Oral Midodrine Hydrochloride for Prevention of Orthostatic Hypotension during Early Mobilization after Hip Arthroplasty

A Randomized, Double-blind, Placebo-controlled Trial

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ABSTRACT

Background: Early postoperative mobilization is essential for rapid recovery but may be impaired by orthostatic intolerance (OI) and orthostatic hypotension (OH), which are highly prevalent after major surgery. Pathogenic mechanisms include an insufficient postoperative vasopressor response. The oral α-1 agonist midodrine hydrochloride increases vascular resistance, and the authors hypothesized that midodrine would reduce the prevalence of OH during mobilization 6 h after total hip arthroplasty relative to placebo.

Methods: This double-blind, randomized trial allocated 120 patients 18 yr or older and scheduled for total hip arthroplasty under spinal anesthesia to either 5 mg midodrine hydrochloride or placebo orally 1 h before mobilization at 6 and 24 h postoperatively. The primary outcome was the prevalence of OH (decrease in systolic or diastolic arterial pressures of > 20 or 10 mmHg, respectively) during mobilization 6 h after surgery. Secondary outcomes were OI and hemodynamic responses to mobilization at 6 and 24 h.

Results: At 6 h, 14 (25%; 95% CI, 14 to 38%) *versus* 23 (39.7%; 95% CI, 27 to 53%) patients had OH in the midodrine and placebo group, respectively, relative risk 0.63 (0.36 to 1.10; $P = 0.095$), whereas OI was present in 15 (25.0%; 15 to 38%) *versus* 22 (37.3%; 25 to 51%) patients, relative risk 0.68 (0.39 to 1.18; $P = 0.165$). At 24 h, OI and OH prevalence did not differ between groups.

Conclusions: Preemptive use of oral 5 mg midodrine did not significantly reduce the prevalence of OH during early postoperative mobilization compared with placebo. However, further studies on dose and timing are warranted since midodrine is effective in chronic OH conditions. **(Anesthesiology 2015; 123:1292-300)**

EARLY postoperative mobilization is essential to avoid postoperative morbidity and in ensuring early recovery.[1,2] Thus, early postoperative mobilization, often on the day of surgery, has become an integral part of several "fast-track" or "enhanced-recovery" protocols, which reduce postoperative morbidity and hospital length of stay (LOS).[3] However, early postoperative mobilization may be hindered by orthostatic hypotension (OH), defined as a decrease in systolic arterial pressure (SAP) greater than 20 mmHg or diastolic arterial pressure (DAP) greater than 10 mmHg,[4] and orthostatic intolerance (OI) defined as symptoms such as dizziness, nausea, vomiting, blurred vision, or syncope during mobilization.[5,6] The prevalence of OI and OH during mobilization 6 h after surgery has been reported to be as high 40 and 50%, respectively, after hip arthroplasty.[7] In addition, OI occurred in up to 60% of patients 6 h after prostatectomy[8,9] and was associated with a prolonged LOS.[9] The use of perioperative goal-directed fluid therapy did not reduce OI during early mobilization,[9] whereas an attenuated

What We Already Know about This Topic

- The oral α1-adrenergic agonist, midodrine, is effective in treatment of chronic orthostatic hypotension
- Orthostatic hypotension is common during early mobilization after surgery and interferes with recovery, but the effects of midodrine in this population have not been tested

What This Article Tells Us That Is New

- In 120 patients undergoing total hip arthroplasty, administration of 5 mg midodrine 1 h before early mobilization at 6 h after surgery did not reduce the incidence of orthostatic hypotension
- Further studies examining other doses and timing are warranted

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postural vasopressor response early after surgery may be an important contributing factor.[7–9]

The oral α1-adrenoreceptor agonist midodrine hydrochloride is a prodrug for desglymidodrine that acts directly on peripheral arteriolar and venous vasculature, thereby increasing the systemic vascular resistance.[10] Midodrine is used for treating recurrent symptomatic OH and OI in patients with various forms of autonomic failure[11] and has, in several randomized controlled trials, demonstrated a reduction in OI symptoms and an improvement in the ability to stand compared with placebo.[12–14] In addition, a 5-mg midodrine dose administered 1 h before head-up-tilt (HUT) markedly reduced the prevalence of HUT-induced neurally mediated syncope.[15]

Therefore, we hypothesized that midodrine may ameliorate the postoperatively attenuated postural vasopressor response and prevent postoperative OH. Consequently, in this double-blind, placebo-controlled, randomized trial, we investigated whether the preemptive administration of 5 mg midodrine hydrochloride could reduce the prevalence of OH and OI during early postoperative mobilization 6 and 24 h after total hip arthroplasty (THA).

Material and Methods

Trial Design and Oversight

The study was a three-center, double-blinded, placebo-controlled, superiority trial and was conducted according to the International Conference on Harmonization guidelines for Good Clinical Practice (GCP) and was approved by the ethics Committee for the Capital Region of Denmark (H-4-2012-097), the Danish Data Protection Agency, and the Danish National Board of Health (EudraCT 2012-002572-13) and registered on ClinicalTrials.gov under the U.S. National Library of Medicine on October 10, 2015 (NCT01707953, principal investigator: Ø.J.). The trial was monitored by the GCP units of the Copenhagen University Hospital, Copenhagen, Denmark, and Odense University Hospital, Odense, Denmark, and was carried out in three high-volume orthopedic surgical centers in Denmark with more than 500 THA procedures per year. Oral and written informed consent was obtained from all patients before participation.

Participants

All patients 18 yr or older, able to give consent, and scheduled for primary unilateral THA were screened for inclusion from October 2012 to October 2013 at the Department of Orthopedic Surgery, Copenhagen University Hospital, Gentofte, Denmark; Copenhagen University Hospital, Hvidovre, Denmark; and Southern Denmark University Hospital, Vejle, Denmark. Exclusion criteria were general anesthesia (GA) for the procedure, digoxin treatment, history of renal or hepatic failure, glaucoma, chronic urinary retention requiring treatment, history of recurrent OI/hypotension, known autonomous nervous system disease, alcohol or drug abuse, current active malignant disease, premenopausal women, treatment with vitamin-K antagonists, body mass index greater than 40 kg/m^2, dementia, cognitive dysfunction, or participation in other trials. Patients were recruited through the participating clinics. Screening for eligibility, enrollment, and allocation of patients was carried out by dedicated research nurses at each participating hospital.

Randomization, Trial Intervention, and Blinding

Patients were randomly assigned to receive an oral administration of either 5 mg midodrine hydrochloride or placebo at 5 and 23 h after surgery (1 h before mobilization at 6 and 24 h postoperatively). The Capital Region pharmacy (Herlev, Denmark), prepared the study drug; generated the randomization list (1:1 allocation ratio); and prepared sequentially numbered, opaque, sealed envelopes that were distributed directly to the participating centers. To ensure balance in the number of patients for each allocation group at each site, block randomization with a block size of 10 was performed. To preserve concealment, both midodrine hydrochloride and placebo were placed in identical capsules and packed in one container per patient labeled with the allocated randomization number. All participating patients, hospital personnel, outcome assessors, and trial investigators were blinded to allocation group. After study termination, the blinded randomization list was dispatched by the Capital Regional Pharmacy to the principal investigator enabling blinded analyses. This list was unblinded with respect to intervention type only after all statistical analyses had been carried out.

Anesthesia and Surgery

All patients were anesthetized by spinal anesthesia with bupivacaine 5 mg/ml at a maximum dose of 15 mg (3 ml) and operated using a standard posterolateral approach. Propofol sedation (1 to 5 mg kg^{-1} h^{-1}) was administered at the discretion of the attending anesthesiologist. One gram tranexamic acid was administered intravenously (IV) immediately after spinal anesthesia. Spinal-induced hypotension was treated at the discretion of the attending anesthesiologist with either IV 10 mg ephedrine or 0.1 to 0.2 mg phenylephrine. Intraoperative fluid therapy included crystalloid infusion (0.9% saline or lactated Ringer's solution) at the discretion of the anesthesiologist, and blood loss was replaced 1:1 using 6% hydroxyethyl starch (Voluven; 130/0.4 Fresenius Kabi AB, Sweden). Transfusion of erythrocytes followed guidelines by the Danish National Board of Health with transfusion thresholds of hemoglobin less than 7.5 g/dl or hemoglobin less than 10.0 g/dl in patients with severe ischemic heart disease.[16] In the postanesthesia care unit

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and the ward, patients were allowed to drink freely, and additional IV fluids were administered only if clinically indicated (hypotension and tachycardia) at the discretion of the attending physician. Discharge from postanesthesia care unit to the ward followed the modified Aldrete criteria.[17]

The perioperative analgesic regime was standardized as follows: 2 g acetaminophen, 400 mg celecoxib, and 600 mg gabapentin preoperatively; 2 g acetaminophen, 200 mg celecoxib, and 300 mg gabapentin on the night of surgery; and followed by 4 g acetaminophen, 400 mg celecoxib, and 900 mg gabapentin daily for the duration of hospital stay. Opioids were administered as rescue analgesia if pain exceeded numeric rating scale (0 to 10) of 3 during rest or 5 during active movement.

Orthostatic Challenge

A standardized mobilization procedure was performed on the day of surgery 1 to 3 h preoperatively and was repeated 6 and 24 h after surgery, defined as the time of wound closure. The mobilization procedure was carried out by trained research nurses and standardized to supine rest (5 min) and was followed by sitting on the bed with feet resting on the floor (3 min). This was followed by standing using a walker (3 min) with patients verbally encouraged to shift body weight from one leg to the other to prevent venous pooling in the legs by activating the muscle pump. The procedure ended with supine rest (5 min).[7–9] The procedure was terminated during the sitting or standing position if patients experienced symptoms of OI (dizziness, syncope, blurred vision, visual disturbance, nausea, or vomiting) or if SAP decreased more than 30 mmHg compared to the supine position.[6] During the entire mobilization procedure, beat-to-beat arterial pressures were recorded noninvasively by photoplethysmography by finger cuffs placed on the second and third fingers of the nondominant hand (CNAP-500; CNSystems, Austria).[18] In addition, a standard three-lead electrocardiogram was recorded during the procedure, and all data were recorded using an AD-converter (PowerLab; ADInstruments Ltd., United Kingdom) and saved for off-line analysis. Pain was reported postoperatively during mobilization for each body position on a numeric rating scale (0 to 10).

Orthostatic Classification

Patients were classified as having OH if SAP decreased greater than 20 mmHg or DAP decreased greater than 10 mmHg in the sitting or standing position compared with supine rest.[4] Patients were classified as having OI if they terminated the mobilization procedure prematurely due to dizziness, syncope, blurred vision, visual disturbance, nausea, or vomiting.[6] Patients having OH who terminated the mobilization procedure due to OI symptoms were classified as having both OH and OI.

Data Collection and Analysis

After patient inclusion, we collected baseline patient demographic variables, the American Society of Anesthesiologists physical status classification score, specific comorbidities, and medications. During the admission, the following perioperative data were collected: intra- and postoperative fluid losses and administration, transfusion of erythrocytes, venous hemoglobin concentration preoperatively and 6 and 24 h after surgery, spinal local anesthetic dose, administration of propofol sedation, postoperative opioid administration, blood pressure before and 1 h after trial drug administration, and LOS. Data were recorded in individual patient case record forms and subsequently entered into an electronic study database. Blood pressure and heart rate (HR) data during mobilization were stored electronically and analyzed off-line using Labchart 7.0 (ADInstruments Ltd.). Before averaging, data were visually inspected for artefacts, and such data were excluded. Values were averaged over 5 min during supine rest and over the last 10 s during the sitting and standing position for both patients completing the mobilization procedure or patients terminating the procedure prematurely due to OI.

Outcome Measures

The primary trial outcome was the prevalence of OH in the sitting or standing position during mobilization 6 h after surgery. The main secondary outcome was OI during mobilization at 6 h. Other secondary outcomes included OH and OI during mobilization at 24 h and blood pressure and HR responses during mobilization. The occurrence of the following predefined possible side effects to the trial drug was recorded at 6 and 24 h after surgery: headache, supine hypertension (SAP > 180 mmHg or DAP > 110 mmHg), pruritus, or urinary retention requiring catheterization. Adverse events (AEs) were recorded and graded according to the International Conference on Harmonization GCP guidelines.

Sample Size Calculation

This study was conducted as a superiority trial. Based on a previous evaluation of early mobilization after THA, which showed a 50% prevalence of OH at 6 h after surgery,[7] we calculated that 110 patients were needed to detect an absolute reduction in OH at 6 h from 50 to 25% with a power (1-beta) of 80% and a two-sized $\alpha = 0.05$. To account for dropouts, we planned to include a total of 120 patients.

Statistical Analysis

The primary outcome and other categorical variables were compared between allocation groups using the chi-square test. All continuous variables were evaluated for normal distribution and compared between allocation groups using the independent-samples *t* test for normally distributed data or the Mann–Whitney U test for variables not following the normal distribution. Categorical variables are reported

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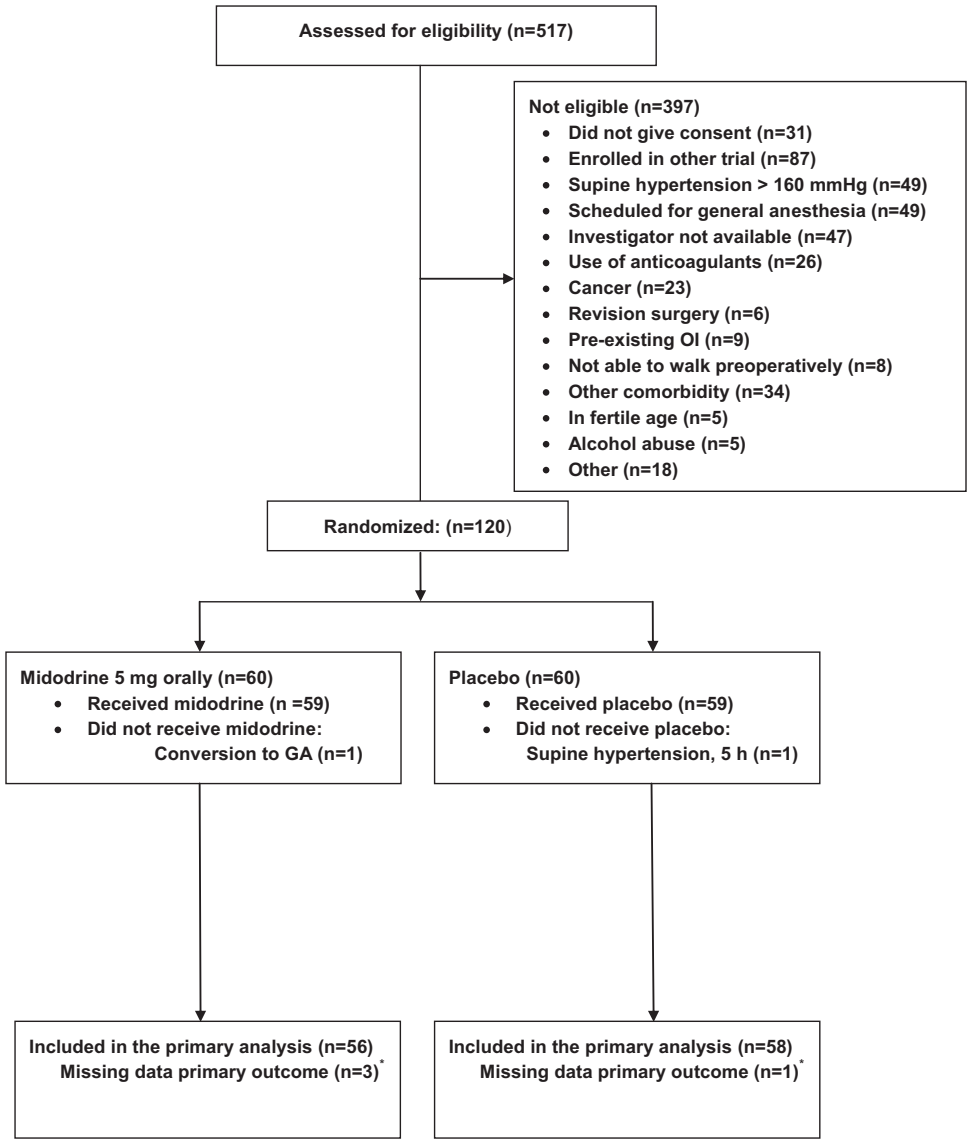

Fig. 1. CONSORT flow diagram for screening, inclusion, and exclusion of trial participants. *Missing data on primary outcome but included in baseline data description and analyses of secondary outcomes. GA = general anesthesia; OI = orthostatic intolerance.

as number (%) and continuous variables reported as mean (±SD) or median with interquartile range as appropriate. Blood pressure and HR responses during mobilization were compared within and between mobilization sessions in a mixed-model ANOVA for repeated measures with subjects included as random effects while body position and mobilization time point (preoperative and 6 and 24 h) were included as fixed effects. If an overall type III effect was found, pairwise comparisons were done using least square means with Dunnett correction with the supine position and preoperative evaluation as control levels.

Statistical analyses were carried out in SPSS version 20.0 (IBM Corp., USA) and SAS version 9.2 (SAS Institute Inc., USA), with a two-sided *P* value of 0.05 representing statistical significance.

Results

A total of 517 patients were screened for inclusion. Of these, 397 were not eligible or did not consent leaving 120 patients for randomization (fig. 1). After randomization, two patients were excluded and did not receive the trial intervention (one due to conversion to GA and one due to severe supine hypertension 5 h after surgery). Due to equipment failure, data regarding the primary outcome were not available in four patients (three in midodrine and one in placebo group), leaving 56 and 58 patients for the modified intention-to-treat analysis of the primary outcome. Baseline characteristics were comparable between allocation groups and are presented in table 1. Likewise, there were no between-group differences in intra- and postoperative data including opioid consumption and fluid administration (table 2). There was

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Table 1. Patient Demographics and Baseline Characteristics by Allocation Group

Variables	Midodrine (n = 59)	Placebo (n = 59)
Age, mean (±SD), yr	69 (9)	68 (9)
Female sex, no. (%)	36 (61.0)	34 (57.6)
Body mass index, mean (±SD), kg/m^2	27 (4)	28 (5)
ASA physical status classification no. (%)		
I	21 (35.6)	17 (28.8)
II	34 (57.6)	36 (61.0)
III	4 (6.8)	6 (5.1)
Comorbidity, no. (%)		
Hypertension	26 (44.1)	30 (50.8)
Ischemic heart disease	3 (5.1)	1 (1.7)
Diabetes	1 (1.7)	2 (3.4)
Cerebrovascular disease	1 (1.7)	1 (1.7)
Pulmonary disease	7 (11.9)	6 (10.2)
Medication, no. (%)		
β-Blocker	7 (11.9)	8 (13.6)
Combined α–β blocker	2 (3.4)	—
Ca^{2+} antagonist	10 (16.9)	14 (23.7)
ACE-II or AT-II antagonist	19 (32.2)	18 (30.5)
Diuretics	8 (13.6)	13 (22.0)
Hemoglobin at baseline (±SD), g/dl	13.8 (1.1)	14.0 (1.0)

ACE = angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; AT-II = angiotensin II.

Table 2. Intraoperative and Postoperative Data

Variables	Midodrine (n = 59)	Placebo (n = 59)	*P* Value
Duration of surgery	53 (18)	54 (21)	0.68
Intraoperative propofol sedation	50 (84.7)	53 (89.8)	0.41
Spinal dose (mg)	13.8 (2.2)	13.9 (2.2)	0.80
Intraoperative			
Crystalloids (ml)	918 (286)	947 (241)	0.56
HES (ml)	250 (270)	244 (246)	0.90
Packed erythrocytes	0	0	—
Blood loss	328 (234)	309 (219)	0.66
PACU and ward 0–6 h			
Crystalloids (ml)	567 (439)	533 (506)	0.70
HES (ml)	334 (388)	300 (368)	0.62
Rescue opioids (mg)	7 (7)	8 (9)	0.41
PACU and ward 6–24 h			
Crystalloids (ml)	397 (408)	438 (404)	0.59
HES (ml)	58 (174)	45 (133)	0.66
Rescue opioids (mg)	15 (18)	18 (23)	0.39
Postoperative hemoglobin concentration			
6 h after surgery	11.1 (1.3)	11.5 (1.3)	0.15
24 h after surgery	11.1 (1.3)	11.2 (1.3)	0.51

Values are reported as mean (±SD) for continuous variables and as number (%) for categorical variables.

HES = hydroxyethyl starch; PACU = postanesthesia care unit.

no difference in intraoperative fluid volume between patients with and without OH ($P = 0.78$) and with and without OI ($P = 0.84$).

Pain scores during mobilization did not differ between allocation groups and their median were (interquartile range) 3 (1.5 to 4.5), 3 (1.5 to 4.5), and 4 (3 to 5) at 6 h and 2 (0.5 to 3.5), 2 (1 to 3), and 2 (0.5 to 3.5) at 24 h during supine, sitting, and standing positions, respectively. No patients received erythrocytes during surgery, but one patient in the placebo group received 2 units of erythrocytes postoperatively on the day of surgery.

Study Outcomes

The primary outcome, OH during mobilization 6 h after surgery was present in 14 patients (25%; 95% CI, 14 to 38%) in the midodrine group *versus* 23 patients (40%; 95% CI, 27 to 53%) in the placebo group ($P = 0.10$; table 3), with an absolute difference in the primary outcome between allocation groups of 15% (95% CI, −2 to 32%). At 6 h, 15 patients (5 while sitting) in the midodrine group *versus* 22 patients (8 while sitting) in the placebo group terminated the mobilization procedure due to OI ($P = 0.17$). At 6 h, 30 (81%) of the OI patients had concomitant OH. Likewise, at 24 h, there was no difference in the prevalence of OH or OI during mobilization (table 3), and six (75%) of the eight OI patients had concomitant OH.

Blood Pressure Responses in Relation to Trial Drug Administration and during Mobilization

In the midodrine group, supine SAP increased by 10 mmHg (6 to 15) ($P < 0.001$) from time of intervention at 5 to 6 h after surgery, whereas SAP were unchanged in the placebo group ($P = 0.28$). Supine (baseline) blood pressure and HR together with changes from supine to termination of mobilization were comparable between allocation groups and are presented in table 4 for all three mobilization sessions (preoperatively, 6 h after surgery, and 24 h after surgery). Preoperatively, no patients experienced OI, but 15 patients (13%) were classified as having OH, 6 (5%) in the midodrine group and 9 (8%) in the placebo group ($P = 0.41$). At 6 h after surgery, SAP decreased while DAP and HR increased in both the midodrine and placebo group during mobilization from supine to standing ($P < 0.05$; fig. 2), and these changes were not different between allocation groups. At 24 h after surgery, SAP, DAP, and HR increased from supine to standing in both allocation groups ($P < 0.05$), with no interaction between treatment allocation.

A comparison of the hemodynamic responses to mobilization at 6 h between orthostatic-intolerant patients (OI) and patients completing the mobilization procedure (OT) is presented in figure 2. In OI patients, both SAP and DAP decreased from supine to standing ($P < 0.001$), whereas HR did not change. In contrast, the responses in OT patients were comparable with the preoperative evaluation and characterized by an increase in SAP, DAP, and HR from supine to standing ($P < 0.001$; fig. 2).

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Table 3. Primary and Secondary Trial Outcomes

Variables	Midodrine (n = 59)	Placebo (n = 59)	Relative Risk (95% CI)	*P* Value
Primary outcome, no/total no. (%)				
OH at 6 h after surgery	14/56 (25.0)	23/58 (39.7)	0.63 (0.36–1.10)	0.10
Secondary outcomes, no/total no. (%)				
OI at 6 h after surgery	15/59 (25.4)	22/59 (37.3)	0.68 (0.39–1.18)	0.17
OH at 24 h after surgery	6/56 (10.7)	11/58 (19.0)	0.57 (0.22–1.42)	0.22
OI at 24 h after surgery	3/59 (5.1)	5/59 (8.5)	0.61 (0.15–2.44)	0.58
Side effects, no/total no. (%)				
Supine hypertension	3/59 (5.1)	1/59 (1.8)	3.00 (0.32–28.0)	0.30
Headache	1/59 (1.8)	2/59 (3.5)	0.50 (0.05–5.37)	0.56
Urinary retention	31/59 (52.5)	27/59 (45.8)	1.15 (0.80–1.66)	0.46
Pruritus	0/59 (0.0)	0/59 (0.0)	—	—

OH = orthostatic hypotension; OI = orthostatic intolerance.

Table 4. Supine Hemodynamics and Changes from Supine to Termination of the Mobilization Procedure during Sitting or Standing before Surgery and 6 and 24 h after Surgery Grouped by Allocation

	Supine		Change during Mobilization	
Variables	Midodrine (n = 59)	Placebo (n = 59)	Midodrine (n = 59)	Placebo (n = 59)
Before surgery				
SAP, mmHg	151 (144 to 157)	146 (140 to 152)	10 (6 to 14)#	5 (1 to 9)§
DAP, mmHg	79 (76 to 82)	79 (77 to 82)	12 (9 to 15)#	8 (5 to 11)#
HR (beats/min)	67 (64 to 70)	68 (65 to 70)	8 (5 to 10)#	6 (3 to 8)#
6 h after surgery				
SAP, mmHg	133 (127 to 140)‡	130 (122 to 137)‡	−7 (−12 to −1)§*	−10 (−17 to −3)*‖
DAP, mmHg	68 (65 to 71)‡	68 (66 to 71)‡	5 (2 to 9)‖	6 (1 to 10)§
HR (beats/min)	70 (67 to 73)*	71 (68 to 74)†	5 (2 to 9)‖	5 (2 to 9)‖
24 h after surgery				
SAP, mmHg	131 (124 to 138)‡	126 (121 to 132)‡	7 (1 to 13)§	5 (−1 to 10)
DAP, mmHg	66 (63 to 69)‡	65 (63 to 68)‡	11 (9 to 14)#	10 (6 to 14)#
HR (beats/min)	73 (70 to 75)‡	73 (71 to 76)‡	9 (6 to 11)#	9 (6 to 12)#

All values are presented as mean (95% CI).

* Different from preoperative value ($P < 0.05$); † different from preoperative value ($P < 0.01$); ‡ different from preoperative value ($P < 0.001$); § different from supine ($P < 0.05$); ‖ different from supine ($P < 0.01$); # different from supine ($P < 0.001$).

DAP = diastolic arterial pressure; HR = heart rate; SAP = systolic arterial pressure.

Side Effects and Safety

All predefined possible side effects to the trial intervention did not differ between treatment allocation and are reported in table 3. The most common event was urinary retention requiring catheterization, whereas all other events were rare. No severe AEs were observed during the trial. One AE (diarrhoea) was observed in the placebo group and was considered unrelated to the trial intervention.

Discussion

The main finding of this randomized, double-blind, placebo-controlled, randomized trial was that the administration of 5 mg midodrine hydrochloride 1 h before mobilization did not significantly reduce the occurrence of OH 6 h after surgery. In addition, we confirmed the high prevalence of OI and OH during same-day mobilization after THA surgery.[7]

Although there is no evidence regarding the optimal time point for initial mobilization after surgery, mobilization on the day of surgery is a realistic goal and is practiced in many institutions, even after major surgery. Thus, measures to avoid OH and OI during same-day mobilization are important.

In agreement with this trial, previous studies have reported a high prevalence of OI after major surgery and have established an attenuated vasopressor response to standing as major mechanism behind postoperative OH and OI.[7–9] Consequently, an attenuated postural response in vascular resistance and in the norepinephrine concentration has been reported in OI patients during early mobilization after surgery, and optimized fluid therapy by goal-directed therapy has not been successful in reducing OI prevalence.[7–9]

In this trial, we hypothesized that the administration of an oral α-1-adrenoreceptor agonist would augment the vasopressor response during postoperative mobilization and thus reduce

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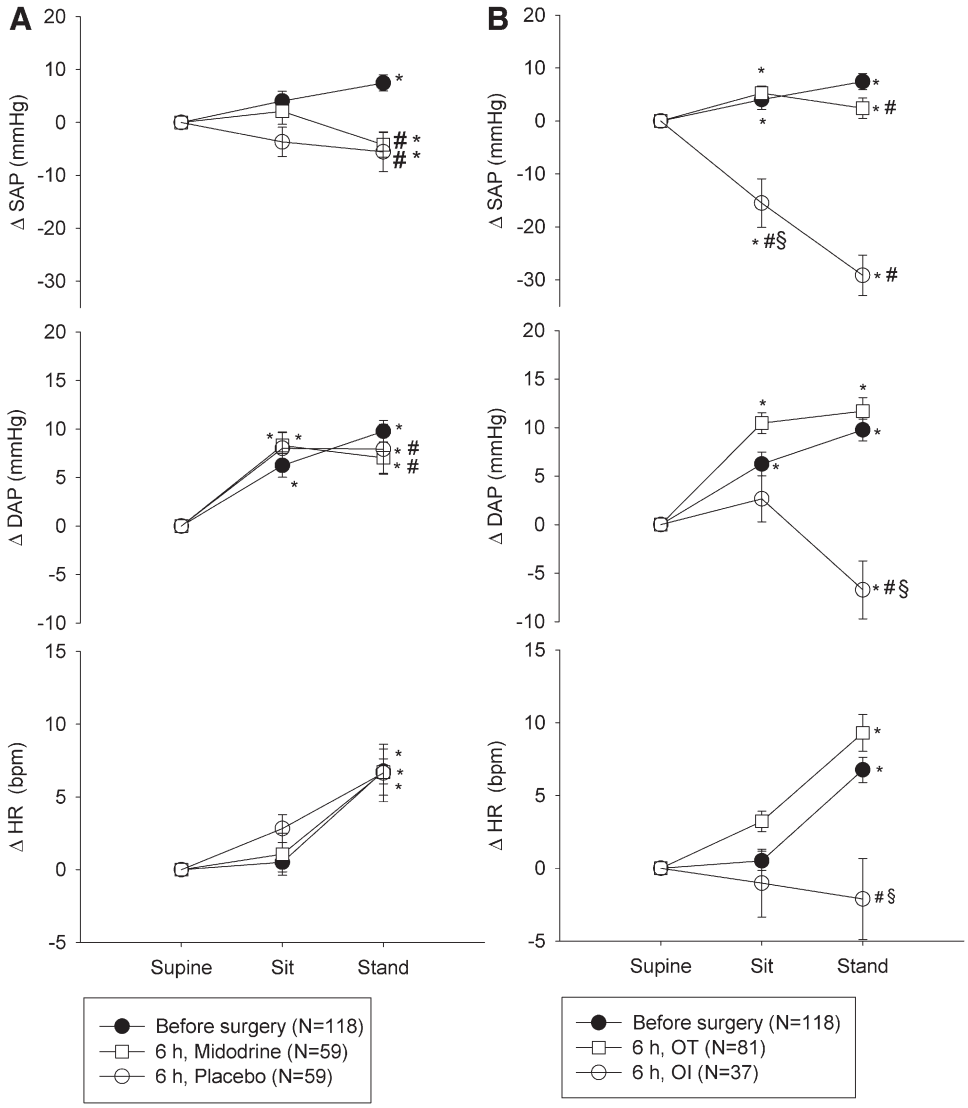

Fig. 2. Changes in arterial pressures and heart rate (HR), grouped by allocation (*A*) and orthostatic competence (*B*), during a standardized mobilization procedure before and 6 h after surgery. DAP = diastolic arterial pressure; OI = orthostatic intolerant; OT = orthostatic tolerant; SAP = systolic arterial pressure. *Different from supine; #different from preoperative evaluation; §different between groups (midodrine *vs.* placebo) or OI *versus* OT.

the occurrence of OH and OI. However, OH and OI occurrence was not significantly reduced among patients receiving midodrine compared with placebo. The lack of a statistically significant effect may be explained by several factors. First, this trial was powered to detect a reduction in OH from 50 to 25% during mobilization 6 h after surgery. However, the OH prevalence in the control group was lower (40%) than the estimated 50% previously reported after THA,[7] and thus our results may have been influenced by lack of statistical power. This is the first study to evaluate the use of midodrine in relation to postoperative mobilization-induced OH and OI. However, when midodrine is administered for treating chronic OH due to various autonomic deficiencies, the dose is usually titrated individually over time from 2.5 to 5 mg up to a dose of 10 mg thrice daily.[11] We used midodrine to treat an acute and transient impairment in cardiovascular regulation postoperatively, and thus we could not perform individual dose titration. Thus, a fixed oral dose of 5 mg may have been insufficient for some patients but was chosen to balance the sympathomimetic effects against the risk of supine hypertension, which is a concern in the postoperative period. Supine hypertension has been observed with increasing midodrine doses,[10] and a supine systolic blood pressure greater than 200 mmHg was reported in 17% of patients receiving a 10-mg dose.[19] Thus, a 5-mg dose was encouraged by a previous trial that demonstrated a reduction from 67 to 17% in neurally mediated syncope induced by HUT when this dose was administered 1 h before HUT.[15] We chose a preemptive administration of midodrine to prevent OH and OI that might lead to delay in early recovery and sometimes to more severe events such as fainting, falls, and even prosthesis dislocation and fracture. Another viable approach may be to administer midodrine to patients who have experienced OI/OH

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during the initial mobilization attempt. However, this therapeutic approach needs to be evaluated in future studies. In this trial, we administered midodrine 1 h before the mobilization period. However, pharmacokinetic data from healthy subjects suggest that at least in some individuals the peak concentration of desglymidodrine is not reached until about 90 min after administration.[10] In contrast to previous studies,[7–9,20] we chose OH and not OI as the main variable of interest. Although the majority of patients experiencing OI have concomitant OH, OI is defined by the appearance of subjective symptoms and may as such be vulnerable to interpretation by the outcome assessors. In contrast, OH is a clearly defined objective measure.[4] However, the definition of OH (decrease in SAP > 20 or DAP > 10 mmHg) has been criticized as it does not account for the relative decrease in blood pressure.[21]

Several factors related to the surgical procedure and anesthesia may contribute to postoperative OH and OI. All patients in this trial received spinal anesthesia, but it is unknown to what extent the type of anesthesia contributes to OI and OH as it has not been compared within the same procedure. Although muscle paralysis is absent during mobilization at 6 h,[7] any residual vasomotor effects of spinal anesthesia cannot be ruled out. A recent study, comparing spinal anesthesia *versus* GA using propofol and remifentanil in THA, demonstrated that more patients in the GA group were able to walk 5 m at 6 h after surgery and reported less dizziness.[22] However, this study did not systematically evaluate OI or OH while other studies have demonstrated a high prevalence of OI in major,[8,9] but not in minor, surgery after GA using short-acting agents.[20] Thus, the type and extent of the surgical trauma and the resulting inflammatory response may be an important factor for the risk of OH and OI.[23] The patient population in this trial was generally healthy, with only 6% being classified as American Society of Anesthesiologist physical status III and consisting of only three patients with diabetes mellitus. Therefore, this trial does not allow us to infer information regarding the prevalence of OH and OI or the efficacy of midodrine in patients with substantial comorbidity.

The strengths of the present trial include a high degree of standardization regarding the perioperative setup in the participating departments. Consequently, all patients received spinal anesthesia using bupivacaine only, thus avoiding intrathecal opioids. Together with an oral multimodal analgesic regimen, this approach has previously resulted in low postoperative pain scores and low doses of rescue opioids,[24] which was also the case in the current study where 40% did not receive any opioids in the first 6 h after surgery. In addition, the mobilization procedure and the perioperative analgesic regime were standardized and the perioperative fluid administration was reported in detail, with the volume administered balanced between allocation groups. Furthermore, this trial is the first to evaluate the use of midodrine in relation to postoperative mobilization and the largest trial to systematically evaluate OH and OI during early postoperative mobilization. However, the present trial is limited by the fact that we did not exclude or stratify patients with preoperative OH as this diagnosis was made during off-line blood pressure analysis. However, this was present only in 13% of the patients and did not differ between allocation groups.

In conclusion, in this randomized, placebo-controlled trial, the preemptive use of 5 mg oral midodrine hydrochloride did not significantly reduce the prevalence of OH during mobilization 6 h after a THA procedure. However, the trend for reduced OH prevalence in the midodrine group calls for further studies on dose and timing of midodrine administration in relation to reducing OH and OI during early postoperative mobilization.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: oeivind.jans@regionh.dk. Raw data available at: oeivind.jans@regionh.dk.

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