Title: High vs. Low Dose Dexamethasone on Complications in the Immediate Postoperative Phase after Mastectomy (DEX-MAS).

NCT number: NCT03125941

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Statistical Analysis Plan

Categorical data are presented as numbers with percentages, and tests for significant differences between the groups are assessed with $\chi_2$test. Continuous data are presented as mean (95% CI) or as median with inter-quartile range or range and assessed for normal distribution with the Kolmogorov-Smirnov/Shapiro-Wilk test. Tests for significant differences between groups are performed with an independent-samples t-test or Mann-Whitney U test when appropriate. The primary outcome is evaluated using $\chi_2$test, and the different modalities in the discharge criterion system and length of stay (secondary outcome) are evaluated using the independent-samples Mann-Whitney U test. Need for seroma drainage, readmissions and wound infections are evaluated using $\chi_2$test.

All available data are used, missing data is not imputed. Data from the questionnaire on PONV and sleep is dichotomized into categories, PONV/no PONV and sleep problems/no sleep problems. A two-sided 5% significance level is chosen for the primary and secondary outcomes. To adjust for multiple comparisons in the tertiary outcome (questionnaire, 40 tests), we chose a Bonferroni corrected significance level of 0.125%.

Data analyses were conducted using SPSS for Windows, version 22 (IBM Corp., New York, USA).

Data processing is done by the investigator, who will continue to be blinded until all results are analyzed, and the abstract is written and accepted by co-authors.

PROTOCOL

Effect of high vs low dose intravenous dexamethasone on complications in the immediate postoperative phase after mastectomy- a randomized, double-blind, controlled trial

EudraCT number: 2017-000227-27

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Appendix 1. Danish Society of Anesthesiology and Intensive Care Medicine (DASAIM)- score, modified.

Introduction

Post-surgery, patients are traditionally observed and treated in post-anesthesia care units (PACU) until they are discharged to the ward (or directly home) assessed by standardized international discharge criteria.

The research project "Why in PACU?" (Rigshospitalet, Denmark), has since the beginning of 2016 systematically collected and analyzed procedure-related complications in the recovery phase. The complications include pain, nausea/vomiting, circulatory and respiratory problems, orthostatic intolerance and cognitive disorders. Common to all the above-mentioned post-operative problems are the possible links to the inflammatory response caused by the surgical trauma.

Glucocorticoids can in this context be central for the reduction of acute postoperative organ dysfunctions, caused by the anti-inflammatory effect. In a number of different surgical procedures, single dose, pre-operative glucocorticoids have been shown to reduce post-operative nausea and vomiting (PONV), acute pain and need of opioids as well as accelerate the convalescence.

Meta-analyses also showed that single-dose administration of glucocorticoids (methylprednisolone and dexamethasone) for surgical patients is safe as opposed to long-term treatment.

Based on positive results in other procedure-specific studies, all mastectomy patients at Rigshospitalet, have received pre-operative high-dose steroids, in the form of 24 mg dexamethasone injection since mid-2015. This has resulted in a decrease in the proportion of patients who need observation in PACU from 30 % to 10 %. The reduction is primarily due to less pain, less sedation, and lower opioid administration.

Whether this is also partly due to a "systemic effect" (Hawthorn effect) as a result of increased focus on the area cannot be excluded.

Prior to creating clinical recommendations and standards, it is required that the results be tested in a randomized, controlled, clinical trial.

The study is not placebo-controlled since the positive effects of dexamethasone 8 mg on PONV have been shown in numerous trials and is already being administered to all patients at the clinic. It would therefore not be ethically correct to withdraw from this practice.

Aim

The aim of this study is to investigate the effect of a single preoperative high-dose steroid injection on complications in the immediate postoperative phase after breast cancer surgery, with removal of the breast (mastectomy). Primary outcome is the proportion patients who require transfer to the post anesthesia care unit (PACU) and the proportion that can be transferred directly to the ward. Secondary outcomes are organ specific complications in the post anesthesia phase, pain and nausea the first 5 days, seroma and wound infection the first 14 days and readmissions the first 30 days after surgery.

The investigators hypothesize that the frequency of transfer to the PACU and organ specific complications will be lower among patients receiving high dose dexamethasone. The investigators hypothesize, that there will be no difference in wound infections, seroma or readmissions.

Outcomes

Primary outcome

The number of patients meeting criteria for postoperative transfer to the post-anesthesia care unit (PACU) according to the DASAIM-score (Appendix

Secondary outcomes

- Discharge score in the operating room (according to discharge criteria, Appendix 1).
- Discharge score at arrival to the ward or PACU (according to discharge criteria, Appendix 1).
- Complications/adverse events in the ward the first 24 h or until discharge.
- Lenght of stay (PACU/Hospital)
- Pain, self-reported in patient questionnaire. Days 0-4.
- Nausea/vomiting, self-reported in patient questionnaire. Days 0-4.
- Analgetics and antiemetics,use of, self-reported in patient questionnaire. Days 0-4.
- Quality of sleep, self-reported in patient questionnaire. Days 0-4.
- Feelings of anxiety, restlessness, fatigue, self-reported in patient questionnaire. Days 0-4.
- Seroma, requiring drainage, the first 14 postoperative days

Methods

Studydesign

Randomized, double-blind, controlled intervention study. Superiority design.

Randomization

Computer generated, double-blind block randomization. Allocation ratio 1:1, block sizes (2,4,6,8) randomly vary and unknown to study personnel.

The allocation sequence with intervention details (24 mg or 8 mg dexamethasone) will be concealed in consecutively numbered (1-130), opaque envelopes by two other investigators not otherwise involved in the trial. Before sealing, 20 % of the envelopes are randomly controlled.

Intervention

A single dose of 24 mg dexamethasone iv (Dexamethasone sodium phosphate, Krka, Novo mesto, Slovenia), (6 ml), administered immediately after anesthesia induction, between 30 and 15 minutes prior to surgery.

Control

A single dose of 8 mg dexamethasone iv (2 ml) with isotonic saline (4 ml), administered immediately after anesthesia induction, between 30 and 15 minutes prior to surgery.

Concealment

The trial drug is 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 re-sealed and signed envelopes.

Blinding

Participants, all healthcare providers, trial personnel, data monitoring committee, principal investigator and outcome adjudicators will be blinded throughout the study. After trial completion, the principal investigator receives the allocation sequence without intervention revealed. The intervention allocation will be revealed after performing statistical analysis and drafting the paper, including comments from all authors.

Time schedule

Study expected to start: March 2017

Study expected to finish: August 2018

Location

Copenhagen University Hospital, Rigshospitalet, Denmark. Department of Breast Surgery and Department of Anesthesiology, Centre of Head and Orthopaedics.

Participants

Number of participants: 130, 65 in each group.

Inclusion criteria

- Planned unilateral mastectomy with or without axillary dessection
- Age 18 years or older
- Able to understand Danish or English and to provide informed oral and written consent.

Exclusion criteria

- Simultaneous contralateral procedure
- Breast conserving surgery
- Daily/current use of glucocorticoids or immunosuppressant medication
- Insulin-dependent diabetes
- Pregnancy or lactation
- Allergies to any of the trial drugs.

Procedures

Inclusion and preoperative treatment

Eligible patients are informed about the trial in relation to the pre-operative appointment.

Enrolled participants are randomized and assigned to consecutive numbers (1-130) at the time of enrollment.

On the morning of surgery, patients received acetaminophen 1 g 1-2 hours before surgery.

Anesthesia and surgery

Participants in the trial follow standard procedures. Anesthesia is induced with propofol 2 mg/kg iv and a total dose of fentanyl 0.25 mg and maintained as total intravenous anesthesia (TIVA) with propofol (5 mg/kg/h) and remifentanil (25µg/kg/h). The airway is handled with a laryngeal mask, or in case of obesity or reflux an endotracheal tube. Intraoperative fluid therapy is standardized with Ringers lactate, 25-30 ml/kg. Ondansetron 4 mg iv is administered 20-30 minutes prior to end of surgery. Local infiltration analgesia at the surgical site (wound infiltration) is performed intraoperatively with 20 ml bupivacaine 2.5 mg/ml by the surgeon. No routine use of drains.

Post-operative treatment

Analgesics: By request, acetaminophen 1 g up to 4 times daily, ibuprofen 400 mg up to three times daily, from the evening of surgery up to and including the fifth postoperative day.. Opioids are only given in hospital, on request based on moderate or severe pain.
Antiemetics: By request, or if vomiting occurs.

Data management

Before patient enrolment, the trial has to be approved by the local ethics committee, the Danish data protection agency and the Danish Medicines Agency. The trial will be registered at ClinicalTrials.gov and EudraCT and will be monitored by the Good Clinical Practice unit at a Copenhagen University Hospital.

Data belongs to sponsor.

Case Report Form

Every patient enrolled will have a case report form signed by investigator. REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Rigshospitalet will be used as case report form. Signed informed consent forms will be kept in a separate folder.

Clinical evaluations and outcome registration

Pain (at rest) is evaluated on a numeric rating scale (NRS) by the patient, assigning pain a number between 0-10. Study personnel assigne a score according to the criteria listed in appendix 1, were NRS 0 = 0 (no pain), 0<NRS≤3 = 1 (light pain), 3<NRS<7 = 2 (moderate pain), NRS≥7 = 3 (severe pain). If patients are not able to assign a number (e.g. due to sedation/doubt), it is accepted with a verbal rating scale (no/light/moderate/severe pain).

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

Length of stay (hospital) is measured as time (hours and minutes) from start of the procedure until discharge from the ward.

Length of stay (PACU) is measured as time from arrival to PACU until the patient is deemed ready to transfer to the ward (as the actual transfer time depends on transport etc.).

The occurrence of seroma requiring drainage is recorded the first 14 postoperative days from patient records.

Readmissions for any reason, except planned procedures or oncological admissions, are collected from patient records for 30 days.

Side-effects and/or complications (any) are registered during hospital stay and up to 60 hours postoperatively. Adverse events/serious adverse events are defined according to ICH-GCP.

Patients receive a questionnaire to fill out on days 0-4. The elements of the questionnaire are:

- 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)

Other collected data

Demographical data (sex, age, height, weight, smoking status, use of alcohol, comorbidities), operative data (date and time of operation, diagnosis, duration of surgery, extent of axillary dissection, intraoperative bleeding). Type and dose of medication given by request.
All data are collected from patient record.

Sample size

After modification of our ERAS 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 ERAS protocol, we chose to compare 24 vs 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 (www.sealedenvelope.com) with a two-sided 5 % significance level, a power of 80 % and an anticipated 10 % exclusion rate.

Appendix 1. Danish Society of Anesthesiology and Intensive Care Medicine (DASAIM)-score, modified.

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

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.

Modality	Score	Criteria
Sedation (nurse evaluation)	3	Sleeping, cannot be aroused
	2	Sleeping, aroused by physical stimuli
	1	Sleeping, aroused by verbal 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) **Numeric Rating Scale (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	