trend for attenuation was found.[9] Furthermore, the prevalence of OI was not found to be associated with the degree of post-operative anemia.[5] Pain and administration of opioids are additional factors that may contribute to OH and OI in the early post-operative period. Thus, the use of larger doses of opioids may potentially cause OH due to their vagotonic effects dampening baroreflex activity.[21] In this study, opioids were only administrated as a rescue analgesic and in small doses, comparable with previous studies.[12,22] In a previous study using the same multimodal opioid-sparing analgesic regimen, no association between similar

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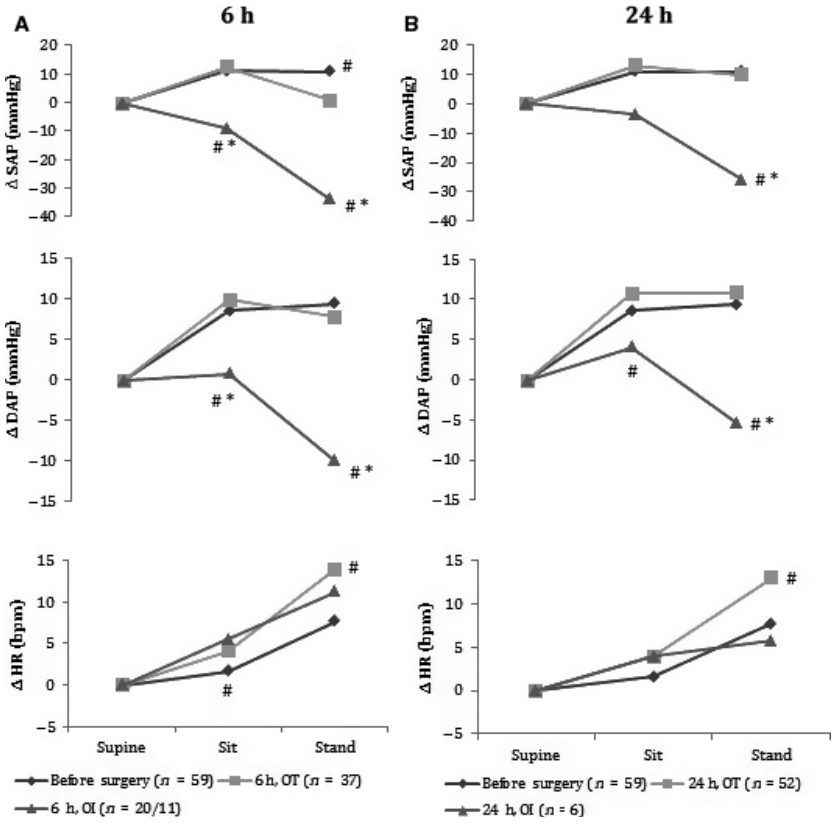

Fig. 3. Changes in arterial pressures and heart rate (HR) during a standardized mobilization procedure 6 (A) and 24 h (B) after surgery compared to before surgery, grouped by orthostatic competence. OI, orthostatic intolerance; OT, orthostatic tolerant; SAP, systolic arterial pressure; DAP, diastolic arterial pressure. * Different between groups (OI versus OT). # Different from pre-operative evaluation.

small doses of opioids and occurrence of OI was found.[5] Likewise, we found no difference in the amount of administered opioid at 0–6 and 6–24 h post-operatively between orthostatic-tolerant and -intolerant patients (data not shown), but less use of opioid from 0–6 h in group MP. Furthermore, gabapentin is known to cause dizziness potentially contributing to OI, but this was a small dose not shown to have side effects.[23]

In addition to the above mentioned factors, the type and extent of surgical trauma and the accompanying inflammatory response may be important pathogenic factors for the risk of OH and OI.[8,24] Thus, an experimental study inducing inflammation by lipopolysaccharide injection in healthy volunteers showed a central downregulation of sympathetic vasomotor tone,[24] suggesting that the magnitude of post-surgical inflammation could represent an important mechanism for impaired vasopressor response during early post-operative mobilization. In our study we monitored the systemic inflammation by CRP-levels, but although an attenuated response was found in group MP at 24 h post-operatively compared to the placebo group, it did not reduce the prevalence of OH and OI. Finally, we found no correlation between the development of OH or OI and levels of plasma CRP (data not shown). However, this study was not powered to evaluate this, and our findings do not exclude the possibility of improving an impaired vasopressor response by reducing the systemic inflammatory response in other types of surgery with more pronounced surgical trauma. Regarding safety, one study solely evaluating high-dose glucocorticoid in elective arthroplasty surgery found no safety issues in terms of infection or other complications.[25]

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The strengths of present study include a high degree of standardization regarding the perioperative setup; all patients received spinal anesthesia using only bupivacaine, thereby avoiding intrathecal opioids. Previously, this approach including a multimodal analgesic regimen resulted in low post-operative pain scores and accompanying low doses of rescue opioids.[12,22] Furthermore, the mobilization procedure was standardized and performed by only two data collectors minimizing the risk of performance bias, and the perioperative analgesic regimen was standardized as well. Perioperative fluid administration was registered in detail and balanced between allocation groups. Finally, this study is the first to evaluate the effect of high-dose glucocorticoid in relation to OH and OI during early mobilization. As OI is defined by appearance of subjective symptoms, the measure may be vulnerable to interpretation by the outcome assessors. In contrast, OH is a clearly defined objective measure[26] which is why we chose OH as the primary outcome. A limitation of our study is that we did not exclude or stratify patients with pre-operative OH as the diagnosis was made during off-line blood pressure analysis. However, this was only present in one patient. Furthermore, remaining motor blockade was ruled out before the mobilization procedure 6 h post-operatively, we cannot exclude any residual effect on the vasomotor action. In addition, although we told patients to pause antihypertensive medications until 48 h post-operatively, we lack specific information on potential post-operative use. Finally, limitations include a short follow-up period and the lack of power to evaluate pain scores, opioid consumption and OH/OI at 24 h post-operatively.

In conclusion, pre-operative 125 mg methylprednisolone did not reduce the prevalence of OH during mobilization 6 or 24 h after THA despite an attenuated inflammatory response.

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Author contributions

V.L.L.: Conceived the study protocol and assessment design, patient recruitment, data collection, blinded statistical analysis, drafting the manuscript, writing the paper.

P.B.P.: Patient recruitment, data collection, blinded statistical analysis, writing the paper.

Ø.J.: Study and assessment design, blinded statistical analysis, writing the paper.

T.B.: Assessment design, patient recruitment, writing the paper.

H.K.: Conceived and designed the study protocol, assessment design, data analysis, writing the paper.

All authors approved the final manuscript.

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