PROTOCOL

Effect of high vs low dose intravenous dexamethasone on complications in the immediate postoperative phase after periacetabular osteotomy- a randomized, double-blind, controlled trial (DEX-GANZ)

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Introduction

Periacetabular osteotomy (PAO) is the joint-preserving treatment of choice in young adults with symptomatic hip dysplasia.[1] There are currently no studies describing pain in the immediate postoperative period after this procedure, but unpublished data from our institution (the research project "Why in PACU?") shows that around 70% of patients have moderate to severe pain in the post anaesthesia care unit (PACU). The procedure, involving three osteotomies in otherwise healthy individuals, is likely to produce a substantial surgical stress response, that potentially could be alleviated by multimodal analgesia including high dose glucocorticoids, similar to results from other orthopaedic procedures.[2,3]

Preoperative low dose glucocorticoids (4-8 mg dexamethasone) are routinely used as a prophylaxis against postoperative nausea and vomiting (PONV).[4,5] Higher doses (>0.11 mg/kg dexamethasone) have been shown to reduce postoperative pain scores (early and late) and opioid consumption across procedures[6], and in a meta-analysis of intravenous glucocorticoid versus placebo in total hip arthroplasty (THA), glucocorticoids (8-40 mg of dexamethasone equivalents) were reported to significantly reduce acute pain and total morphine consumption, without increasing complications.[7]

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 PAO (primarily pain).Thus, in order to investigate if a high dose of dexamethasone was superior to the low/intermediate dose used routinely for PONV prophylaxis in decreasing immediate pain and other complications after PAO, we conduct a randomised, double-blind trial of 48 mg versus 8 mg of dexamethasone. The primary

hypothesis is that patients who are given 48 mg of dexamethasone (equivalent to approximately 250 mg of methylprednisolone) will be less likely to have moderate or severe pain in the immediate postoperative period (at the operating room and PACU) compared to patients given 8 mg of dexamethasone.

Secondary outcomes include other complications requiring treatment in the immediate postoperative phase (circulatory and respiratory complications, sedation and PONV), length of stay (in PACU and in hospital), readmissions, wound infections, self-reported pain and sleep problems, the first four days after the operation. The investigators hypothesize that patients receiving 48 mg of dexamethasone will have fewer complications and report lower pain scores. The investigators hypothesize that there will be no differences between groups in frequency of wound infections, readmissions or length of stay.

Outcomes

Primary outcome

The proportion of patients reporting moderate to severe pain at rest (>3 out of 10 on a Numeric Rating Scale from 0-10 (NRS)) in the immediate postoperative phase (after extubation in the operating room, and in the PACU until transfer to the ward).

Secondary outcomes

- Differences between groups in average and maximal level of pain in the immediate postoperative phase
- Occurrence of any complications requiring treatment in the PACU (nausea, circulatory or respiratory events)
- Complications/adverse events in the ward the first 24 h
- Length of stay (PACU/Hospital)

- Pain, self-reported. Days 0-4.
- Nausea/vomiting, self-reported. Days 0-4.
- use of opioid and/or antiemetic treatment other than standard, during hospital stay and up to postoperative day 4
- Quality of sleep. Days 0-4.
- Feelings of anxiety, restlessness, fatigue. Days 0-4.
- Any complications (including wound infections) up to 30 days postoperatively days

Methods

Study design

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

Randomization

Computer generated, double-blind block randomization. Allocation ratio 1:1, block sizes =8, unknown to study personnel.

The allocation sequence with intervention details (48 mg or 8 mg dexamethasone) will be concealed in consecutively numbered (1-64), 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 48 mg dexamethasone iv (Dexamethasone sodium phosphate, Krka, Novo mesto, Slovenia), (12 ml), administered immediately after anesthesia induction, around 30 minutes prior to surgery.

Control

A single dose of 8 mg dexamethasone iv (2 ml) with isotonic saline (10 ml), administered immediately after anesthesia induction, around 30 minutes prior to surgery.

Concealment

The trial drug is contained in a syringe with 12 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 2019

Location

Copenhagen University Hospital, Rigshospitalet, Denmark. Department of Orthopedic Surgery, and Department of Anesthesiology, Centre of Head and Orthopedics.

Participants

Number of participants: 64, 32 in each group.

Inclusion criteria

- Planned PAO
- Age 18 years or older
- Able to understand Danish or English and to provide informed oral and written consent.

Exclusion criteria

- Previous enrolment in the trial
- Planned simultaneous cheilectomy procedure

- Daily/current use of glucocorticoids or immunosuppressant medication
- Insulin-dependent diabetes
- Pregnancy or lactation
- Allergies to any of the trial drugs.

Procedures

Inclusion and randomization

Eligible patients are informed about the trial in relation to the pre-operative appointment. Enrolled participants are randomized and assigned to consecutive numbers (1-64) at the morning of surgery.

Standard care procedures

Pre-operative medication	Thromboprophylaxis (low molecular weight heparin) (on the morning of surgery, continued to discharge)
	Acetaminophen 1g (oral, 1-2 hours before surgery)
	Gabapentin 600 mg (oral, 1-2 hours before surgery)
Anaesthesia	
- Induction	Propofol ~ 2 mg kg^{-1} i.v.
- Maintenance	Total intravenous anaesthesia with propofol (5 mg kg^{-1} h^{-1}) and remifentanil (25 µg kg^{-1} h^{-1})*.
- Relaxant	Cicatracurium 0.1 mg kg^{-1} (before skin incision)
- airway	Endotracheal tube. Extubation only after train of four ratio >0.9
Intraoperative fluid therapy/medication	Ringers lactate, 25-30 ml kg^{-1}
	Dicloxacillin 2 gram (continued for 24 hours, every 8^{th} hour)
	Morphine 0.25 mg kg^{-1} (i.v., 45-30 minutes prior to the end of surgery).
	Ondansetron 4 mg (i.v., 30-20 min prior to end of surgery)
Local wound injection	A thin catheter is placed in the wound cavity for injection of local anaesthetics of 0.2% ropivacaine and 0.25 mg epinephrine (100 ml) prior to closure. Every 8^{th} hour for the first 24 hours after surgery, 20 ml 0.75% ropivacaine and 0.25 mg epinephrine are injected through the catheter.
Post-operative medication	Acetaminophen 1g (oral, 4 times daily, for up to 14 days)
	Ibuprofen 400 mg (oral, 3 times daily, for up to 14 days)
	Oxycodone 10 mg (oral, 2 times daily, for up to 7 days)
	Antiemetics (ondansetron 4 mg) on request
Discharge criteria	Acceptable radiologic control of the hip and clinical control of the wound. Patients should be able to mobilise in and out of bed, walk safely and climb one flight of stairs supported by crutches without other complications hindering discharge.

*However, the dosage could vary depending on indication and decision by the responsible anaesthetist. Data on accurate dosage is collected.

Data management

Before patient enrolment, the trial is 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 (NRS) at rest is evaluated every 15th minute in the PACU. The patient is asked to assign pain a number between 0 (no pain) and 10 (worst pain imaginable). Numbers are transformed into a 4 level-score (NRS 0 = 0 (no pain), NRS 1-3 = 1 (light pain), NRS 4-6 = 2 (moderate pain), NRS 7-10 = 3 (severe pain)). If patients are unable to assign a number (sedation), a verbal rating scale (no/light/moderate/severe pain) is used. Maximal level of pain is defined as the single highest pain score from the time of extubation until PACU discharge to the ward. The average level of pain is calculated for each patient by dividing the cumulated pain scores with the number of measurements from the time of extubation and during PACU stay.

Nausea is evaluated by patients on a four-point NRS (0, none; 1, slight; 2, moderate; 3, severe nausea). Opioid and antiemetic treatment is evaluated through electronic patient records. To allow comparison, opioids are converted into oral morphine equivalents (OMEQs) in mg, using the equianalgesic ratios[8]. Pain, nausea and sedation **a**re assessed from the time of extubation and

every 15 minutes in the operating room, at transfer from the operating room and the PACU and upon arrival at the ward. Side-effects are registered up to 60 hours postoperatively. Adverse events/serious adverse events were defined according to ICH-GCP. Complications requiring treatment during the first 24 hours (including PACU and ward) are defined as; pain requiring opioids, nausea requiring antiemetics, bleeding resulting in transfusion or reoperation, hypotension requiring the use of vasopressors, >2 l min^{-1} oxygen supplement or additional lung physiotherapy (CPAP etc.). Complications (any) are registered during hospital stay and up to 30 days postoperatively. Data on potential wound infections were collected from patient records and defined as superficial (involving skin and/or subcutaneous tissue) or deep (involving tissues down to and including the fascia, muscle and bone), based on clinical and microbiological evidence. Hospital length of stay (LOS) is defined as the time (hours and minutes) from start of operation until discharge to home, PACU LOS is defined as the time (hours and minutes) from transfer from the operating room until discharge to the ward. Readmission within the first 30 days are defined as any readmission to hospital.

To explore duration of possible effects and evaluate effect on wellbeing/sleep we include a questionnaire with variables as tertiary outcomes. Self-reported pain and nausea, quality of sleep, presence of fatigue, restlessness, and sadness are investigated by a questionnaire once a day from the day of surgery until the fourth postoperative day. The elements of the questionnaire are; average and worst pain (NRS), average and worst nausea 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, duration of surgery, intraoperative bleeding). Type and dose of medication given by request.
All data are collected from patient record.

Sample size

The estimated sample size for the primary outcome was based on unpublished data from our institution where 70% of patients had moderate and/or severe pain at some point during the PACU stay. We considered a 50% reduction in the proportion of patients with moderate/severe pain from 70% to 35% in the 48 mg vs. 8 mg dexamethasone group clinically relevant. A two-sided significance level of 5% and power of 80% was chosen, with equal allocation to two treatment arms, resulting in the requirement of 32 patients in each arm. As patients were included and randomized at the time of operation, no dropout rate was expected.

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