ANESTHESIOLOGY

Dexamethasone Dose and Early Postoperative Recovery after Mastectomy

A Double-blind, Randomized Trial

Kristin Julia Steinthorsdottir, M.D.,
Hussein Nasser Awada, Bc.Med., Hanne Abildstrøm, Ph.D.,
Niels Kroman, D.M.Sc., Henrik Kehlet, M.D., Ph.D.,
Eske Kvanner Aasvang, Ph.D.

ANESTHESIOLOGY 2020; 132:678–91

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Dexamethasone is an effective antiemetic and may facilitate initial postoperative recovery after mastectomy
- Whether 24 mg is more effective than 8 mg remains unknown

What This Article Tells Us That Is New

- Dexamethasone (24 mg) did not increase the number of patients eligible to skip the postanesthetic care unit
- Pain scores were low and nausea rare in both groups
- Dexamethasone 24 mg was not preferable to 8 mg

ABSTRACT

Background: Pain and nausea are the most common challenges in postoperative recovery after mastectomy. Preventive measures include multimodal analgesia with preoperative glucocorticoid. The aim of this study was to investigate whether 24 mg of preoperative dexamethasone was superior to 8 mg on early recovery after mastectomy in addition to a simple analgesic protocol.

Methods: In a randomized, double-blind trial, patients 18 yr of age or older having mastectomy were randomized 1:1 to 24 mg or 8 mg dexamethasone, and all received a standardized anesthetic and surgical protocol with preoperative acetaminophen, total intravenous anesthesia, and local anesthetic wound infiltration. The primary endpoint was number of patients transferred to the postanesthesia care unit according to standardized discharge criteria (modified Aldrete score). Secondary endpoints included pain and nausea at extubation, transfer from the operating room and upon arrival at the ward, length of stay, seroma occurrence, and wound infections.

Results: One hundred thirty patients (65 in each group) were included and analyzed for the primary outcome. Twenty-three (35%) in each group met the primary outcome, without significant differences in standardized discharge scores (odds ratio, 1.00 [95% CI, 0.49 to 2.05], $P > 0.999$). More patients had seroma requiring drainage in the 24 mg *versus* 8 mg group, 94% *versus* 81%, respectively (odds ratio, 3.53 [95% CI, 1.07 to 11.6], $P = 0.030$). Median pain scores were low at all measured time points, numeric rating scale less than or equal to 2 *versus* less than or equal to 1 in the 24 mg *versus* 8 mg group, respectively. Six patients in each group (9%) experienced nausea at any time during hospital stay ($P > 0.999$). Length of stay was median 11 and 9.2 h in the 24 and 8 mg group, respectively ($P = 0.217$).

Conclusions: The authors found no evidence of 24 mg *versus* 8 mg of dexamethasone affecting the primary outcome regarding immediate recovery after mastectomy. The authors observed a short length of stay and low pain scores despite a simple analgesic protocol.

(*ANESTHESIOLOGY 2020; 132:678–91*)

Across different surgical procedures, preoperative glucocorticoid has been shown to reduce postoperative nausea and vomiting,[1,2] acute pain, and need of opioids,[3] and has been suggested to accelerate recovery (*e.g.*, increased speed of return to diet after bowel surgery,[1] earlier fulfillment of discharge criteria after vascular surgery,[4] shorter mean length of stay after major abdominal surgery,[5] and lower risk of prolonged length of stay after arthroplasty surgery[6]), without increasing complications.[1,4–9] The established dose for postoperative nausea and vomiting prevention is 4 to 8 mg dexamethasone,[1,2] but higher doses of glucocorticoid (up to 125 mg of methylprednisolone, equivalent to 24 mg of dexamethasone) have been shown superior to placebo in decreasing postoperative pain and opioid use in different surgical procedures.[3] The rationale behind preoperative

glucocorticoid administration is control of the inflammatory response to surgery occurring at the first incision stressor and lasting up to several days, but whether high-dose glucocorticoids have effects on recovery in the immediate postoperative phase is not fully investigated.[10]

In breast cancer surgery, problems in early recovery primarily comprise pain and nausea, despite being partly alleviated by implementation of enhanced recovery after surgery protocols, including 8 mg preoperative dexamethasone.[11,12] Randomized, placebo-controlled studies on 8 mg dexamethasone[13,14] and betamethasone[15] (equivalent to dexamethasone) in breast cancer surgery have shown reduced postoperative nausea and vomiting, pain, and analgesic consumption in the immediate postoperative phase, with no difference in the rate of surgical complications.[13,14] One study also found a

potentially positive effect on respiration, although this may be attributable to reduced opioid consumption.[14]

In our institution, patients undergoing breast cancer surgery have been treated according to an enhanced recovery after surgery protocol since 2008, undergoing regular evaluation and changes according to available evidence. In 2015, 125 mg methylprednisolone (equivalent to 24 mg dexamethasone) was implemented as part of an existing enhanced recovery after surgery protocol (before including 8 mg dexamethasone).[16] This resulted in a marked reduction in length of stay and frequency of transfer to the postanesthesia care unit (PACU), allowing for a majority of mastectomies to be performed as true day-case surgeries.[16] These promising results prompted an investigation of the isolated effects of 24 mg compared with 8 mg dexamethasone on recovery and need for observation in the PACU after breast cancer surgery in an already well-implemented enhanced recovery after surgery set-up. We tested the hypothesis that patients having mastectomies who are given 24 mg of dexamethasone are more likely to bypass the PACU than those given 8 mg of dexamethasone.

Materials and Methods

Before patient enrollment, the trial was approved by the local ethics committee (reg. no. H-17002847), the Danish data protection agency, and the Danish Medicines Agency. The trial was registered at ClinicalTrials.gov on March 28, 2017 (NCT03125941) and EudraCT on January 27, 2017 (2017-000227-27) and was monitored by the Good Clinical Practice unit at a Copenhagen University Hospital (Copenhagen, Denmark; Principal Investigator: Kristin Julia Steinthorsdottir, M.D.).

This trial was a single-center, prospective, randomized, double-blind study with a superiority design. Participants were randomized 1:1 in parallel groups by block randomization. A blocked randomization list was computer generated by an independent physician (Pelle Baggesgaard Petersen, M.D., Surgical Pathophysiology Unit, Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark) not otherwise involved in the trial, using Sealed Envelope Ltd 2017.[17] Block sizes (2, 4, 6, 8) randomly varied and were unknown to study personnel. The allocation sequence with intervention details (24 mg or 8 mg dexamethasone) was concealed in consecutively numbered (1 to 130), opaque envelopes by two other investigators not otherwise involved in the trial. Before sealing, 20% of the envelopes were randomly controlled by Dr. Petersen. The allocation sequence was stored by Dr. Petersen.

From March 2017 to April 2018, all patients undergoing unilateral mastectomy at Copenhagen University Hospital, Rigshospitalet, Denmark were consecutively screened for inclusion. Patients considered were 18 yr of age or older, able to understand Danish or English, and able to provide informed oral and written consent. Exclusion criteria were simultaneous contralateral procedure, breast conserving surgery, daily/current use of glucocorticoids or immunosuppressant medication, insulin-dependent diabetes, pregnancy or lactation, or allergies to any of the trial drugs.

Trial personnel consisted of the principal investigator (Dr. Steinthorsdottir), a project nurse, and a project medical student. All patient enrollment and data collection were performed by one of the three. Participants, all healthcare providers, trial personnel, data monitoring committee, principal investigator, and outcome adjudicators were blinded throughout the study. After trial completion, the principal investigator received the allocation sequence without intervention revealed. The intervention allocation was revealed after performing statistical analysis and drafting the paper, including comments from all authors.

Patients were informed about the trial in relation to the preoperative appointment. Enrolled participants were randomized and assigned to consecutive numbers (1 to 130) at the time of enrollment. On the morning of surgery, nurses not otherwise involved in the trial opened the sealed envelope and prepared the trial drug. The 24 mg group received a single dose of 24 mg dexamethasone IV (Dexamethasone sodium phosphate, Krka, Novo mesto, Slovenia; 6 ml). The 8 mg group received a single dose of 8 mg dexamethasone (2 ml) with isotonic saline (4 ml) IV. The trial drug was contained in a syringe with 6 ml solution, transparent and identical in appearance regardless of dose, labeled with patient identification, and handed to trial personnel together with the resealed and signed envelopes. Trial personnel or an anesthesia nurse (not otherwise involved in the trial) administered the trial drug immediately after anesthesia induction, between 30 and 15 min before surgery.

Participants in the trial followed standard procedures. On the morning of surgery, patients arrived at the hospital and received acetaminophen 1 g, 1 to 2 h before surgery. Per protocol, anesthesia was induced with propofol 2 mg/kg IV and a total dose of fentanyl 0.25 mg and maintained as total intravenous anesthesia with propofol (5 mg · kg^{-1} · h^{-1}) and remifentanil (25 µg · kg^{-1} · h^{-1}). However, dosage could vary depending on indication and decision by the responsible anesthetist. Data on accurate dosage were collected. The airway was handled with a laryngeal mask, or in case of obesity or reflux an endotracheal tube. Intraoperative fluid therapy was standardized with Ringers lactate, 25 to 30 ml/kg. Ondansetron 4 mg IV was administered 20 to 30 min before the end of surgery. Intraoperative anesthesia was primarily handled by board-certified anesthetic nurses. Local infiltration analgesia at the surgical site (wound infiltration) was performed intraoperatively with 20 ml bupivacaine 2.5 mg/ml by the surgeon. Surgery was mastectomy with or without axillary dissection (sentinel node or axillary dissection level I + II). No drains were used.

After extubation patients were observed and assessed by the anesthetic nurse in the operating room at least 15 min according to a standardized discharge criterion scoring system (Danish Society of Anesthesiology and Intensive Care

Medicine [DASAIM] score, a modified version of the Aldrete discharge score[18]. The score consists of six modalities (sedation, oxygen saturation, blood pressure, heart rate, pain [at rest], and nausea), with a score of 0 to 3 in each modality/criterion. Patients are considered dischargeable to the ward when the score sum of all criteria is four or less and no single score is above one, on two consecutive assessments greater than or equal to 15 min apart (appendix 1). Otherwise, patients should be observed in the PACU or discharged to the ward after consultation with an anesthesiologist.

Postoperative analgesics were optional and consisted of acetaminophen 1 g up to four times daily and ibuprofen 400 mg up to three times daily, from the evening of surgery up to and including the fifth postoperative day. Opioids were only given in the hospital, on request based on moderate or severe pain.

Patients were discharged to their own home on the day of surgery, unless having any complications, older than 80 yr of age, or living alone/unaccompanied by an adult the first night. After discharge, patients were followed up in an outpatient clinic 5 to 7 days postoperatively or on demand, and seroma drainage was performed as transcutaneous aspiration when the fluid collection was estimated to be greater than 50 ml. The former protocol for the outpatient program, forming the basis for our protocol has previously been described.[16]

Involved healthcare providers and trial personnel were informed and instructed about the trial, standard procedures, and the importance of following protocol, before and during the trial, but only the intervention was different from normal procedures. There were no changes to our methods during the trial.

The primary endpoint was the number of patients meeting criteria for postoperative transfer to the PACU according to the DASAIM score. Secondary endpoints were the effects on the various modalities in the discharge criterion score system, in the operating room (at extubation and discharge), and upon arrival to the ward. Sedation was evaluated by nurses and assigned a score from 0 (fully awake) to 3 (sleeping, cannot be aroused). Oxygen saturation, systolic blood pressure, and heart rate were measured continuously (oxygen saturation and heart rate) or every 5 min (systolic blood pressure), and the exact values were recorded in the patient chart. Study personnel assigned a score to each modality according to the criteria listed in appendix 1.

Pain (at rest) was evaluated on a numeric rating scale by the patient, assigning pain a number between 0 and 10. Study personnel assigned a score according to the criteria listed in appendix 1, were numeric rating scale $0 = 0$ (no pain), $0 <$ numeric rating scale $\leq 3 = 1$ (light pain), $3 <$ numeric rating scale $< 7 = 2$ (moderate pain), numeric rating scale $\geq 7 = 3$ (severe pain). If patients were not able to assign a number (e.g., because of sedation/doubt), it was accepted with a verbal rating scale (no/light/moderate/severe pain).

Nausea was evaluated by patients and assigned a score from 0 (no nausea) to 3 (severe nausea or vomiting). The

effect on length of stay (hospital and PACU), need for seroma drainage, readmission the first 30 days, wound infections, and secondary transfers from ward to the PACU, were also evaluated.

Tertiary Outcome

Self-reported pain and nausea, analgesic- and antiemetic requirements, quality of sleep, presence of fatigue, restlessness, and sadness were investigated by a questionnaire. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Rigshospitalet.[19] Baseline data were collected from patient records. Pain, nausea, and sedation were assessed at extubation and every 15 min until and at transfer from the operating room, and at arrival to the PACU and the ward.

The primary endpoint was assessed by calculating the modified standardized discharge criterion score upon transfer from the operating room. Patients could be discharged to the ward when the total discharge score was at or below 4 and no single score was greater than 1.

Acknowledging that the standardized discharge criteria do not cover all complications that may be considered relevant for PACU referral, the actual transfer (ward or PACU) was also registered. The standardized discharge criterion score was assessed upon arrival at the ward. Length of stay (hospital) was measured as time (hours and minutes) from start of the procedure until discharge from the ward. Length of stay (PACU) was measured as time from arrival to PACU until the patient was deemed ready to transfer to the ward (as the actual transfer time depended on transport, etc.). The occurrence of seroma requiring drainage was recorded the first 14 postoperative days and was individually based on symptoms from patients; no measurement of seroma volume was registered. Readmissions for any reason, except planned procedures or oncologic admissions, were collected from patient records for 30 days.

Side-effects or complications (any) were registered during hospital stay and up to 60 h postoperatively. Adverse events/serious adverse events were defined according to the International Conference on Harmonisation guideline for Good Clinical Practice. Patients received a questionnaire to fill out on days 0 to 4. The elements of the questionnaire were:

- pain on average and at worst on the 11-point numeric rating scale (0 no pain, and 10 worst pain imaginable)
- nausea on average and at worst on the four-point numeric scale (0, none; 1, slight; 2, moderate; 3, severe) and vomiting (if any)
- use of analgesics
- feelings of sadness, restlessness or fatigue (yes/no)
- quality of sleep (good, difficulty falling asleep, frequent awakenings, no sleep)

There were no changes to trial outcomes after the trial commenced.

Sample Size

After modification of our enhanced recovery after surgery protocol introducing high-dose glucocorticoids (125 mg methylprednisolone, equivalent to 24 mg dexamethasone), we observed a 30% to 10% decrease in PACU referral after mastectomy. To test the isolated effect of the increased glucocorticoid dosage in a well-implemented enhanced recovery after surgery protocol, we chose to compare 24 *versus* 8 mg dexamethasone. Considering the observed 20% absolute (66% relative) reduction in need for PACU transfer clinically relevant, a sample size of 130 patients (65 in each group) was calculated (http://www.sealedenvelope.com; accessed February 28, 2017) with a two-sided 5% significance level, a power of 80%, and an anticipated 10% exclusion rate.

Statistical Analysis

Categorical data are presented as numbers with percentages, and tests for significant differences between the groups were assessed with χ^2 test. Continuous data are presented as mean ± SD or as median with interquartile range or range and assessed for normal distribution with the Kolmogorov-Smirnov/Shapiro-Wilk test. Tests for significant differences between groups were performed with an independent-samples *t* test or Mann–Whitney *U* test when appropriate. The primary outcome was evaluated using χ^2 test, and the different modalities in the discharge criterion system and length of stay (secondary outcome) were evaluated using the independent-samples Mann–Whitney *U* test. Need for seroma drainage, readmissions, and wound infections were evaluated using χ^2 test. To investigate for a linear trend between the extent of lymph node dissection and proportion of patients with a seroma, a Cochran-Armitage test of trend was performed.

All available data were used. For the primary outcome, outcomes from the excluded patients were analyzed as observed (transfer to PACU). Missing data otherwise were assumed to be missing at random or missing completely at random and were ignored by pairwise deletion (no imputation). Data from the questionnaire on postoperative nausea and vomiting and sleep were dichotomized into categories, postoperative nausea and vomiting/no postoperative nausea and vomiting and sleep problems/no sleep problems. A two-sided 5% significance level was chosen for the primary and secondary outcomes. To adjust for multiple comparisons in the tertiary outcome (questionnaire, 40 tests [eight tests repeated on five days]), we chose a Bonferroni corrected significance level of 0.125%.

Data analyses were conducted using SPSS for Windows, version 22 (IBM Corp., USA). Dr. Steinthorsdottir conducted all analyses, which were evaluated by Dr. Kvanner Aasvang.

Results

Two hundred twenty-six patients were assessed for eligibility, and 130 were included and randomized. Three patients were excluded after allocation but before receiving the intervention (postrandomization exclusion). This was a result of the decision to change the procedure (one immediate reconstruction, one bilateral mastectomy, and one breast conserving surgery) after randomization. All randomized patients were analyzed for the primary outcome according to the intention-to-treat approach. All patients receiving intervention were analyzed for secondary outcomes according to the per-protocol approach (fig. 1). One hundred eight patients (83%) returned the questionnaire. The missing questionnaires were equally distributed in the two groups (24 mg: n = 9 [7%], 8 mg: n = 13 [10%]). There were no differences between baseline pre- and perioperative patient characteristics (tables 1 and 2).

There was no statistically significant difference between groups in number of patients meeting criteria for transfer to PACU according to the standardized discharge score, 46 (35%) in total, with 23 (35%) in both groups (odds ratio, 1.00 [95% CI, 0.49 to 2.05]), a difference of 0.0% (95% CI, −16.4 to 16.4%), P > 0.999 (primary outcome). There was no statistically significant difference between groups in patients actually transferred to PACU, n = 24 (18%) in total, n = 12 (18%) in both groups (odds ratio, 1.00 [95% CI, 0.41 to 2.43]), a difference of 0.0% (95% CI, −13.3 to 13.3%), P > 0.999. Reasons for transfer were primarily pain (table 3).

There was no significant difference between groups in the standardized discharge total or subscores in the operating room or upon arrival at the ward, except significantly higher pain scores in the 24 mg group at extubation (fig. 2; appendix 2). Only 12 patients (9%) experienced postoperative nausea and vomiting at any time during hospital stay, n = 6 in each group, P < 0.999. Of these only three patients (2%) experienced moderate postoperative nausea and vomiting and no patients experienced severe postoperative nausea and vomiting. Most patients experienced no or only light pain at transfer from the operating room (n = 84, 65%) or upon arrival at the ward (n = 82, 63%). However, pain was the most frequent single score above one, with 37 patients (29%) experiencing moderate pain and six patients (5%) experiencing severe pain at transfer from the operating room (fig. 3). Median pain scores were 0 in both groups at extubation (interquartile range 0 in both groups, range 0 to 4 in the 24 mg group and 0 to 2 in the 8 mg group; P = 0.018), 0.5 (25th, 75th percentiles: 0, 3) in the 24 mg group and 0 (25th, 75th percentiles: 0, 3) in the 8 mg group at transfer from the operating room (P = 0.034), and 2 (25th, 75th percentiles: 1, 3) in the 24 mg group and 1 (25th, 75th percentiles: 0, 3) in the 8 mg group upon arrival at the ward (P = 0.097).

Length of stay (hospital) for all patients was median 10.6 h (interquartile range, 7.8 to 23.7 h), median 11 h (interquartile range, 8.1 to 23.5 h) in the 24 mg group, median 9.2 h (interquartile range, 7.4 to 24.4 h) in the 8 mg group (P = 0.217). PACU length of stay was median 1.5 h (interquartile range, 1.4 to 2.1 h), median 1.5 h (interquartile range, 1.4 to 1.6 h) in the 24 mg group *versus* median 2.0 h (interquartile range, 1.4 to 2.4 h) in the 8 mg group, P = 0.350.
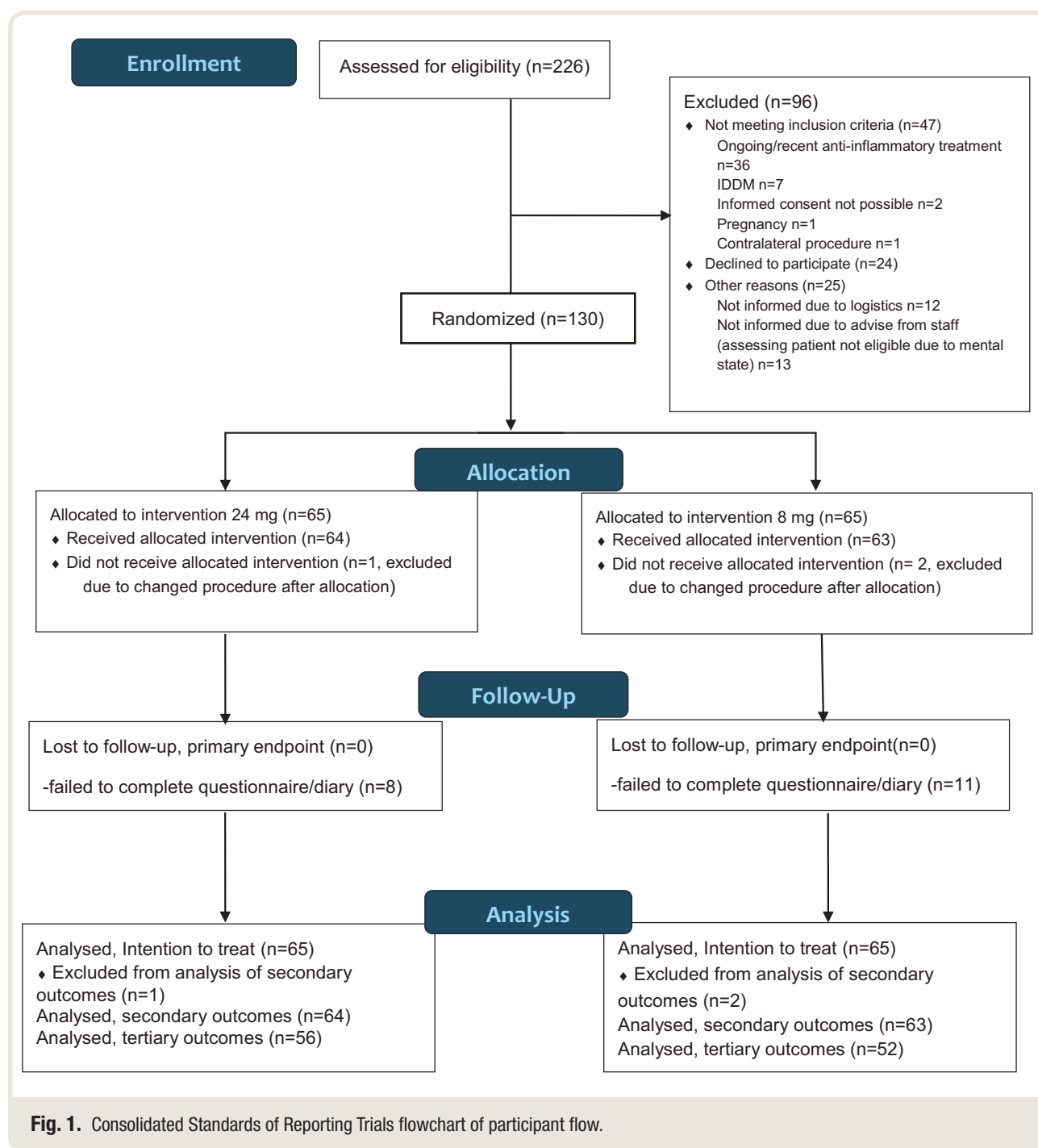
Enrollment

Assessed for eligibility (n=226)

Excluded (n=96)
- Not meeting inclusion criteria (n=47)
  Ongoing/recent anti-inflammatory treatment n=36
  IDDM n=7
  Informed consent not possible n=2
  Pregnancy n=1
  Contralateral procedure n=1
- Declined to participate (n=24)
- Other reasons (n=25)
  Not informed due to logistics n=12
  Not informed due to advise from staff (assessing patient not eligible due to mental state) n=13

Randomized (n=130)

Allocation

Allocated to intervention 24 mg (n=65)
- Received allocated intervention (n=64)
- Did not receive allocated intervention (n=1, excluded due to changed procedure after allocation)

Allocated to intervention 8 mg (n=65)
- Received allocated intervention (n=63)
- Did not receive allocated intervention (n= 2, excluded due to changed procedure after allocation)

Follow-Up

Lost to follow-up, primary endpoint (n=0)

-failed to complete questionnaire/diary (n=8)

Lost to follow-up, primary endpoint(n=0)

-failed to complete questionnaire/diary (n=11)

Analysis

Analysed, Intention to treat (n=65)
- Excluded from analysis of secondary outcomes (n=1)
Analysed, secondary outcomes (n=64)
Analysed, tertiary outcomes (n=56)

Analysed, Intention to treat (n=65)
- Excluded from analysis of secondary outcomes (n=2)
Analysed, secondary outcomes (n=63)
Analysed, tertiary outcomes (n=52)

Fig. 1. Consolidated Standards of Reporting Trials flowchart of participant flow.

There was no difference in readmissions (24 mg group: n = 4; 8 mg group: n = 4; odds ratio, 1.02 [95% CI, 0.243 to 4.3]), a difference of 0.1% (95% CI, −0.084 to 0.086), and there were no secondary transfers from the ward to the PACU (n = 0). There were statistically significantly more patients requiring seroma drainage in the 24 mg group; n = 60 (94%) *versus* n = 51 (81%) in the 8 mg group (odds ratio, 3.53 [95% CI, 1.07 to 11.6]), $P = 0.030$, a difference of 12.8% (95% CI, 1.43 to 24.2%), $P = 0.027$. We tested whether there was a linear trend between extent of lymph node dissection and the proportion of patients with seroma. The extent of lymph node dissection was none (n = 18), sentinel node (n = 88), and full axillary dissection (n = 21), and the proportion of patients with seroma was 0.94, 0.84, and 0.95, respectively, a nonstatistically significant trend, $P = 0.855$. There were no statistically significant differences between groups in the incidence of wound infection (the 24 mg group: n = 3; the 8 mg group: n = 1; odds ratio, 0.33

Steinthorsdottir *et al.*

Table 1. Demographic Characteristics of Patients Receiving 24 mg or 8 mg Dexamethasone for Mastectomy

Patient Characteristics	24 mg (n = 65)	8 mg (n = 65)	Total (n = 130)
Age , yr	63 (24–85)	66 (28–87)	65 (24–87)
Sex, female	65 (100%)	63 (97%)	128 (98%)
BMI, kg/m^2	26 ± 5	25 ± 5	25 ± 5
Disease (breast cancer)	62 (95%)	64 (98%)	126 (97%)
Smoking*			
Never	43 (66%)	35 (55%)	78 (60%)
Former	12 (18%)	13 (20%)	25 (19%)
Present	10 (15%)	16 (25%)	42 (33%)
Alcohol†			
Nothing	23 (35%)	19 (30%)	42 (33%)
Within national guidelines‡	34 (52%)	36 (56%)	70 (54%)
Above national guidelines‡	8 (12%)	9 (14%)	17 (13%)
Comorbidities			
None	29 (45%)	23 (35%)	52 (40%)
Hypertension	23 (35%)	19 (29%)	42 (32%)
Cardiac disease	2 (3%)	3 (5%)	5 (4%)
Chronic obstructive lung disease	3 (5%)	5 (8%)	8 (6%)
Atrial fibrillation	4 (6%)	1 (2%)	5 (4%)
Other	22 (34%)	31 (48%)	53 (41%)

Values are mean ± SD or (range) and numbers (percentages).

*Missing data for one patient.†Missing data for one patient (not the same patient as *). ‡National guidelines (Denmark): seven units per week (females), 14 units per week (males).

[95% CI, 0.03 to 3.24]), a difference of 3.1% (95% CI, −2.3 to 9.2%), P = 0.315. All wound infections were superficial and successfully treated with oral antibiotics.

Results from the questionnaire (questionnaire post-operative day 0 to 4; on pain, nausea, analgesic and anti-emetic requirements, quality of sleep, and mental health) are described in appendix 3. Corrected for multiple

Table 2. Perioperative Characteristics of Patients Receiving 24 mg or 8 mg Dexamethasone for Mastectomy

Variable	24 mg (n = 65)	8 mg (n = 65)	P Value
Anesthesia used			
Propofol, mg · kg^{-1} · h^{-1}	4 ± 1	4 ± 1	0.767
Remifentanil, µg · kg^{-1} · h^{-1}	31 ± 9	30 ± 6	0.459
Morphine equivalent (excluding remifentanil) administered during surgery, mg	26 ± 6	25 ± 6	0.141
Deviation from standard protocol	8 (13%)	8 (13%)	0.973
Reoperation (previous BCS)	12 (19%)	20 (31%)	0.103
Lymph node dissection			0.801
Axillary	10 (15%)	12 (18%)	
Sentinel node	47 (72%)	43 (66%)	
None	8 (12%)	10 (15%)	
Duration of surgery, h	2.03 ± 0.55	1.78 ± 0.42	0.004
Bleeding, ml	0 [0, 94]	50 [0, 100]	0.476

Values are mean ± SD, median [25th,75th] and numbers (percentages). BCS, breast conserving surgery.

Table 3. Reasons for Transfer to the Postanesthesia Care Unit after Mastectomy in Patients Receiving 24 mg or 8 mg Dexamethasone

Reason, n	24 mg	8 mg
Pain	5	5
ASA class 3	2	2
Sedation/confusion	2*	1
Respiratory complications	2†	0
Blood pressure monitoring	0	2
Hyponatremia	1	0
Unknown/other	0	2‡

ASA, American Society of Anesthesiologists classification.

*One patient transferred because of both sedation and low oxygen saturation. †One patient had preoperative pneumonia. ‡Indications not specified.

comparisons, there were no significant differences between groups. There was no significant difference between patients requiring rescue analgesics or antiemetics at any time (appendix 4).

Adverse Events

There were 24 adverse events in a total of 21 patients (n = 11 [9 patients] in the 24 mg group, n = 13 [12 patients] in the 8 mg group). Of these, eight were considered serious adverse events (n = 3 in the 24 mg group, n = 5 in the 8 mg group), but none was assessed to be related to the study drug. There was no significant difference between the groups (appendix 5).

Discussion

In this single-center randomized trial, 24 mg dexamethasone did not result in fewer patients transferred to the PACU, or less pain, nausea, or other organ-specific complications after mastectomy, compared with 8 mg dexamethasone. We found more patients with seromas requiring drainage in the 24 mg group, and although our trial was not designed primarily for this outcome and we cannot rule out type I error, this may contribute to a growing literature of prevention of postoperative seroma.[20–22]

Of the modalities in the discharge score, the most frequent complication was moderate/severe pain, and if high-dose glucocorticoids should have influenced postoperative transfers in this population, it would have been a consequence of a superior analgesic effect in this population. However, although pain was the most frequent complication, intensity was low with a maximum median of numeric rating scale 2. The only pain scores with a statistical difference was pain immediately after extubation and at transfer from the operating room (in favor of the 8 mg group), and we do not consider this clinically relevant as median pain scores were zero in both groups at extubation and 0.5 and 0 in the 24 mg and 8 mg group, respectively, at transfer from
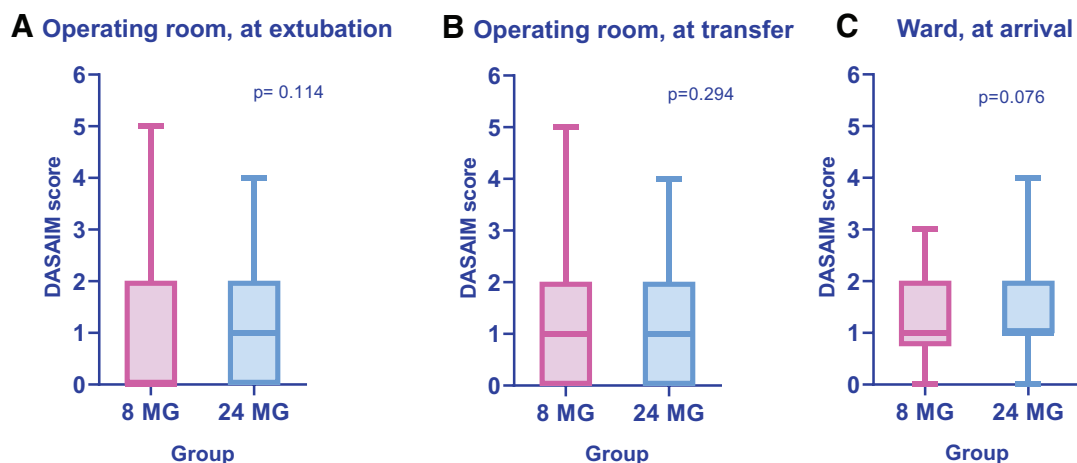
Fig. 2. Box plots of postoperative Danish Society of Anesthesiology and Intensive Care Medicine (DASAIM) score in the operating room, at extubation and transfer, and at arrival to the ward. *Boxes* indicate 25th, 75th percentiles; *lines* indicate median; *whiskers* indicate range (minimum to maximum).

the operating room. The analgesic effects of preoperatively administered glucocorticoids have previously been shown in a number of surgical procedures, with a meta-analysis concluding that 8 mg of dexamethasone was associated with small but statistically significant reductions in postoperative pain and opioid consumption in many, but not all procedures.[23] The mechanisms of postoperative pain are complex, but the physiologic mechanisms of analgesic effects of preoperative glucocorticoids can in part be explained by the reduction in inflammation.[24] Differences in the magnitude of the inflammatory response to different surgical procedures may explain the procedure-specific findings and warrant further procedure specific studies on the effects of preoperative glucocorticoids.

Placebo-controlled studies on 8 mg dexamethasone in breast cancer surgery have shown significant reductions in pain scores, use of rescue analgesics, and reduced nausea and vomiting up to 24 h after mastectomy,[13–15] but the effect of even higher doses of glucocorticoids on further reduction in complications had not been established before our study. Despite including only patients undergoing mastectomy, with 17% having full axillary dissection, pain scores in our study were lower than those found in the intervention groups of the previous randomized controlled trials on 8 mg glucocorticoid *versus* placebo in breast cancer surgery (including both mastectomy and breast conserving surgery),[13–15] where up to 74% of patients in the betamethasone group had a pain score of numeric rating scale at or above 3 at 0 to 3 h
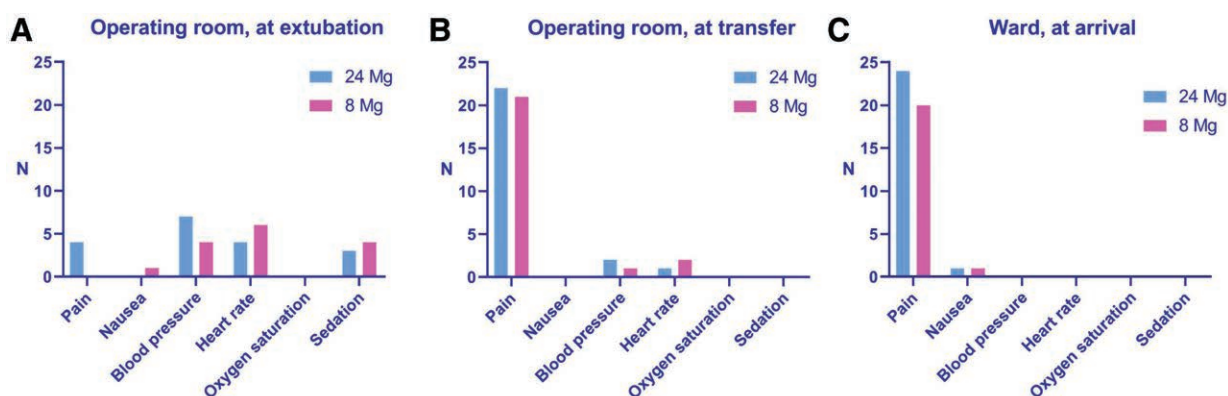

Fig. 3. Histogram of complications comprised in Danish Society of Anesthesiology and Intensive Care Medicine score, single score greater than 1 at the operating room at extubation and transfer, and at arrival to the ward.

postoperatively,[15] compared with 34% in total in our study. Surgical and anesthetic practices vary between the studies, and of note, none of them administered local infiltration analgesia, an easy and inexpensive addition to postoperative analgesic treatment,[25] and in only one study[15] patients received premedication (acetaminophen), shown to effectively reduce postoperative pain and patient reported quality of recovery.[26]

In recent years, several studies on various regional analgesic blocks have been reported to show positive effects on postoperative pain after especially major breast surgery.[27–29] However, the effects of these more invasive techniques remain untested in a population receiving a standardized multimodal, opioid-sparing analgesic regime.[29] A randomized trial testing pectoral bloc on pain and quality of life found no differences in quality of life and no clinically significant effect on pain after breast cancer surgery.[30] In a population of patients undergoing simple mastectomy, the addition of invasive regional blocks with the inherent risk of rare but serious complications may not be warranted. However, nerve blocks may be appropriate in specific populations (patients with chronic pain, preoperative opioid use) but the limited 6 to 14 h duration should be considered.

Pain was assessed using a numeric rating scale (0 to 10) because it is easy to understand and use, and it does not require patients to be able to see (as with the visual analog scale), which can be a problem in the operating room (lack of eyeglasses, sedation, etc.).[31] However, there are only few validation studies of its use in acute pain, and studies suggest that the score often indicates greater pain than that actually experienced by the patient.[32,33] This also seems to be the case in this study, where only half of patients with moderate or severe postoperative pain received rescue analgesics. Again, this illustrates a potential problem with the discharge criteria, as patients with moderate or severe pain scores accordingly should be transferred to the PACU, but often are transferred directly to, and are handled sufficiently at, the ward. In otherwise healthy patients, with uncomplicated breast cancer surgery, pain alone may not be indicative of need for observation at the PACU.

The total number of wound infections (3%) was low compared with previous reported incidence (5% to 19%),[34–36] and although there were numerically more patients in the 24 mg group with a wound infection compared with the 8 mg group (without significant differences), we do not consider this a safety issue.

Limitations

This study has several limitations. The study design included broad inclusion and few exclusion criteria and most procedures followed standard care, ensuring high internal validity. But because our primary outcome was based on discharge criteria, which are supplemented by clinical evaluations of the practitioners, we found a discrepancy between the number of patients meeting criteria on transfer to PACU according to the discharge criteria and the actual number of patients transferred. The actual number of patients

transferred (18%) was lower than the expected 30%, but according to the discharge criteria, the number of patients requiring transfer to PACU was 35%. Our power calculation was based on observations from a prospective quality assurance assessment, and the results may have been influenced by a systemic (Hawthorne) effect, and thereby optimistic. However, there was no signal of a difference in the primary outcome (and the number of patients meeting criteria was similar to the expected number), and for the primary outcome we do not believe that the study was underpowered.

We could have formally trained all involved personnel to avoid the discrepancy found in theoretic and actual transfers, but then our internal validity would have decreased. Because we did not observe any complications in the ward requiring subsequent transfer to the PACU, the evaluations of the practitioners as a supplement to the discharge criteria seem valuable and a re-evaluation of the discharge criteria to align with the current standard of care and specific competencies at the ward might be just.

Although the dose for simple postoperative nausea and vomiting prophylaxis is usually 4 mg dexamethasone, we based our choice of 8 mg dexamethasone for the active control group upon the available procedure-specific evidence where this is the investigated dosage, and to our knowledge no studies of 4 mg *versus* 8 mg for mastectomy exists. Thus, we cannot rule out that we might have found an effect of 24 mg dexamethasone when compared with 4 mg (or placebo), but meta-analyses on postoperative nausea and vomiting after various procedures have not shown dose-dependency between 4(–5) mg and 8(–10) mg dexamethasone.[2,23]

Three patients were excluded after randomization because of a change in procedure after enrollment. This could have been avoided if we had waited with the randomization to the day of surgery. We included the patients in the analysis for primary outcome, but not secondary outcomes, because this kind of exclusion should not introduce bias.[37] The questionnaire used in this trial was not validated, and although the outcomes from the questionnaire were tertiary and exploratory, we could have considered using and expanding a validated recovery after surgery score, such as the Quality of Recovery-15[38] or Quality of Recovery-40.[39]

Conclusion

An increase in preoperative dexamethasone from 8 to 24 mg did not show an effect on the primary outcome of early recovery after mastectomy. Overall, a simple analgesic and antiemetic regime resulted in low levels of postoperative pain and practically no occurrence of postoperative nausea and vomiting. Length of stay was short both in the PACU and in total. We did observe a higher proportion of patients with a seroma in the 24 mg group, and based on that no outcomes were improved and we do not recommend 24 mg of dexamethasone for mastectomy.

Acknowledgments

Research Support

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Steinthorsdottir: Rigshospitalet dep. 2043, Blegdamsvej 9, 2200 Copenhagen, Denmark. kste0050@regionh.dk. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. DREAMS Trial Collaborators and West Midlands Research Collaborative: Dexamethasone versus standard treatment for postoperative nausea and vomiting in gastrointestinal surgery: Randomised controlled trial (DREAMS Trial). BMJ 2017; 357:j1455

2. Oliveira GS De, Castro-Alves LJS, Ahmad S, Kendall MC, McCarthy RJ: Dexamethasone to prevent postoperative nausea and vomiting. Anesth Analg 2013; 116:58–74

3. Oliveira GS De, Almeida MD, Benzon HT, McCarthy RJ: Perioperative single dose systemic dexamethasone for postoperative pain: A meta-analysis of randomized controlled trials. ANESTHESIOLOGY 2011; 115:575–88

4. la Motte L de, Kehlet H, Vogt K, Nielsen CH, Groenvall JB, Nielsen HB, Andersen A, Schroeder T V, Lönn L: Preoperative methylprednisolone enhances recovery after endovascular aortic repair: A randomized, double-blind, placebo-controlled clinical trial. Ann Surg 2014; 260:540–8

5. Srinivasa S, Kahokehr AA, Yu TC, Hill AG: Preoperative glucocorticoid use in major abdominal surgery: Systematic review and meta-analysis of randomized trials. Ann Surg 2011; 254:183–91

6. Jørgensen CC, Pitter FT, Kehlet H; Lundbeck Foundation Center for Fast-track Hip and Knee Replacement Collaborative Group: Safety aspects of preoperative high-dose glucocorticoid in primary total knee replacement. Br J Anaesth 2017; 119:267–75

7. Kehlet H, Lindberg-Larsen V: High-dose glucocorticoid before hip and knee arthroplasty: To use or not to use-that's the question. Acta Orthop 2018; 89:477–9

8. Toner AJ, Ganeshanathan V, Chan MT, Ho KM, Corcoran TB: Safety of perioperative glucocorticoids in elective noncardiac surgery: A systematic review and meta-analysis. ANESTHESIOLOGY 2017; 126:234–48

9. Sauerland S, Nagelschmidt M, Mallmann P, Neugebauer EA: Risks and benefits of preoperative high dose methylprednisolone in surgical patients: A systematic review. Drug Saf 2000; 23:449–61

10. Steinthorsdottir KJ, Kehlet H, Aasvang EK: Surgical stress response and the potential role of preoperative glucocorticoids on post-anesthesia care unit recovery. Minerva Anestesiol 2017; 83:1324–31

11. Gärtner R, Kroman N, Callesen T, Kehlet H: Multimodal prevention of pain, nausea and vomiting after breast cancer surgery. Minerva Anestesiol 2010; 76:805–13

12. Chiu C, Aleshi P, Esserman LJ, Inglis-Arkell C, Yap E, Whitlock EL, Harbell MW: Improved analgesia and reduced post-operative nausea and vomiting after implementation of an enhanced recovery after surgery (ERAS) pathway for total mastectomy. BMC Anesthesiol 2018; 18:41

13. Gómez-Hernández J, Orozco-Alatorre AL, Domínguez-Contreras M, Oceguera-Villanueva A, Gómez-Romo S, Alvarez Villaseñor AS, Fuentes-Orozco C, González-Ojeda A: Preoperative dexamethasone reduces postoperative pain, nausea and vomiting following mastectomy for breast cancer. BMC Cancer 2010; 10:692

14. Cortés-Flores AOO, Jiménez-Tornero J, Morgan-Villela G, Delgado-Gómez M, Zuloaga-Fernández del Valle CJ, García-Rentería J, Rendón-Félix J, Fuentes-Orozco C, Macías-Amezcua MDD, Ambriz-González G, Alvarez-Villaseñor ASS, Urias-Valdez D, Chavez-Tostado M, Contreras-Hernández GI, González-Ojeda A: Effects of preoperative dexamethasone on postoperative pain, nausea, vomiting and respiratory function in women undergoing conservative breast surgery

for cancer: Results of a controlled clinical trial. Eur J Cancer Care (Engl) 2018; 27:e12686

15. Olanders KJ, Lundgren GA, Johansson AM: Betamethasone in prevention of postoperative nausea and vomiting following breast surgery. J Clin Anesth 2014; 26:461–5

16. Duriaud HM, Kroman N, Kehlet H: Feasibility and safety of outpatient breast cancer surgery. Dan Med J 2018; 65:A5458

17. Sealed Envelope LTD, 2017. Available at: https://www.sealedenvelope.com/simple-randomiser/v1/lists. Accessed January 1, 2020.

18. Aldrete JA, Kroulik D: A postanesthetic recovery score. Anesth Analg 1970; 49:924–34

19. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42:377–81

20. Okholm M, Axelsson CK: No effect of steroids on seroma formation after mastectomy. Dan Med Bull 2011; 58:A4241

21. Qvamme G, Axelsson CK, Lanng C, Mortensen M, Wegeberg B, Okholm M, Arpi MR, Szecsi PB: Randomized clinical trial of prevention of seroma formation after mastectomy by local methylprednisolone injection. Br J Surg 2015; 102:1195–203

22. Agrawal A, Ayantunde AA, Cheung KL: Concepts of seroma formation and prevention in breast cancer surgery. ANZ J Surg 2006; 76:1088–95

23. Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS: Impact of perioperative dexamethasone on postoperative analgesia and side-effects: Systematic review and meta-analysis. Br J Anaesth 2013; 110:191–200

24. Holte K, Kehlet H: Perioperative single-dose glucocorticoid administration: Pathophysiologic effects and clinical implications. J Am Coll Surg 2002; 195:694–712

25. Tam KW, Chen SY, Huang TW, Lin CC, Su CM, Li CL, Ho YS, Wang WY, Wu CH: Effect of wound infiltration with ropivacaine or bupivacaine analgesia in breast cancer surgery: A meta-analysis of randomized controlled trials. Int J Surg 2015; 22:79–85

26. Oliveira GS De, Rodes ME, Bialek J, Kendall MC, McCarthy RJ: Single dose systemic acetaminophen to improve patient reported quality of recovery after ambulatory segmental mastectomy: A prospective, randomized, double-blinded, placebo controlled, clinical trial. Breast J 2018; 24:240–4

27. Versyck B, van Geffen GJ, Van Houwe P: Prospective double blind randomized placebo-controlled clinical trial of the pectoral nerves (Pecs) block type II. J Clin Anesth 2017; 40:46–50

28. Kulhari S, Bharti N, Bala I, Arora S, Singh G: Efficacy of pectoral nerve block *versus* thoracic paravertebral block for postoperative analgesia after radical mastectomy: A randomized controlled trial. Br J Anaesth 2016; 117:382–6

29. Jones MR, Hadley GR, Kaye AD, Lirk P, Urman RD: Paravertebral blocks for same-day breast surgery. Curr Pain Headache Rep 2017; 21:35

30. Kamiya Y, Hasegawa M, Yoshida T, Takamatsu M, Koyama Y: Impact of pectoral nerve block on postoperative pain and quality of recovery in patients undergoing breast cancer surgery: A randomised controlled trial. Eur J Anaesthesiol 2018; 35:215–23

31. Hawker GA, Mian S, Kendzerska T, French M: Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011; 63 Suppl 11:S240–52

32. Dijk JFM van, Kappen TH, Schuurmans MJ, Wijck AJM van: The relation between patients' NRS pain scores and their desire for additional opioids after surgery. Pain Pract 2015; 15:604–9

33. van Dijk JF, van Wijck AJ, Kappen TH, Peelen LM, Kalkman CJ, Schuurmans MJ: Postoperative pain assessment based on numeric ratings is not the same for patients and professionals: A cross-sectional study. Int J Nurs Stud 2012; 49:65–71

34. Fraser VJ, Nickel KB, Fox IK, Margenthaler JA, Olsen MA: The epidemiology and outcomes of breast cancer surgery. Trans Am Clin Climatol Assoc 2016; 127:46–58

35. Witt A, Yavuz D, Walchetseder C, Strohmer H, Kubista E: Preoperative core needle biopsy as an independent risk factor for wound infection after breast surgery. Obstet Gynecol 2003; 101:745–50

36. Vilar-Compte D, Rosales S, Hernandez-Mello N, Maafs E, Volkow P: Surveillance, control, and prevention of surgical site infections in breast cancer surgery: A 5-year experience. Am J Infect Control 2009; 37:674–9

37. Fergusson D, Aaron SD, Guyatt G, Hébert P: Post-randomisation exclusions: The intention to treat principle and excluding patients from analysis. BMJ 2002; 325:652–4

38. Kleif J, Waage J, Christensen KB, Gögenur I: Systematic review of the QoR-15 score, a patient- reported outcome measure measuring quality of recovery after surgery and anaesthesia. Br J Anaesth 2018; 120:28–36

39. Gornall BF, Myles PS, Smith CL, Burke JA, Leslie K, Pereira MJ, Bost JE, Kluivers KB, Nilsson UG, Tanaka Y, Forbes A: Measurement of quality of recovery using the QoR-40: A quantitative systematic review. Br J Anaesth 2013; 111:161–9

Appendix 1. Danish Society of Anesthesiology and Intensive Care Medicine (DASAIM) Score, Modified

Modifications: Pain score is numeric rating scale 0 to 10 instead of visual analogue scale 0 to 100 mm. Oxygen saturation was measured with 2 l supplementary oxygen in the operating room. Respiratory rate as category is omitted.

Modality	Score	Criteria
Sedation (nurse evaluation)	3	Sleeping, cannot be aroused
	2	Sleeping, aroused by verbal stimuli
	1	Sleeping, aroused by physical stimuli
	0	Fully awake
Oxygen saturation, %	3	< 85
	2	85–89
	1	90–93
	0	≥ 94
Blood pressure, systolic, mmHg (automatic NIBP)	3	< 80
	2	80–89 or > 220
	1	90–99
	0	100–220
Heart rate; pr. min. (automatically derived from ECG)	3	< 40 or > 130
	2	40–49 or 121–130
	1	101–120
	0	50–100
Pain (at rest), NRS 0–10 (patient evaluation)	3	Severe (NRS ≥ 7)
	2	Moderate (3 < NRS < 7)
	1	Light (0 < NRS ≤ 3)
	0	None (NRS = 0)
Nausea (patient evaluation and nurse observation)	3	Severe
	2	Moderate
	1	Light
	0	None
Total	Sum	

Patients are considered dischargeable to the ward when the score sum of all criteria is four or less and no single score is above one.
ECG, electrocardiogram; NIBP, non-invasive blood pressure; NRS, numeric rating scale.

Appendix 2. Subscores, Danish Society of Anesthesiology and Intensive Care Medicine (DASAIM) Score, Modified (see appendix 1)

Operating Room, At Extubation

Modality	24 mg (n)	8 mg (n)	P Value
Sedation (score)			0.804
Sleeping, cannot be aroused	0	0	
Sleeping, aroused by verbal stimuli	3	4	
Sleeping, aroused by physical stimuli	17	14	
Fully awake	44	45	
Oxygen saturation, %			0.713
< 85	0	0	
85–89	0	0	
90–93	4	3	
≥ 94	60	60	
Blood pressure, systolic, mmHg			0.096
< 80	2	0	
80–89 or > 220	5	4	
90–99	11	6	
100–220	46	53	
Heart rate, beats per min			0.747
< 40 or > 130	1	0	
40–49 or 121–130	3	6	
101–120	3	2	
50–100	57	55	
Pain (at rest), numeric rating scale (NRS) 0–10			0.009
Severe (NRS ≥ 7)	0	0	
Moderate (3 < NRS < 7)	4	0	
Light (0 < NRS ≤ 3)	5	3	
None (NRS = 0)	54	61	
Nausea			0.545
Severe	0	0	
Moderate	0	1	
Light	1	1	
None	62	60	

Operating Room, At Transfer

Modality	24 mg (n)	8 mg (n)	P Value
Sedation (score)			0.977
Sleeping, cannot be aroused	0	0	
Sleeping, aroused by verbal stimuli	0	0	
Sleeping, aroused by physical stimuli	6	6	
Fully awake	58	57	
Oxygen saturation, %		0	0.304
< 85	0	0	
85–89	0	3	
90–93	1	60	
≥ 94	63	60	
Blood pressure, systolic, mmHg			0.652
< 80	0	1	
80–89 or > 220	0	0	
90–99	3	1	
100–220	59	61	
Heart rate, beats per min.			0.136
< 40 or > 130	0	0	
40–49 or 121–130	0	2	
101–120	8	1	
50–100	55	60	
Pain (at rest), numeric rating scale (NRS) 0–10			0.435
Severe (NRS ≥ 7)	3	3	
Moderate (3 < NRS < 7)	19	18	
Light (0 < NRS ≤ 3)	10	4	
None (NRS = 0)	32	38	

(Continued)

Appendix 2. (Continued)

	24 mg	8 mg	
Nausea			0.676
Severe	0	0	
Moderate	0	0	
Light	3	2	
None	59	58	

Ward, At Arrival

Modality	24 mg (n)	8 mg (n)	P Value
Sedation (score)			0.321
Sleeping, cannot be aroused	0	0	
Sleeping, aroused by verbal stimuli	0	0	
Sleeping, aroused by physical stimuli	1	0	
Fully awake	63	63	
Oxygen saturation, %			0.321
< 85	0	0	
85–89	0	0	
90–93	1	0	
≥ 94	63	63	
Blood pressure, systolic, mmHg			> 0.999
< 80	0	0	
80–89 or > 220	0	0	
90–99	0	0	
100–220	64	63	
Heart rate, beats per min			0.055
< 40 or > 130	0	0	
40–49 or 121–130	0	0	
101–120	6	1	
50–100	58	62	
Pain (at rest), numeric rating scale (NRS) 0–10			0.250
Severe (NRS ≥ 7)	4	1	
Moderate (3 < NRS < 7)	20	19	
Light (0 < NRS ≤ 3)	29	26	
None (NRS = 0)	11	16	
Nausea			0.968
Severe	0	0	
Moderate	1	1	
Light	2	2	
None	61	59	

Appendix 3. Results from Questionnaire on Pain, Pain Medication, Nausea, Sadness, Restlessness, Fatigue, and Sleep Problems, Postoperative Days 0 to 4

	POD0			POD1			POD2			POD3			POD4		
	24 mg	8 mg	P Value	24 mg	8 mg	P Value	24 mg	8 mg	P Value	24 mg	8 mg	P Value	24 mg	8 mg	P Value
Pain average, NRS (25th,75th)	2 (1,4)	2 (0,4)	0.755	1 (1,2)	2 (0,3)	0.616	1 (0,2)	1 (0,3)	0.585	1 (0,1)	1 (0,2)	0.193	1 (0,1)	1 (0,2)	0.527
Pain worst, NRS (25th,75th)	3 (1,5)	3 (0,6)	0.526	2 (1,3)	2 (0,4)	0.757	2 (0,3)	2 (0,4)	0.660	1 (0,2)	1 (0,3)	0.436	1 (0,2)	1 (0,3)	0.420
Intake of analgesics (paracetamol/NSAID), n (%)	55 (98)	49 (96)	0.350	53 (95)	47 (90)	0.478	48 (86)	46 (89)	0.671	38 (68)	45 (87)	0.021	32 (46)	38 (54)	0.083
PONV, n (%)	11 (20)	6 (12)	0.248	10 (18)	6 (12)	0.356	9 (16)	6 (12)	0.496	6 (11)	7 (14)	0.661	6 (11)	7 (14)	0.661
Sadness, n (%)	18 (32)	14 (27)	0.553	13 (23)	13 (26)	0.784	18 (32)	14 (27)	0.553	20 (36)	14 (27)	0.326	12 (22)	14 (27)	0.538
Restlessness, n (%)	20 (36)	17 (33)	0.741	9 (16)	9 (16)	0.828	8 (14)	14 (27)	0.103	8 (14)	11 (21)	0.349	13 (23)	13 (25)	0.828
Fatigue, n (%)	28 (50)	26 (50)	1.000	27 (48)	11 (21.2)	0.003	17 (30)	16 (31)	0.963	17 (30)	14 (27)	0.693	15 (27)	14 (27)	0.987
Sleep problems (total)*	39	31	0.276	22	20	0.930	18	24	0.136	17	18	0.637	16	17	0.734

25th,75th, 25th and 75th percentile; NRS, numeric rating scale; NSAID, nonsteroid anti-inflammatory drug; POD, postoperative day; PONV, postoperative nausea and vomiting.

*Sleep problems comprise any of the choices; trouble falling asleep, frequent awakenings, no sleep.

Appendix 4. Ancillary Analyses: Number of Patients Requiring Opioids or Antiemetics during Hospital Stay and Morphine Equivalent Doses of Opioids Administered

	24 mg	8 mg	Odds Ratio (95% CI)	P Value
No. of patients requiring opioids (not including remifentanil), (n) and (total)				
In the operating room	10 (64)	9 (63)	1.11 (0.42 to 2.95)	0.832
In the postanesthesia care unit	5 (12)	7 (12)	0.51 (0.101 to 2.59)	0.414
Upon arrival at the ward	6 (64)	6 (63)	0.98 (0.299 to 3.23)	0.977
No. of patients requiring antiemetics (n)				
In the operating room	1 (64)	0 (63)	0.98 (0.95 to 1.02)	> 0.999
In the postanesthesia care unit	0	0		
Upon arrival at the ward	1 (64)	1 (63)	1.02 (0.06 to 16.6)	> 0.999
Morphine equivalent doses (not including remifentanil), (median, range)				
In the operating room	0 (0 to 20)	0 (0 to 23)		0.933
In the postanesthesia care unit	0 (0 to 13)	0 (0 to 43)		0.485
Upon arrival at the ward	0 (0 to 3)	0 (0 to 3)		0.429

Appendix 5. Description of Adverse and Serious Adverse Events

Adverse Events (n)	24 mg	8 mg	Total
Wound hemorrhage/hematoma	3 (SAE n = 3)	6 (SAE n = 5)	9
Respiratory event*	1	2	3
Cardiac event†	0	2	2
Rash (allergic reaction to bandage)	1	1	2
Blood glucose >10 mmol	1	0	1
Headache	1	0	1
Hyponatremia	1	0	1
Blushing	1	0	1
Restlessness	1	0	1
Wound dehiscence	1	0	1
Fainting	0	1	1
Falling	0	1	1

SAE indicates serious adverse event.

*High respiratory rate (n = 1), low oxygen saturation requiring continuous positive airway pressure (n = 1), or inhalation with bronchodilator (n = 1). †Hypertension (n = 1), atrial fibrillation (n = 1). Both patients were known with a history of hypertension/intermittent atrial fibrillation.