

**Preoperative high-dose Steroids in Total Knee and Hip Arthroplasty
Protocols for three randomized controlled trials**

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Preoperative high-dose Steroids in Total Knee and Hip Arthroplasty – Protocols for three randomized controlled trials.

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Conflicts of interest:

HK is a member of the advisory board at "Rapid Recovery" by Zimmer Biomet.

KG and HH received financial research support and speaker fees from Zimmer Biomet unrelated to this study. NBF received speaker fees from Zimmer Biomet unrelated to this study.

Abstract:

Background:

Patients undergoing total knee arthroplasty (TKA) / total hip arthroplasty (THA) still experience moderate-severe postoperative pain despite optimized pain management regimes. Patients already on opioid-treatment, and pain catastrophizers (PCs) have a higher risk of postoperative pain.

The use of preoperative intravenous high-dose glucocorticoids decreases postoperative pain after TKA and THA, but optimal dose is yet to be found, and the effect on subpopulations at high pain risk is unknown.

Aim:

To investigate the effect of a higher than previously used dose of glucocorticoids (dexamethasone (DXM)), administered intravenously before surgery, as part of standardized fast-track regimen, on postoperative pain in TKA/THA subgroups.

Method:

Three separate randomized, double-blinded, controlled trials are planned to compare a new higher dose DXM (1 mg/kg) to the earlier used high-dose DXM (0.3 mg/kg). Study 1: predicted Low Pain TKA; study 2: predicted High Pain Responder (HPR) TKA; study 3: predicted HPR THA. Predicted HPR groups consist of either PCs with PCS-score of ≥ 21 and/or history of ongoing opioid-treatment of 30 mg/day of morphine or equivalents >30 days. 408 patients in total are planned for inclusion (160 Low Pain TKA, 88 HPR TKA, 160

HPR THA).

Primary outcome: Pain upon ambulation in a 5-meter walk test 24 hours after surgery. Secondary outcomes include use of analgesics, rescue-opioids, antiemetics, cumulated pain, CRP, OR-SDS, QoR-15, quality of sleep, length of stay (LOS), reasons for hospitalization, readmission, morbidity and mortality. Patients are completed for follow-up on day 90. Recruiting commenced February 2019 and is expected to finish September 2020.

1: Introduction

Primary total knee arthroplasty (TKA) and total hip arthroplasty (THA) for osteoarthritis is a frequently performed procedure, worldwide. They represent an ever growing proportion of surgical patients each year, and is expected to increase in numbers within the next decades because of the growing elderly population¹⁻³.

TKA and THA can be performed in a FAST-TRACK regimen to ensure a low perioperative morbidity and mortality and facilitate early rehabilitation, with the main object of perioperative interventions being the attenuation of postoperative pain and fatigue, which is the most pronounced inhibitors of early mobilization and discharge⁴⁻⁶.

Studies have shown that the use of low to intermediate doses of glucocorticoids is effective in suppressing the systemic inflammatory part of the surgical stress response, thereby attenuating dynamic pain during the first hours after surgery⁷⁻¹¹. Different doses have been investigated, and intermediate dose (earlier high dose ~ 25 mg of DXM) glucocorticoids is considered safe and part of the standard care in many arthroplasty centers performing primary TKA and THA^{12,13}. In spite of the analgesic effect of intermediary dose glucocorticoids pain is still a significant problem, but the potential additive effect of higher dose of glucocorticoids has not been investigated.

Such higher doses, up to 2-5 mg/kg of DXM equivalents, have been investigated in several other types of surgery, including among others lung, liver, esophageal and major abdominal surgery and a recent meta-analysis concludes that there are no unwanted adverse effects as a result of the glucocorticoid administration in these higher doses¹⁴⁻¹⁷.

Importantly, the effect of glucocorticoid therapy in specific patient groups at high risk of acute

postoperative pain has not been investigated. Studies have found that hip and knee arthroplasty patients with prior opioid-treatment and patients categorized as pain catastrophizers (PCs), identified by the Pain Catastrophizing Scale (PCS)¹⁸⁻²⁰ had an increased risk of poorly controlled postoperative pain (high pain responders, HPR), and may have a higher risk of developing chronic pain after surgery²¹⁻²³.

A higher dose of glucocorticoids could be more effective in controlling postoperative pain after TKA/THA, and this effect could potentially be different in patients described as HPR, calling for separate acute pain trials in the different groups²⁴.

1.1: Aim

To investigate the effect of a new higher dose of a preoperative glucocorticoid, DXM, on acute postoperative pain upon well-defined ambulation 24 hours after TKA and THA and compare it to current standard intermediate dose treatment, in TKA in general and in HPR TKA and THA subgroups.

2: Methods

2.1: Trial design

To investigate the effect of a higher dose of glucocorticoid, 3 separate randomized double blinded controlled trials are planned, comparing a new higher dose of glucocorticoid equivalent to 1.0 mg/kg of DXM to the earlier high dose(intermediate) 0.3 mg/kg of DXM.

The 3 parallel RCT's contains 3 distinct groups with different postoperative pain profiles, in which postoperative pain is still a significant issue, despite intermediate dose glucocorticoid (see figure 1-3):

Study 1: Low Pain TKA group, title: High-dose Steroids in Total Knee Arthroplasty – A randomized double-blinded controlled trial.

Study 2: HPR TKA group, title: High-dose Steroids in High Pain Responders undergoing Total Knee Arthroplasty – A randomized double-blinded controlled trial.

Study 3: HPR THA group, title: High-dose Steroids in High Pain Responders undergoing Total Hip Arthroplasty – A randomized double-blinded controlled trial.

All 3 groups will have a separate randomization. All patients will be receiving evidence-based basic multimodal analgesia.

The studies are planned to be carried out on 2 different sites, Hvidovre Hospital, Dept. of Orthopedics, Capital Region of Denmark, and Vejle Sygehus, Dept. of Orthopedics, Region of Southern Denmark.

2.2 Approvals

The three RCTs were approved by the Local Ethics comity: De Videnskabetiske Komiteer for Region

Hovedstaden, Kongens Vænge 2, 3400 Hillerød, ref. numbers H-18034756, H-18034778 and H-18034782, and by the knowledge-Centre for Data Protection, ref. numbers VD-2018-528, VD-2019-04 and VD-2019-05. The three studies were also approved by the Danish Medicine Agency (DKMA) with the following EudraCT-numbers 2018-002634-20, 2018-002635-23, 2018-002636-25

All three studies are registered at ClinicalTrials.gov, ID NCT03758170, NCT03763760 and NCT03763734.

2.3 Study population and procedures

Patients undergoing unilateral TKA and THA in spinal anesthesia, between the age of 40 and 90, both included.

All surgery is performed in a standardized fast-track setting by experienced surgeons specialized in TKA and THA surgery. All patients will undergo surgery in planned spinal anesthesia using standardized fluid management, pre- and postoperative tranexamic acid (TXA), absence of drains and a standardized physiotherapeutic functional mobilization protocol. All THAs will be performed using a standard posterolateral approach. TKAs will be performed using the medial parapatellar approach with application of local infiltration analgesia (LIA). Patients are discharged to their homes when fulfilling the standard functional discharge criteria²⁵.

In-hospital thromboprophylaxis will be administered if LOS \leq 5 days, and no use of pneumatic compression devices or compression stockings. If LOS > 5 days, prophylaxis will be prescribed according to local guidelines on thromboprophylaxis²⁶.

2.4 Analgesic regimen

All patients included in the studies will be undergoing surgery in a planned spinal anesthesia with between 10-12.5 mg bupivacaine 0.5% (plain for THA and hyperbaric for TKA).

Propofol intravenously for perioperative sedation is optional. Patients who receive primary spinal anesthesia but later require general anesthesia are not excluded. The patients undergoing TKA will also receive LIA as per standard protocol²⁷.

Oral analgesic-regimen will start preoperatively on the morning of surgery with 1g Paracetamol and 400 mg Celecoxib and continue postoperatively with 1 g paracetamol x 4 daily, Celecoxib 200 mg x 2 daily and 10-20 mg of morphine or other opioids in equivalent doses as rescue opioids²⁷.

2.5 Grouping

The predicted HPR groups are compiled of patients scoring >20 on the PCS scale^{19,28,29} and/or patients with a daily opioid intake of 30 mg of morphine or equivalents. The duration of the opioid treatment had to be at least 30 days prior to surgery.

2.6 Inclusion and exclusion criteria

All patients must be able to understand and read Danish and must be able to cooperate with a patient-filled pain-diary and must give written informed consent after receiving and understanding the information for the studies.

Exclusion criteria contain ongoing treatment with glucocorticoids (apart from those inhaled and topically applied), neurologic deficiencies blurring the pain-sensation from the surgical area, insulin-dependent diabetes, allergies for the study-treatment, pregnancy/breast feeding and anti-psychotic treatment and bipolar and schizophrenic disorders.

TKA patients with PCS score <21 and no history of ongoing opioid-treatment >30 days, are included in study 1: Low Pain TKA.

TKA patients with PCS score ≥ 21 and/or history of ongoing opioid-treatment of 30 mg/day of morphine or equivalents >30 days are included in study 2: High Pain TKA.

THA patients with PCS score ≥ 21 and/or history of ongoing opioid-treatment of 30 mg/day of morphine or equivalents >30 days are included in study 3: High Pain THA.

No Low pain THA patients are included in the studies, because their pain upon ambulation 24 hours postoperatively is already low with moderate dose glucocorticoid.

2.7 Data collection

Patient demographics including age, gender, height, weight, history of alcohol consumption and smoking status, morbidity, prior opioid treatment and PCS-score will be obtained prior to surgery along with baseline pain-score at rest, after a 5-meter walk-test and pain during the nights. Preoperative quality of sleep the night before surgery will be registered.

Also, preoperative levels of CRP will be tested.

All pain scores are made by patients by marking with a pen on a 10 cm predefined line, representing a VAS of 0-100 mm, 0 mm being no pain at all, and 100 mm being the worst pain imaginable.

Surgical data as well as perioperative data on anesthesia are obtained during the procedure.

Postoperative data collected upon arrival in the Post Anesthesia Care Unit (PACU) or the specialized ward, 4, 24 and 48 hours after the end of surgery. If the patient is discharged before the 48-hour mark, an out-patient follow-up is done.

At all follow-up points after surgery a pain score after a 5-meter walk-test, at rest, at passive leg raise, and overall during the night is done.

Also, quality of sleep is assessed, and patients fill in the QoR-15 and OR-SDS questionnaires along with CRP-samples preoperatively and at 24 and 48 hours. The use of rescue analgesics and antiemetics is

registered the first 7 days postoperatively.

After the 48-hour follow-up, an instruction in the patient-filed diary is done, monitoring pain, use of analgesics and rescue-opioids every evening and morning until the 7th day after surgery.

Follow-ups are planned at 14 days, 30 days and 90 days, either electronically or by phone.

All data will be collected in a patient specific case-report-form (CRF) and be processed using the REDCap research database program.

2.7.1 Serious Adverse Events (SAE)

According to the international Good Clinical Practice (GCP) guideline³⁰ the SAE's during the project will be reported as required by law.

2.8 Outcomes

2.8.1 Primary outcome:

Pain upon walking during a 5-meter walk test 24 hours after TKA and THA.

2.8.2 Secondary outcomes:

The use of multimodal non-opioid analgesics, rescue opioids and antiemetics within the first 48 hours and up to 7 days after surgery.

Inflammation due to surgery (and the attenuation/decrease of this) as indicated by level of C-reactive protein pre- and 24/48 hours postoperatively.

Cumulated pain the first 48 hours by cumulating the T₀, T₄, T₂₄ and T₄₈.

Cumulated pain the first 7 days registered by patient-filed pain diary.

Questionnaires: Quality of recovery (QoR-15)³¹ and Opioid Related Symptom Distress Scale (OR-SDS)^{32,33}.

Quality of sleep measured by a 0-10 numeric rank scale.

Reasons why the patient is still admitted to the hospital at time T₄, T₂₄ and T₄₈ (Why Still in Hospital²⁵).

Length of stay, number of days at hospital.

Readmission within the first week, and reasons why.

Morbidity and mortality within first 90 days. A systematic assessment of the patient's medical record is made at day 14, 30 and 90. Follow-up is secured using the patient's unique social security number.

All admissions with overnight stay, and/or medical contacts with a possible adverse event is identified and evaluated using patient and discharge records. All complications will be categorized according to the attending physician's assessment, diagnosis, treatment and follow-up.

All complications will be graded according to the Clavien-Dindo³⁴ classification

All reasons for admission, and all serious adverse events and timing of these will be evaluated in relation to index surgery and recorded.

2.9 Statistics

2.9.1 Sample-size calculation

Power calculation on each RCT was performed separately. We performed the analysis based on all the studies having the power to detect a 50% reduction in the number of patients experiencing VAS >30 when ambulated in a 5-meter walking-test 24 hours after surgery to be clinically relevant. We set a 90% power and two-sided level of significance to 0.05 in a superiority design. The sample-size calculation was based on data from earlier TKA and THA studies from the Lundbeck Foundation Center for Fast-Track Hip and Knee Replacement Collaborative Group, two on pain profiles after, with intermediate dose glucocorticoids and one on pain levels in PCs and one in opioid using patients^{7,8,20,35}.

From the earlier studies in the Lundbeck Foundation Center for Fast-Track Hip and Knee Replacement Collaborative Group, we knew the incidence of VAS >30 (moderate and severe pain) upon ambulation 24 hours after surgery in knee-replacements to be 0.5 with intermediate dose glucocorticoids⁸.

No data exists on the expected pain scores on HPR TKA group with intermediate glucocorticoids, but from other studies, we knew the incidence of VAS >30 to be 0.9 in patients with high PCS, and 0.86 in patients with ongoing opioid treatment, but none of the two groups had glucocorticoid treatment^{20,35}. We estimated a reduction in pain from the intermediate dose of glucocorticoids to correlate with an incidence of VAS >30 to be 0.7.

In the THA group median VAS upon ambulation 24 hours after surgery was > 30 in 30% of patients in a mixed group of patients receiving intermediate dose glucocorticoids. We assumed an expected HPR THA group to have an incidence of VAS >30 to be 0.5, based on data from the PCS and ongoing opioid treatment studies mentioned above. This led to the following power calculations, all with a significance of 0.05 and power 0.9.

Project 1 LPR TKA: A 50% reduction required 77 patients in each arm. Added up to 80 patients in each arm to allow for fallouts, n = 160.

Project 2 HPR TKA: A 50% reduction required 41 patients in each arm. Added up to 44 patients in each arm to allow for fallouts, n= 88.

Project 3 HPR THA: Based on data from the earlier TKA studies and the THA and glucocorticoid vs. placebo study we predicted a 50% reduction required 77 patients in each group. Added up to 80 patients in each

arm to allow for fallouts, n = 160.

2.9.2 Analysis

All primary data will be tested with Chi square test and described by Odds ratio with two-sided confidence-intervals.

Secondary data consisting of continuous data will be tested with T-test and dichotomous data with Chi-squared or Pearson's Exact test. Level of significance 0.05.

Statistical data will be processed with SPSS statistics (IBM, New York, USA), v.18 or higher.

All changes to the statistical plan will be accounted for upon publication. The final detailed statistical plan will be included in the manuscripts.

3 Discussion/Strengths/Limitations

To our knowledge this is the first study with a single preoperative administration of a new higher dose (>24mg) of DXM in TKA and THA. Simultaneously, it is the first study to evaluate the effect of glucocorticoids specifically on a selected group of anticipated HPR in TKA and THA as requested by Gilroy/Kehlet 2019²⁴.

The aim of the present studies is to evaluate the potential effect of a higher dose of glucocorticoids on TKA in general, but also to be able to evaluate this specifically in TKA and THA patients with more specialized pain issues.

Earlier studies have primarily targeted the general population of arthroplasty surgery patients as a homogenous group^{7,8}, and the aim of targeting specific pain responders is of great relevance to the clinical daily challenges faced by clinicians and nurses on the specialized ward for TKA and THA patients. Our present knowledge does not allow us to conclude specifically on HPR patients as to the effects of our analgesic interventions, a problem which is exacerbated by the international increase in chronic opioid users.

Reasons for delayed discharge or challenges in the early phases of convalescence after TKA and THA include pain, nausea and vomiting (PONV), circulatory and respiratory problems, orthostatic intolerance and cognitive difficulties²⁵. These complaints are all potentially associated with the surgical stress response (SSR) which is both neurohumoral and inflammatory.

The acute postoperative pain following TKA and THA is well described with up to 75% of patients undergoing TKA, reporting moderate to severe pain on the first postoperative day, and 30-40% reporting continued pain after 2 weeks after TKA³⁶⁻³⁸. Acute postoperative pain predisposes to the development of chronic pain conditions and is a key factor in delaying mobilization after surgery^{39,40}.

The mechanism of action for glucocorticoids is thought to be a general attenuation of the SSR. This has

been shown previously with a significant decrease in endothelial damage and systemic inflammation in TKA-patients^{8,41}, as well as a significant reduction in pain, fatigue and PONV in studies testing preoperative glucocorticoids vs. placebo⁸.

The strengths in the study setting includes the double-blinded randomization and the elimination of the effects of treatment assignment and selection bias. Another strength is the use of a well-established FAST-TRACK setting in the two facilities⁵ participating in the “Lundbeck-group” cooperation which, to some extent, have the same setting of their FAST-TRACK setup⁴². Also, the small number of evaluators is a strength to avoid assessment bias. Further, the same personnel who evaluate the patients will be responsible of entering the data into our REDCap database. A double entry of primary outcome will be executed to ensure data quality.

Limitations include the patient-reported pain-diary for post discharge pain beyond 48 hours, but it is not logistically possible to do a 7-day pain evaluation of the participating patients who, for the most part, leave the facility on the day after surgery. Another limitation involves patient selection bias. Two of our three parallel studies are designed to include anticipated HPR, who we identify by opioid-consumption or the PCS with a total score of 21 or more. No data is available on the different incidence of HPR in different centers or if selection bias for participating in studies exists amongst these patients, but it is not possible to rule out the limitation of a bias in patients declining to participate.

Declarations

Consent of publication

The participating patients are informed verbally and in writing and are required to fill in an informed consent confirming their agreement to participate in the study and the publication of data and findings throughout the study.

Availability of data

No data was generated during the design of the study and therefore cannot be made available to sharing. Datasets generated and analyzed during the study itself will be made available on reasonable request to the corresponding author.

Conflict of interest

HK is a member of the advisory board at “Rapid Recovery” by Zimmer Biomet.

KG and HH received financial research support and speaker fees from Zimmer Biomet unrelated to this study. NBF received speaker fees from Zimmer Biomet unrelated to this study.

Authors contribution

NN, HK, HH, KG, and NBF drafted the protocols and the manuscript for this paper was made by NN, HK and NBF and in collaboration with KG, AT, HH, CV, PKA, LER, and HM.

All authors have read and approved the final manuscript. NBF is sponsor and NN is principal investigator.

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Figure 1:

Study 1: Low Pain TKA

Enrolment

Assessed for eligibility

Inclusion criteria:

- ◆ 40 – 90 years old
- ◆ Primary unilateral TKA
- ◆ Signed informed consent
- ◆ Understanding Danish language.
- ◆ PCS <21 and no history of ongoing opioid-treatment >30 days.

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Figure 2

Study 2: High Pain TKA

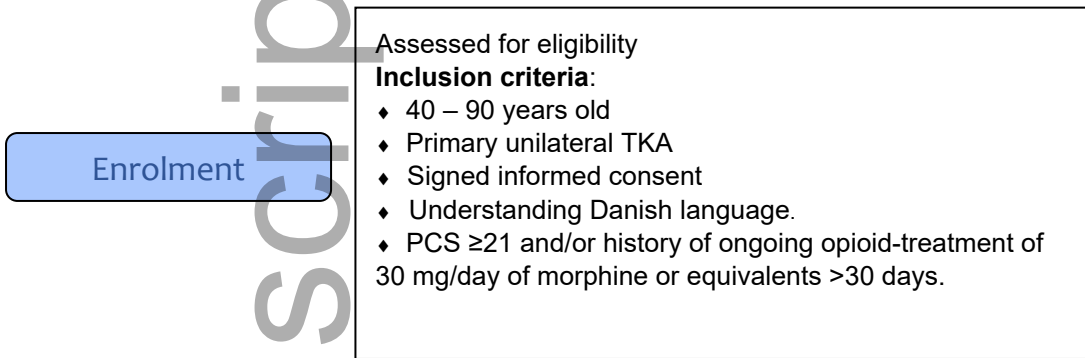


Figure 3

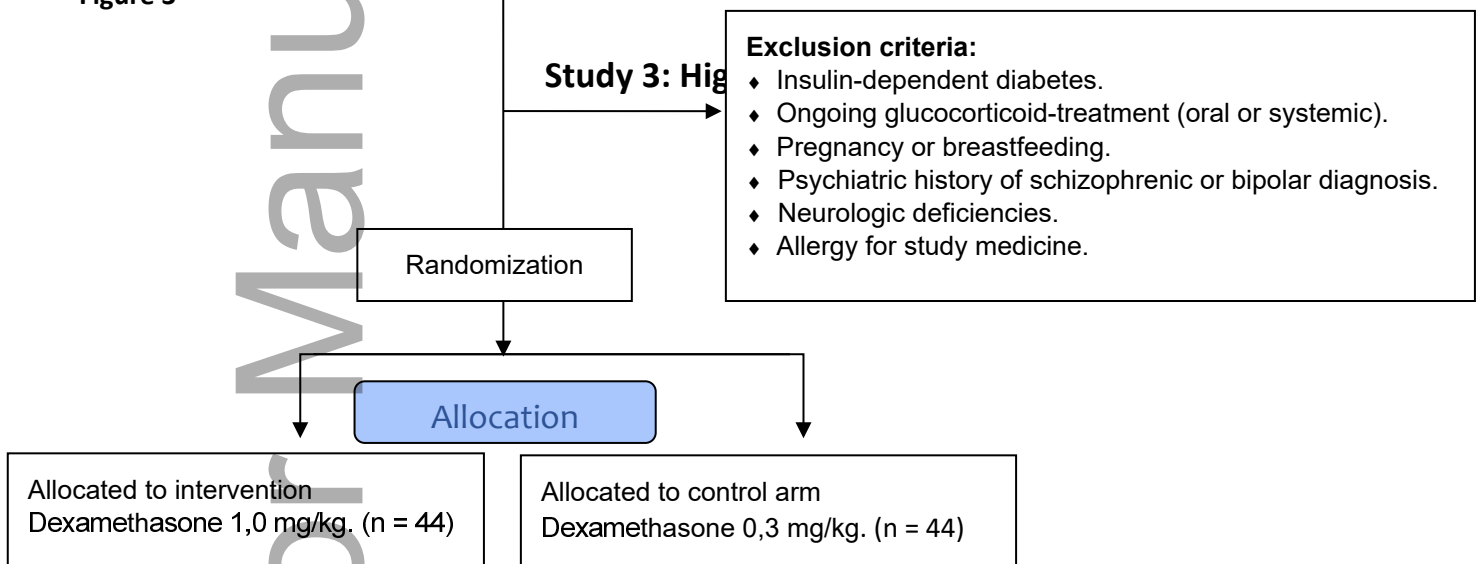
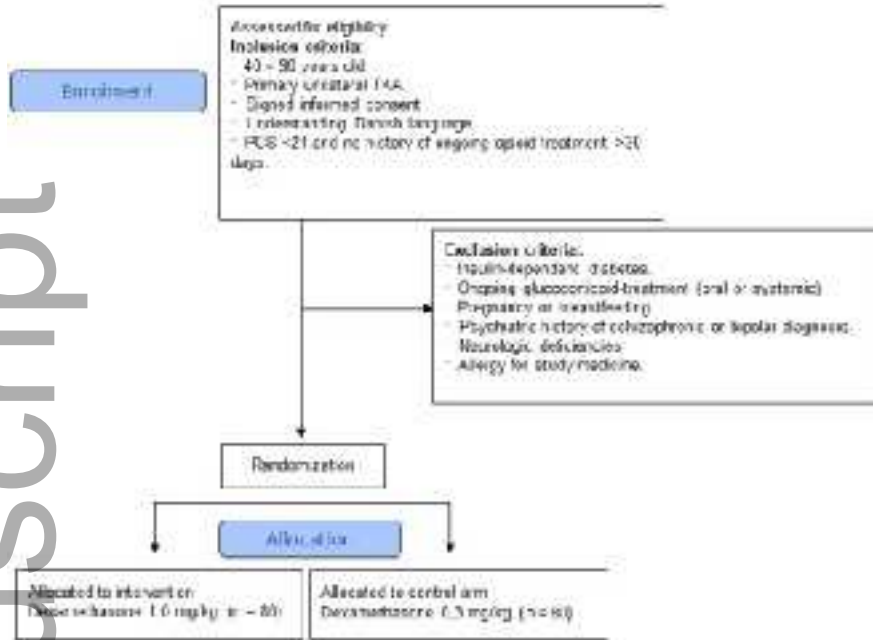
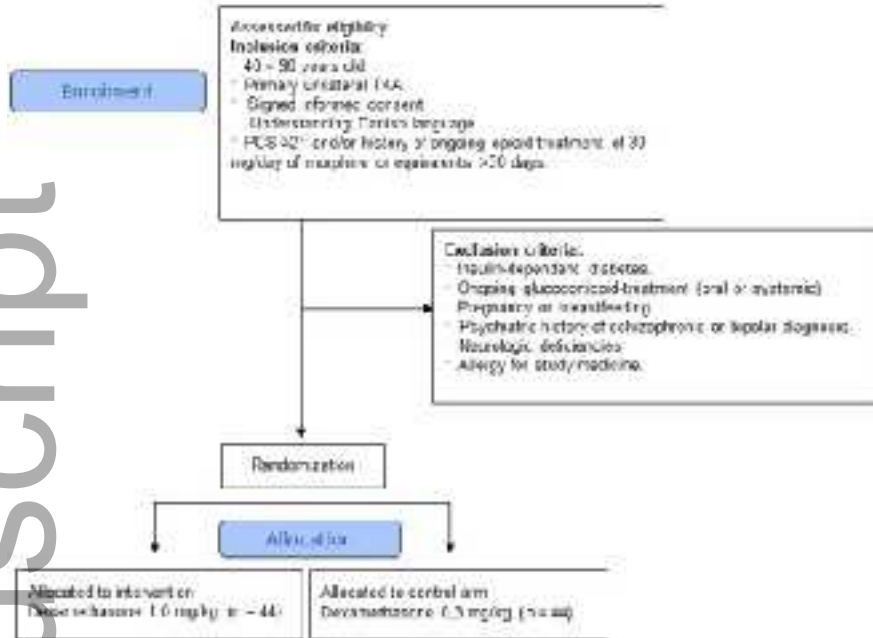


Figure 1:
Study 1: Low Pain TKA



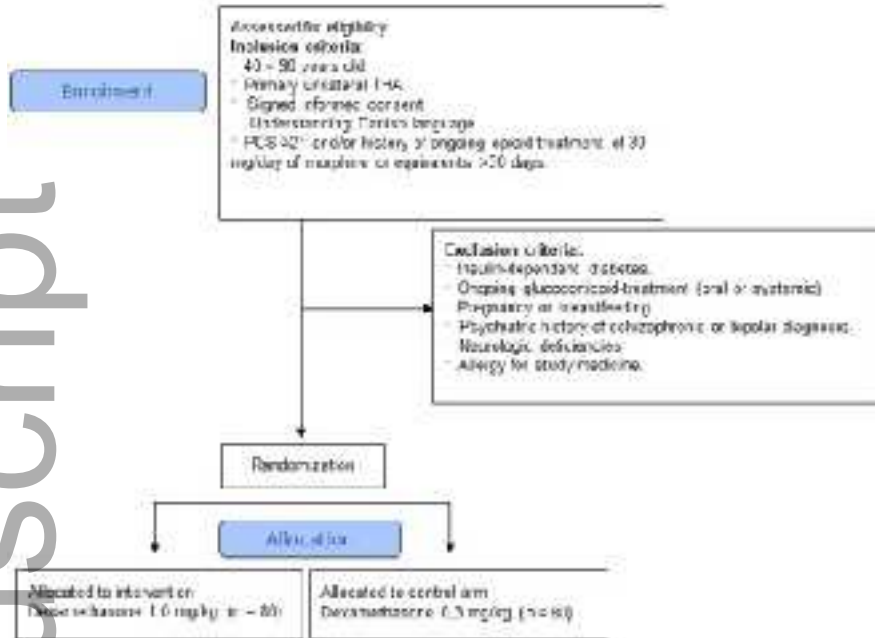
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Figure 2:
Study 2: High Pain TKA



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Figure 3:
Study 3: High Pain THA



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