High-volume Local Infiltration Analgesia in Hip and Knee Arthroplasty

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The thesis is based on the following papers:


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Introduction

Administration of local anesthetics to the surgical wound with intraoperative infiltration or continuous postoperative wound infusion is increasingly used for postoperative pain management, since these techniques are simple and documented by an increasing number of randomized clinical studies reporting analgesic efficacy across surgical specialties. However, in spite of improvements in regional anesthetic techniques and multimodal analgesia, total hip arthroplasty (THA) and total knee arthroplasty (TKA) are still associated with moderate to severe postoperative pain, especially in the case of total knee arthroplasty. Traditionally, postoperative pain is managed with administration of local anesthetic to the peripheral nerves (peripheral nerve block) which may be continued with pump-infusions after discharge from hospital, while the use of continuous epidural analgesia is not recommended due to the relatively high risk of side-effects. Peripheral nerve block techniques are effective in postoperative pain management in hip and knee arthroplasty, but these techniques are associated with a risk of motor blockade of the muscles innervated by the affected nerves, which may delay early mobilization along with a delay in recovery and discharge from hospital. Recently, continuous peripheral nerve block have been demonstrated to increase the risk of patient falls after both TKA and THA. Furthermore, peripheral nerve block techniques may require high levels of technical expertise and equipment (ultrasound, electrical simulating catheters etc.) and may be expensive. As an alternative to peripheral nerve block techniques, high-volume local infiltration analgesia (LIA) was introduced as a modality for postoperative pain management in hip- and knee arthroplasty by Dr. Kerr and Dr. Kohan, Sydney, Australia. The initial experience reporting effective analgesia along with early mobilization and early discharge from hospital (1-2 days) has led to widespread use of the technique in recent years, especially in Scandinavia. However, relatively few randomized clinical studies have evaluated the high-volume local infiltration analgesia technique for hip and knee...
arthroplasty\textsuperscript{3, 5, 7-9, 20-41, 44-45, 46}, and most of these with inadequate definitions on the different components of the technique as initially reported by the inventors, not allowing final recommendations on how LIA is best applied in hip- and knee arthroplasty. Therefore there is a need for clinical trials to systematically evaluate the analgesic efficacy of each component in the LIA technique.
**Aim and hypothesis**

The specific aim of this doctoral thesis was to investigate the optimal analgesic design of the LIA technique in hip and knee arthroplasty. Each distinct component of the LIA technique was investigated separately in the 10 trials upon which the thesis is based. These clinical trials were consecutively designed to distinctly evaluate each component of the LIA technique and were based on the following hypothesis:

  a) Intra-operative high-volume wound infiltration with ropivacaine has superior analgesic effect compared to placebo in TKA when both groups receive identical systemic analgesia (Study I)

  b) A compression bandage prolongs the analgesic effect of LIA in TKA when both groups receive identical systemic analgesia (study II)

  c) Injection of ropivacaine to the extraarticular tissue through a wound catheter has superior analgesic effect compared to placebo in TKA when both groups receive identical systemic analgesia (Study III and VII)

  d) Local Infiltration Analgesia in a well-defined fast-track setting leads to acceptable postoperative pain and rehabilitation up to one month after TKA and THA (Study IV)

  e) Intra-capsular administration of ropivacaine has superior analgesic effect compared to intra-articular administration in TKA when both groups receive identical systemic analgesia (Study V)

  f) Multi-holed catheters placed in the wound in THA cause increased wound spread compared to triple-lumen catheters with injection of a radio-active isotope thereby serving as a basis for future efficacy studies (Study VI)
g) Intra-operative infiltration with ropivacaine of the subcutaneous tissue has improved analgesic efficacy compared to placebo in TKA when both groups receive identical systemic analgesia (Study VII)

h) Post-operative subcutaneous wound injection with ropivacaine has superior analgesic effect compared to placebo in TKA when both groups receive identical systemic analgesia (Study VII)

i) Postoperative administration of ropivacaine in similar dose but different volume/concentration has similar analgesic effect after TKA when both groups receive identical systemic analgesia (Study VIII)

j) intra-operative high-volume wound infiltration with ropivacaine has superior analgesic effect compared to placebo in THA when both groups receive identical systemic analgesia (Study IX)

Furthermore, the aim of this thesis is to provide a critical review of the methodology and outcomes of the existing randomized controlled trials performed with the high-volume local infiltration analgesia technique in hip- and knee arthroplasty, which was evaluated in a systematic review (Study X). Specific emphasis is placed on each component of the LIA technique, and each of the studies on which this thesis is based is discussed.

Finally, this thesis provides suggestions for future research strategies in this area.
Methods

Randomized controlled trials included in this review were identified by searching the PubMed database, Google Scholar and the Cochrane Library without language, age or gender restrictions. Search was performed using the terms “local infiltration analgesia”, “LIA”, “hip arthroplasty”, “THA”, “knee arthroplasty” and/or “TKA”. The reference list of each identified trial was reviewed to ensure inclusion of all randomized controlled trials investigating LIA for THA or TKA. Trials published until June 1st 2013 were included. A narrative review of the included literature was conducted with a detailed discussion of methods and outcome of randomized trials investigating LIA for THA and TKA together with a systematic review, despite that the published trials differ substantially in methods, including choice of systemic analgesia which was not comparable between active treatment groups and control groups, and because the type and method of performing LIA was different in the published trials.

To specifically address each of the hypothesis listed (“Aims and hypothesis”) we conducted 9 prospective and consecutive trials. First, the LIA technique was evaluated using a placebo-controlled design in both bilateral hip and bilateral knee arthroplasty to specifically evaluate the analgesic effect of high-volume ropivacaine and epinephrine wound infiltration compared to similar administration of saline. The analgesic potential of each component in the LIA technique was subsequently evaluated in randomized clinical trials, including the investigation of a compression bandage to prolong the analgesic efficacy of LIA, and the post-operative administration of local anesthetic through intraarticular or extra-articular wound catheters. The analgesic difference between using local anesthetic in high versus low concentration was investigated in a separate randomized trial. Pain and side-effects after discharge from hospital (up to 1 month...
postoperatively) after THA and TKA with LIA was investigated separately in an observational study.  

Each of these 9 trials were performed under comparable and standardized fast-track settings with similar and well-defined discharge criteria and with similar standardized systemic analgesia with slow-release paracetamol 2g/12h, celecoxib 200 mg/12h and gabapentin 300+600 mg initiated preoperatively and continued until 6 days postoperatively. Anesthesia was standardized and all patients were operated in spinal anesthesia with similar amount of local anesthetic. All trials were performed using identical criteria for enrollment with exclusion of patients with a condition potentially influencing pain perception, such as (but not restricted to) diabetes (neuropathy), rheumatoid arthritis or history of stroke, to minimize bias in pain recording. Furthermore, all trials applied similar functional discharge criteria. Pain was assessed under fairly similar and well-defined, broadly accepted and optimal settings in all trials (rest, flexion, extension and during walk) by one of two investigators. The intra-operative infiltration of local anesthetic + epinephrine was conducted in a similar manner in all these trials and by one of two experienced orthopedic surgeons, to minimize differences in surgical technique. In this manner, all variables were fairly standardized other than the specific component subject to study in each trial. Aspects of the randomization and blinding procedures are described in the articles, and data were widely presented in accordance with the Consolidated Standards of Reporting Trials (CONSORT-statement), although not entirely.

Post-hoc analysis

The results from post-hoc analysis with longitudinal mixed models statistics along with corrections for multiple analyses is included in tables 1-7 and in the description of each randomized trial upon which this thesis is based. The purpose of a longitudinal re-analysis of data is to quantify the
intra-individual changes in a response variable and to find explanations for systematic inter-individual differences in the data obtained, for instance the influence of an intervention, gender or age. All seven sets of data are characterized by very few missing observations. The data from most trials comprise 5 or more repeated measurements of each individual patient. As described in the following, the results obtained from analysis of data with longitudinal mixed models are in accordance with the results reported in the original published trials, even when corrections for multiple analyses is included.


This trial was designed to specifically evaluate the analgesic effect of high-volume ropivacaine+epinephrine wound infiltration in TKA. 12 consecutive patients operated with bilateral TKA were included. Due to the strict exclusion criteria applied, the study period was long (8 months). The study was designed with patients serving as their own control receiving active treatment in one knee and saline injections in similar volume in the opposite knee. This design is optimal to minimize or even exclude inter-individual variation in pain response, which is of major importance in clinical studies assessing post-operative pain, since variation in pain between individuals is pronounced in spite of similar surgery.

A valid power-analysis could not be performed prior to the study, since previous trials with LIA had only been performed in unilateral TKA and with a wide discrepancy in design regarding systemic analgesia. To perform a power-analysis on pain data obtained from unilateral surgery does not translate with validity into bilateral surgery, where the pain response and dispersion of data may be
different. As demonstrated, this trial was probably not underpowered, since the difference in pain between groups was statistically significant, but this potential weakness of the study may be taken into consideration when interpreting the results. However, the risk of the results being due to a chance-finding is highly unlikely, as evident from the statistical analysis. Finally, the design is optimal as a hypothesis-generating study on the potential efficacy of LIA in TKA due to the specific assessment in bilateral TKA.

Data were analysed using Wilcoxon Signed Ranks test between groups and data was presented in figures with data pooled for all patients. This is a simple non-parametric analysis comparing data from each group at each distinct time-point. Another valid method to analyze the longitudinal data collected in this trial would be to apply linear mixed models including analysis of the changes over time in each individual patient’s pain response. The results from these analyses are presented in Table 1, and do not alter results as presented in the original article also when corrections for multiple analyses are included.

Other options to compare groups would also have been possible, such as asking patients about most/least painful knee. Although this is an alternative method to present data, such data were not included in the study since the main objective was to present and compare pain data from each knee which are best presented by using the Visual Analogue Scale (VAS).

It may be argued that data should be corrected for multiple analyses, for instance by using the Bonferroni method, since multiple testings were performed. These conservative methods were not applied to the data presented, and may be taken into consideration as a limitation to the results reported from this trial, but as described (Table 1) the accepted linear mixed models analysis of data demonstrated similar clinically relevant analgesia with LIA versus placebo.

Other limitations to this trial may include the lack of preoperative pain data, preoperative functional data from each knee as well as the lack of description of pre-operative x-ray findings assessing the
degree of osteoarthritis in each knee. However, no correlations between these specific parameters and the degree of acute postoperative pain have been reported in the literature, and therefore the risk of bias in pain perception between groups is hypothetical. Furthermore, because randomization was performed, such data were probably not important and therefore not included.

As described in the original article, all knees were operated and infiltrated in a similar technique, and in all patients the left knee was operated first, independent of randomization.

The change in pain responses after post-operative intra-articular injections with ropivacaine were not analysed in this trial, but the pooled changes in data are presented. Consequently, no conclusions regarding the analgesic efficacy of postoperative intra-articular injections are made in the article.

The use of saline may be argued not to be a true placebo, since the injection of saline does not mimic the clinical situation of no injection and because slight analgesic effect of saline administration has been reported in arthroscopic knee surgery. However, to ensure blinding of both patients, caretakers and the single investigator recording postoperative pain data, this method was chosen, since sham- or no injections would highly increase the risk of impairing the blinding procedure. Furthermore, the use of saline as placebo is well accepted in other trials.

In conclusion: this double-blind, randomized and placebo-controlled trial provides data to support the analgesic efficacy of intraoperative high-volume infiltration of ropivacaine in combination with epinephrine. Considering the limitations, this trial was original to provide evidence of the analgesic efficacy of high-volume local infiltration analgesia with ropivacaine and epinephrine in TKA.

The original LIA-technique involves the application of a compression bandage to the wound intended to reduce absorption and re-distribution of ropivacaine and thereby prolong analgesia. To evaluate if a compression bandage results in improved and prolonged overall analgesia in the first 8 hours after TKA using the LIA technique, we randomized 48 patients to receive a compression or a non-compression bandage and all patients completed the study. This study demonstrated reduced pain at rest and with flexion/straight elevated leg in the group of patients treated with a compression bandage for the first 8 hours postoperatively and the pooled data for each group was presented graphically. Statistics were performed comparing groups at each specific time-point using the non-parametric Mann-Whitney U test. At the time the study was performed, no transferrable data on pain with the use of LIA for unilateral TKA operated in spinal anesthesia had been published, and although a formal power-analysis using data from studies in TKA treated with other analgesic modalities could have been performed, such sample-size calculations would be without validity in assessing the magnitude and dispersion in pain data in patients operated with TKA using LIA and with the same systemic analgesia in both groups. For this reason, no valid sample-size calculation could be performed, which may be a limitation to the interpretation of the results presented in this trial. The nature and aim of this study was to record the overall pain intensity in the first 24 hours after surgery, which naturally implies recording of multiple and similar data. However, correction for multiple analyses was not performed, and the statistical differences reported may therefore also have been due to chance findings, although the presentation of multiple statistically significant differences between groups makes this unlikely. Furthermore, the comparison of pooled data
between groups at every time-point does not take into account the longitudinal nature of the data collected which may be considered a limitation of the study.

For these reasons, results from post-hoc analysis of data using linear mixed models with Bonferroni corrections for multiple analyses are included in this thesis (table 2). As stated, the application of these statistical methods does not alter the results originally presented even when the conservative Bonferroni correction is applied (Table 2).

This trial was not blinded due to the obvious difference in the bandage, and this is a limitation to the study.

*In conclusion:* this first randomized trial demonstrated an overall reduced level of early postoperative pain with the application of a compression bandage as part of the LIA-technique in TKA. Although the limitations should be considered, this trial clearly describes the importance of a compression bandage as part of the LIA-technique and should be considered in future trials of LIA in TKA.


This trial was designed to evaluate the analgesic efficacy of a key-component in the original LIA-technique which involves uniform injection of local anesthetic to the extra-articular wound area upon retraction/removal of the intra-articular catheter. In the original technique, as described by the inventors [18], ropivacaine+epinephrine is injected upon removal of the intra-articular catheter in an
attempt to prolong analgesia 24 hours after surgery by injecting the extraarticular wound area. The analgesic efficacy of extra-articular infiltration by this technique had not been investigated and it was unknown whether a specific anatomic application of the local anesthetic would improve analgesia. We therefore randomized 32 patients who were all operated with TKA with LIA to receive either ropivacaine or saline in the extra-articular wound space upon catheter removal. Previous trials had investigated the analgesic efficacy of administration of local anesthetic to the intra-articular wound space after TKA, and found no analgesic effect with intra-articular administration, but no studies investigating the analgesic efficacy of extra-articular wound administration of local anesthetic after TKA had been performed. For this reason, the key question presented in this trial is of major importance with the LIA technique: whether extra-articular administration of local anesthetic is effective in the treatment of postoperative pain after TKA.

The study demonstrated overall low pain scores and no statistically significant difference between groups. Postoperative pain data was collected consecutively for 4 hours after injection and data were presented pooled for each group. Statistical comparisons were performed using Mann-Whitney U test at each time point. This study has several limitations which include the lack of a formal power-analysis which could not be validly performed since this trial was the first to investigate pain with extra-articular wound administration of local anesthetic after TKA. Another limitation is the low number of observations (n=32) and the fact that data were not analysed using longitudinal models. The results of such analysis of data are included in this thesis (Table 3) and do not alter the results and conclusions made in the original publication.

In conclusion: this trial is original in the key question – whether local anesthetics are most effective when administered intra-articularly or to the extra-articular wound space. However, due to the above-mentioned limitations, results can only be interpreted with caution and should be
considered preliminary and hypothesis generating. The results only support that extra-articular injections may have only slightly, if any, improved analgesic efficacy in TKA.


To evaluate pain and function after discharge from hospital, we conducted this prospective, observational study in 100 patients operated with TKA (n=50) and THA (n=50) treated with LIA with a similar technique and in a standardized fast-track setting. The immediate preoperative as well as per- and postoperative treatment was standardized (up to 6 days postoperatively), and all patients received an analgesic regimen consisting of paracetamol (4 g/day), celecoxib (400 mg/day) and gabapentin (900 mg/day) along with intraoperative LIA performed by one of 2 surgeons using a similar technique. Furthermore, anesthesia was performed by the same 2 anesthetists and all patients were operated in spinal anesthesia. Patients were asked to evaluate their average pain intensity during each day 1-10 and 30 days postoperatively along with an indication on functional rehabilitation (ability to leave home after discharge). Furthermore, the use of oral analgesics was recorded 1 month postoperatively along with a description of the incidence of nausea and vomiting (opioid related side-effects).

This study describes in detail that postoperative pain is pronounced after TKA with more than two-thirds of patients reporting moderate or severe pain (VAS>30 mm, 0-100 mm) when walking one month after surgery. In THA more than 95% of patients reported a VAS-pain <30 mm one month after surgery, and the use of oral analgesic was equally low. Furthermore, pre-operative pain and/or use of opioids did not correlate to the degree of postoperative pain in this material.
Some limitations apply to this trial due to its observational design without a control-group. Furthermore, the calculation of correlation between preoperative and early postoperative pain data to pain one month after surgery was constricted to calculation on “raw” pain data, and not incorporating the diverse nature of pain (such as measurements in patients individual psychological pain tolerance etc.) and these correlations may therefore not be entirely conclusive. However, the aim of this study was to provide data on the amount of postoperative pain up to 1 month postoperatively and to correlate these raw pain data.

In conclusion: Although not randomized, this first detailed study provides a clear picture of the actual degree of 30 days postoperative pain in 100 patients treated with LIA for TKA and THA, and clearly describes acceptable postoperative pain relief after THA but not TKA in spite of an identical and standardized perioperative analgesic regimen. The study therefore serves as a rational basis for designing future studies with a required prolonged analgesic treatment in TKA.


Post-operative injections of local anesthetic is a central component in the LIA-technique aimed at prolonging the analgesic efficacy of intraoperative wound infiltration. Since nearly all available studies with intra-articular injection of local anesthetic after TKA have not shown any analgesic efficacy\(^{58}\), we conducted this trial to compare intra-capsular and intra-articular injections in the postoperative period. 60 patients operated with TKA with LIA were randomized to receive a catheter tunneled through the anterior part of the joint capsule *versus* an intraarticular catheter in
which 100 mg ropivacaine was administered 6 and 24 hours post-operatively. It was concluded that intra-capsular administration of local anesthetic has similar analgesic efficacy compared to intra-articular injection after TKA. This study is the first and only study to examine the clinically relevant question of potential differences in analgesic efficacy with application of local anesthetic to distinct anatomic locations in the LIA technique, except for the authors previous study.\textsuperscript{3}

Some limitations apply to these findings, since this was a clinical trial without a placebo control group. For this reason, it is not possible to conclude whether intra-capsular injection of local anesthetic has an analgesic effect after TKA, but only that it may be comparable to intra-articular injection in the early (<24 hours) postoperative period. Conclusions as to whether intra-capsular injections have an analgesic and/or opioid-sparing effect after TKA would have required a placebo control group which was not the case in this study design. Furthermore, it may be argued that it is not known if intra-capsular injections should be performed in the anterior or posterior part of the knee joint capsule. However, injections in the posterior part of the capsule may be associated with a risk of damage to the popliteal nerve and/or adjacent popliteal artery, although this has not been investigated. For this reason, and because it is the anterior part of the joint capsule which is incised during TKA and therefore subject to the surgical trauma, we chose to investigate injection in the anterior part of the joint capsule.

Since data were analysed using non-parametric Mann-Whitney U test for continuous numerical data, it may be suggested that the use of linear mixed models may provide a better statistical analysis. As can be seen in Table 4 in this thesis, the post-hoc analysis with application of these statistical models does not alter the overall conclusions originally presented.

\textit{In conclusion:} Although this study has some limitations which should be considered when interpreting the results, it was the first study to investigate and to demonstrate that intracapsular
post-operative catheter injections do not provide superior analgesia compared to intra-articular injections in the early post-operative period. These results have been supported by a recent study.\textsuperscript{27}


This trial was designed to evaluate whether any large difference in the area over which a fluid disperses in the wound after THA may result from the use of different types of catheter, i.e. multifenestrated versus epidural catheter. Such data are required as hypothesis-generating data before large randomized trials are performed on the analgesic efficacy of different catheter types. Since such measurements are difficult to perform in vivo, we injected technetium Tc 99m diethylenetriaminepentaacetic acid labeled saline postoperatively and wound spread for 10 minutes was recorded with a double-head gamma camera (2 projections). 16 patients operated with THA were randomly assigned to receive either a multi-holed catheter or an epidural catheter placed under the fascia in the mid-point of the surgical wound. This study was double blinded and randomization was not revealed until wound spread area was calculated and compared by using the t test for equality of means since the collected continuous numeric data were normally distributed. This trial does not permit any conclusions on the analgesic efficacy of the different types of catheter which is a limitation to the study. Furthermore, the small number of observations make this trial preliminary in its design.

*In conclusion:* Although this trial should be considered preliminary due to the small number of observations (n=16), it was demonstrated that only a small, if any, difference may be present in
wound spread area with the use of different types of catheters. The clinical relevance of potential difference in analgesic efficacy between catheter types is therefore questioned and was not studied further.


In this randomized, double-blind and placebo-controlled trial we investigated the analgesic value of subcutaneous intra-operative wound infiltration with ropivacaine compared to saline along with the analgesic effect of injection of ropivacaine to the subcutaneous part of the wound 24 hours postoperatively. The aim was to conclude if subcutaneous intra-operative infiltration as well as postoperative injection of local anesthetic had any clinically relevant analgesic efficacy or if this component of the LIA technique could be omitted in the future. We included 16 patients operated with bilateral TKA, based upon a well-defined power analysis which was performed from previous pain-data collected in bilateral TKA. Due to the bilateral model, patients were their own control group, minimizing the inter-individual variation in pain response. From the pain-data collected, we demonstrated reduced pain in the early postoperative period (1-6 hours) with ropivacaine infiltration in the subcutaneous part of the wound compared to similar infiltration with saline. At 24 hours postoperatively, we calculated the difference in the decline in VAS pain scores which was observed after injection in both groups. The change in pain scores is the most clinically relevant aspect after a bolus injection with local anesthetic. At this time-point, no difference could be demonstrated between groups.
The total intra-operative dose of ropivacaine used in this trial was 500 mg, which is the largest dose of ropivaine administered in any trial so far investigating LIA. No side-effects were observed in the study.

The study may have some limitations, since correction for multiple analyses was not performed and because the statistical analysis did not include linear mixed models (Table 5). Instead the non-parametric Wilcoxon Signed Ranks test was applied to test for significant differences between groups in all data. The results from analyses with linear mixed models are presented in Table 5, and some of the original statistically significant differences are not present with this type of analysis. Although this limitation to the study should be considered, the overall conclusions from the data are likely to be true as evident from the supplemental statistical analysis (Table 5). Another limitation is the use of large amounts of locally infiltrated ropivacaine, which may result in systemic absorption and systemic analgesia. However, this theoretical limitation should be considered minimal since patients were their own control, and a potential systemic analgesic effect would be present in both groups. It may be, however, that a difference in the reduction in pain scores could have been observed if no systemic analgesic effect of ropivacaine was present 24 hours postoperatively, although plasma-ropivacaine concentrations have diminished at this time point.

In conclusion: This first and only double-blind and placebo-controlled trial demonstrates that intra-operative subcutaneous ropivacaine infiltration cannot be excluded from the intra-operative LIA-technique without impairment of postoperative analgesic efficacy. Furthermore, subcutaneous catheter placement may be of less analgesic value, since no difference in analgesia could be demonstrated in this material. The statistical analysis applied may be considered a limitation to the trial, and for this reason results from other types of analysis are presented in the post-hoc analysis (Table 5).
Study VIII: Andersen LØ, Husted H, Kristensen BB, Otte KS, Gaarn-Larsen L, Kehlet H.


The analgesic efficacy from postoperative local anesthetic wound administration may be depend on the volume, concentration or total dose of the specific local anesthetic. Because no clinical trials had compared these variables with postoperative wound administration, we conducted this randomized and double-blind trial to compare administration of 100 mg ropivacaine injected in high versus low volume/concentration 6 and 24 hours postoperatively through an intra-capsular catheter. 48 patients operated with TKA were enrolled and 43 patients completed the study. No statistically significant difference in analgesia was observed between groups although a reduction in pain scores was observed in both groups after local anesthetic administration 24 h postoperatively at rest, with knee flexion and upon walking. Although patients who were randomized to receive injection with high volume ropivacaine used less oxycodone (12 vs. 20 mg) in the initial (cumulated) 24 hours after surgery compared to the low-volume injection group, this is probably of minor clinical importance since this difference is small and because the pain data are without differences even if this could be attributed to the increased opioid administration in the low-volume group. The limitations to this trial involve the analysis of data using Mann-Whitney U test instead of longitudinal models. As can be seen from the additional post-hoc statistical analysis provide results in support of the initial conclusions made (Table 6).

In conclusion: This trial was original and the only to investigate the potential difference in analgesic efficacy with administration of local anesthetic in different volumes and concentrations but similar total dose. The results demonstrate limited analgesic efficacy in both treatment groups, but are
limited by statistical considerations which are addressed in Table 6 and shown to be of minor importance.


This trial was designed to specifically evaluate the analgesic effect of high-volume ropivacaine+epinephrine wound infiltration in THA and the design is similar to the trial performed in bilateral TKA. 12 consecutive patients operated with simultaneous bilateral THA were included. Because bilateral THA is only rarely performed and due to the strict exclusion criteria described, the study period was long (3 years). This period would have been shorter if exclusion criteria had been abandoned, but the aim of the study was to collect as unbiased pain data possible to evaluate whether LIA has any analgesic effect when combined with a multimodal analgesic regimen consisting of celecoxib, paracetamol and gabapentin. For this reason patients were their own control receiving active treatment in one hip and saline injections in similar volume in the opposite hip. The surgical and anesthetic techniques were similar and unaltered in the 3-year study period. Patients in this trial reported very low pain scores without differences in pain from the hip receiving LIA and saline. Due to the design, opioid consumption could not be compared but was equally low (mean 43 mg in the initial 48 hours postoperatively).

No valid preliminary calculation of sample size could be performed from the data published in unilateral THA with LIA since this is a different surgical procedure. The risk of the study being under-powered inflicts a major limitation to the study which served as an important hypothesis-generating trial since the findings questioned common clinical practice to use LIA in THA based
upon data from trials where systemic analgesia was not standardized and similar between groups. Based upon these negative results, a larger (n=120) trial in unilateral THA under similar clinical settings was therefore performed. The results from this larger trial\textsuperscript{33} were similar, confirming our preliminary data. The design of this preliminary trial was therefore optimal to improve the design of larger studies.

LIA was investigated on top of an optimal analgesic regimen, as is the case for every trial upon which this thesis is based. This may be considered a limitation to the study, since an analgesic effect of LIA may exist in THA when a multimodal analgesic regimen is not applied.

Data were analysed using Wilcoxon Signed Ranks test between groups and data was presented in figures with data pooled for all patients. This is a simple non-parametric analysis comparing data from each group at each distinct time-point, and another valid method to analyze the longitudinal data collected in this trial is presented in Table 7 and the results are similar.

\textit{In conclusion:} this first and at that time only double-blind, randomized and placebo-controlled trial demonstrated that local infiltration with ropivacaine and epinephrine may have no analgesic effect in conjunction with a multimodal analgesic regimen with paracetamol, celecoxib and gabapentin. The low number of observations and risk of this trial being underpowered necessitated confirmation of our results in a larger trial, which was published recently with similar findings.\textsuperscript{33} Consequently, LIA is not recommended in THA.\textsuperscript{10, 59}
High-volume Local Infiltration Analgesia

1. Background and evidence

Kerr and Kohan have reported a local infiltration analgesia technique (“LIA”) for the control of postoperative pain after hip and knee arthroplasty. In a case series of 325 patients (86 TKA, 54 THR, 185 hip resurfacing) a mixture of local anesthetic (ropivacaine 0.2%), NSAID (ketorolac 30 mg) and adrenaline (10 μg/mL) (“RKA”-mixture) was injected intraoperatively at the surgical sites in total volumes of 150-200 mL along with an additional postoperative injection (15-20 hours postoperatively) through an intra-articular catheter where 15 mL of the RKA-mixture was injected into the joint and 35 mL spread in the wound upon catheter removal. This technique, as reported by the inventors, included application of a compression bandage to the surgical site, application of ice-packs for the initial 4 hours postoperatively along with ibuprofen 400 mg/4-hourly. The results reported were surprisingly low postoperative pain levels without the need for opioid in two-thirds of patients, limited side-effects and discharge from hospital the day after surgery in 71% of patients. These encouraging results raise several questions since the technique includes multiple analgesic components. Thus, the analgesic efficacy of each component requires separate evaluation in randomized clinical trials in order to provide a clear answer on how the technique is best applied to enhance early recovery after major joint arthroplasty. In particular, the claimed long duration of the LIA-technique, which may be in contrast to the 4-6 hour duration when applied to wounds in other procedures, calls for detailed evaluation. Until June 1st 2013, the analgesic efficacy of local infiltration analgesia (LIA), defined as intraoperative periarticular injections of local anesthetic with or without addition of adrenaline, NSAID and/or opioid, has been investigated in 17 randomized clinical trials in knee arthroplasty (Table 8) and in 10 randomized clinical trials in hip arthroplasty (Table 9).
Knee arthroplasty:

An initial, single-blind, randomized controlled trial with administration of LIA for unicompartmental knee arthroplasty (UKA) investigated the safety and efficacy (in functional outcome measures) of intraoperative LIA along with accelerated discharge 24 hours after surgery, and found early discharge (1.5 days) to be possible with acceptable long-term functional outcome and high levels of patient satisfaction with application of LIA in an accelerated protocol. This study did not assess the analgesic efficacy of LIA per se for knee arthroplasty, and only suggests that LIA may be part of the analgesic regimen in an accelerated fast-track protocol without apparent side-effects or impairment in functional outcome measures. Essving and colleagues performed another study in unicompartmental knee arthroplasty where 40 patients were randomized to intraoperative LIA along with postoperative bolus injection of ropivacaine and ketorolac versus no intraoperative injections and postoperative injection of saline. In this study 2 patients were excluded from analysis and in the remaining 38 patients, LIA resulted in reduced length of hospital stay (median 1 day vs. 3 days in the placebo group), reduced pain up to 27 hours after surgery and reduced need for opioid in the first 2 days after surgery compared to saline. However, no control for injections with ketorolac was included in the placebo-group. Furthermore, systemic non-opioid analgesics included only paracetamol in this trial, which may have resulted in higher pain scores than could be expected from trials including multiple opioid-sparing analgesics.

The first evidence of analgesic efficacy of LIA in total knee arthroplasty (TKA) was reported in a study in 64 patients randomized to periarticular injection of ropivacaine, ketorolac, morphine and epinephrine or no injection. This clinical trial reported a reduction in immediate (4 hours) postoperative pain and a reduction in opioid requirements (0-24 hours postoperatively) with LIA compared to no intraoperative injections. However, this was not a double-blind or placebo-controlled trial. Furthermore, the control-group did not receive NSAID and opioids, and therefore
The achieved analgesia in the LIA group may be the result of systemic effects of these drugs. The analgesic potential of periarticular injection with local anesthetic was supported by a trial in 42 patients operated with TKA who were randomized to periarticular infiltration with ropivacaine, epinephrine and ketorolac or no injection. However, the same limitation applies to this trial, since both opioid and NSAID were injected along with the local anesthetic but not in the control group. For this reason, clear evidence of analgesic efficacy of LIA cannot be drawn from these trials, since analgesia may have been the results of a systemic effect of the supplementary analgesics administered. With the limited evidence from these preliminary clinical trials investigating LIA in knee arthroplasty, one investigation compared continuous peripheral nerve block to LIA. In this non-blinded clinical trial, 80 patients operated with TKA were randomized to receive a continuous femoral nerve block (FNB) or LIA for postoperative pain management. The femoral nerve block consisted of injection with 200 mg ropivacaine in combination with continuous peri-neural infusion (ropivacaine 20 mg/h) for 48 hours postoperatively as well as intraarticular injection with morphine (4 mg) and bupivacaine (50 mg) at the end of surgery. LIA consisted of a combination of ropivacaine (300 mg), NSAID (ketorolac 30 mg) and epinephrine (0.5 mg) administered with intraoperative infiltration of the wound. This trial reported reduced pain only on the day after surgery, along with reduced need for rescue opioids as well as improved mobilization and range of knee motion in patients treated with LIA compared to femoral nerve block. However, several limitations may apply to these findings: this was not an observer blinded trial; patients with regular preoperative use of opioids were included in the study possibly inferring bias to the calculations of opioid consumption, and because postoperative pain was assessed by multiple investigators (nursing staff, physiotherapists, patients themselves). Furthermore, the fact that opioid was administered intraarticularly in one group (FNB) and NSAID infiltrated in the wound in the other group (LIA) makes it difficult to draw valid conclusions on the analgesic efficacy of local
anesthetic infiltration to the wound in TKA from these data. Finally, FNB has been reported to be more effective in other trials\textsuperscript{13, 14} and remain the gold standard for TKA.\textsuperscript{15} The results may therefore have been influenced also by the FNB technique and expertise. More recently, continuous femoral nerve block was compared to LIA in a randomized and double-blind trial.\textsuperscript{26} However, many of the same limitations may apply to this trial, and the groups were not similar with respect to the amount of ketorolac administered. Furthermore, the group treated with continuous femoral nerve block also received local infiltration with ropivacaine (100 mg), ketorolac (30 mg) and epinephrine in part of the wound, making it difficult to draw any conclusions on the analgesic efficacy from a continuous femoral nerve-block compared to LIA from this trial.

Two additional trials have compared analgesia with the femoral nerve block technique to femoral nerve block combined with LIA.\textsuperscript{31, 32} In one trial, LIA provided additional pain relief when administered in combination with femoral nerve block, but this trial is limited by injection of morphine and ketorolac with LIA but not in the control group and the trial was not observer blinded.\textsuperscript{31} Thus, analgesia may have arisen from morphine and NSAID infiltration. In the other trial, the posterior joint capsule was infiltrated in combination with a femoral nerve block, and the results showed similar pain levels and opioid requirements when compared to a femoral nerve block alone.\textsuperscript{32} Local infiltration of ropivacaine, ketorolac and epinephrine was compared to femoral nerve block in 40 patients operated with TKA, and this trial also demonstrated similar levels of postoperative pain and opioid requirements in the initial 24 hours after surgery.\textsuperscript{20} This trial was not blinded, but administration of NSAID was similar in both groups. To specifically evaluate the analgesic efficacy of a high-volume local anesthetic infiltration we performed a randomized, double-blind and placebo-controlled trial in a bilateral knee replacement model.\textsuperscript{1} In this trial 12 patients were randomized to receive systematic intraoperative infiltration with ropivacaine and adrenaline in the wound along with supplemental postoperative intra-articular injections 6 and 24
hours postoperatively in one knee and similar treatment with saline in the opposite knee. Pain was assessed for 48 hours postoperatively and we recorded significantly reduced pain scores in the knee infiltrated with ropivacaine and adrenaline up to 32 hours after surgery, both at rest and with knee movement. Another trial in 48 patients operated with TKA found reduced pain scores up to 48 hours after surgery along with reduced need for rescue-opioid in the LIA-group compared to placebo. Again, no control for injections with ketorolac was included in the placebo-group and systemic non-opioid analgesics included only paracetamol in this trial, which may have resulted in higher pain scores than could be expected from trials including multiple opioid-sparing analgesics.

More recently, LIA was compared to epidural analgesia after TKA in 3 randomized clinical trials. In the study by Spreng and co-workers, 99 patients were randomized in 3 active treatment groups; LIA with local infiltration of NSAID and opioid vs. LIA with intravenous injection of NSAID and opioid vs. epidural analgesia. This study concluded that LIA was less effective than epidural analgesia on the day of surgery but resulted in better analgesia and reduced need for rescue analgesics 24-72 hours after surgery. Furthermore, the study concluded that local infiltration of NSAID and opioid provided superior analgesia compared to intravenous administration of the same drugs. Systemic analgesia consisted of paracetamol and morphine PCA. However, this study was limited by incomplete blinding of study participants and because morphine was administered with LIA but not with epidural analgesia, making groups difficult to compare. Also, the statistical differences in pain scores between groups were small and probably without any relevant clinical significance. In the study comparing epidural analgesia to LIA by Andersen and co-workers, epidural analgesia was not as effective as otherwise reported in the literature, and this trial reported reduced pain with LIA versus epidural analgesia up to 72 hours after surgery. This trial was not blinded and pain was recorded at poorly defined time-points by patients themselves and not by a dedicated investigator, which makes the overall analgesic effect of LIA hard to interpret from this
trial. Furthermore, epidural analgesia was not as effective as otherwise reported in the literature and systemic opioid-sparing analgesia was insufficient with only paracetamol. The report by Thorsell and colleagues\textsuperscript{38} compared LIA to an insufficiently described epidural regimen, and lacks sufficient data on pain recordings and this study was also not blinded, but concludes that LIA is equally effective to epidural analgesia for postoperative pain management and that LIA has the advantage of faster mobilization (without description on how this was achieved). Due to the incomplete design and blinding, no firm conclusions can be drawn from this report. Finally, one prospective, randomized and double-blind trial randomized 40 patients operated with bilateral TKA to periarticular infiltration with a mixture of bupivacaine (2 mg/kg body weight), fentanyl (100 µg) and methylprednisolone (40 mg) or no injection.\textsuperscript{61} This trial reported reduced pain (between 1-3 on a numerical ratingscale from 0-10) in the initial postoperative period (until discharge) and also 2 and 4 weeks postoperatively along with improved functional outcome measures (improved knee flexion, reduced extensor lag) from the day of discharge until 4 weeks postoperatively. Although the bilateral design in this trial may provide evidence of a local effect of the infiltrated drug mixture, it is not possible to draw any valid conclusion on the analgesic potential of local infiltration with bupivacaine, methylprednisolone or fentanyl, since all drugs were administered in combination. Furthermore, the volume of the infiltrated drug-mixture is not reported. Similar limitations apply to results reported by Parvataneni and colleagues who compared wound infiltration with a mixture of ropivacaine, morphine, epinephrine and prednisolone (and antibiotics) to analgesia with the use of a femoral nerve block.\textsuperscript{35} Results from this non-blinded trial were similar pain levels and functional outcome measures in both groups.

More recently, LIA was compared to intrathecal administration of morphine for postoperative analgesia in 49 patients operated with TKA.\textsuperscript{30} LIA resulted in reduced pain and opioid requirements and length of hospital stay was reduced 25 % (4 vs 3 days). However, no control for ketorolac was
included in the control group, and intrathecal morphine is not recommended as part of the postoperative analgesic regimen in TKA. Another trial including 57 patients demonstrated similar analgesic efficacy with a multimodal peri-articular injection with bupivacaine, ketorolac, morphine and epinephrine compared to 0.2 mg intra-thecal morphine. No control for local infiltration with morphine and ketorolac was given to the control group imposing a risk of bias in this trial.

In conclusion: Intraoperative high-volume infiltration with ropivacaine and adrenaline may provide effective analgesia after knee arthroplasty in the early postoperative period (< 24 hours). Published literature comparing LIA to continuous femoral nerve block or continuous epidural analgesia are few and contradicting and all limited by incomplete blinding or unmatched administration of systemic analgesics. Compared to intra-thecal morphine, the data are limited and inconclusive due to insufficient design. Overall, most trials have not included a systemic control for locally infiltrated ketorolac with LIA in the control group, and/or have applied different systemic or insufficient systemic analgesia in study groups making final conclusions difficult on the analgesic efficacy of LIA per se.

Hip arthroplasty:

A randomized and placebo-controlled clinical trial in 37 patients operated with THA reported reduced pain in the early postoperative period (up to 8 hours postoperatively) as well as 1 and 2 weeks after surgery. This trial also reported reduced opioid requirements 8-96 hours after surgery along with improvements in physical function and reduced joint stiffness 1 week after surgery with application of the LIA technique. Hospital stay was short (mean 2.7 days). The LIA-technique applied in this trial was similar to the technique invented by Kerr and Kohan, with inclusion of ketorolac to the injected ropivacaine-epinephrine mixture, but no control for systemic effects of
ketorolac was included in the control group. For this reason, final evidence on analgesic efficacy of high-volume local anesthetic infiltration cannot be provided by this otherwise well conducted trial. Another trial randomized 75 patients to receive LIA or continuous epidural analgesia for postoperative pain treatment. In this trial, LIA resulted in reductions in pain intensity 20-96 hours postoperatively along with reduced need for opioid in the postoperative period. Furthermore, length of hospital stay (4.5 versus 7 days) and adverse events were reduced in the LIA group. Although encouraging, the results from this trial do not provide conclusive evidence to recommend LIA for hip replacement surgery, since this was not a blinded trial and since different analgesic regimens were administered in the two groups (ketorolac was given in the LIA group and morphine in the epidural group). Furthermore, epidural analgesia is not recommended for THA and the analgesic effect depends on the dose-regimen and drug concentration, which may not have been sufficient in this trial. An additional trial randomized 64 patients to LIA or no intraoperative injection and found statistically significant reduced postoperative pain and opioid requirements in the LIA group, but since analgesic regimens were different and not comparable between the two groups, with administration of morphine and ketorolac in the LIA group, this trial does not provide any further evidence on the analgesic efficacy of LIA in hip arthroplasty. Recently, a randomized and placebo-controlled trial in 80 patients operated with THA concluded that local infiltration analgesia with a mixture of bupivacaine (30 mg), morphine (5 mg) and betamethasone (1 mL, dose not reported) in a total volume of 60 mL resulted in a reduction in opioid administration (approximately 32 mg vs. 48 mg morphine 0-48 hours postoperatively) and reduced pain (around 10 mm on the VAS during activity 36 hours postoperatively) compared to similar injection of saline. However, this trial is confounded by incomplete description of data on study outcomes (pain, opioid consumption) and by the administration of morphine and glucocorticoid in the LIA group but not in the control group. Similar limitations apply to another trial in which 71 patients operated with THA were randomized.
to receive periarticular infiltration with a mixture of bupivacaine, morphine, epinephrine, prednisolone and antibiotics or no infiltration.\textsuperscript{35} This trial reported reduced pain with periarticular infiltration of these drugs, but the trial is not double-blind and contains no precise description of the systemic analgesia otherwise administered in the study period, and therefore no evidence of an analgesic effect of LIA can be derived.

We conducted a randomized, placebo-controlled trial in 12 patients operated with bilateral hip arthroplasty, who were randomized to intraoperative injection with ropivacaine (340 mg) and epinephrine (10 μg/mL) in one hip (170 mL) or saline in the opposite hip.\textsuperscript{9} All 12 patients received treatment with gabapentin, celecoxib and paracetamol. The results from this trial were that postoperative pain scores were very low and without any difference between groups. To confirm these findings, our trial was followed by a large double-blind, randomized trial in which 120 patients undergoing unilateral hip arthroplasty were randomized to receive LIA versus similar intra- and postoperative injections with saline. The results from this largest trial were similar, and it was concluded that LIA does not provide additional analgesia in hip arthroplasty when combined with a multimodal analgesic regimen consisting of gabapentin, celecoxib and paracetamol.\textsuperscript{33} Similar results have been reported in a prospective randomized trial in 92 patients operated with THA who were randomized to receive intra-operative local infiltration analgesia with levo-bupivacaine (200 mg/160 mL) or no injection.\textsuperscript{43} In this trial, patients reported very low postoperative pain scores even though systemic analgesia consisted of only morphine and paracetamol. A trial comparing intra-operative infiltration with levo-bupivacaine (150 mg/60 mL) to saline in 91 patients operated with THA reported no difference in analgesia between groups.\textsuperscript{34} In this trial only morphine-PCA was administered as adjuvant systemic analgesic, and although the trial was not double-blind and with limitations to the method of pain data collection, it may confirm our initial finding of limited analgesic value with LIA in THA even when only a limited systemic analgesic regimen is applied.
In a randomized trial by Liu and co-workers, 80 patients operated with THA were randomized to receive LIA consisting of bupivacaine, morphine, betamethasone and epinephrine or placebo. This trial reported reduced pain and opioid requirements in the LIA group, but no control for betamethasone or morphine was included in the control group, and the risk of bias in these results is high.

In conclusion: Data in favor of LIA for THA are confounded by uncontrolled administration of NSAID, steroid and/or opioid, and excellent postoperative pain control has been reported with administration of paracetamol alone or in combination with celecoxib and gabapentin with no additional analgesia from LIA in both bilateral and unilateral THA.

2. Drug mixture

a. Local anesthetic type

So far, most published trials have used ropivacaine as local anesthetic for high-volume infiltration analgesia in hip and knee arthroplasty. Ropivacaine is a long-acting amide-type local anesthetic equally effective to bupivacaine for local infiltration analgesia but with lower lipid solubility, and produces less cardiac and central nervous system side-effects compared to bupivacaine with intravenous administration in healthy volunteers. Ropivacaine may have the most favorable side-effects profile of the long-acting local anesthetics available. So far, no studies have been published comparing analgesic efficacy of different types of local anesthetics for high-volume local infiltration analgesia in hip and knee arthroplasty.
b. Volume vs. concentration of local anesthetic

The main factor for local anesthetic efficacy with wound infiltration may be volume, concentration and/or total dose of local anesthetic. To evaluate the potential difference in analgesic efficacy with administration of ropivacaine in high volume/low concentration compared to low volume/high concentration, we conducted a double-blind clinical trial in which 48 patients operated with TKA were randomized to receive injection with 100 mg ropivacaine in high volume (20 ml, 0.5%) versus low volume (10 ml, 1.0%) 6 and 24 hours postoperatively through a multi-holed catheter tunneled through the anterior joint capsule of the knee joint. This trial showed similar analgesic efficacy with local infiltration of ropivacaine in high-volume versus high concentration 6 and 24 hours postoperatively both at rest and with mobilization. However, there was a significant reduction in supplementary need for oxycodone in the early postoperative period (0-24h) in the group of patients receiving local anesthetic in a higher volume (12.5 mg versus 20 mg).

c. Epinephrine

Although ropivacaine may have vasoconstrictive properties at low concentrations, all studies investigating local infiltration analgesia for hip and knee arthroplasty have added epinephrine to the injected mixture in a concentration of 1:100,000 (Tables 8 and 9). No clinical studies have assessed the need for epinephrine infiltration to prolong analgesia and reduce systemic absorption of the local anesthetic with LIA.

d. Non-steroidal anti-inflammatory drugs

Evidence of an enhanced peripheral analgesic action compared with systemic administration of non-steroidal anti-inflammatory drugs is limited, although some evidence for a clinically relevant peripheral analgesic action with intra-articular administration of NSAID in knee arthroscopy has been concluded from a systematic review. This review concluded that intra-articular
administration of ketorolac 60 mg or tenoxicam 20 mg compared to similar i.v. administration resulted in reduced VAS pain scores of 11-25 mm up to 6 hours after surgery. No evidence for a peripheral analgesic action of local wound infiltration in a variety of surgical procedures (mastectomy, herniorrhaphy) with NSAID could be demonstrated in 3 out of 5 studies included in the review. More recently, Spreng and colleagues concluded that local infiltration with ketorolac and morphine in combination, as part of the LIA-mixture in TKA, provided better postoperative analgesia compared to similar intravenous administrations. However, although statistically significant, the reductions in VAS pain scores were only about 5-10 mm up to 72 hours after surgery, limiting the clinical relevance of these findings. Furthermore, this trial does not permit any conclusion on a peripheral analgesic action of ketorolac, since morphine was infiltrated along with the NSAID. Andersen and colleagues randomized 60 patients undergoing TKA to receive intraoperative LIA (ropivacaine 300 mg and epinephrine 0.5 mg) combined with either ketorolac 30 mg or saline and concluded that local infiltration of ketorolac resulted in a reduction in opioid requirements along with reduced pain up to 48 hours after surgery. In general, no clinical data are available on the potential adverse events with NSAID local wound infiltration (e.g. increased bleeding, delayed wound healing etc.).

In conclusion: No randomized clinical trials have compared infiltration of different types of local anesthetic and so far ropivacaine remains the drug of choice due to its long-acting properties and more favorable side-effect profile compared to other local anesthetics. Addition of adrenaline to the local anesthetic is without evidence, and a conclusive clinically relevant analgesic effect of local infiltration with NSAID compared to systemic administration has not been demonstrated with the LIA technique.
3. Injection technique

The injection technique does not differ substantially in the studies published in both TKA and THA (Tables 1 and 2), and involves systematic infiltration of all tissue incised, handled or otherwise instrumented, as originally described by the inventors. In TKA, the injections are performed systematically to ensure delivery of local anesthetic to all structures in the knee joint including the posterior and anterior joint capsule and subcutaneous tissues as well as soft tissues surrounding the joint. For hip arthroplasty, the anatomical compartments are less well defined, and injections are made in the periacetabular tissues including the anterior capsule where retractors are placed. After insertion of the femoral component local anesthetic is injected in the cut rotators, gluteus minimus muscle and into the femoral muscle laterally where the guide-pin is placed during the procedure. Finally the gluteus medius and maximus muscle are injected. The procedure has been described in detail by Otte and co-workers. Only one randomized trial has investigated different injection techniques and found the subcutaneous infiltration to be of clinical value in early postoperative analgesia after TKA.

In conclusion: The subcutaneous component of the LIA technique may be necessary for adequate postoperative analgesia with the LIA-technique, but detailed randomized clinical studies investigating the remaining optimal sites for intraoperative injections are lacking.
4. Compression bandaging

A compression bandage, applied from the foot to the mid-thigh, has been reported to result in reduced intraarticular pressure and swelling of the knee following TKA. In this study, 150 patients were randomized to receive a compression bandage or non-compression bandage with or without suction drain to the knee. The study also reported improved knee function on discharge when a compression bandage was applied after TKA. However, no clinical data on analgesia has been provided on the use of a compression bandage after TKA or THA. The use of a combined compression/cooling dressing (Cryo-Cuff ®) may result in reduced postoperative pain, but compression and cold therapy may have similar analgesic efficacy in the early postoperative period after TKA.

In the original design of the LIA technique, the inventors applied a firm compression dressing in both hip and knee arthroplasty, in an attempt to prolong analgesia and reduce absorption of local anesthetic from the wound. To evaluate this component of the technique, we conducted a clinical trial in which 48 patients operated with TKA were randomized to receive either a compression or non-compression bandage. This study demonstrated reduced pain with a compression bandage, both at rest and with mobilization up to 8 hours postoperatively.

In conclusion: Although the mechanism of action is unknown (reduced swelling or different pharmacokinetics) a compression bandage is recommended to improve analgesia with the LIA technique in TKA, but no data are available for THA.
5. Systemic analgesics

Systemic analgesia may comprise alpha-2 receptor agonists (clonidine) or alpha-2-delta agonists (gabapentin/pregabalin), selective serotonin and norepinephrine reuptake inhibitors (duloxetine), conventional or COX-2 selective non-steroidal anti-inflammatory drugs, NMDA-antagonists (ketamine), paracetamol, glucocorticoids and opioids. Furthermore, future options may include the use of capsaicin or selective serotonin reuptake inhibitors (SSRIs), but so far, no conclusive procedure-specific evidence is available in major orthopedic surgery.

Total knee arthroplasty: although pain after knee arthroplasty is complex and remains an unresolved issue, overall recommendations include the use of a continuous femoral nerve block combined with conventional NSAID or COX-2 selective inhibitors along with paracetamol and weak opioids for low-moderate intensity pain and strong opioid for high-intensity pain. A single preoperative administration of high-dose glucocorticoid has been demonstrated to result in reduced postoperative pain, PONV, fatigue and C-reactive protein after TKA and reduced pain after THA but detailed studies assessing the safety of administration of glucocorticoid in major orthopedic surgery have not been performed. Opioids should preferably be delivered with intravenous patient-controlled analgesia pumps, due to a higher degree of patient satisfaction with this modality. For TKA there is insufficient procedure-specific evidence for analgesic efficacy of perioperative clonidine.

Pregabalin (300 mg/24 hours) was reported to reduce the need for opioids in the acute postoperative period along with a reduction in the incidence of chronic neuropathic pain after TKA in a randomized, placebo-controlled trial in 240 patients. Also, the analgesic efficacy of pregabalin/gabapentin has been demonstrated in other procedures including hip arthroplasty where 24-hour morphine consumption may be reduced 50% with administration of pregabalin 300 mg prior to surgery. Side-effects to pregabalin/gabapentin include sedation, and studies on the optimal dose-response for postoperative analgesia are required. Several of the clinical trials
assessing the analgesic efficacy of the LIA technique in TKA have applied different systemic analgesia than these general recommendations (Table 8). In one trial, only morphine-PCA was given. In another trial, only paracetamol was administered as systemic analgesia. In our trials, gabapentin was part of the systemic analgesic regimen (along with a COX-2 selective inhibitor and paracetamol) for 6 days postoperatively, due to the overall evidence of analgesic efficacy from related procedures, although no procedure-specific evidence has been published so far. In 2 trials, systemic analgesia was sufficient, consisting of NSAID and paracetamol along with a strong opioid for rescue analgesia. However, in one of these trials comparing LIA to PNB, strong opioid was administered at regular intervals, and not titrated to effect with PCA-pumps, as recommended. Duloxetine, a selective serotonin/norepinephrine reuptake inhibitor (SNRI), has been demonstrated to reduce postoperative morphine requirements from around 30 to 20 mg 48 hours after surgery in knee replacement surgery. Future clinical studies are required to assess the analgesic potential of duloxetine as a part of the multimodal perioperative analgesic regimen in TKA.

**Total hip arthroplasty:** overall recommendations for postoperative pain management include regional anesthetic techniques with femoral or lumbar plexus nerve block along with opioids (strong or weak opioid, depending on pain intensity) in combination with paracetamol and conventional NSAID or COX-2 selective inhibitors. However, in only four of the randomized trials investigating LIA for THA (table 9), an NSAID/COX-2 inhibitor (celecoxib) was part of the systemic analgesic regimen. In two trials, gabapentin was also part of the multimodal analgesic regimen, which resulted in low postoperative pain scores without additional analgesic effect of LIA. In the remaining trials, systemic analgesia consisted only of paracetamol and strong opioids. In one trial, caffeine was also part of the analgesic regimen, even though no evidence on the analgesic efficacy of caffeine for THA has been published so far.
In conclusion: most of the trials investigating LIA for TKA have inadequate systemic analgesic regimens, thereby hindering sufficient interpretation of a potential analgesic efficacy of LIA, when administered with an optimal multimodal analgesic regimen. Postoperative pain after THA is lower than after TKA, and LIA or peripheral nerve-block techniques are not required when a multimodal systemic analgesic regimen is applied.
6. Catheter techniques for postoperative administration of local anesthetic in the wound

Continuous wound infusion of local anesthetic may be effective for postoperative pain management across surgical specialties, including cardiothoracic surgery, abdominal surgery as well as back or upper limb orthopedic surgery. However, to evaluate the analgesic efficacy of postoperative administration of local anesthetic to the wound, clear definitions of each component of the catheter techniques are needed. Primarily, the anatomic location of the inserted catheter needs to be clearly defined, since pain may originate from different sites in different surgical procedures.

In knee arthroplasty, a catheter may be inserted in the subcutaneous, intracapsular or intraarticular part of the wound. In the hip, the joint capsule is less well defined, restricting placement of a catheter to either the subcutaneous part of the wound (above the fascia/iliofemoral ligament) or intra-articular placement (below the fascia). Local anesthetics may be delivered through catheters at different flow-rates and in different volumes and concentrations, potentially resulting in clinical differences in analgesia. Finally, different types of catheters exist (i.e. single-, few- or multiholed catheters), and potential differences in wound spread as well as the analgesic potential need to be evaluated in randomized clinical trials. Most trials investigating the analgesic efficacy of LIA have not specifically addressed analgesic efficacy of local anesthetic catheter injections in hip or knee arthroplasty, apart from one trial in THA which was designed to specifically evaluate the analgesic efficacy of postoperative catheter injections and found no analgesic effect of injections with ropivacaine in combination with epinephrine and ketorolac. One trial has demonstrated reduced pain and a reduction in opioid consumption in the early postoperative period (0-48 h) after minimally invasive hip arthroplasty in 72 patients randomized to receive postoperative infusion of ropivacaine 12 mg/h or saline. In this trial, patients reported higher pain scores than in other trials and systemic analgesia was restricted to paracetamol along with morphine-PCA.
Evidence of the potential analgesic efficacy of postoperative local anesthetic wound administration in hip and knee arthroplasty is limited. One study has reported decreased pain and opioid requirements in a mixed population of 37 patients operated with THA or TKA (of these 8 were TKA) with postoperative subcutaneous catheter infusion of local anesthetic.\(^9^1\) This study is limited by the inclusion of patients undergoing unmatched surgical procedures. Continuous intra-articular infusion of ropivacaine was reported to be effective for postoperative pain management in total knee arthroplasty.\(^9^2\) In this placebo-controlled trial 50 patients operated with TKA were randomized to postoperative infusion of ropivacaine 2 mg/mL (10 mg/h) or saline. A reduction in postoperative pain of around 20 mm on a VAS scale was recorded with intraarticular infusion of ropivacaine for the first 3 days postoperatively along with reduced need for opioid (38% of patients in placebo group vs. 14% in ropivacaine group required opioid on the day of surgery). A similar study in 87 patients operated with TKA reported decreased pain and opioid consumption with continuous intra-articular infusion of ropivacaine compared to similar infusion of saline.\(^4^1\) However, these results are in contrast to other published data; in one randomized and double-blind trial in 66 patients comparing continuous intra-articular infusion of ropivacaine (10-18.75 mg/h) to placebo for 48 hours postoperatively no analgesia could be demonstrated with intra-articular infusion of ropivacaine in TKA.\(^9^3\) Similar results were reported from 49 patients randomized to continuous intraarticular infusion of bupivacaine (2 ml/h, 10 mg/h) or saline for 48 hours postoperatively.\(^9^4\) In this trial, pain levels and opioid requirements were similar in the initial 48 hours after surgery, in spite of continuous intra-articular infusion of bupivacaine. Furthermore, the positive results with intraarticular infusion of local anesthetic are in opposition to previously published data from randomized clinical trials demonstrating no or very limited analgesia from intraarticular bolus injection of local anesthetic in TKA.\(^5^3-5^8, 9^5\) Intra- and extra-articular infusion of ropivacaine in
combination with LIA has been compared in a small study (n=36), and in this double-blind trial no difference in analgesia was observed, apart from reduced pain upon mobilization 24 hours postoperatively. In another trial, postoperative infusion of ropivacaine was compared to infusion of saline both with and without LIA, and this trial reported reduced pain with intra-articular ropivacaine infusion up to 48 hours postoperatively. However, this trial is limited by uncontrolled infiltration of ketorolac and because pain was recorded with poor definitions and by multiple investigators. More recently, Ikeuchi and co-workers compared intraarticular catheter injections with a mixture of 150 mg ropivacaine + 6.6 mg dexamethasone 12-hourly for the initial 48 hours after surgery and reported reduced pain 1 and 3 days postoperatively pain along with a reduction in CRP and drain volume in 40 patients. This study does not specify which treatment was given to the control group and the analgesic effect may be explained by steroid injections and/or local anesthetic. A similar study from the same group compared postoperative injections with versus without dexamethasone in 40 patients operated with TKA and concluded that the analgesic effect was attributable to the steroid injections.

The original LIA technique, as invented by Dr. Kerr and Dr. Kohan, involves placement of an intraarticular epidural catheter in both TKA and THA. The local anesthetic (ropivacaine) is administered as bolus injections twice (around 6 and 24 hours) postoperatively, to flood the joint with local anesthetic and prolong analgesia. Furthermore, 30 mL ropivacaine (60 mg) is injected uniformly as the catheter is withdrawn from the intraarticular space through the joint capsule and muscular/subcutaneous part of the wound, in an attempt to (re-)infiltrate the wound and prolong analgesia 24 hour postoperatively. We conducted a randomized and placebo-controlled trial to specifically evaluate this component of the technique. In this trial 32 patients operated with TKA were randomized to receive injection with ropivacaine or saline in the extra-articular part of the wound upon catheter removal. The results were inconclusive, and no difference in analgesia was
observed for 3 hours following injections. However, this trial was original in the key question asked; whether local anesthetic is most effective with administration to the intra- or extra-articular wound space in TKA. In another trial we randomized 60 patients operated with TKA to intraoperative placement of a multiholed catheter tunneled through the anterior part of the joint capsule (intracapsular placement) or an intraarticular catheter. This trial demonstrated equal analgesic efficacy of intraarticular and intracapsular injections of ropivacaine (20 mL/100 mg) 6 and 24 hours postoperatively. Furthermore, the analgesic effect of injections in both anatomic locations was only modest and with limited – if any - clinical value for postoperative pain management after TKA. A subgroup analysis in patients reporting moderate to severe pain prior to injection demonstrated a non-universal trend towards improved analgesia with intracapsular administration and potential confirmation of these findings requires larger-scale studies. We subsequently compared intracapsular injections with ropivacaine in high volume/low concentration (20 mL, 5 mg/mL) to low volume/high concentration (10 mL/10 mg/mL). In this randomized trial, equivalent total dose of ropivacaine (100 mg) was injected 6 and 24 hours postoperatively in a multiholed intracapsular catheter. The results from this trial confirmed the previously reported data that analgesia was only modest with intracapsular administration in TKA, and no difference in analgesia was observed between the two types of administration. We also investigated the analgesic efficacy of intraoperative subcutaneous infiltration along with postoperative subcutaneous catheter injections of ropivacaine in bilateral knee arthroplasty. In this trial, 16 patients operated with bilateral knee arthroplasty were randomized to intraoperative infiltration with ropivacaine or saline in the subcutaneous part of the wound. To evaluate the analgesic efficacy of postoperative subcutaneous local anesthetic administration, a multiholed catheter was placed in the subcutaneous tissues in both knees with administration of ropivacaine or saline in either knee 6 and 24 hours postoperatively. In summary, this trial confirmed the analgesic efficacy of subcutaneous wound
infiltration as a component of the LIA technique, while postoperative subcutaneous bolus administration of ropivacaine did not show improved analgesia compared to similar administration of saline. Finally, we compared wound spread of radio-labeled saline administered through a triple-orifice epidural catheter or a 15 cm multiholed catheter, by the use of a dual-head gamma-camera recording the area over which the radioactive isotope spread after a single bolus injections. In this trial 16 patients operated with total hip arthroplasty were randomized to receive a triple-orifice epidural catheter or a 15 cm (40-holed) catheter placed below the fascia in total hip arthroplasty. In this trial no significant difference in wound spread was observed, and we concluded that demonstration of any potential increase in wound spread with multiholed catheters would require large study populations with concomitant limited clinical relevance. This is supported by our bilateral THA study where satisfactory pain control with a COX-2 inhibitor, paracetamol and gabapentin without additional benefits of intraoperative high-volume local infiltration analgesia or supplemental intraarticular injections in a placebo-controlled trial could be demonstrated.

Specht and co-workers have performed a double-blind trial in which 60 patients operated with THA and LIA were randomized to postoperative intraarticular injections with a mixture of ropivacaine (100 mg), ketorolac (15 mg) and adrenaline (0.5 mg) versus placebo. Intraarticular injections with the “RKA”-mixture or placebo were administered 10 and 22 hours postoperatively, and no statistically significant differences in pain scores or opioid consumption were recorded. These findings further support the conclusion, that postoperative intra- or periarticular administration of local anesthetic may be of limited clinical value in the treatment of postoperative pain after THA as well as TKA.

In conclusion: Most of the available studies were not designed to assess the analgesic efficacy of postoperative local anesthetic administration in TKA or THA, and have made use of an intra-articular catheter for postoperative injection as part of the LIA technique but without evaluation of
the analgesic efficacy of postoperative injections. Administration of local anesthetic through wound catheters has no or limited analgesic efficacy in hip and knee arthroplasty, regardless of anatomic placement (intra-articular, anterior joint capsule or subcutaneous part of wound) and with no relevant analgesic difference in relation to volume/concentration of local anesthetic.
7. Length of hospital stay

The randomized clinical trials with LIA for THA and TKA have reported very variable data on length of hospital stay (LOS), and potential reasons for the differences in LOS are not described (Table 10). The choice of analgesic technique may have very limited impact on LOS beyond 24 hours, and organizational issues, with a well-organized fast-track setup, may be the most important factor for achieving a short stay around 2-3 days after TKA. This conclusion is supported by a randomized study where both groups received LIA for unicompartmental knee arthroplasty comparing traditional vs. fast-track setup, where LOS was reduced from 4.3 to 1.5 days with a fast-track setup in spite of similar analgesic technique. The LOS reported from randomized trials with LIA varies from 1-6 days in TKA and 2.5-7 in THA, and discharge criteria are different between studies or are not well defined (Table 10).

Conclusion: LOS depends on organizational issues and the LIA technique is only a minor component to determine the length of hospitalization.
8. Discharge and recovery

Most of the published trials have evaluated the early postoperative outcome with LIA for TKA or THA, although similar knee range of motion was demonstrated with LIA versus placebo\textsuperscript{24} and similar long-term functional outcome and analgesic efficacy after knee arthroplasty (3 and 6 months after surgery).\textsuperscript{28, 29} Functional and analgesic outcome were similar with LIA vs. placebo 6 weeks after surgery in THA.\textsuperscript{23} The initial investigation of LIA concluded that early discharge was possible with application of the LIA-technique in TKA, but no data were provided on pain and recovery after discharge from hospital.\textsuperscript{60}

To evaluate the prevalence and intensity of subacute postoperative pain after discharge from hospital 1-10 and 30 days after surgery, we conducted a prospective observational trial in 100 patients operated with TKA or THA.\textsuperscript{4} In this descriptive trial we reported moderate to severe pain in 68\% of patients operated with TKA when walking 1 month after surgery with a concomitant increase in the use of strong opioids, in spite of multimodal analgesia with paracetamol, celecoxib and gabapentin initiated preoperatively and continued for 6 days after surgery. In contrast, fast-track total hip arthroplasty with early discharge (< 3 days) resulted in acceptable levels of pain with concomitant low use of opioids in > 95\% of patients after discharge before day 10. No increase in pain or analgesic requirements were present 30 days after surgery.

\textit{In conclusion:} Few trials have incorporated long-term assessment of LIA for hip and knee arthroplasty. In spite of comprehensive multimodal analgesia in the perioperative period, LIA may result in insufficient analgesia after total knee arthroplasty after hospital discharge, and further improvement with additional components in the multimodal regimen is necessary in TKA, but probably not in THA.
9. Safety aspects

In the largest cohort of patients treated with LIA for THA and TKA, the inventors reported the results from 325 consecutive and unselected patients. This study reported a zero-incidence of side-effects attributable to the LIA technique during the first 10 days postoperatively. In particular, no cardiac or neurological adverse-events were encountered over the 2-year study period, and no catheter-related infections were recorded.\textsuperscript{18}

The results from randomized clinical trials in TKA are similar. In total, 962 patients have been included in trials comparing LIA to placebo or other kinds of postoperative analgesia techniques (epidural analgesia, peripheral nerve block, intrathecal morphine etc.) (Table 8), and so far none have reported any occurrence of cardiotoxic or neurological side-effects or catheter related infection. Two randomized trials in TKA\textsuperscript{24,29} have measured plasma ropivacaine concentrations below the toxic threshold, as defined by Knudsen.\textsuperscript{64} In our trial in TKA, LIA was administered bilaterally in the largest total volume/dose of ropivacaine 250 mL/500 mg with inclusion of a total of 2 mg epinephrine to the drug mixture, and no clinical side-effects were recorded.\textsuperscript{7} In hip arthroplasty, the results are similar, although fewer patients (n=748) have been included in these trials (Table 9).

All trials have excluded epinephrine from the subcutaneous component of the drug mixture, due to a potential risk of cutaneous blister formation, in spite of only casuistic reports of this adverse effect so far.

\textit{In conclusion:} reports of systemic toxicity of local anesthetic with epinephrine infiltrated in large volumes and doses have not been reported in the randomized trials available so far, but a conclusive and large-scale safety study assessing the potential adverse-effects of LIA has not been conducted.
Conclusions

Knee arthroplasty:

The intraoperative high-volume infiltration of ropivacaine seems to be effective for early postoperative analgesia, since these findings have been confirmed in all clinical trials in knee arthroplasty (Table 8) despite limitations in study designs. However, this conclusion is especially supported by the results reported in the placebo-controlled trial in bilateral TKA. All trials comparing LIA to continuous epidural analgesia are limited by unmatched administration of systemic analgesics or insufficient study design, and epidural analgesia is not recommended in TKA. Trials comparing LIA to continuous peripheral nerve block techniques also have these same limitations, and final recommendations are not possible to make from these trials, although some evidence has been provided of enhanced postoperative mobilization with LIA versus PNB.

The LIA technique should make use of a compression bandage to prolong analgesia in the early postoperative period (0-24 hours), although this is supported by limited data only. Postoperative injection of local anesthetic through wound catheters is not recommended due to the lack of clinically relevant analgesia with intra-articular, intracapsular and subcutaneous postoperative wound administration. The potential risk of catheter-related wound infection has not been fully evaluated. High-pain responders may potentially benefit from intra-capsular administration.

Finally, there is no evidence of difference in wound spread area with the use of different types of catheter, but no trials comparing different types of catheter have been conducted in TKA. LIA does not result in sufficient analgesia 2-30 days after TKA with intraoperative local infiltration analgesia, and multimodal analgesia with paracetamol, NSAID/cox-2 selective inhibitors and gabapentin should be continued after discharge from hospital. No side-effects have been reported with the use of LIA, but long-term and large-scale safety studies are required to make final conclusions regarding safety.
In conclusion: Intra-operative LIA is effective and recommended for early postoperative pain management after TKA.  

Hip arthroplasty:

Combined with a multimodal oral analgesic regimen consisting of paracetamol, celecoxib and gabapentin, high-volume LIA does not provide additional analgesia. Combined with a multimodal oral analgesic regimen consisting of paracetamol, celecoxib and gabapentin, high-volume LIA does not provide additional analgesia. Randomized clinical trials reporting analgesic efficacy with intraoperative LIA for THA are few and all confounded by uncontrolled local infiltration of NSAID or by the local infiltration of multiple drugs in combination without sufficient control groups.

The use of wound catheters is not recommended for THA since no clinically relevant analgesic action has been documented with postoperative, intra-articular injections of local anesthetic and because the potential risk of infection has not been sufficiently evaluated. There is no clinically relevant difference in wound spread with the use of different types of catheter.

In conclusion: LIA provides no additional analgesic effect when combined with a multi-modal analgesic regimen and is therefore not recommended in THA.
Contribution

This thesis contributes to our understanding of how high-volume local infiltration analgesia is best applied in hip and knee arthroplasty and helps define future areas of research relevant to the technique. All trials upon which the thesis is based have been performed under well-defined fast-track settings with evidence-based peri-operative anesthetic, analgesic, surgical and rehabilitation techniques to provide a coherent and systematic evaluation of each individual component in the LIA technique. Until now, this thesis provides the largest series of systematic clinical trials to evaluate the analgesic efficacy of LIA for TKA and THA. The clinical trials upon which this thesis is based are widely cited and have contributed to further debate and research on the issue of local infiltration analgesia for major joint arthroplasty.

The thesis concludes on each of the initial hypothesis presented (“Aims and hypothesis”).

Finally, the thesis itself contributes with an updated qualitative review of published clinical trials investigating LIA for THA and TKA. The comprehensive review of the literature published so far is summarized to provide recommendations for future research strategies in this area.

Overall, the thesis therefore provides a clear contribution to our knowledge on how to treat pain with local infiltration analgesia after hip and knee replacement surgery and these 9 trials and 1 systematic review have had an impact on clinical practice.
Future research strategy

Although LIA provides an effective means for satisfactory pain management with limited side-effects along with the possibility for early mobilization in the initial 24 hours after surgery in TKA, further improvements in long-term pain management are necessary to optimize recovery. Future studies should evaluate the analgesic potential of additional components in the multimodal analgesic regimen: glucocorticoids, capsaicin infiltration to the wound/joint capsule, the use of gabapentin, duloxetine, selective serotonin reuptake inhibitors and/or ketamine and its optimal dosing should be defined in both TKA and THA. The impact of an effective multimodal regimen on chronic postoperative pain needs detailed evaluation in randomized and properly designed clinical trials. In many trials, patients receiving strong opioids preoperatively have been excluded. However, these patients may pose specific analgesic problems postoperatively and should be studied regarding optimal multimodal analgesia.

The peripheral actions of NSAID infiltration should be evaluated more conclusively, to determine whether any clinically relevant peripheral action of NSAID infiltration exists in TKA and THA, along with assessment of potential side-effects. Furthermore, the effects and safety of locally injected epinephrine should be investigated in large-scale studies.

The large inter-individual variation in postoperative pain, especially demonstrated in our prospective observational study, calls for investigations to predict preoperatively which patients are likely to be low-pain responders who may be treated with simple multimodal oral analgesics. In contrast, high-pain responders may need more effective analgesics including glucocorticoids and continuous femoral nerve-block in TKA.

Recently, the adductor canal block, which may have limited motor side-effects as demonstrated in a small study in healthy volunteers, has been suggested as an alternative
analgesic method in TKA.\textsuperscript{105, 108, 109} So far, the analgesic efficacy from reported data are relatively minor but deserve further evaluation. This technique may be useful in combination with LIA to reduce pain further on the day of surgery.\textsuperscript{104}

Finally, the potential development of local anesthetic formulations with prolonged duration of action\textsuperscript{110, 111} would be of significant clinical interest to prolong the analgesic efficacy of infiltration analgesia, not only in major joint arthroplasty, where improved analgesia has been demonstrated with the use of a liposomal formulation of bupivacaine compared to bupivacaine HCl\textsuperscript{112}, but across surgical specialties.

As suggested by others, LIA is a promising technique in arthroplasty surgery\textsuperscript{113-115} and across surgical specialties in many countries\textsuperscript{116} and future clinical trials need clear definitions of each distinct component in the technique\textsuperscript{117} which should be investigated separately and under controlled and standardized conditions\textsuperscript{118} as presented in this doctoral thesis. Finally, LIA should be compared with the best analgesic alternatives available.
Danish summary


Postoperative smerter kan i denne sammenhæng behandles effektivt ved administration af lokalbedøvelsesmidler omkring nerverne der forsyner det opererede led (perifer nerveblokade), men teknikken medfører hyppigt at muskelfunktionen i benet bedøves i en sådan grad at patienten ikke kan mobiliseres efter operationen. Immobilisering af patienten er uhensigtsmæssigt og har flere ulemper, eksempelvis i form af behov for blodfortyndende behandling til forebyggelse af blodprop i benets vener, øgede krav til afdelingens plejepersonale og fysioterapi, ligesom nedsat kraft i benets muskler øger risikoen for at patienten falder i dagene efter operation. Der kan desuden argumenteres for at teknikken med perifer nerveblokade kræver højt specialiseret personale til anlæggelse af nerveblokaden og at teknikken hyppigt kræver brug af ultralydsapparatur hvilket medfører en økonomisk udgift. Derfor afprøves hvorvidt postoperativ smertebehandling kan ske ved administration af et stort volumen lokalbedøvelsesmiddel som anlægges i såret under operationen, idet denne teknik er simpel og ikke medfører svækkelse af muskelfunktionen.

Teknikken kaldes Lokal Infiltrations Analgesi (LIA) og blev introduceret af Dr. Kerr og Dr. Kohan, Sydney, Australien, som har publiceret resultater fra 325 patienter opereret med total hofte eller knæaloplastik behandlet med LIA. I denne serie af patienter blev 71% udskrevet dagen efter operation og kun få patienter havde brug for supplerende smertebehandling med morfinpræparater. Disse resultater har medført at teknikken er blevet meget udbredt, særligt i Skandinavien, til trods for at kun få randomiserede, kliniske studier har undersøgt teknikken fyldestgørende.
Denne afhandling baseres på 10 studier omhandlende LIA til knæ- og hoftealloplastik. Studierne er blevet systematisk designet til at evaluere LIA-teknikkens enkelte delkomponenter: den intraoperative infiltration af lokalbedøvelsesmiddel, brugen af komprimerende forbinding, brugen af katetre til indgift af yderligere lokalbedøvelse i det postoperative forløb samt undersøgelse af smerter og funktion op til en måned efter udskrivelse fra hospital.

Den tilgængelige litteratur med anvendelse af LIA til knæ- og hoftealloplastik gennemgås systematisk, og sammenfattende konkluderes det, at LIA er effektivt til behandling af smerter i det tidlige postoperative forløb efter knæalloplastik (0-32 timer postoperativt) men at LIA ikke har nogen supplerende smertestillende virkning til hoftealloplastik hvis patienterne behandles med et multimodalt analgetisk regime bestående af gabapentin, paracetamol og celecoxib. Samlet set findes der ikke evidens for brugen af katetre til administration af lokalbedøvelsesmidler i perioden efter operation ved hverken knæ eller hoftealloplastik, uanset katetrets type eller anatomiske placering.


Fremtidige forskningsprojekter anbefales til at belyse virkningen af et effektivt smertestillende regime til knæalloplastik med inklusion af potentielt smertestillende medikamina som ikke anvendes rutinemæssigt i dag. Der er desuden brug for studier til at belyse hvilket patienter der er i risiko for at få svære smerter i perioden efter operation.


47. Husted H, Holm G. Fast Track in total hip and knee arthroplasty - experiences from Hvidovre University Hospital, Denmark. Injury, Int J Care Injured 2006;37:S31-S35.


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<tr>
<td>Flexion (6-8)</td>
<td>No differences</td>
<td>No differences</td>
<td>Significant effect of time; no effect of group or treatment</td>
<td>Significant effect of time; no effect of group or treatment</td>
</tr>
<tr>
<td>Standing (6-8)</td>
<td>No differences</td>
<td>Significant difference between groups; no effect of treatment</td>
<td>Near-significant difference between groups; no effect of treatment</td>
<td>Significant difference between groups; no effect of treatment</td>
</tr>
<tr>
<td>Rest (24-26)</td>
<td>No differences</td>
<td>Significant effect of time, no effect of treatment</td>
<td>Significant effect of time; no effect of treatment</td>
<td>Significant effect of time; no effect of treatment</td>
</tr>
<tr>
<td>Flexion (24-26)</td>
<td>No differences</td>
<td>Significant effect of time, no effect of treatment</td>
<td>Significant effect of time; no effect of group or treatment</td>
<td>Significant effect of time; no effect of group or treatment</td>
</tr>
<tr>
<td>Standing (24-26)</td>
<td>No differences</td>
<td>Near-significant effect of time</td>
<td>Significant effect of time; no effect of treatment</td>
<td>Significant effect of time; no effect of treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition (hours after surgery)</th>
<th>Analyses from publication</th>
<th>Simple analyses</th>
<th>Nonparametric longitudinal analysis</th>
<th>Linear Mixed Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest (4-9)</td>
<td>No differences</td>
<td>No differences</td>
<td>-</td>
<td>No differences</td>
</tr>
<tr>
<td>Flexion (4-9)</td>
<td>No differences</td>
<td>No differences</td>
<td>-</td>
<td>No differences</td>
</tr>
<tr>
<td>Rest (24-48)</td>
<td>Significant difference at 32 hours</td>
<td>No differences</td>
<td>-</td>
<td>No differences</td>
</tr>
<tr>
<td>Flexion (24-48)</td>
<td>No differences</td>
<td>No differences</td>
<td>-</td>
<td>Significant effect of time; no other significant effects</td>
</tr>
<tr>
<td>Author, year</td>
<td>Procedure (no. patients)</td>
<td>Study design</td>
<td>Intraoperative injection, type, (total volume)</td>
<td>Catheter placement</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------</td>
<td>-------------</td>
<td>-----------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Busch CA 2006</td>
<td>TKA (64)</td>
<td>Intraoperative local infiltration vs. no injection</td>
<td>Ropivacaine 400 mg Ketorolac 30 mg Epinephrine 5 mg Epinephrine 1:100.000 (100 mL)</td>
<td>-</td>
</tr>
<tr>
<td>Vendittioli 2006</td>
<td>TKA (42)</td>
<td>Intraoperative local infiltration vs. no injection</td>
<td>Ropivacaine 275mg Epinephrine 1:100.000 Ketorolac 30 mg (160 mL) Intra-articular ~20h/15ml/ Ropivacaine 150 mg</td>
<td>↓ pain (24, 48h) ↓ opioid (8, 16, 24, 48 h) ↔ROM (5 days)</td>
</tr>
<tr>
<td>Tofthahl 2007</td>
<td>TKA (80)</td>
<td>Intraoperative local infiltration vs. femoral nerve block</td>
<td>Ropivacaine 300 mg Ketorolac 30 mg Epinephrine 0.5 mg (150 mL) Intra-articular 8h and 24h/20+20ml/ Ropivacaine 200 mg Ketorolac 30 mg Epinephrine 0.5 mg</td>
<td>-</td>
</tr>
<tr>
<td>Parvataneni 2007</td>
<td>TKA (60)</td>
<td>Intraoperative local infiltration vs. femoral nerve block + PCA</td>
<td>Ropivacaine 2-400 mg Morphine 4-10 mg Epinephrine 0.3 mg Prednisolone 40 mg Cefuroxime 750 mg</td>
<td>-</td>
</tr>
<tr>
<td>Andersen LØ 2008</td>
<td>Bilateral TKA (12)</td>
<td>Intraoperative local infiltration vs. placebo</td>
<td>Ropivacaine 340 mg Epinephrine 1.2 mg (170 mL) Intra-articular 8 and 24 h/20+50 mL/ Ropivacaine 40/100mg Epinephrine (1:100,000)</td>
<td>-</td>
</tr>
<tr>
<td>Essving P 2009</td>
<td>UKA (38)</td>
<td>Intra- and postoperative local infiltration/saline (postop. injection)</td>
<td>Ropivacaine 200 mg Ketorolac 30 mg Epinephrine 0.5 mg</td>
<td>Intra-articular 21 h/22 mL/ Ropivacaine 150 mg Ketorolac 30 mg Epinephrine 0.1mg</td>
</tr>
</tbody>
</table>

Table 8. Randomized clinical trials investigating the analgesic efficacy of local infiltration analgesia for knee arthroplasty.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Procedure</th>
<th>Study design</th>
<th>Intraoperative injection, type, (total volume)</th>
<th>Outcome, LIA vs control</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen LØ, 2010</td>
<td>Bilateral TKA (16)</td>
<td>Double-blind design</td>
<td>Subcutaneous Ropivacaine 500 mg Epinephrine 2 mg (250 mL) - Subcutaneous 6 and 24 h/20 mL Ropivacaine 100 mg</td>
<td>↓Pain 1-6 h</td>
<td>Systemic analgesia with paracetamol (slow release) 2g/12h, celecoxib 200mg/12h and gabapentin (300+600 mg)</td>
</tr>
<tr>
<td>Essving P, 2010</td>
<td>TKA (48)</td>
<td>Double-blind design</td>
<td>Intra-articular Ropivacaine 400 mg Ketorolac 30 mg Epinephrine 0.5 mg (166 mL) - Intra-articular &gt;21 h/22 mL Ropivacaine 200 mg Ketorolac 30 mg Epinephrine 0.1 mg</td>
<td>↓opioid (0-48h)</td>
<td>Plasma ropivacaine conc. below toxic levels (n=8)</td>
</tr>
<tr>
<td>Spreng UJ, 2010</td>
<td>3 study groups: a) epidural analgesia (48 h)</td>
<td></td>
<td>Epidural analgesia not as effective as otherwise reported</td>
<td></td>
<td>Epidural analgesia not as effective as otherwise reported</td>
</tr>
<tr>
<td>Andersen KV, 2010</td>
<td>TKA (48)</td>
<td>Not observer-blinded</td>
<td>Intra-articular 50 mg</td>
<td></td>
<td>Incomplete information on pain data and method of recording</td>
</tr>
<tr>
<td>Thorsell M, 2010</td>
<td>TKA (65)</td>
<td>Not observer-blinded</td>
<td>Intra-articular 4.8% mepivacaine 100 mg with 1mg epinephrine</td>
<td></td>
<td>Systemic analgesia with opiods alone</td>
</tr>
<tr>
<td>Author, year</td>
<td>Procedure (no. patients)</td>
<td>Study design</td>
<td>Intraoperative injection, type, (total volume)</td>
<td>Catheter placement</td>
<td>Postop. injection(s) time/volume/type</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------</td>
<td>--------------</td>
<td>-----------------------------------------------</td>
<td>-------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Carli F 2010 26</td>
<td>TKA (40)</td>
<td>Intraoperative local infiltration and postoperative intra-articular infusion vs. continuous femoral nerve block</td>
<td>Ropivacaine 300 mg Ketorolac 45 mg Epinephrine 0.75 mg (200 mL)</td>
<td>Intra-articular</td>
<td>24 h/50 mL Ropivacaine 250 mg Ketorolac 30 mg Epinephrine 0.25 mg</td>
</tr>
<tr>
<td>Dobrydnjov I 2011 27</td>
<td>TKA (36)</td>
<td>Intraoperative LIA with intra- vs. extraarticular postoperative infusion</td>
<td>Ropivacaine 300 mg Ketorolac 30 mg Epinephrine 0.5 mg (156 mL)</td>
<td>Intra-articular vs. extra-articular (soft tissue)</td>
<td>0.48 h/ 2 mL/h Ropivacaine 5 mg/mL</td>
</tr>
<tr>
<td>Essving P 2011 30</td>
<td>TKA (49)</td>
<td>Intraoperative local infiltration and postoperative intra-articular injections vs. intrathecal morphine</td>
<td>Ropivacaine 400 mg Ketorolac 30 mg Epinephrine 0.5 mg (166 mL)</td>
<td>Intra-articular</td>
<td>21 and 45 h/22 mL Ropivacaine 200 mg Ketorolac 30 mg Epinephrine 0.1 mg</td>
</tr>
<tr>
<td>Affas F 2011 32</td>
<td>TKA (40)</td>
<td>Intraoperative local infiltration vs. femoral nerve block</td>
<td>Ropivacaine 300 mg Ketorolac 30 mg Epinephrine 0.5 mg (156 mL)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Zhang S 2011 34</td>
<td>TKA (80)</td>
<td>3 study groups: a) LIA + postop ropivacaine infusion b) LIA + postop saline infusion c) postop saline infusion</td>
<td>Ropivacaine 300 mg Ketorolac 30 mg Epinephrine 0.5 mg (152 mL)</td>
<td>Intra-articular</td>
<td>0.48 h/4mL/h Ropivacaine 2 mg/mL or saline 0.9%</td>
</tr>
<tr>
<td>Author, year</td>
<td>Procedure (no. patients)</td>
<td>Study design</td>
<td>Intraoperative injection, type, (total volume)</td>
<td>Catheter placement</td>
<td>Postop. injection(s) time/volume/type</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------</td>
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<td>-------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Koh IJ 2011</td>
<td>TKA (87)</td>
<td>Intraoperative local infiltration + cFNB vs cFNB</td>
<td>Ropivacaine 300 mg Morphine 10 mg Ketorolac 30 mg Epinephrine 0.3 mg Cefuroxime 750 mg (100 mL)</td>
<td>-</td>
<td>↓ pain (0-48h) ↓ opioid (0-24h) ↔ ROM (7 days postop.) ↔ LOS</td>
</tr>
</tbody>
</table>
### Table 9. Randomized trials investigating local infiltration analgesia for hip arthroplasty.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Procedure (no. patients)</th>
<th>Study design</th>
<th>Intraoperative injection (total volume)</th>
<th>Catheter placement</th>
<th>Postop. injection(s) time/volume/type</th>
<th>Outcome (time after surgery) LIA vs. control</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen LJ 2007</td>
<td>THA (37)</td>
<td>Intraoperative periarticular inj. vs placebo</td>
<td>Ropivacaine (300 mg) Ketorolac (30 mg) Epinephrine (0.5 mg) (151.5 mL)</td>
<td>Intra-articular</td>
<td>24 h/21.5 ml Ropivacaine 300 mg Ketorolac 30 mg Epinephrine 0.5 mg</td>
<td>↓ pain (4h, 8h, POD 1-4, 1-2 weeks) ↓ opioid (8-96h) ↑ physical function (1 week)</td>
<td>• Double-blind design • No control for ketorolac • Systemic analgesia with paracetamol 1g/6h and oxycodone p.a.</td>
</tr>
<tr>
<td>Andersen KV 2007</td>
<td>THA (75)</td>
<td>Intraoperative periarticular inj. vs epidural</td>
<td>Ropivacaine (200 mg) Ketorolac (30 mg) Epinephrine (0.5 mg) (102 mL)</td>
<td>Intra-articular</td>
<td>8 h/20 ml Ropivacaine 150 mg Ketorolac 30 mg Epinephrine 0.5 mg</td>
<td>↓ pain (20-96h) ↓ opioid (0-20h) ↑ ability to walk (8h) ↓ LOS (4.5 vs. 7 days) ↓ side-effects</td>
<td>• Non-blinded design • No control for morphine (epidural group) or ketorolac (LIA group) in either group • Systemic analgesia with paracetamol 1g/6h and oxycodone p.a.</td>
</tr>
<tr>
<td>Parvataneni 2007</td>
<td>THA (71)</td>
<td>Intraoperative local infiltration vs. PCA</td>
<td>Bupivacaine 2-400 mg Morphine 4-10 mg Epinephrine 0.3 mg Prednisolone 40 mg Cefuroxime 750 mg</td>
<td>-</td>
<td>-</td>
<td>↓ pain (POD 1,2 and 3) ↑ satisfaction (POD 1) ↓ LOS (3.2 vs. 4.2 days) ↔mobilization (6 weeks and 3 months)</td>
<td>• Not double-blinded • Groups not comparable with injection of morphine and steroid only in LIA group and undefined opioid-PCA in control group only • Inadequate definition of systemic analgesia</td>
</tr>
<tr>
<td>Busch CA 2010</td>
<td>THA (64)</td>
<td>Intraoperative periarticular inj. vs no injection</td>
<td>Ropivacaine (400 mg) Ketorolac (30 mg) Morphine (5 mg) Epinephrine (0.6 mg)</td>
<td>-</td>
<td>-</td>
<td>↓ opioid (6,24 h) ↓ pain on activity (PACU) ↔pain at rest ↔patient satisfaction ↔postoperative complications ↔mobilization dose below toxic level (n=5) ↔ LOS</td>
<td>• No control for morphine or NSAID in active treatment group • multiple anaesthetic procedures (general/regional) • Pain assessment time poorly defined • Pain on activity poorly defined • Systemic analgesia with Morphine-PCA and oral paracetamol, caffeine, codeine and oxycodone.</td>
</tr>
<tr>
<td>Andersen LO 2010</td>
<td>Bilateral THA (12)</td>
<td>Intraoperative periarticular inj. vs placebo</td>
<td>Ropivacaine (340 mg) Epinephrine (1.2 mg)</td>
<td>Intra-articular</td>
<td>8-24 h/20+50 ml Ropivacaine 40+100 mg Epinephrine (1:100,000)</td>
<td>↔pain (0-48 h) ↔mobilization (6 weeks and 3 months) ↓ side-effects</td>
<td>• Double-blind design • Systemic analgesia with gabapentin, celecoxib and paracetamol resulted in low postoperative pain scores.</td>
</tr>
<tr>
<td>Lunn TH 2011</td>
<td>THA (120)</td>
<td>Intraoperative periarticular inj. vs placebo</td>
<td>Ropivacaine (300 mg) Epinephrine (1.5 mg) (150 mL)</td>
<td>-</td>
<td>-</td>
<td>↔pain (0-8 h) ↔opioid (0-8 h)</td>
<td>• Double-blind design • Systemic analgesia with gabapentin, celecoxib and paracetamol resulted in low postoperative pain scores.</td>
</tr>
<tr>
<td>Author, year</td>
<td>Procedure (no. patients)</td>
<td>Study design</td>
<td>Intraoperative injection (total volume)</td>
<td>Catheter placement</td>
<td>Postop. injection(s) time/volume/type</td>
<td>Outcome (time after surgery)</td>
<td>LIA vs. control</td>
</tr>
<tr>
<td>--------------</td>
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<td>----------------------------------------</td>
<td>-------------------</td>
<td>--------------------------------------</td>
<td>---------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Specht K 2011 26</td>
<td>THA (54)</td>
<td>Intraoperative periarticular inj. with postoperative injection of LIA vs placebo</td>
<td>Ropivacaine (200 mg) Ketorolac (30 mg) Epinephrine (1 mg) (102 mL)</td>
<td>Intra-articular</td>
<td>10+22 h/51+51 mL Ropivacaine 100 mg Ketorolac 15 mg Epinephrine 0.5 mg</td>
<td>↓ pain (12-24 h) ↓ opioid (0-24 h) ↔ LOS</td>
<td>Double-blind design</td>
</tr>
<tr>
<td>Murphy TP 2011 34</td>
<td>THA (91)</td>
<td>Intraoperative periarticular inj. vs placebo</td>
<td>Levobupivacaine (150 mg) (60 mL)</td>
<td>-</td>
<td>-</td>
<td>↓ pain (0-72 h) ↓ opioid (0-48 h) ↔ PONV</td>
<td>No description of how pain data was collected Surgeon was not blinded to injection type Systemic analgesia with Morphine-PCA 0-48h.</td>
</tr>
<tr>
<td>Dobie I 2012 45</td>
<td>THA (92)</td>
<td>Intraoperative periarticular inj. vs no injection</td>
<td>Levobupivacaine (200 mg) Epinephrine (1:200,000) (160 mL)</td>
<td>-</td>
<td>-</td>
<td>↑ pain (7+12 h) ↔ opioid (0-24 h) ↔ mobilization (24 h) ↔ LOS</td>
<td>No clear description of how pain data was collected Systemic analgesia with IV Morphine (10 mg/4-6h) and paracetamol 1g/6h. Low post-op. pain scores in both groups.</td>
</tr>
<tr>
<td>Aguirre J 2012 42</td>
<td>Minimally invasive THA (72)</td>
<td>Postoperative epicapsular infusion of ropivacaine vs saline.</td>
<td>Ropivacaine (60 mg) (20 mL)</td>
<td>Epi-capular</td>
<td>0-48 h/6 ml h⁻¹ ropivacaine 12 mg h⁻¹</td>
<td>↓ opioid (0-48 h) ↓ pain (4-24 h + 3 months)</td>
<td>Double-blind design Systemic analgesia with Morphine-PCA and paracetamol 1g/6h in both groups. Inadequate systemic analgesia resulting in higher postoperative pain levels than normal.</td>
</tr>
<tr>
<td>Rikalainen-Salmi 2012 44</td>
<td>THA (60)</td>
<td>Intraoperative periarticular inj. vs intra-thecal morphine</td>
<td>Levobupivacaine (125 mg) Ketorolac (30 mg) Epinephrine (0.5 mg) (106 mL)</td>
<td>Intra-articular</td>
<td>24 h/21 mL Levobupivacaine 100 mg Ketorolac 30 mg</td>
<td>↑ pain (0-48 h) ↑ opioid (0-24 h) ↑ mobilization (6+24 h) ↔ PONV</td>
<td>Patient and investigator blinded No control for ketorolac in intra-thecal morphine group Systemic analgesia with paracetamol 1g/6h and ibuprofen 400 mg/12h.</td>
</tr>
<tr>
<td>Liu W 2012 45</td>
<td>THA (80)</td>
<td>Intraoperative periarticular inj. vs placebo</td>
<td>Bupivacaine (30 mg) Morphine (5 mg) Betamethasone (1 mL) Epinephrine (1:1000) (60 mL)</td>
<td>-</td>
<td>-</td>
<td>↓ opioid (0-36 h) ↓ pain (0-36 h) ↓ ROM (24 h, POD 2+7)</td>
<td>Double-blind design No control for morphine or betamethasone in control group Systemic analgesia with morphine-PCA and celecoxib 200 mg/12h.</td>
</tr>
</tbody>
</table>
Table 10. Length of Hospital Stay (LOS) in randomized trials using LIA for unilateral Hip and Knee Arthroplasty.

<table>
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<tr>
<th>Study</th>
<th>LOS, LIA</th>
<th>LOS, control</th>
<th>Well-defined discharge criteria (+ / -)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TKA</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Busch, 2006</td>
<td>mean 5.2</td>
<td>5.2</td>
<td>-</td>
</tr>
<tr>
<td>Vendittoli, 2006</td>
<td>mean 4.8</td>
<td>5.2</td>
<td>+</td>
</tr>
<tr>
<td>Toftdahl, 2007</td>
<td>median 5</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Parvataneni, 2007</td>
<td>not reported</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td>Andersen LØ, 2008</td>
<td>mean 2.8</td>
<td>3.3</td>
<td>+</td>
</tr>
<tr>
<td>Andersen LØ, 2008</td>
<td>not reported</td>
<td>not reported</td>
<td>+</td>
</tr>
<tr>
<td>Krenzel, 2009</td>
<td>not reported</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td>Essving, 2009</td>
<td>median 1</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Essving, 2010</td>
<td>median 3</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>Spreng, 2010</td>
<td>mean 3.5 and 4</td>
<td>5.5</td>
<td>+</td>
</tr>
<tr>
<td>Andersen KV, 2010</td>
<td>median 4</td>
<td>4</td>
<td>+</td>
</tr>
<tr>
<td>Carli, 2010</td>
<td>median 5</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Thorsell, 2010</td>
<td>mean 4.7</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Dobrydnjov, 2011</td>
<td>mean 3</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Essving, 2011</td>
<td>median 3</td>
<td>4</td>
<td>+</td>
</tr>
<tr>
<td>Affas, 2011</td>
<td>not reported</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td>Zhang, 2011</td>
<td>not reported</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td><strong>THA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersen LJ, 2007</td>
<td>mean 2.6</td>
<td>2.8</td>
<td>+</td>
</tr>
<tr>
<td>Andersen KV, 2007</td>
<td>median 4.5</td>
<td>7</td>
<td>+</td>
</tr>
<tr>
<td>Parvataneni, 2007</td>
<td>not reported</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td>Busch, 2010</td>
<td>mean 5.2</td>
<td>5.8</td>
<td>-</td>
</tr>
<tr>
<td>Lunn, 2011</td>
<td>mean 2.7</td>
<td>2.5</td>
<td>+</td>
</tr>
<tr>
<td>Specht, 2011</td>
<td>median 3</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Murphy, 2011</td>
<td>not reported</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td>Dobie, 2012</td>
<td>mean 3.5</td>
<td>3.9</td>
<td>-</td>
</tr>
<tr>
<td>Aguirre, 2012</td>
<td>not reported</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td>Rikalainen-Salmi</td>
<td>4</td>
<td>4</td>
<td>+</td>
</tr>
</tbody>
</table>

data presented as days in hospital unless otherwise stated.