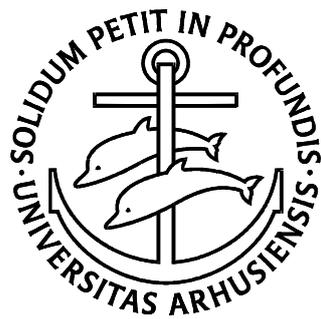


Postoperative pain relief after total hip and knee replacement

PhD thesis

Karen Vestergård Andersen

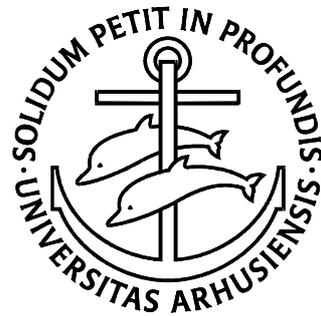


Faculty of Health Sciences
University of Aarhus
2010

Postoperative pain relief after total hip and knee replacement

PhD thesis

Karen Vestergård Andersen



Faculty of Health Sciences
University of Aarhus

Supervisors

Kjeld Søballe, Professor, MD, DMSc
Department of Orthopedics
Aarhus University Hospital, Denmark

Lone Nikolajsen Associated Professor, MD, PhD
Department of Anesthesiology and Danish Pain Research Center
Aarhus University Hospital, Denmark

Evaluation committee

Sten Rasmussen, Associate Professor, MD, PhD (chairman)
Department of Orthopedics
Aalborg Hospital – University Hospital of Aarhus, Denmark

Narinder Rawal, Professor, MD, DMSc
Department of Anesthesiology and Intensive Care
Örebro University, Sweden

Søren Solgaard, MD, DMSc
Department of Orthopedics
Hillerød Hospital, Denmark

Public Defense of this PhD thesis

The public defense is scheduled for June 11th 2010.

Location: Auditorium 1, Aarhus University Hospital, Aarhus Hospital, Tage Hansens
Gade 2, DK-8000.

Preface

This thesis was carried out at the Department of Orthopedics, Aarhus University Hospital in the period 2006 – 2009. Part of the research was performed at the Department of Anesthesiology at Glostrup Hospital.

I am greatly indebted to a number of persons who have made this work possible.

First of all, I wish to thank all the patients who volunteered to participate in the trials and spent their valuable time.

I wish to thank the care staff at Aarhus University Hospital and Glostrup Hospital, without their efforts in registration of data none of these studies would have been possible.

Especially I wish to express my sincere gratitude to my two enthusiastic supervisors Professor Kjeld Søballe MD., D.M.Sc, and Associate Professor Lone Nikolajsen MD, PhD, for their valuable and skilful guidance and support.

Associate Professor Niels Trolle Andersen, Lic. Scient, Department of Biostatistics is thanked for valuable guidance with statistics. I am also grateful to Birgitte V. Christensen, MD, for her help at Glostrup Hospital and her friendship. Secretary Tina Stenumgaard is thanked for her help with various subjects.

I also, wish to thank my fellow PhD students in the research group for our valuable discussions to research meetings and especially my friend Mette Krintel Petersen, Cand.Scient.San., PhD for her support, advice and for her friendship.

Finally, I would like to thank my family and friends for always supporting me. Most of all, my deepest gratitude goes to my best friend and partner Hans Jørgen Wolf Andersen for his support.

Acknowledgements

I received generous financial support from Aarhus Hospital, Aarhus University Hospital and Forskningsinitiativet Aarhus hospital, Aarhus University Hospital.

Aarhus, 28 February 2010.

Karen Vestergård Andersen

List of papers:

- I. **Reduced hospital stay and narcotic consumption and improved mobilization with local and intraarticular infiltration after hip arthroplasty**
Karen V. Andersen, Mogens Pfeiffer-Jensen, Viggo Haraldsted, Kjeld Søballe. Acta Orthopaedica 2007; 78(2):180-186.
- II. **A Randomized Controlled Trial of Local Infiltration Analgesia vs. Epidural Infusion for Total Knee Arthroplasty**
Karen V. Andersen, Marie Bak, Birgitte V. Christensen, Jørgen Harazuk, Niels A. Pedersen, Kjeld Søballe - Submitted to Acta Orthopaedica 2010.
- III. **A comparison of participants and non-participants in a randomized controlled trial involving 156 patients scheduled for primary total knee arthroplasty**
Karen V. Andersen, Anne F. Christensen, Mette K. Petersen, Birgitte V. Christensen, Niels A. Pedersen, Kjeld Søballe - Submitted to Acta Orthopaedica 2010.

Contents

1. English summary.....	5
2. Danish summary	7
3. Introduction.....	9
3.1 Total hip replacement surgery	9
3.2 Total knee replacement surgery	10
Fast track surgery	11
3.3 Postoperative analgesia	11
4. Aim of the thesis	16
5. Design	17
The Randomized Controlled Trial	17
6. Materials & methods.....	19
Ethical issues	19
Patients.....	19
Study I.....	19
Studies II and III	20
Intervention.....	21
Control and intervention groups study I.....	21
Control and intervention group study II.....	23
Study III	24
Outcomes	25
Outcome measures in study I to II.....	25
Outcome study I	26
Outcome study II.....	27
Outcome study III	27
Statistics	28
Sample size	28
Statistical methods	28
7. Results	29
Study I.....	29
Study II.....	30
Study III	32
8. Discussion.....	34
Key findings	34
Consideration of possible mechanism and explanations	34
Comparison with relevant findings from other studies	34
Limitations.....	37
Selection bias	38
Random allocation	39
Blinding and information bias.....	39
9. Conclusion.....	40
10. Perspectives and future research	41
11. References.....	42
Appendices.....	50
Papers 1 to 3	53

Abbreviations

In alphabetic order

ASA	American Society of Anesthesiology
IA	Intraarticular
CAS	Cumulated Ambulation Score
EA	Epidural Analgesia
HB	Hemoglobin
HHS	Harris Hip Score
IV	Intravenous
LIA	Local Infiltration Analgesia
LOS	Length of stay
NSAID	NonSteroidal Anti-Inflammatory Drugs
PONV	Postoperative Nausea and Vomiting
PCA	Patient Controlled Analgesia
PNB	Peripheral Nerve Blockade
THR	Total Hip Replacement
TKR	Total Knee Replacement
UKR	Unicompartmental Knee Arthroplasty
VAS	Visual Analogue Scale

1. English summary

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are reliable and common surgical procedures to relieve pain and restore function among patients with degenerative or damaged hip and knee joints. However, the procedures are associated with moderate to severe postoperative pain which can contribute to delayed rehabilitation. During the last decade several techniques have been used for postoperative analgesia after THA and TKA, and recently local infiltration analgesia consisting of a high volume wound infiltration combined with intraarticular injection with multimodal drugs through a catheter has been introduced.

The aims of this thesis were in a randomized controlled design to investigate the efficacy of local infiltration analgesia compared with epidural treatment for postoperative analgesia after THA (study I) and TKA (study II) and to evaluate the external validity of study II (study III).

In study I, we randomized 80 patients scheduled for elective primary hip arthroplasty to receive either continuous epidural analgesia (control group) with local anesthetic and morphine or local infiltration analgesia (intervention group) with multimodal drugs. Primary outcome was pain intensity at rest and during mobilization, and secondary outcomes were opioid consumption, occurrence of side effect, early mobilization ability, and length of stay (LOS).

Even though we found that the local infiltration technique significantly reduced the consumption of opioids, we did not demonstrate differences in pain intensity score during active treatment. We did find a significant reduction in the occurrence of side effects and LOS and an improved ability to implement early mobilization. No differences in complications or readmission were observed.

In study II, we investigated 49 prospectively randomized patients undergoing elective primary knee arthroplasty. One group received wound infiltration combined with continuous intraarticular infusion with local anesthetics and nonsteroidal anti-inflammatory drugs (NSAID). The other group received continuous epidural infusion of local anesthetics and intravenous NSAID. Primary outcome was opioid consumption and secondary outcomes included pain intensity scores at rest and during mobilization, occurrence of side effect and LOS.

We found significant differences in opioid consumption, pain intensity scores, occurrence of urinary retention, and constipation in favor of the local infiltration group. No differences in LOS, complications or readmission were observed.

In study III, we studied the distribution of preoperative characteristics and postoperative clinical outcome variables among participants and nonparticipants in study II. In the randomized controlled trial, 157 patients were identified as potential participants; 97 patients were excluded and 11 patients declined to participate. The excluded patients were less healthy, used more often walking devices, and needed more help from the home care system preoperatively. Furthermore, they were hospitalized longer and were more often readmitted during a 30-days follow-up.

Postoperative pain relief with local infiltration analgesia after THA and TKA compared with conventional treatment with epidural analgesia gives excellent pain relief with a minimum of side effects.

The local infiltration technique is simple and easy to use and can be recommended for postoperative analgesia following total hip and knee arthroplasty.

Because nonparticipants differed significantly from participants, our results underline the need to provide additional information about the recruitment process and readily available quantitative data in order to avoid biased estimates of treatments effects and misleading assessments regarding the degree to which the results may be generalized

2. Danish summary

Total hofte alloplastik (THA) og total knæ alloplastik (TKA) er pålidelige og meget anvendte kirurgiske procedurer til at afhjælpe smerte og genoprette funktion hos patienter med degenereret eller beskadiget hofte- eller knæled. Men de kirurgiske indgreb er ofte forbundet med moderate til svære postoperative smerter, som kan medvirke til forsinket rehabilitering. I løbet af det sidste årti er flere forskellige teknikker blevet anvendt til postoperativ smertebehandling efter THA og TKA hvoraf en af de nyeste er lokal infiltration analgesi som består af en høj volumen sår infiltration kombineret med intra-artikulær injektion med multimodale smertestillende midler gennem et kateter.

Formålet med denne afhandling var i et randomiseret, kontrolleret design at undersøge effekten af lokal infiltrations analgesi sammenlignet med epidural behandling for postoperativ smertebehandling efter THA (studie I) og TKA (studie II) samt at evaluere den eksterne validitet af undersøgelse II (studie III).

I studie I, randomiserede vi 80 patienter der var planlagt til elektiv primær hofte alloplastik til at modtage enten kontinuerlig epidural analgesi (kontrol gruppe) med et lokal bedøvelsesmiddel tilsat morfin eller lokal infiltration analgesi (interventions gruppe) med multimodale smertestillende midler. Det primære effektmål var smerteintensitet i hvile og under mobilisering og sekundære effektmål var opioid forbrug, forekomst af bivirkninger, evne til tidlig mobilisering og indlæggelsestid.

Selv om vi kunne konstatere, at den lokale infiltrations teknik reducerede forbruget af opioider væsentligt kunne vi ikke påvise en forskel i smerteintensitets score i løbet af den aktive behandlingsperiode. Vi fandt en signifikant reduktion i forekomsten af bivirkninger og indlæggelsestid samt en forbedret evne til tidlig mobilisering. Der blev ikke observeret nogen forskel i forekomsten af komplikationer eller genindlæggelser.

I studie II undersøgte vi 49 prospektivt randomiserede patienter, der gennemgik elektiv primær knæ alloplastik. En gruppe fik sår infiltration kombineret med kontinuerlig intra-artikulær infusion af et lokal bedøvelsesmiddel tilsat et non steroid anti-inflammatorisk lægemiddel (NSAID). Den anden gruppe fik kontinuerlig epidural infusion med et lokalt bedøvelsesmiddel og intravenøs injektion af NSAID. Det primære effektmål var opioid forbrug og sekundære effektmål bestod af

smerteintensitet score i hvile og under mobilisering, forekomst af bivirkninger og indlæggelsestid.

Vi fandt signifikante forskelle i opioid forbrug, smerte intensitet score, forekomst af urinretention og obstipation til fordel for den lokale infiltrations gruppe. Der blev ikke observeret forskel i indlæggelsestid eller i forekomsten af komplikationer eller genindlæggelser.

I studie III, undersøgt vi fordelingen af præoperative karakteristika og postoperative kliniske variabler blandt deltagere og ikke-deltagere i undersøgelse II.

I det randomiserede kontrollerede forsøg, blev 157 patienter identificeret som potentielle deltagere hvoraf 97 patienter blev ekskluderet og 11 patienter afslog at deltage.

De ekskluderede patienter var mindre raske, anvendte oftere ganghjælpemidler og havde større behov for hjælp fra hjemmeplejen præoperativt. Desuden var de indlagt i længere tid og blev oftere genindlagt indenfor en 30 dags opfølgingsperiode efter operationen.

Postoperativ smertelindring opnået ved lokal infiltration analgesi giver en god smertelindring med et minimum af bivirkninger sammenlignet med konventionel behandling med epidural analgesi efter THA og TKA. Den lokale infiltrations teknik er simpel, billig samt let at anvende og kan anbefales til postoperativ smertebehandling efter total hofte og knæalloplastik.

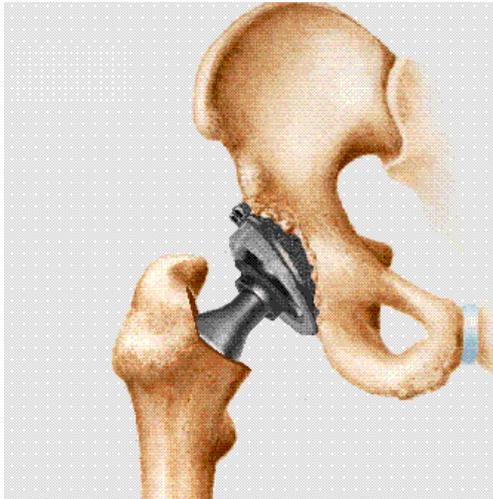
Fordi ikke-deltagere afveg væsentligt fra deltagerne understreger vores resultater behovet for at give yderligere oplysninger om rekrutteringsprocessen. De indikerer også vigtigheden af at supplere med let tilgængelige kvantitative data for at undgå misvisende skøn over behandlings effekter og vildledende vurderinger af, i hvilket omfang resultaterne kan generaliseres.

3. Introduction

3.1 Total hip replacement surgery

Total hip arthroplasty (THA) is a very common surgical procedure nationally as well as worldwide. It involves surgical removal of the diseased cartilage and bone of the femoral head and acetabulum, which are then replaced with an artificial ball joint that includes a stem inserted to the femur with a ball on the top and an artificial acetabular socket with a liner inside (Fig. 1).

Fig. 1: Total hip Replacement



The history of THA began in 1925 with the intervention of the “mold arthroplasty” by Marius N. Smith-Peterson from Boston, Massachusetts, USA. He molded a piece of glass into the shape of a hollow hemisphere and fitted it over the ball of a patient’s hip joint (1;2). Sir John Charnley from England was the first to demonstrate, in 1961, long-term success by using a prosthetic implant attached to bone with self-curing acrylic cement. Since then, many improvements regarding fixation, cementing techniques, and refinements in design of the prosthesis have been made (3;4). In Denmark in 2006, 47% of THAs were performed using an uncemented cup and uncemented stem, 22.4% with an uncemented cup and cemented stem, and 30.6% with both a cemented cup and stem (5).

The operational indication for THA is a combination of symptoms, objective signs, and radiological findings. The symptoms are dominated by pain at rest, leading to disability or threaten loss of working ability. Objective signs can be reduced movement, instability, and locking in the hip joint. The accompanying radiological findings are narrowing of the joint space, increased sclerosis of the head and acetabulum, cysts in the head or acetabulum, osteophytes and later loss of sphericity

of the femoral head (6;7) On basis of these indications, the main diagnosis for patients receiving a primary THA is primary osteoarthritis, which accounts for more than 79% of patients treated with a THA (5). Secondary reasons are, among others, fresh fracture of the femoral neck, late sequelae from fracture of the proximal femur, acetabular fracture, atraumatic necrosis of the femoral head, and rheumatoid arthritis (5;6). THA surgery is usually considered when conservative treatment (e.g. pain medication and physiotherapy) are insufficient.

The incidence rate of primary THA procedures is consentingly increasing due to improved surgical techniques and demographic changes owing to an ageing population (8). In Denmark, the incidence rate at risk for primary THA procedures were 131 and 141 per 100,000 inhabitants in 2001 and 2006, respectively. From 2002 to 2020 the expected future demands of THA in Denmark have been estimated to increase with between 22% and 210% (9).

3.2 Total knee replacement surgery

Total knee arthroplasty (TKA) like THA is a common surgical procedure that has become the treatment of choice for people with intractable joint pain and disability due to chronic arthropathy who fail to benefit from conservative management (7) The history of total knee arthroplasty (TKA) has a line of development parallel to that seen with THA. In the early 1970s John Insall designed what has become the prototype for current TKA. This prosthesis is made of three components which resurfaced all three surfaces of the knee (the femur, tibia, and the patella) and is fixed with bone cement. Since then, significant improvements have been introduced (10;11).

Fig. 2: Total knee replacement



Today, a TKA is typically composed of a metal shield to the femur, a metal platform to the tibia, a mobile work of hardened plastic that rest on the metal platform, and

the patella is often replaced with metal or plastic. These three to four parts are referred to as the arthroplasty (Fig. 2).

The commonly accepted indications for TKA are joint pain, disability, and arthritic changes seen on radiography during weight bearing (12). On these indications, the most common diagnosis in 2006 for patients receiving a TKA was primary osteoarthritis, accounting for 84.9%.

The incidence rate per 100,000 inhabitants for primary knee replacement was 135 in 2007 and the incidence is increasing (13).

Being subjected to THA or TKA consists, however, of much more than the operation itself, and numerous factors should be taken into account. A rather new concept for optimizing the perioperative period in terms of reducing the surgical stress response and minimize pain and discomfort is fast-track surgery, also referred to as accelerated intervention, multimodal intervention, and clinical pathway.

Fast track surgery

Fast-track surgery involves a coordinated effort to combine preoperative patient education, preoperative optimization, attenuation of surgical stress response, optimized pain relief, enforced mobilization, and nutritional support (14-16). The concept of fast-track has been developed in order to shorten the time needed for convalescence, especially after major surgical procedures, and to reduce perioperative complications (17).

Major orthopedic surgery such as THA and TKA is associated with moderate to severe postoperative pain which can contribute to immobility-related complications, delay in hospital discharge, and interfere with functional outcome (18;19). Adequate pain relief is a prerequisite for optimal recovery and may be achieved using a combination of analgesic agents or techniques (14).

3.3 Postoperative analgesia

Over the last decade, several techniques have been available to treat pain after THA and TKA, such as intravenous patient controlled analgesia (PCA) (20), peripheral nerve blocks (21;22), and continuous epidural analgesia (23;24). Although there are a number of treatments options for postoperative pain, a “gold standard” has not been established.

Opioids continue to play a major role in pain management even though they may contribute to increased morbidity and hospital costs, and patients may be at significant risk for opioid-related adverse effects (25-27).

Multimodal analgesia

The concept of multimodal analgesia was introduced in the early 90s with the aim of enhancing analgesia in terms of targeting the various pathways and neurotransmitters involved in nociception by incorporating the use of analgesic adjuncts with additive or even synergistic effects (28). This approach may allow a reduction in the dose of each individual analgesic and thereby reduce the drug-related side effects.

In this Thesis we focus on, epidural and local infiltration techniques with local anesthetics for postoperative analgesia following THA and TKA.

Literature search

Reports of prospective randomized controlled trials (RCTs), reviews, meta-analysis, and overview articles were systematically sought. The search was performed using the PubMed database with restriction to the English language. The literature was reviewed using MeSH terms "*Arthroplasty, Replacement, Hip*" or "*Hip Prosthesis*" or "*Hip Joint*" and "*Knee Joint*" or "*Arthroplasty, Replacemen, Knee*" or "*Knee Prosthesis*" and "*Pain Postoperative*" and "*Anesthetics, Local*" and "*injections, Intra-Articular*". Further, we reviewed the PubMed literature using free text search "*local infiltration analgesia*" and "*Hip*" or "*Knee*". Finally the PubMed literature was reviewed using MeSH terms "*Randomized Controlled Trials*" and "*Reproducibility of Results*" or "*Patient Participation*" or "*Patient Selection*" and in combination with free text search "*external validity*" or "*non-participants*" or "*nonparticipation*". Additional reports not obtained in the primary search were identified from reference lists of retrieved reports and review articles.

Epidural Analgesia

The use of continuous epidural analgesia with local anesthetics with or without opioids is well established for the treatment of moderate to severe pain and their use has been popular in major orthopedic surgery like THA and TKA during recent decades (23;24;29;30). A meta-analyzes (N=100 RCT) comparing epidural therapy with parenteral opioids after various surgical procedures showed that epidural analgesia regardless of analgesic agent, location of catheter placement, and type and time of pain assessment, provided better postoperative analgesia compared with parenteral opioids (31). A systematic review from 2003 comparing lumbar epidural blockade with systemic opioid analgesia after THA and TKA reported better dynamic pain scores in the epidural group but no difference in the incidence of overall side effects (32).

Perioperative infiltration and intraarticular infusions

The use of local anesthetics at incision sites or as intraarticular (IA) infusion for analgesia has gained increased attention and seems an attractive method for the management of postoperative pain after various surgical procedures because of the low side-effect profile, ease of use, and low cost (33). Local anesthetics can be administered as single-dose infiltrations, and or via catheters to infuse the wound at the end of the procedure (34;35).

Moiniche et al. reviewed 20 double-blind RCTs of a single-dose IA administration of local anesthetics compared with placebo or no treatment after arthroscopic knee surgery (36). In 12 studies, improved pain relief was shown, and the authors concluded that there was weak evidence for a reduction of postoperative pain.

Marret et al. found significantly better analgesia with IA local anesthetics infiltration after arthroscopic knee surgery with ropivacaine 0.75 % compared with bupivacaine 0.5%, whereas no difference in pain intensity scores was documented between the bupivacaine and placebo groups (37).

The effect of IA administration of opioids after knee arthroscopic surgery has been investigated (38;39) and a short-term analgesic effect has been shown.

The use of IA analgesia following TKA has been investigated with diverging results (40-44). Badner et al evaluated IA injection of 30 ml bupivacaine 0.5% compared with placebo for 24 h, and found a not statistically significant decrease in opioid consumption (40). Mauerhan et al. evaluated the use of IA bupivacaine (50 mg) and/or morphine injection for 48 h. Results indicated a modest short-term reduction in pain scores in favor of the local anesthetics and morphine groups (42). In contrast, Ritter et al. found no significant differences between IA bupivacaine (25 mg) and/or morphine injection for 24 h (44). Browne et al. evaluated the use of IA bupivacaine (100 mg) compared with placebo injection for 24 h. The local anesthetics group had lower pain scores and reduced narcotic consumption during the 24 h postoperative period, but the differences were not statistically different (43). In an open intervention study Rasmussen et al. reported significantly improved motion and decreased opioid use in groups receiving continuous IA infusion of local anesthetics and morphine compared with no treatment (41)

Infiltration and IA injection of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) has also been investigated. A review from 2000 reported that two out of three studies showed significant pain relief with local infiltration with NSAIDs compared with placebo. The authors concluded that the results were inconclusive. In the same

review four out of four studies demonstrated a significant reduction of pain with IA administration compared with similar systemic administration of NSAIDs (45). The analgesic effect of IA administration of NSAIDs (ketorolac) has been confirmed by others (46-49).

Bianconi et al. investigated the effectiveness of local anesthetic wound infiltration (200 mg ropivacaine) combined with continuous subcutaneous wound infusion of ropivacaine (550 mg) during 55 h with IV morphine 0.5 mg/h and ketorolac 3.6 mg/h for 24 h after THA and TKA. The local anesthetics group had significantly lower pain score beginning at 8 h postoperatively and continuing to 72 h postoperatively and the consumption of rescue medication was also significantly reduced (50).

A systematic review from 2006 examining the use of continuous wound catheters in multiple surgical procedures concluded that this technique was advantageous with regard to improved analgesia, reduced opioid use, and side effect (34).

In 2005 we became aware of a multimodal local infiltration analgesic technique (LIA) consisting of high volume infiltration combined with an IA re-injection with a mixture of ropivacaine, ketorolac, and epinephrine for management of postoperative pain after THA and TKA. The technique was developed by Lawrence Kohan and Dennis Kerr from Sydney, Australia, but first detailed described and published in 2008 (51).

Only two nonblinded RCTs that investigated this multimodal wound infiltration analgesic technique for postoperative pain relief after TKA and THA could be identified up to 2007 (52;53) (Table 1).

Table 1. Randomized controlled trials, nonblinded local anesthetic infiltration after total knee arthroplasty.

Authors, year, n,	Local anesthetic regime	Control regime	Analgesic consumption	Pain intensity scores
Busch et al. (52) 2006, n=64	Periarticular infiltration ropivacaine 400 mg + ketorolac 30 mg + epimorphine 5 mg + epinephrine (100 ml)	No infiltration	Reduced for up to 24 h postoperatively	Reduced for up to 4 h postoperatively
Vendittoli et al. (53) 2006, n=44	Periarticular infiltration ropivacaine 275 mg + ketorolac 30 mg + epinephrine (160 ml) Intra-articular re-injection 24 h postoperatively 250 mg ropivacaine (15 ml)	No infiltration and no re-injection	Reduced for up to 48 h postoperatively	Reduced for up to 48 h postoperatively

Busch et al. compared the efficacy of multimodal infiltration with 400 mg ropivacaine, 30 mg ketorolac, 5 mg epimorphine, and 0.6 mg epinephrine with no infiltration for 24 h after TKA. Results showed a significantly decrease in overall morphine consumption during the 24 h study period and significantly lower scores for pain intensity (VAS) until 4 h postoperatively (52). Vendittoli et al. evaluated the effect of multimodal infiltration (275 mg ropivacaine, 30 mg ketorolac and 0.5 mg epinephrine) combined with one IA injection with local anesthetics (150 mg ropivacaine) as compared with no treatment. Narcotics consumption and pain scores were significantly reduced for up to 48 h postoperatively in favor of the local infiltration group (53) (Table 1).

In conclusion, we were not able to find evidence for the use of local infiltration analgesia as treatment for postoperative pain after TKA and THA. However the technique may have potential usefulness (30)

4. Aim of the thesis

The aims of the thesis were as follows:

Study I To investigate the efficacy of local infiltration analgesia compared with continuous epidural infusion after total hip replacement surgery.

Study II To investigate the efficacy of continuous local infiltration analgesia compared with continuous epidural infusion after total knee replacement surgery.

Study III To evaluate the external validity of an RCT investigating the efficacy of local infiltration analgesia after total knee replacement surgery.

5. Design

Different designs were used according to the particular question under investigation. Because all studies were experimental, they were longitudinal and prospective, and a randomized controlled design was used.

When evaluating the results from the present studies, several considerations regarding design and methods used to determine outcome must be taken into account since they all may influence the results obtained.

The Randomized Controlled Trial

The randomized Controlled Trial (RCT) is often used to test the efficacy or effectiveness of healthcare services or health technologies. It involves the random allocation of different interventions and is considered as being the “gold standard” for determining the efficacy of different interventions (54-56).

The purpose of the randomization in trials is to ensure that every patient who entered the study has the same, known probability of receiving one or the other of the treatments being compared and thereby ensuring that the groups only differ with respect to the interventions being compared (57).

In the present study patients were randomized according to a computer-generated sequence made by a person with no relation to the study. Each patient in the studies was assigned to a control or intervention group by opening a sequentially numbered, opaque sealed envelope prior to surgery.

Blinding of patients and healthcare staff is another important issue to minimize bias in RCTs and it must be attempted if possible because lack of masking can lead to different placebo effects and information bias (58).

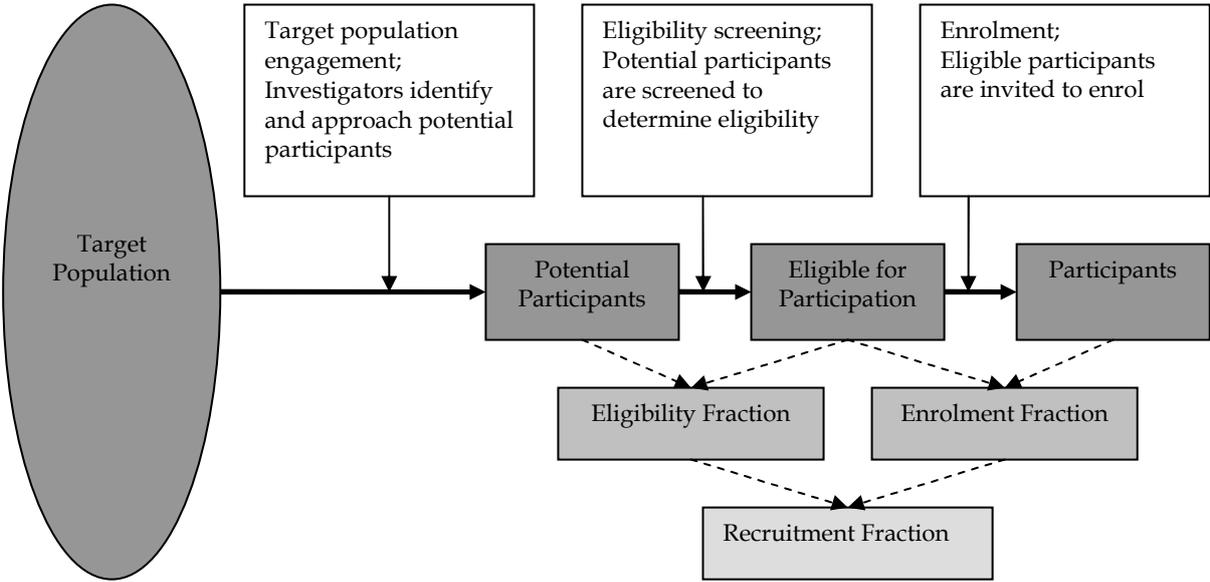
In the present study blinding was not attempted due to two reasons: firstly, because of the potential risk of infection with the use of two invasive catheters and secondly, because the treatments used are obviously different regarding side effects.

Results of well-designed and well-conducted RCTs cannot be relevant to all patients and settings, but to be useful for clinicians, the results must be relevant to a definable group of patients in a particular clinical setting; this is generally termed external validity, applicability, or generalizability. To obtain high internal validity by eliminating the possibility of bias, most results of RCTs are obtained in a tightly controlled environment with selective eligibility criteria, with the intent to include a strictly homogeneously sample to reduce confounding. Strict eligibility criteria can diminish the external validity in RCTs, and therefore they should at least be available for scrutiny (56;59)

Even if the randomized comparison in clinical trials is not biased by exclusion per se, external validity of trial results depends on the representativeness of the study sample (60;61) A step-wise model to describe the recruitment process is recommended Fig. 3 (54).

If only a proportion of potentially eligible patients is enrolled in a trial, it is important to evaluate how participants differ from nonparticipants as a result of eligibility criteria or other factors (54;62)

Fig. 3: The steps in the recruitment process [Gross CP et al. 2002] (54)



The external validity of an RCT also depends on whether the outcome measure is clinically relevant and on the duration of treatment and/or follow-up.

6. Materials & methods

Ethical issues

The procedures followed in the three studies were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration.

Study I was approved by the Ethics Committee of the County of Aarhus (J. no. 20040199) and registered in The Danish Data Protection Agency (J. no. 2005-41-4840), and the Clinical Trial Register (NCT00289419)

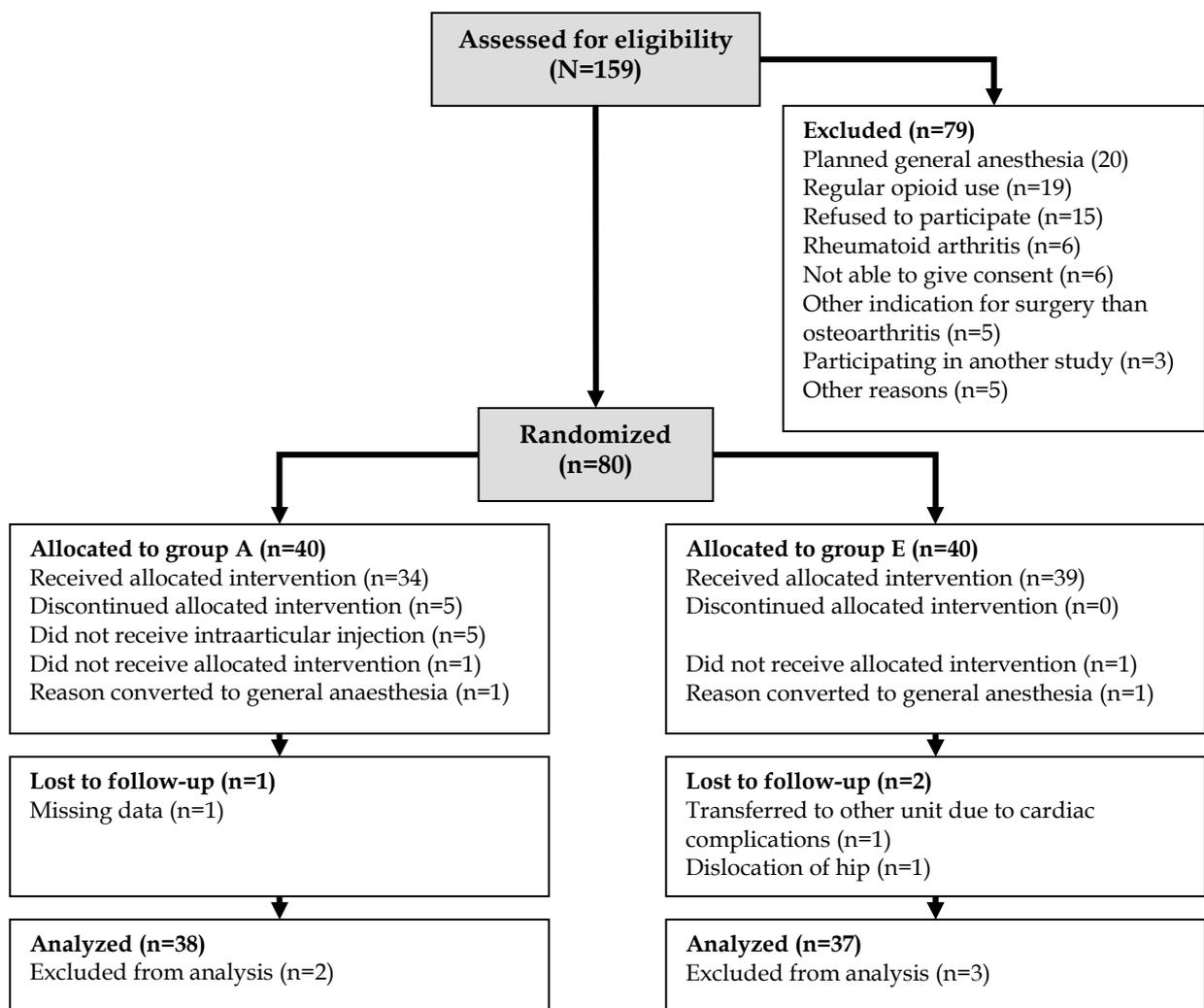
Study II (III) was approved by the Ethics Committee of the County of Copenhagen (20060134), The Danish Medicines Agency (EudraCT.no. 2006-004638-33), and monitored by the GCP unit of Copenhagen. The study was also registered in The Danish Data Protection Agency (J. no. 2006-41-7334) and the Clinical Trial Register (NCT00421967)

Patients

Study I

All consecutive patients awaiting elective primary unilateral THA at Aarhus Hospital, Aarhus University Hospital, were prospectively screened according to entry criteria from February 2005 – February 2006. Exclusion criteria were known allergy to study drugs, simultaneous bilateral THA, planned general anesthesia, obesity (body mass index $> 35 \text{ kg/m}^2$), regular opioid use, rheumatoid arthritis, inability to comprehend pain scales and patients with alcohol or drug abuse. Suitable patients were counseled before giving informed consent. During the study period, 159 patients were identified as potential participants, 79 were excluded, and 80 patients were enrolled and randomized. Progression through the phases of Study I is shown in Fig. 4.

Fig.4: Flowchart of participants' progress through the phases of study I.

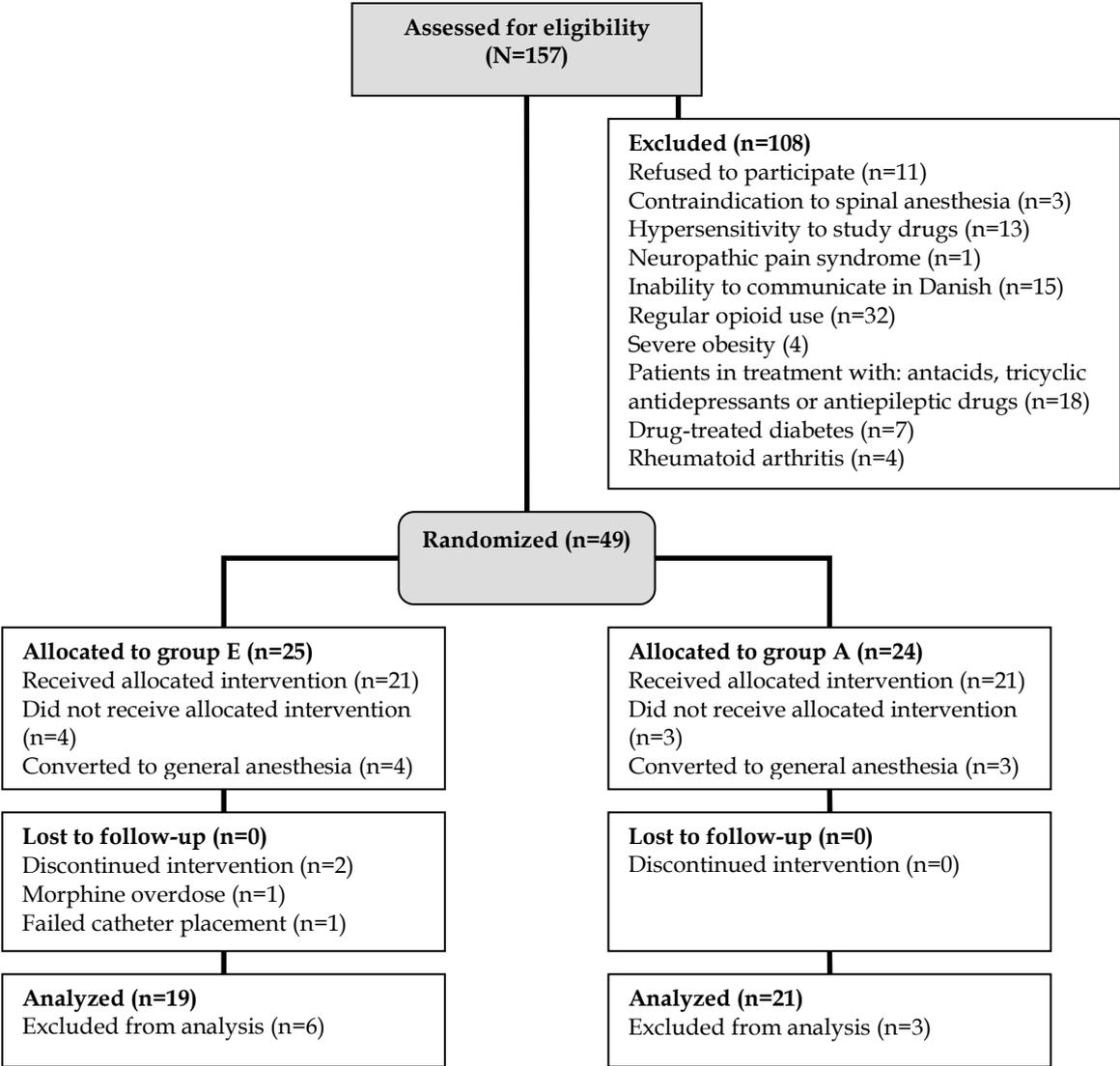


Studies II and III

Patients >18 years of age scheduled for elective, unilateral, primary TKA at Glostrup Hospital from January 2007 until March 2008 were identified as potential participants. The exclusion criteria were contraindications to spinal anesthesia or epidural analgesia, hypersensitivity to study drugs, neuropathic pain or sensory disorders in the leg to be operated on, inability to communicate in Danish, regular narcotic use, rheumatoid arthritis, severe obesity (body mass index >40 kg/m²), drug-treated diabetes, patients in treatment with antacids, tricyclic antidepressants and/or antiepileptic drugs and pregnant women. Patients who meet the inclusion criteria were invited to participate and given written and oral information about the study at the initial visit. Those who were interested gave their written informed consent.

In the study period, 157 patients were identified as potential participants (patients enrolled in study III). Ninety-seven patients were excluded according to exclusion criteria and eleven patients declined to participate. Forty-nine patients were enrolled and randomized (study II) to receive either the current procedure (epidural analgesia) or intervention (local infiltration analgesia). A flowchart of participants' progress through the phases of study II and study III is shown in Fig. 5.

Fig.5: Flowchart of progression through the phases of study II and study III.



Intervention

Control and intervention groups study I

One the day of surgery, patients received oral premedication of 1000 mg acetaminophen and 5 to 10 mg diazepam.

All patients were operated using a posterior approach under spinal anesthesia, with 15 mg bupivacaine 5 mg/ml (Marcaïne Spinal Plain) administered via the L2/L3 or L3/L4 vertebral interspace.

To reduce blood loss, tranexamic acid 10 mg/kg was given at the beginning of surgery and repeated 3 h postoperatively. Dicloxacillin 2000 mg (Diclocil) was given intravenously preoperatively, and 1000 mg was administered every 8 h until 24 h postoperatively. A negative-pressure vacuum suction drain was placed near the arthroplasty under the fascia before wound closure. For thromboprophylaxis fondaparinux 2.5 mg (Arixtra) was administered once daily for 7 days postoperatively.

Oral analgesia consisted of 1000 mg acetaminophen 4 times daily starting in the recovery room. Break-through pain (VAS>30 mm) at rest was relieved by immediate-release oxycodone hydrochloride (Oxynorm) 5 to 10 mg or in the case of persisting severe pain (VAS>5) intravenously nicomorphine (Vilan) 5 to 10 mg. There were no restrictions regarding the frequency of drug administration or the overall daily dose. Starting at 20 h postoperatively oxycodone hydrochloride (OxyContin) 10 to 20 mg was given as analgesic treatment twice daily.

Patients received as a laxative 10 mg bisacodyl (Perilax) daily, and in the case of postoperative nausea and vomiting (PONV), 2 to 4 mg ondansetron (Zofran) was given. Disposal catheters were used when urine retention >350 ml as documented by ultrasound bladder scan (63).

At 8 hours postoperatively, patients were instructed how to get out of bed and to walk with walking devices. On a daily basis, a physiotherapist coached patients in mobilization (gait training, exercises focusing on strengthening the hip muscles, and how to avoid restricted movements).

Intervention group

Patients received local infiltration analgesia (LIA) consisting of an infiltration with a mixture of 100 ml ropivacaine 2 mg/ml, 1 ml ketrorolac 30 mg/ml, and 0.5 ml epinephrine 1 mg/ml. The mixture was loaded into 50 ml syringes which the surgeon used to infiltrate one layer at a time. The first syringe was used to infiltrate the capsule around exposed gluteal and adductor muscles and extern rotators. The second syringe was used to infiltrate the subcutaneous tissues under the wound. Immediately before wound closure, a multihole catheter was tunneled under direct visualization and placed with the catheter tip in the joint. A bacterial filter was then connected, and 1 to 2 ml of the mixture was injected through the catheter to ensure patency.

Eight hours postoperatively a re-injection was performed with 20 ml ropivacaine 7.5 mg/ml, 1 ml ketorolac 30 mg/ml, and 0.5 mg epinephrine 1mg/ml (total volume 21.5 ml). The mixture was injected by hand through the bacterial filter.

Approximately 15 ml of the solution was injected before the catheter was removed and then the rest spread evenly throughout the wound as the catheter was withdrawn and removed. The wound drain was removed before re-injection through the catheter in order to prevent drug loss through the drain.

Control group

A combined spinal-epidural technique was used. On regression of the spinal block, a test dose of 3 ml lidocaine-adrenaline 20 mg/5 µg/ml was given to confirm extradural positioning. No priming dose was given. Postoperatively, analgesia within the first 20 h was attained with continuous epidural infusion (flow rate 4ml/h) of 2mg/ml ropivacaine with 5 µg/ml morphine. Patients were instructed to take epidural bolus as needed (4 ml, lockout 15 min, and total bolus limit of 2 per h) when VAS >30 mm at rest and VAS >50 mm during mobilization. To obtain adequate pain relief, the flow rate could be increased by 2 ml/h.

Control and intervention group study II

Patients did not receive premedication. Spinal anesthesia was induced with 15 mg bupivacaine 5 mg/ml (Marcaine Spinal) administered via the L2/L3 vertebral interspace. Surgery was performed using a standard medial parapatellar approach in a bloodless field obtained by the use of a femoral tourniquet. To reduce blood loss tranexamic acid 10 mg/kg was given at the beginning of surgery and repeated 3 h postoperatively. Drains or bladder catheters were not used. Low molecular weight heparin 5000 IE subcutaneously was administered at 6 to 8 h postoperatively for thromboprophylaxis and once daily until 5 days postoperatively. All patients received laxatives and ondansetron (Zofran), and metoclopramide (Emperal) were used for the treatment of PONV.

For analgesic treatment, 1000 mg acetaminophen was given 4 times daily. Break-through pain was controlled with IV Patient Controlled Analgesia (PCA) morphine (1mg/ml, dose 2.5 mg, lockout 10 min). The PCA pump was removed after 48 h, and oxycodone hydrochloride (OxyContin) 10 mg was administered twice a day. Disposal catheters were used when urine retention >350 ml documented by ultrasound bladder scan (63)

All patients received physiotherapy daily and were discharged with a home-training exercise program.

Intervention group

A solution of 151 ml consisting of 150 ml ropivacaine 2 mg/ml and 1 ml ketorolac 30 mg/ml was prepared. Fifty ml of the solution was loaded into one 50 ml syringe and to the remaining quantity was added 0.5 ml epinephrine 1 mg/ml and loaded into two 50 ml syringes.

The first 50 ml was injected into the posterior joint capsule after the bone surfaces had been prepared. After the components were inserted, the deep tissues around the medial and lateral collateral ligaments and wound edges were injected with 50 ml. The remaining 50 ml of solution without epinephrine was used to infiltrate the subcutaneous tissue. Before wound closure, a multihole catheter was placed with the tip anterior to the posterior capsule. A bacterial filter was then connected, and 1 to 2 ml of the mixture was injected through the catheter to ensure patency. An infusion pump (Multirate infusor Baxter) was then connected, delivering a continuous (4 ml/h) infusion of 8 mg/h ropivacaine 2mg/ml and 1.25 mg/h ketorolac 30 mg/ml for 48 h postoperatively.

Control group

A combined spinal-epidural technique was used. On regression of the spinal block, a test dose of 3 ml lidocaine 20 mg/ml – adrenaline 5 µg/ml was given to confirm extradural positioning, followed by a dose of 7 ml ropivacaine 2mg/ml.

For 48 h postoperatively, analgesia was attained by continuous epidural infusion (Infusion pump CADD AstraTech) 4 ml/h with ropivacaine 2 mg/ml and IV 0.5 ml ketorolac 30 mg/ml given perioperatively and 3, 20, 28, 34, and 42 h postoperatively.

Study III

The study was a prospective cohort study with an embedded RCT (study II). To evaluate the external validity of study II, we used a standardized abstraction instrument, as recommended by Gross (54).

The trial terminology and a participant's progress through the phases of the study are shown in table 3. Baseline data and peri- and postoperative variables for potential participants were collected prospectively to estimate differences between eligible consenters, excluded patients, and nonconsenters.

Table 3: A participant's progress through the phases of studies II and III

Term	Definition	Population under investigation
Target population	Location and characteristics of potentially eligible persons; represents the individuals to whom the trial results are expected to apply	Patients >18 years of age, scheduled for elective primary unilateral TKA (N=157)
Eligibility fraction	Proportion of potential participants who undergo eligibility screening and are eligible to enroll	Reason for exclusion of enrolment (n=97) <ul style="list-style-type: none"> • Contraindications to spinal anesthesia or epidural analgesia (n=3) • Hypersensitivity to study drugs (n=13) • Neuropathic pain or sensory disorders in the leg to be operated on (n=1) • Inability to communicate in Danish (n=15) • Regular narcotic use (n=32) • Patients in treatment with antacids (n=9) • Rheumatoid arthritis (n=4) • Severe obesity Body Mass Index > 40 (n=4) • Drug-treated diabetes (n=7) • Patients in treatment with tricyclic antidepressants (n=8) • Patients in treatment with antiepileptics (n=1)
Enrolment fraction	Proportion of patients who are eligible for participation and who actually enroll	Patients asked for informed consent (n=60)
Recruitment fraction	Proportion of potential participants who are actually enrolled and randomized	Enrolled and randomized patients (n=49)

Outcomes

Outcome measures in study I to II

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (64).

The measurement of pain can be performed using many different methods depending on which aspect of pain is under investigation (65;66).

There is no gold standard regarding the measuring of pain intensity, but the most simple and frequently used instruments are Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), and Verbal Rating Scale (VRS).

The VRS is a 4-point categorical scale using explanatory words: none, mild, moderate, and severe pain. The NRS is based on an 11-point scale, with zero denoting no pain and 10 signifying the worst imaginable pain.

The classic VAS is a 100-mm line with anchors indicating extremes Fig. 6.

(65-72). In the present studies we used the classic VAS as a measurement for pain intensity after surgery.

Fig. 6: Visual Analogue Scale



VAS is a generic, nondisease specific instrument (66). It can be used to measure pain before, under, and after treatment, but it is also possible to use as a “pain diary” (73). VAS has shown to be reliable and is a valid instrument to measure pain intensity in adults without cognitive problems (65;70;74); however, the measurement of changes in pain is only meaningful if changes in the use of analgesic requirements is recorded simultaneously (75).

Length of hospital stay (LOS) was registered from the day of surgery to the day of discharge. Although the use of hospitalization as an outcome is frequently used the validity of LOS can be questioned. In order to minimize bias, we used standardized discharge criteria as recommended (16).

Outcome study I

Primary outcome was hip pain intensity at rest and during mobilization. Secondary outcomes included opioids requirements, occurrence of side effects, LOS and postoperative complications and readmissions during 3 months’ follow-up.

Pain intensity was registered by patients themselves using the Visual Analogue Scale (VAS) during three periods: at rest for 2 – 96 h postoperatively and during deep coughing and while walking for 2 – 20 and 20 – 96 hours postoperatively. The consumption of opioids was determined from the hospital registration system. Side effects consisting of the occurrence of PONV, constipation and itching were registered by the patients themselves every 2 h on the day of surgery and every 4 h from 24 h – 96 h postoperatively, excluding at night. Constipation was defined according to department guidelines as no bowel function for 72 h. Urine retention was defined as >350 ml documented by ultrasound bladder scan. Adverse reactions or events related to the local anesthetic instillation were recorded on a daily basis and abstracted from the evaluation charts.

LOS was recorded using standardized discharge criteria. Patients were considered for discharge if sufficient pain relief was obtained (VAS score < 30 mm at rest and < 50 mm during mobilization), patients were able to maintain personal hygiene, being

able to perform home exercises, helping aids delivered and installed, walk with walking sticks, and able to climb stairs. All patients were seen in the outpatient clinic at Aarhus Hospital, Aarhus University Hospital 90 days after discharge for a 3-month follow-up and could here give information regarding readmissions and complications.

Outcome study II

Opioids consumption was the primary outcome. Secondary endpoints were knee pain intensity at rest and during mobilization, occurrence of adverse events, the day patients fulfilled discharge criteria, LOS, and postoperative complications and readmissions during the first month after surgery.

Data on opioid consumption were abstracted from portable CADD-Legacy PCA infusion pumps, model 6300 (Smiths Medical MD, Inc.). Pain intensity at rest (2 - 72 h postoperatively) and during deep coughing (2 - 4 h postoperatively) and during walking (4 - 72 h postoperatively) was registered by patients themselves in diaries using the Visual Analogue Scale. PONV, constipation, and itching were registered by patients themselves in diaries from 2 - 72 h postoperatively. Constipation was defined according to department guidelines as no bowel function for 72 h. Urine retention was defined as >350 ml documented by ultrasound bladder scan. Adverse events or reactions related to the local anesthetic instillation were recorded on a daily basis and abstracted from evaluation charts.

LOS was recorded using standardized discharge criteria. Patients were considered for discharge if sufficient pain relief was obtained (VAS score < 30 mm at rest and < 50 mm during mobilization), patients were able to maintain personal hygiene, walk safely with walking sticks, able to perform home exercises, able to climb stairs, uncomplicated wound-healing process, uncomplicated clinical and radiographic outcomes, no evidence of deep vein thrombosis, satisfactory hemoglobin level and at least 90° of knee flexion

All patients were contacted by phone 30 days after discharge to give information regarding readmissions and complications.

Outcome study III

In order to investigate possible differences between participant and nonparticipants, data were abstracted from evaluation charts. The form included information regarding preoperative and postoperative variables. Discharge criteria and LOS were measured and registered in the same way as in study II.

Statistics

All data were entered twice using EpiData 3.1(EpiData Association, Odense, Denmark).

In study I, analyses were performed using NCSS 2000 statistical software (Kaysville, Utah, USA). In studies II and III, analyses were performed using STATA 10.0, (StataCorp, Texas, USA).

Sample size

With a significance level of 5% and a power of 80%, sample size was estimated to be 70 patients based on an expected reduction in pain intensity score (0-100 mm VAS) of 25%, (SD; 22). To compensate for patient dropout, we planned to enroll 80 patients.

Calculation of sample size in study II was based on an expected difference of 10 mg IV rescue opioid (SD 15). With a power of 80% and a significance level of 5%, sample size was estimated to be 72 patients. To allow for incomplete data collection, a conservative sample size of 80 patients was chosen.

Sample size was not calculated in study III, because of the study design.

Statistical methods

Frequencies were compared using Fisher's exact test. Normally distributed data were presented as means, SD with 95% confidence intervals (CIs), and statistically tested with Student's T test. Data that did not fulfill the assumptions of normal distribution were described by medians with interquartile range (IQR) and analyzed with the Mann-Whitney U test. The level of significance was chosen to be 0.05.

7. Results

Study I

Patients were randomized to receive either local infiltration analgesia (LIA group) or epidural analgesia (EA group) for 20 h after THA. The two groups were similar at trial entry in terms of preoperatively baseline variables. Groups were also comparable in relation to perioperative variables.

The analysis of the primary outcome pain intensity at rest and during coughing showed no significant differences in group LIA compared with the EA group during the active treatment period (0 – 20 h post) (Table 4).

Table 4. Pain intensity (Visual Analogue Scale, VAS 0 – 100 mm) at rest and during mobilization in a randomized control trial (n=75)

	Group LIA (n=38)	Group EA (n=37)	P value
Highest pain score at rest			
0 - 20 h, median (IQR)	30 (12 - 33.5)	16 (6 - 40.5)	0.2
24 - 48 h, median (IQR)	8 (0 - 22.5)	20 (3.5 - 39)	0.02
48 - 72 h, median (IQR)	0 (0 - 0)	11 (5.5 - 24)	< 0.001
Highest pain score during mobilization*			
0 - 20 h, median (IQR)	28 (14 - 41)	22 (07 - 45)	0.4
24 - 48 h, median (IQR)	27 (0 - 46)	42 (20 - 64.5)	0.04
52 - 96 h, median (IQR)	6 (0 - 26.25)	30 (15 -45)	< 0.01

* From 0 – 20 h postoperatively during coughing and from 24 – 96 h postoperatively during walking. Mann-Whitney U test.

At cessation of treatment, the median VAS pain score was significantly reduced in group LIA both at rest ($P = 0.02$) and during walking ($P = 0.04$) from 24 – 48 h postoperatively. This difference in pain intensity continued until 96 h postoperatively (Table 4).

The median (IQR) consumption of opioids (0 – 20 h postoperatively) was significantly reduced in group LIA 17.5 mg (0 – 40.5) relative to group EA 26 mg (31 – 52) ($P = 0.004$). This difference in opioid consumption persisted during the whole period of observation ($P < 0.05$) group LIA 258 mg (167 – 366) compared with group EA 324 mg (221 – 543).

The occurrence of PONV between groups was not significant. Patients in the control group experienced more often urinary retention ($P=0.001$), constipation ($P < 0.001$), and itching ($P = 0.01$) than patients in the intervention group (Table 5).

Table 5. Comparison of side effects in a randomized control trial (n=75)

Side effects	Group LIA (n=38)	Group EA (n=37)	P value
Nausea, n	8 / 38	14 / 37	0.1
Vomiting, n	2 / 38	8 / 37	0.05
Urinary retention, n	3 / 38	32 / 37	0.001
Itch, n	0 / 38	6 / 37	0.01
Constipation, n	5 / 38	24 / 37	<0.001

Fisher's exact test.

The number of patients able to walk at 8 hours postoperatively was significantly increased in group LIA (frequency 33 / 38) relative to group EA (13 / 37) ($P < 0.001$). A 36% reduction in LOS was observed in group LIA median (IQR) 4.5 (3– 6) relative to group EA 7 (5.5 – 7) days, ($P < 0.001$).

We did not observe any adverse reactions or events in relation to the ropivacaine instillation.

During the follow-up period, two patients in each group developed deep vein thrombosis, and one patient in group LIA developed a deep infection.

Study II

Patients were allocated to receive either intervention treatment (LIA group) or control treatment (EA group) during the first 48 h postoperatively.

Patients were followed for 72 h and contacted by phone 30 days postoperatively.

Based on sample-size calculation, 72 patients should have been enrolled in the study.

Due to a prolonged inclusion period, it was decided to terminate the study when 40 patients had completed the study protocol.

No significant differences in baseline variables were observed between the two groups.

The analysis of PCA opioid intake during active treatment (0 – 48 h postop.) showed a significant reduction in favor of the LIA group compared with group EA: median (IQR) 11.25 mg (3.75 – 22.5) and 32.5 mg (20 – 40), respectively ($P = 0.01$).

As shown in table 6 pain intensity scores both at rest and during mobilization were significantly lower in group LIA compared with group EA during the whole period of observation, with the exception of pain intensity scores during mobilization 0 - 24 h postoperatively ($P = 0.05$)

Table 6. Pain intensity (Visual Analogue Scale, VES 0 - 100 mm) at rest and during movement in a randomized control trial (n=49)

	Group LIA (n=)	Group EA (n=)	<i>P</i> value
Highest pain score at rest			
0 - 24 h, median (IQR)	7 (3 - 25)	30 (10 - 44)	< 0.01
24 - 48 h, median (IQR)	5 (2 - 21)	33 (9 - 38)	0.02
48 - 72 h, median (IQR)	8 (3 - 21)	23 (14 - 42)	0.02
Highest pain score during mobilization			
0 - 24 h, median (IQR)	13 (4 - 41)	37 (12 - 53)	0.05
24 - 48 h, median (IQR)	14 (7 - 35)	41 (27 - 51)	0.02
48 - 72 h, median (IQR)	17 (5 - 36)	41 (24 - 53)	0.02
Mann-Whitney U test.			

Most side effects recorded were found to be similar. These included itching and PONV, with the exception of the frequency of vomiting at 24 - 48 h postoperatively in favor of the LIA group ($P = 0.02$).

Patients in the EA group had a longer duration of urinary retention ($P = 0.03$) and a higher incidence of constipation ($P = 0.004$) than observed in the LIA group.

The median (IQR) LOS in the LIA group was 3 (3 - 3.5) and 4 (3 - 5), days in the EA group. This difference was not significant ($P = 0.2$), however, discharge criteria were met earlier in group LIA 3 (3 - 3.5) compared with group EA 4 (3 - 5) ($P < 0.004$).

We did not observe any adverse reactions or events in relation to the ropivacaine instillation.

During the follow-up period, two patients in the EA group had wound complications and one of these patients was hospitalized. One patient in the LIA group developed a deep infection after a spinal abscess.

Study III

During the inclusion period 157 patients were identified as potential participants. Among the potential participants, 49 patients were enrolled, 97 patients were excluded, and 11 patients declined to participate.

Excluded patients were characterized by a higher BMI ($P = 0.01$), more often classified in ASA group II or III ($P < 0.001$), more often had a chronic disease ($P < 0.0001$), more often were on transfer income ($P = 0.04$), more often used walking devices ($P < 0.0001$), and more often received help from the home care service system preoperatively ($P < 0.0001$) (Table 7).

Table 7. Preoperative baseline characteristics of participants, excluded, and nonconsenters.

Variables	Participants (n=49)	Excluded (n=97)	Nonconsenters (n=11)	P value*
Age, mean (SD) [95%]	67.4 (8.5) [65-70]	70.4 (9.8) [68-72]	67.5 (10.6)	0.06 ¹
Gender				
Male / Female	16 / 33	31 / 66	6 / 5	0.93 ²
BMI, median (IQR)	28 (25-31,5)	30 (28-34)	30 (25-32)	0.01 ³
ASA classification				0.0001 ⁴
ASA class I	11	4	1	
ASA class II	36	58	10	
ASA class III	2	35	0	
Chronic disease				<0.0001 ²
Yes / No	7 / 42	70 / 27	3 / 7	
Smoking				0.81 ²
Yes / No	7 / 42	17 / 80	2 / 9	
Social factors				0.21 ²
Married / Single	33 / 16	54 / 43	2 / 9	
Occupational factors				0.04 ⁴
Employed	10	10	0	
Old-age pensioner	36	73	9	
Invalidity pensioner	3	14	2	
Preoperative home care service				<0.0001 ²
Yes / No	1 / 49	38 / 59	2 / 9	
Preoperative walking devices				<0.0001 ²
Yes / No	8 / 41	58 / 39	4 / 11	

*Participants and excluded were compared statistically. Nonconsenters are described.
¹Student's T test; ²Fisher's exact test; ³Mann-Whitney U test; ⁴Kruskal-Wallis test

LOS differed between excluded patients and participants ($P < 0.0001$) and excluded patients were more often readmitted within 30 days after surgery than were participants (Table 8)

Table 8. Postoperative variables of participants, excluded and nonconsenters.

Variables	Participants (n=49)	Excluded (n=97)	Nonconsenters (n=11)	P value*
Anesthesia				0.145 ¹
General	7	24	4	
Spinal	42	73	7	
Duration of surgery, min mean (SD) [95%]	106 (30) [98-115]	105 (30) [99-112]	94 (41)	0.86 ²
Length of stay, median (IQR)	4 (4-5)	8 (6-9)	5 (3-7)	<0.0001 ³
Readmission				0.04 ¹
Yes	2	15	2	
No	47	82	9	

*Participants and excluded were compared statistically. Nonconsenters are described.
¹Fisher's exact test, ²Student's T test, ³Mann-Whitney U test

8. Discussion

The following section will discuss the findings presented in this thesis in relation to the existing literature and the clinical implications of our findings.

Key findings

To our knowledge, these studies are the first to examine the efficacy of LIA compared with epidural analgesia after THA and TKA. We also believe that study II is the first study which has taken the systemic effect of a NSAID given via the LIA technique into account.

This thesis gives evidence that local infiltration analgesia with multimodal drugs gives excellent pain relief with a minimum of side effects after total hip and knee replacement surgery.

We also demonstrated that excluded patients differed significantly with regard to baseline variables as well as in postoperative outcome variables, which indicates the importance of eligibility criteria and the need for providing sufficient information about the recruitment process.

Consideration of possible mechanism and explanations

We believe that the observed reduction in opioid intake and pain intensity scores between the intervention group and the control group in study I as well as in study II was achieved primarily because the LIA treatment gives better pain relief. In both studies opioids were given as patient-controlled analgesia, in study I as self-administered immediate-released oral oxycodone and in study II via IV morphine PCA infusion pumps. Postoperative analgesia was in both studies supplemented with acetaminophen 1000 mg four times daily.

We have no explanation for the finding in study I that in patients who had received LIA, a positive effect on pain intensity scores could be seen after the end of active treatment. A explanation could be the local application of NSAID because similar result have been obtained in other studies (50;76).

Comparison with relevant findings from other studies

Studies I–II

Between 2006 and 2009, we identified a further five RCTs dealing with local infiltration analgesia interventions in THA (76), TKA (77-79), and unicompartamental

knee arthroplasty (UKA) (80) (Table 9). Two other RCTs were identified that investigated the site of placement of the catheter (81) and a compression bandage (82)

Table 9. Randomized controlled trials of local anesthetic infiltration after total knee arthroplasty (TKA), total hip arthroplasty (THA) and unicompartmental knee arthroplasty (UKA)

Authors, year, n	Local anesthetic regime	Control regime	Analgesic consumption / Pain intensity scores
P Essving et al. (80), 2009, n=40 (UKA)	Peri and intraarticular ropivacaine 300 mg + ketorolac 30 mg + epinephrine (106 ml) Intraarticular re-injection 21 h postoperative ropivacaine 150 mg + ketorolac 30 mg + epinephrine (22 ml)	No infiltration Intraarticular re-injections saline (22 ml)	Reduced for up to 48 h after surgery / Reduced for up to 27 h after surgery during flexion and at 6 h and 22 h postoperatively at rest
CA Busch et al. (78), 2009, n=64 (THA)	Peri and intraarticular ropivacaine 400 mg + ketorolac 30 mg + morphine 5 mg + epinephrine (100 ml)	No infiltration	Reduced for up to 24 h after surgery / Reduced in the post anesthetic care unit
LØ Andersen et al (77), 2008, n=12 (bilateral TKA)	Peri and intraarticular ropivacaine 340 mg + epinephrine (170 ml) Intraarticular re-injection at 8 and 24 h postoperatively ropivacaine 40 mg + epinephrine (20 ml) and ropivacaine 100 mg + epinephrine (50 ml)	Peri and intraarticular saline (170 ml) Intraarticular re-injections saline (20 ml) + (50 ml)	Not possible due to study design / Reduced for up to 32 h after surgery
LJ Andersen et al (76), 2007, n=37 (THA)	Peri and intraarticular ropivacaine 300 mg + 30 mg ketorolac + epinephrine (150 ml) Intraarticular re-injection 24 h postoperative ropivacaine 150 mg + ketorolac 30 mg + epinephrine (21,5 ml)	Peri and intraarticular saline (150 ml) Intraarticular re-injections saline (21,5 ml)	Reduced for up to 96 h after surgery / Reduced for up to 14 days after surgery
K Toftdahl et al. (79), 2007, n=77 (TKA)	Peri and intraarticular ropivacaine 300 mg + 30 mg ketorolac + epinephrine (150 ml) Intraarticular re-injection 24 h postoperative ropivacaine 200 mg + ketorolac 30 mg + epinephrine (21,5 ml)	Femoral nerve block with catheter, bolus ropivacaine 1%, 20 ml and continuous infusion ropivacaine 0.2%, 10 ml/h	Reduced for up to 24 h after surgery / Reduced during physiotherapy on postoperative day 1

Regarding the effect of LIA on postoperative pain intensity and additional need for opioids after THA, the results of our study (I) are in accordance with the study by Andersen et al. 2007 (76). They assessed the value of LIA after THA compared with placebo, and showed a significant reduction in pain intensity score (VAS) and rescue morphine consumption. They showed, comparable with ours, satisfactory pain intensity score at rest and during mobilization after the LIA intervention. Our results are also in accordance with the study by Busch et al. 2009 that showed a significant reduction in analgesic requirements during 24 h postoperatively for THA, when using peri- and intraarticular infiltration compared with no infiltration (78).

The effect of LIA after TKA has been studied compared with placebo (77), continuous femoral nerve block (79), and no treatment (52;53). All studies comparing the LIA treatment with control regimes or no treatment show superior analgesia in favor of the infiltration group (Table 9).

With the exception of one study (77), all studies, including ours, use a combination of various drugs for the infiltration technique.

In topical review from 2009 on LIA with local anesthetics for postoperative analgesia after total hip and knee replacement, the authors conclude that further data from randomized double-blind, placebo-controlled trials that address the single components of the multimodal technique (LIA) are needed (83). The authors reasoned that the use of multiple drugs and treatment modalities makes interpretation of the available studies difficult. In our study (II) both groups received the same amount of NSAID and local anesthetic but administered in different ways. Andersen et al. studied the effect of LIA in bilateral knee arthroplasty. Patients received infiltration with 340 mg ropivacaine plus epinephrine combined with two re-injections at 8 h (40 mg ropivacaine) and 24 h (100 mg) postoperatively or placebo. Results showed significantly lower NRS pain scores from 4 to 25 h at rest and until 32 h postoperatively during mobilization in the knee infiltrated with local anesthetic. One study has compared LIA with the ropivacaine, ketorolac and epinephrine mixture to placebo after UKA and found significantly reduced pain intensity and opioid consumption in favor of the LIA treatment (80).

In 2008 Kerr and Kohan published their results from a case study of 325 patients in which they described their development of the technique of “local infiltration analgesia” (LIA) for the control of pain following THA, TKA, and hip resurfacing.

Our results (study I and study II) are in accordance with the results obtained in the case study by Kerr and Kohan. They showed satisfactory pain control (0–3 NRS) and no need for additional opioids in two-third of the patients. The mean (SD) time for the ability to walk independently for THA and TKA patients was 24 (9.2) h and 20 (9.6) h, respectively. Side effects were limited, and mean LOS for THA and TKA patients were 4.3 and 3.2 nights, respectively (51).

We did not use compression bandaged in our studies as did Kerr and Kohan (51), and we therefore do not know whether greater pain relief could have been obtained, but a study by Andersen et al. showed a reduction in pain intensity up to 8 h after surgery with the use of compression bandaging after TKA. (82).

Regarding site placement of catheters Andersen et al. found no differences in pain relief after bilateral TKA in patients receiving intaarticular and extraarticular local anesthetics injection compared with intaarticular local anesthetics injection and extraarticular saline injection (81).

Study III

Despite the potentially important implications of disparities between participants, excluded patients and nonconsenters only a few studies have previously supplied preoperative and postoperative data in sufficient detail to allow comparison. The nonparticipants in our study were significantly different from participants at baseline and with regard to clinical outcome variables, which is in agreement with the findings in clinical studies (84-86).

A previous study investigating the efficacy of fast-track programs in Denmark after THA showed that nonconsenters were significantly older, less healthy, needed more help from the home care system, and were hospitalized longer compared with participants (87;88). The characteristics of these nonconsenters seem similarly to the excluded patients in our study.

Regarding LOS, our results are in agreement with the findings of Husted et al. (89).

Limitations

In the assessing of the validity of the findings from the studies, alternative explanations for the findings have to be examined.

It can be discussed whether our choice of control intervention in the two studies (I and II) is optimal. Firstly, even though epidural analgesia provides superior

analgesia, it is associated with hypotension, urinary retention, and motor blockade that limits ambulation and therefore may not be the first choice of treatment for postoperative pain following total knee replacement and total hip replacement surgery.

A recent review from 2008 comparing epidural analgesia with peripheral nerve blockade (PNB) after major knee surgery found no significant difference in pain score and morphine consumption between the two groups as well as no difference in postoperative nausea and vomiting (PONV); however, urinary retention and hypotension occurred more frequently among patient who received epidurals (90). The use of unilateral peripheral nerve blockade after THA has also been investigated, and analgesia and surgical outcomes similar to those of continuous epidural analgesia have been reported, but with fewer side effects (91-93). Despite these advantages, the placement of nerve blocks requires advanced regional anesthetic skills (94) and can have serious potential side effects, including, among others, patient falls and injury (95) and nerve injury (96). Secondly, epidural analgesia is not merely epidural, and therefore it can be argued that our treatment was not the “ideal” epidural regime.

Selection bias

Selection bias occurs when the association between exposure and outcome differs for those who participate and those who do not participate in a study (97).

In the THA and TKA studies, we used consecutive inclusion. Even though we used rather broad eligibility criteria in study I, we did exclude 40% and furthermore 10% refused to participate. To what extent participants, nonconsenters, and excluded patients differed with regard to important prognostic variables and how that could influence the external validity of study I remains uncertain.

In study II we excluded 62% based on the exclusion criteria and 9% refused to participate. Substantial proportions lost at any stage in an RCT have important implications for the external validity, since the resulting participants may no longer be representative of those eligible for the intervention (54;56). The results in study III show that participants and nonparticipants differed significantly regarding important prognostic factors and subsequent clinical outcome variables. A basic prerequisite of a clinical trial is that the study sample should be realistically representative of the target population for future treatment.

Our data underline the need for those conducting clinical trials to provide additional information about the recruitment process supplemented with readily available quantitative data to avoid misleading assessments regarding the degree to which the results may be generalized and thereby bias estimates of treatments effects (56;98;99).

Random allocation

The objective of any trial is to provide an unbiased comparison of the differences between the treatments being compared. The randomization of participants between the treatment groups is the paramount statistical element that allows one to claim that the study is unbiased (100).

We do believe that the randomization procedures using sequentially-numbered, opaque, sealed envelopes and the use of a third person to provide and store the randomization sequences in both studies succeeded and thereby reduced the risk of a serious imbalance in known and unknown factors at baseline that could influence our outcome. However we are aware of that it is unjustified to conclude that variables that are not significantly differently distributed between groups can not have affected the results of the trials.

However, although randomization is necessary, it alone is not sufficient to provide an unbiased study. We did not succeed in providing data for an intention-to-treat analysis in any of the studies. This was not possible because of missing data of primary outcome variables, and we therefore may have introduced bias since we did not maintain treatment groups.

Blinding and information bias

In contrast to random allocation, blinding can not always be successfully implemented in RCTs. Blinding prevents ascertainment bias and protects the sequence after allocation (58;101).

We did not achieve blinding of participants, investigators and outcome assessors in the studies (I and II) due the choice of comparator (epidural analgesia). There for we may have introduced ascertainment bias also referred to, as information bias, which occurs when results are systematically distorted by knowledge of which intervention each participant is receiving. Most outcomes variables in the studies (I and II) were measured by patients themselves. To which extent psychological effects could arise from patients knowing that they received a new untested treatment or a thoroughly tested standard treatment and how that may influence their evaluation of outcome remains uncertain. The choice of primary outcome in study I (i.e. pain intensity scores) makes the possibility of introducing ascertainment bias even greater since obviously, more subjective outcomes present greater opportunities for bias.

The lack of blinding of investigators and care staff can lead to the introduction of information bias. However the potential for information bias, in this context, seems limited by the standardized treatment regime.

9. Conclusion

Based on the results obtained and our considerations regarding potential bias in the three studies, we drew the following conclusions:

Studies I–II

We found that high-volume wound infiltration combined with one IA re-injection was associated with significantly reduced opioid consumption, reduced occurrence of side effects, reduced length of stay, and improved early walking ability compared with epidural analgesia after total hip replacement surgery.

Compared with epidural analgesia, high-volume wound infiltration combined with IA continuous infusion after total knee replacement surgery resulted in a significant reduction in opioid consumption and reduced pain intensity. Time spent in the recovery room and days until discharge criteria were met were shorter in favor of the infiltration group.

The effect of local infiltration analgesia has been shown to be superior to placebo, femoral nerve blocks, and epidural analgesia after total knee and hip replacement surgery. Even though the local infiltration technique seems promising, there are still many questions that need to be addressed. Combining different drugs makes interpretation of the studies difficult and more randomized controlled trials are warranted to address the effect of the single components in the multimodal mixture.

Study III

We found that excluded patients differed from participants with regard to both preoperative characteristics and postoperative outcome. Our findings demonstrate the importance of eligibility criteria in RCTs evaluating the efficacy of perioperative interventions for postoperative pain relief. Furthermore, our data underline the need for those conducting clinical trial to provide additional information about the recruitment process and supplemental quantitative data about patients to avoid biased estimates of treatments effects and misleading assessments regarding the degree to which the results may be generalized.

10. Perspectives and future research

The studies presented in this thesis demonstrate that excellent pain relief can be achieved with local infiltration analgesia after major orthopedic surgery. We hope that our studies have contributed to a greater awareness of local infiltration techniques for postoperative analgesia after total hip and knee replacement surgery. However, there is still a need for research on the local infiltration analgesia technique regarding several specific issues. What role has the specific analgesic agents used and what role plays the use of other treatment modalities such as compression bandaging and cooling. We hope that we can continue to contribute to this sustained development in analgesic techniques.

We are currently performing randomized double-blind, placebo-controlled trials that investigate the role of wound and intraarticular administration of NSAID after TKA and THA and the possible effect of repetitive postoperative intraarticular infusions after THA. We are also planning studies evaluating the effect of continuous intraarticular infusion versus intermitted bolus injections after TKA.

In addition to the studies mentioned above are we, in collaboration with others conducting studies in the areas of one-stage revision surgery, enhancement of recovery by optimization of pain therapy, patient satisfaction and quality of life, deep vein thrombosis prophylaxis and physiotherapy to investigate to which extent the different elements contributes to improvements in perioperative and postoperative outcomes in the context of fast-track surgery.

11. References

- (1) Gomez PF, Morcuende JA. Early attempts at hip arthroplasty--1700s to 1950s. *Iowa Orthop J* 2005; 25:25-29.
- (2) Pramanik S, Agarwal AK, Rai KN. Chronology of total hip joint replacement and materials development. *Trends in Biomaterials and Artificial Organs* 2005; 19(1):15-26.
- (3) Charnley J. Arthroplasty of the hip. A new operation. *Lancet* 1961; 1(7187):1129-1132.
- (4) Charnley J, Cupic Z. The nine and ten year results of the low-friction arthroplasty of the hip. *Clin Orthop Relat Res* 1973;(95):9-25.
- (5) Danish Hip Arthroplasty Registry. [Annual report 2007]. 2007.
- (6) Danish Orthopedic Society [Reference Program 2006]. 2006.
- (7) Brady OH, Masri BA, Garbuz DS, Duncan CP. Rheumatology: 10. Joint replacement of the hip and knee--when to refer and what to expect. *CMAJ* 2000; 163(10):1285-1291.
- (8) Wells VM, Hearn TC, McCaul KA, Anderton SM, Wigg AE, Graves SE. Changing incidence of primary total hip arthroplasty and total knee arthroplasty for primary osteoarthritis. *J Arthroplasty* 2002; 17(3):267-273.
- (9) Pedersen AB, Johnsen SP, Overgaard S, Soballe K, Sorensen HT, Lucht U. Total hip arthroplasty in Denmark: incidence of primary operations and revisions during 1996-2002 and estimated future demands. *Acta Orthop* 2005; 76(2):182-189.
- (10) Gunston FH. Polycentric knee arthroplasty. Prosthetic simulation of normal knee movement. *J Bone Joint Surg Br* 1971; 53(2):272-277.
- (11) Ranawat CS. History of total knee replacement. *J South Orthop Assoc* 2002; 11(4):218-226.
- (12) The Danish National Board of Health [Reference Program of Kneearthrosis]. Copenhagen: The Danish National Board of Health 2007. 2007.
- (13) Danish Knee Arthroplasty Registry. [Annual report 2007]. 2007.

- (14) Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002; 183(6):630-641.
- (15) Wilmore DW, Kehlet H. Management of patients in fast track surgery. *BMJ* 2001; 322(7284):473-476.
- (16) Kehlet H, Wilmore DW. Fast-track surgery. *Br J Surg* 2005; 92(1):3-4.
- (17) Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; 362(9399):1921-1928.
- (18) Pang WW, Hsu TC, Tung CC, Hung CP, Chang DP, Huang MH. Is total knee replacement more painful than total hip replacement? *Acta Anaesthesiol Sin* 2000; 38(3):143-148.
- (19) Bonica JJ. The management of pain. 2 ed. Philadelphia: Lea & Febiger, 1990.
- (20) Biboulet P, Morau D, Aubas P, Bringuier-Branch, Capdevila X. Postoperative analgesia after total-hip arthroplasty: Comparison of intravenous patient-controlled analgesia with morphine and single injection of femoral nerve or psoas compartment block. a prospective, randomized, double-blind study. *Reg Anesth Pain Med* 2004; 29(2):102-109.
- (21) Horlocker TT, Kopp SL, Pagnano MW, Hebl JR. Analgesia for total hip and knee arthroplasty: a multimodal pathway featuring peripheral nerve block. *J Am Acad Orthop Surg* 2006; 14(3):126-135.
- (22) Boezaart AP. Perineural infusion of local anesthetics. *Anesthesiology* 2006; 104(4):872-880.
- (23) Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology* 1995; 82(6):1474-1506.
- (24) Axelsson K, Johanson E, Essving P, Weckstrom J, Ekback G. Postoperative extradural analgesia with morphine and ropivacaine. A double-blind comparison between placebo and ropivacaine 10 mg/h or 16 mg/h. *Acta Anaesthesiol Scand* 2005; 49(8):1191-1199.
- (25) Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *J Pain* 2002; 3(3):159-180.
- (26) Philip BK, Reese PR, Burch SP. The economic impact of opioids on postoperative pain management. *J Clin Anesth* 2002; 14(5):354-364.
- (27) Oderda GM, Evans RS, Lloyd J, Lipman A, Chen C, Ashburn M et al. Cost of opioid-related adverse drug events in surgical patients. *J Pain Symptom Manage* 2003; 25(3):276-283.
- (28) Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993; 77(5):1048-1056.

- (29) Kehlet H, Werner M, Perkins F. Balanced analgesia: what is it and what are its advantages in postoperative pain? *Drugs* 1999; 58(5):793-797.
- (30) Fischer HB, Simanski CJ. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement. *Anaesthesia* 2005; 60(12):1189-1202.
- (31) Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Jr., Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 2003; 290(18):2455-2463.
- (32) Choi PT, Bhandari M, Scott J, Douketis J. Epidural analgesia for pain relief following hip or knee replacement. *Cochrane Database Syst Rev* 2003;(3):CD003071.
- (33) Rawal N. Incisional and intra-articular infusions. *Best Pract Res Clin Anaesthesiol* 2002; 16(2):321-343.
- (34) Liu SS, Richman JM, Thirlby RC, Wu CL. Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. *J Am Coll Surg* 2006; 203(6):914-932.
- (35) Moiniche S, Mikkelsen S, Wetterslev J, Dahl JB. A qualitative systematic review of incisional local anaesthesia for postoperative pain relief after abdominal operations. *Br J Anaesth* 1998; 81(3):377-383.
- (36) Moiniche S, Mikkelsen S, Wetterslev J, Dahl JB. A systematic review of intra-articular local anesthesia for postoperative pain relief after arthroscopic knee surgery. *Reg Anesth Pain Med* 1999; 24(5):430-437.
- (37) Marret E, Gentili M, Bonnet MP, Bonnet F. Intra-articular ropivacaine 0.75% and bupivacaine 0.50% for analgesia after arthroscopic knee surgery: a randomized prospective study. *Arthroscopy* 2005; 21(3):313-316.
- (38) Gupta A, Bodin L, Holmstrom B, Berggren L. A systematic review of the peripheral analgesic effects of intraarticular morphine. *Anesth Analg* 2001; 93(3):761-770.
- (39) Kalso E, Tramer MR, Carroll D, McQuay HJ, Moore RA. Pain relief from intra-articular morphine after knee surgery: a qualitative systematic review. *Pain* 1997; 71(2):127-134.
- (40) Badner NH, Bourne RB, Rorabeck CH, MacDonald SJ, Doyle JA. Intra-articular injection of bupivacaine in knee-replacement operations. Results of use for analgesia and for preemptive blockade. *J Bone Joint Surg Am* 1996; 78(5):734-738.
- (41) Rasmussen S, Kramhoft MU, Sperling KP, Pedersen JH. Increased flexion and reduced hospital stay with continuous intraarticular morphine and

- ropivacaine after primary total knee replacement: open intervention study of efficacy and safety in 154 patients. *Acta Orthop Scand* 2004; 75(5):606-609.
- (42) Mauerhan DR, Campbell M, Miller JS, Mokris JG, Gregory A, Kiebzak GM. Intra-articular morphine and/or bupivacaine in the management of pain after total knee arthroplasty. *J Arthroplasty* 1997; 12(5):546-552.
- (43) Browne C, Copp S, Reden L, Pulido P, Colwell C, Jr. Bupivacaine bolus injection versus placebo for pain management following total knee arthroplasty. *J Arthroplasty* 2004; 19(3):377-380.
- (44) Ritter MA, Koehler M, Keating EM, Faris PM, Meding JB. Intra-articular morphine and/or bupivacaine after total knee replacement. *J Bone Joint Surg Br* 1999; 81(2):301-303.
- (45) Romsing J, Moiniche S, Ostergaard D, Dahl JB. Local infiltration with NSAIDs for postoperative analgesia: evidence for a peripheral analgesic action. *Acta Anaesthesiol Scand* 2000; 44(6):672-683.
- (46) Brill S, Plaza M. Non-narcotic adjuvants may improve the duration and quality of analgesia after knee arthroscopy: a brief review. *Can J Anaesth* 2004; 51(10):975-978.
- (47) Convery PN, Milligan KR, Quinn P, Scott K, Clarke RC. Low-dose intra-articular ketorolac for pain relief following arthroscopy of the knee joint. *Anaesthesia* 1998; 53(11):1125-1129.
- (48) Ng HP, Nordstrom U, Axelsson K, Perniola AD, Gustav E, Rytberg L et al. Efficacy of intra-articular bupivacaine, ropivacaine, or a combination of ropivacaine, morphine, and ketorolac on postoperative pain relief after ambulatory arthroscopic knee surgery: a randomized double-blind study. *Reg Anesth Pain Med* 2006; 31(1):26-33.
- (49) Calmet J, Esteve C, Boada S, Gine J. Analgesic effect of intra-articular ketorolac in knee arthroscopy: comparison of morphine and bupivacaine. *Knee Surg Sports Traumatol Arthrosc* 2004; 12(6):552-555.
- (50) Bianconi M, Ferraro L, Traina GC, Zanolli G, Antonelli T, Guberti A et al. Pharmacokinetics and efficacy of ropivacaine continuous wound instillation after joint replacement surgery. *Br J Anaesth* 2003; 91(6):830-835.
- (51) Kerr DR, Kohan L. Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery: a case study of 325 patients. *Acta Orthop* 2008; 79(2):174-183.
- (52) Busch CA, Shore BJ, Bhandari R, Ganapathy S, MacDonald SJ, Bourne RB et al. Efficacy of periarticular multimodal drug injection in total knee arthroplasty. A randomized trial. *J Bone Joint Surg Am* 2006; 88(5):959-963.

- (53) Vendittoli PA, Makinen P, Drolet P, Lavigne M, Fallaha M, Guertin MC et al. A multimodal analgesia protocol for total knee arthroplasty. A randomized, controlled study. *J Bone Joint Surg Am* 2006; 88(2):282-289.
- (54) Gross CP, Mallory R, Heiat A, Krumholz HM. Reporting the recruitment process in clinical trials: who are these patients and how did they get there? *Ann Intern Med* 2002; 137(1):10-16.
- (55) Jadad AR, Rennie D. The randomized controlled trial gets a middle-aged checkup. *JAMA* 1998; 279(4):319-320.
- (56) Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet* 2005; 365(9453):82-93.
- (57) Altman DG. *Practical statistics for medical research*. 1 ed. London: Chapman & Hall, 1991.
- (58) Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; 273(5):408-412.
- (59) Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA* 2007; 297(11):1233-1240.
- (60) Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C. Threats to applicability of randomised trials: exclusions and selective participation. *J Health Serv Res Policy* 1999; 4(2):112-121.
- (61) Swanson GM, Ward AJ. Recruiting minorities into clinical trials: toward a participant-friendly system. *J Natl Cancer Inst* 1995; 87(23):1747-1759.
- (62) Charlson ME, Horwitz RI. Applying results of randomised trials to clinical practice: impact of losses before randomisation. *Br Med J (Clin Res Ed)* 1984; 289(6454):1281-1284.
- (63) Rosseland LA, Stubhaug A, Breivik H. Detecting postoperative urinary retention with an ultrasound scanner. *Acta Anaesthesiol Scand* 2002; 46(3):279-282.
- (64) Pain Terms, A current List with Definitions and Notes on Usage. In: Merskeynad H, Bogduk N, editors. *Classification of Chronic Pain Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. seattle: 1994: 209-214.
- (65) Coll AM, Ameen JR, Mead D. Postoperative pain assessment tools in day surgery: literature review. *J Adv Nurs* 2004; 46(2):124-133.
- (66) Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983; 17(1):45-56.

- (67) Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; 113(1-2):9-19.
- (68) Jensen MP, Turner JA, Romano JM, Fisher LD. Comparative reliability and validity of chronic pain intensity measures. *Pain* 1999; 83(2):157-162.
- (69) Jensen MP. The validity and reliability of pain measures in adults with cancer. *J Pain* 2003; 4(1):2-21.
- (70) Lundeberg T, Lund I, Dahlin L, Borg E, Gustafsson C, Sandin L et al. Reliability and responsiveness of three different pain assessments. *J Rehabil Med* 2001; 33(6):279-283.
- (71) Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975; 1(3):277-299.
- (72) Ohnhaus EE, Adler R. Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. *Pain* 1975; 1(4):379-384.
- (73) Ahles TA, Ruckdeschel JC, Blanchard EB. Cancer-related pain--II. Assessment with visual analogue scales. *J Psychosom Res* 1984; 28(2):121-124.
- (74) Gift AG. Visual analogue scales: measurement of subjective phenomena. *Nurs Res* 1989; 38(5):286-288.
- (75) Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94(2):149-158.
- (76) Andersen LJ, Poulsen T, Krogh B, Nielsen T. Postoperative analgesia in total hip arthroplasty: a randomized double-blinded, placebo-controlled study on peroperative and postoperative ropivacaine, ketorolac, and adrenaline wound infiltration. *Acta Orthop* 2007; 78(2):187-192.
- (77) Andersen LO, Husted H, Otte KS, Kristensen BB, Kehlet H. High-volume infiltration analgesia in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. *Acta Anaesthesiol Scand* 2008; 52(10):1331-1335.
- (78) Busch CA, Whitehouse MR, Shore BJ, MacDonald SJ, McCalden RW, Bourne RB. The Efficacy of Periarticular Multimodal Drug Infiltration in Total Hip Arthroplasty. *Clin Orthop Relat Res* 2009.
- (79) Toftdahl K, Nikolajsen L, Haraldsted V, Madsen F, Tonnesen EK, Soballe K. Comparison of peri- and intraarticular analgesia with femoral nerve block after total knee arthroplasty: a randomized clinical trial. *Acta Orthop* 2007; 78(2):172-179.

- (80) Essving P, Axelsson K, Kjellberg J, Wallgren O, Gupta A, Lundin A. Reduced hospital stay, morphine consumption, and pain intensity with local infiltration analgesia after unicompartmental knee arthroplasty. *Acta Orthop* 2009; 80(2):213-219.
- (81) Andersen LO, Kristensen BB, Husted H, Otte KS, Kehlet H. Local anesthetics after total knee arthroplasty: intraarticular or extraarticular administration? A randomized, double-blind, placebo-controlled study. *Acta Orthop* 2008; 79(6):800-805.
- (82) Andersen LO, Husted H, Otte KS, Kristensen BB, Kehlet H. A compression bandage improves local infiltration analgesia in total knee arthroplasty. *Acta Orthop* 2008; 79(6):806-811.
- (83) Dahl JB, Moiniche S. Relief of postoperative pain by local anaesthetic infiltration: efficacy for major abdominal and orthopedic surgery. *Pain* 2009; 143(1-2):7-11.
- (84) de Jong Z, Munneke M, Jansen LM, Runday K, van Schaardenburg DJ, Brand R et al. Differences between participants and nonparticipants in an exercise trial for adults with rheumatoid arthritis. *Arthritis Rheum* 2004; 51(4):593-600.
- (85) Fossa SD, Skovlund E. Selection of patients may limit the generalizability of results from cancer trials. *Acta Oncol* 2002; 41(2):131-137.
- (86) Ros A, Carlsson P, Rahmqvist M, Backman K, Nilsson E. Non-randomised patients in a cholecystectomy trial: characteristics, procedures, and outcomes. *BMC Surg* 2006; 6:17.
- (87) Petersen MK, Madsen C, Andersen NT, Soballe K. Efficacy of multimodal optimization of mobilization and nutrition in patients undergoing hip replacement: a randomized clinical trial. *Acta Anaesthesiol Scand* 2006; 50(6):712-717.
- (88) Petersen MK, Andersen KV, Andersen NT, Soballe K. "To whom do the results of this trial apply?" External validity of a randomized controlled trial involving 130 patients scheduled for primary total hip replacement. *Acta Orthop* 2007; 78(1):12-18.
- (89) Husted H, Holm G, Jacobsen S. Predictors of length of stay and patient satisfaction after hip and knee replacement surgery: fast-track experience in 712 patients. *Acta Orthop* 2008; 79(2):168-173.
- (90) Fowler SJ, Symons J, Sabato S, Myles PS. Epidural analgesia compared with peripheral nerve blockade after major knee surgery: a systematic review and meta-analysis of randomized trials. *Br J Anaesth* 2008; 100(2):154-164.
- (91) Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and

- duration of rehabilitation after major knee surgery. *Anesthesiology* 1999; 91(1):8-15.
- (92) Singelyn FJ, Deyaert M, Joris D, Pendeville E, Gouverneur JM. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. *Anesth Analg* 1998; 87(1):88-92.
- (93) Singelyn FJ, Gouverneur JM. Postoperative analgesia after total hip arthroplasty: i.v. PCA with morphine, patient-controlled epidural analgesia, or continuous "3-in-1" block?: a prospective evaluation by our acute pain service in more than 1,300 patients. *J Clin Anesth* 1999; 11(7):550-554.
- (94) Ranawat AS, Ranawat CS. Pain management and accelerated rehabilitation for total hip and total knee arthroplasty. *J Arthroplasty* 2007; 22(7 Suppl 3):12-15.
- (95) Ilfeld BM, Ball ST, Gearen PF, Le LT, Mariano ER, Vandeborne K et al. Ambulatory continuous posterior lumbar plexus nerve blocks after hip arthroplasty: a dual-center, randomized, triple-masked, placebo-controlled trial. *Anesthesiology* 2008; 109(3):491-501.
- (96) Siddiqui ZI, Cepeda MS, Denman W, Schumann R, Carr DB. Continuous lumbar plexus block provides improved analgesia with fewer side effects compared with systemic opioids after hip arthroplasty: a randomized controlled trial. *Reg Anesth Pain Med* 2007; 32(5):393-398.
- (97) Rothman KJ. *Epidemiology, An Introduction*. Oxford University Press, 2002.
- (98) Bornhoft G, Maxion-Bergemann S, Wolf U, Kienle GS, Michalsen A, Vollmar HC et al. Checklist for the qualitative evaluation of clinical studies with particular focus on external validity and model validity. *BMC Med Res Methodol* 2006; 6:56.
- (99) Green LW, Glasgow RE. Evaluating the relevance, generalization, and applicability of research: issues in external validation and translation methodology. *Eval Health Prof* 2006; 29(1):126-153.
- (100) Lachin JM. Statistical considerations in the intent-to-treat principle. *Control Clin Trials* 2000; 21(3):167-189.
- (101) Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. *Ann Intern Med* 2002; 136(3):254-259.

Appendices

THESES FROM THE ORTHOPAEDIC RESEARCH GROUP

PhD and Doctoral Theses from the Orthopaedic Research Group, www.OrthoResearch.dk, University Hospital of Aarhus, Denmark

PhD Theses

1. In vivo and vitro stimulation of bone formation with local growth factors
Martin Lind, January 1996
www.OrthoResearch.dk
2. Gene delivery to articular cartilage
Michael Ulrich-Vinther, September 2002
www.OrthoResearch.dk
3. The influence of hydroxyapatite coating on the peri-implant migration of polyethylene particles
Ole Rahbek, October 2002
www.OrthoResearch.dk
4. Surgical technique's influence on femoral fracture risk and implant fixation. Compaction versus conventional bone removing techniques
Søren Kold, January 2003
www.OrthoResearch.dk
5. Stimulation and substitution of bone allograft around non-cemented implants
Thomas Bo Jensen, October 2003
www.OrthoResearch.dk
6. The influence of RGD peptide surface modification on the fixation of orthopaedic implants
Brian Elmengaard, December 2004
www.OrthoResearch.dk
7. Biological response to wear debris after total hip arthroplasty using different bearing materials
Marianne Nygaard, June 2005
www.OrthoResearch.dk
8. DEXA-scanning in description of bone remodeling and osteolysis around cementless acetabular cups
Mogens Berg Laursen, November 2005
www.OrthoResearch.dk
9. Studies based on the Danish Hip Arthroplasty Registry
Alma B. Pedersen, 2006
www.OrthoResearch.dk
10. Reaming procedure and migration of the uncemented acetabular component in total hip replacement
Thomas Baad-Hansen, February 2007
www.OrthoResearch.dk
11. On the longevity of cemented hip prosthesis and the influence on implant design
Mette Ørskov Sjøland, April 2007
www.OrthoResearch.dk
12. Combination of TGF- β 1 and IGF-1 in a biodegradable coating. The effect on implant fixation and osseointegration and designing a new in vivo model for testing the osteogenic effect of micro-

- structures in vivo
Anders Lamberg, June 2007
www.OrthoResearch.dk
13. Evaluation of Bernese periacetabular osteotomy; Prospective studies examining projected load-bearing area, bone density, cartilage thickness and migration
Inger Mechlenburg, August 2007
Acta Orthopaedica (Suppl 329) 2008;79
 14. Rehabilitation of patients aged over 65 years after total hip replacement - based on patients' health status
Britta Hørdam, February 2008
www.OrthoResearch.dk
 15. Efficacy, effectiveness, and efficiency of accelerated perioperative care and rehabilitation intervention after hip and knee arthroplasty
Kristian Larsen, May 2008
www.OrthoResearch.dk
 16. Rehabilitation outcome after total hip replacement; prospective randomized studies evaluating two different postoperative regimes and two different types of implants
Mette Krintel Petersen, June 2008
www.OrthoResearch.dk
 17. CoCrMo alloy, *in vitro* and *in vivo* studies
Stig Storgaard Jakobsen, June 2008
www.OrthoResearch.dk
 18. Adjuvant therapies of bone graft around non-cemented experimental orthopaedic implants. Stereological methods and experiments in dogs
Jørgen Baas, July 2008
Acta Orthopaedica (Suppl 330) 2008;79
 19. The Influence of Local Bisphosphonate Treatment on Implant Fixation
Thomas Vestergaard Jakobsen, December 2008
www.OrthoResearch.dk
 20. Surgical Advances in Periacetabular Osteotomy for Treatment of Hip Dysplasia in Adults
Anders Troelsen, March 2009
Acta Orthopaedica (Suppl 332) 2009;80
 21. Polyethylene Wear Analysis. Experimental and Clinical Studies in Total Hip Arthroplasty.
Maiken Stilling, June 2009
www.OrthoResearch.dk
 22. Step-by-step development of a novel orthopaedic biomaterial: A nanotechnological approach.
Thomas H.L. Jensen, September 2009
www.OrthoResearch.dk
 23. Osteoclastic bone resorption in chronic osteomyelitis
Kirill Gromov, November 2009
www.OrthoResearch.dk
 24. Use of medications and the risk of revision after primary total hip arthroplasty
Theis Thillemann, December 2009
www.OrthoResearch.dk
 25. Different fixation methods in anterior cruciate ligament reconstruction
Ole Gade Sørensen, February 2010
www.OrthoResearch.dk

Doctoral Theses

1. Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs
Kjeld Søballe, 1993
Acta Orthop Scand (Suppl 255) 1993;54
2. Growth factor stimulation of bone healing. Effects on osteoblasts, osteomies, and implants fixation
Martin Lind, October 1998
Acta Orthop Scand (Suppl 283) 1998;69
3. Calcium phosphate coatings for fixation of bone implants. Evaluated mechanically and histologically by stereological methods
Søren Overgaard, 2000
Acta Orthop Scand (Suppl 297) 2000;71
4. Adult hip dysplasia and osteoarthritis. Studies in radiology and clinical epidemiology
Steffen Jacobsen, December 2006
Acta Orthopaedica (Suppl 324) 2006;77
5. Gene therapy methods in bone and joint disorders. Evaluation of the adeno-associated virus vector in experimental models of articular cartilage disorders, periprosthetic osteolysis and bone healing
Michael Ulrich-Vinther, March 2007
Acta Orthopaedica (Suppl 325) 2007;78

Papers 1 to 3

- 1) **Reduced hospital stay and narcotic consumption and improved mobilization with local and intraarticular infiltration after hip arthroplasty**
Karen V. Andersen, Mogens Pfeiffer-Jensen, Viggo Haraldsted, Kjeld Søballe.
Acta Orthopaedica 2007; 78(2):180-186.
- 2) **A Randomized Controlled Trial of Local Infiltration Analgesia vs. Epidural Infusion for Total Knee Arthroplasty**
Karen V. Andersen, Marie Bak, Birgitte V. Christensen, Jørgen Harazuk, Niels A.. Pedersen, Kjeld Søballe – Submitted to Acta Orthopaedica 2010
- 3) **A comparison of participants and non-participants in a randomized controlled trial involving 156 patients scheduled for primary total knee arthroplasty**
Karen V. Andersen, Anne F. Christensen, Mette K. Petersen, Birgitte V. Christensen, Niels A.. Pedersen, Kjeld Søballe – Submitted to Acta Orthopaedica 2010

