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Regional anesthesia and total knee arthroplasty

Anesthetic and pharmacological considerations

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Table of contents

Chapter 1  General introduction 7
Chapter 2  Femoral nerve catheter versus local infiltration analgesia in fast track total knee arthroplasty: short-term and long-term outcome 21
Chapter 3  Pharmacokinetics of 400 mg ropivacaine after periarticular local infiltration analgesia for total knee arthroplasty 39
Chapter 4  Pharmacokinetics of 400 mg locally infiltrated ropivacaine after total knee arthroplasty without perioperative tourniquet use 51
Chapter 5  Influence of a tourniquet on opioid consumption after local infiltration analgesia for total knee arthroplasty 63
Chapter 6  Improving performance by monitoring the success rate of peripheral nerve blocks 73
Chapter 7  General discussion 83
Chapter 8  Conclusions 95

Summary
Nederlandse samenvatting
Dankwoord
Curriculum vitae
Bibliography
Research Data Management
Theses Sint Maartenskliniek
Chapter 1

General introduction
General introduction

In this thesis several aspects providing postoperative pain relief after orthopedic surgery, with specific interest in total knee arthroplasty, will be discussed. This first chapter starts by laying out the different aspects of anesthesia and analgesia, which can be used to create a condition to perform surgery safely and with a minimum of postoperative pain.

Total knee arthroplasty is a commonly performed surgery to improve chronic refractory joint pain and improve mobility, knee function and quality of life in patients suffering from severe osteoarthrosis.1,2 The history of total knee arthroplasty goes back to the late 19th century when the German surgeon Themistocles Gluck implanted the first hinged knee prosthesis, which was back then made of ivory.3 Over the second half of the 20th century the number of total knee arthroplasties performed annually increased exponentially, and this increase is expected to continue in the next decades.4–7 In this period the component materials varied from acryl to cobalt-chrome and finally to the development of the modern metal-on-polyethylene arthroplasty.8 During the seventies and eighties of the 20th century, several improvements in materials, geometry and fixation were established. Since then, developments have merely focused on durability of the prosthesis, accurate sizing, more natural biomechanics and improving range of motion. Despite all the improvements still 20% of patients undergoing total knee arthroplasty are not satisfied with their clinical outcome. Persistent (chronic) pain, reduced quality of life and lack of functional improvement are main predictors of dissatisfaction.9

Total knee arthroplasty is still associated with severe acute postoperative pain. This is not only uncomfortable for the patient, but has several other detrimental effects. In the short run, pain may hamper early mobilization, recovery and hospital discharge. While in the long run, acute postoperative pain is also a predictor of chronification of pain,10 which is a major setback for both patient and society. Therefore adequate postoperative analgesia is mandatory.11

General versus neuraxial anesthesia

General anesthesia is characterized by systemic administration of several types of drug, usually at least an opioid and an anesthetic agent. Opioids obtund the pain stimulus, while the administration of an anesthetic agent provides a state of unconsciousness, thus facilitating all kinds of surgery. Neuraxial anesthesia only anesthetizes the lower part of the body without altering the state of consciousness. Therefore, neuraxial anesthesia can only be used for lower abdominal or lower extremity surgery. Neuraxial anesthesia is performed by placing a needle between the spinous processes of two vertebrae and injecting a local anesthetic, with or without adjuvants, into the subarachnoid (for spinal anesthesia) or epidural (for epidural anesthesia) space. (Fig. 1)

Although spinal12 and epidural13,14 anesthesia were described long before the first total knee arthroplasty was performed, general anesthesia was the dominant form in anesthesia utilized for total knee arthroplasty in its early days. However, since the mid-eighties of the last century, neuraxial anesthesia has been gaining popularity.

Compared to central neuraxis blockade, general anesthesia has been associated with higher rates of postoperative nausea, vomiting, and itching. On the other hand neuraxial anesthesia
is associated with rare but serious complications such as spinal hematoma, epidural abscess, and nerve injury.\textsuperscript{18} Furthermore, a patient's coagulation status should be suitable for neuraxial anesthesia, which might be hindered by anticoagulant medication or bleeding disorders. Finally, even in experienced hands, in a small amount of patients the intrathecal space may not be identified, abolishing the possibility to perform neuraxial anesthesia.

**Figure 1. Needle positioning in spinal and epidural anesthesia.**

When focusing on total knee arthroplasty, large databases have shown positive results at several levels when performing neuraxial anesthesia for total knee arthroplasty: spinal anesthesia has been shown to be associated with lower wound infection and blood transfusion rates, and a decrease of overall number of complications, length of hospital stay and 30-day mortality.\textsuperscript{18} These beneficial effects of neuraxial anesthesia are particularly pronounced in patients with comorbidities.\textsuperscript{17} In addition, fast-track or enhanced recovery protocols are designed to enhance postoperative recovery, reduce morbidity and reduce length of hospital stay.\textsuperscript{18} These protocols usually incorporate the use of spinal anesthesia. Spinal anesthesia is usually performed using a single shot technique. After administration of a local anesthetic into the intrathecal space, sensory block is usually intense enough to perform surgery without the need for additional sedation. Using a hyperbaric solution offers the possibility to establish a predominantly unilateral block by placing the patient in the lateral decubitus position for about 20 minutes following intrathecal injection. With this technique the dose of local anesthetic can be reduced with approximately 30%,\textsuperscript{30} thus accelerating the regression of sensory and motor block and facilitating early mobilization.

Epidural anesthesia is nowadays usually performed in combination with spinal anesthesia (combined spinal-epidural) or with general anesthesia. A benefit of epidural anesthesia compared to spinal anesthesia is the option to prolong the duration of analgesia through an indwelling catheter. Several types of drugs\textsuperscript{18,28} can be administered through the epidural catheter, but often a mixture of a local anesthetic with an opioid is prescribed. However, the continuous administration of local anesthetic not only provides analgesia by blocking sensory nerve fibers, it can also prolong motor and sympathetic blockade, delaying mobilization and recovery as consequence.

Because of the aforementioned benefits, spinal anesthesia is the preferred and standard anesthetic technique in the fast-track protocols of many centers around the world.

**Multimodal analgesia**

Considering that severe postoperative pain can delay rehabilitation\textsuperscript{18,19} and is a prognostic factor for chronic pain,\textsuperscript{24,25} postoperative analgesia is a cornerstone in rehabilitation after surgery. In the past, intermittent opioid administration was the main cure to relieve postoperative pain. In 1987, the use of a novel electric pump to provide patient controlled analgesia (PCA-pump) was first described in the literature.\textsuperscript{27} Opioids are strong analgesics which can relieve pain adequately, but are commonly associated with side effects such as nausea, vomiting, drowsiness, respiratory depression, obstipation and itching.

To avoid or diminish these unwanted side effects, postoperative opioid consumption has to be reduced. A multimodal analgesic regimen is therefore standard in fast-track protocols, aiming for adequate pain relief with a minimum of side effects. Paracetamol, in combination with a NSAID, (oral) opioids, gabapentin and a local or regional anesthetic technique are frequently used constituents of fast-track protocols. Paracetamol, a NSAID and gabapentin are usually started preemptively before surgery; dexamethasone can be administered intravenously during surgery with the objective of prolonging the duration of local anesthetics and decrease the incidence of postoperative nausea.\textsuperscript{28} In general, administration of a COX-2 inhibitor before surgery decreases postoperative pain scores, opioid consumption, pruritus, and nausea or vomiting without increasing bleeding complications.\textsuperscript{29} More specifically for total knee arthroplasty, the use of etoricoxib leads to a decrease in postoperative opioid use without an increase in side effects.\textsuperscript{30}

Gabapentin can be prescribed to patients undergoing total knee arthroplasty. Although there is no evidence that gabapentin decreases acute postoperative pain,\textsuperscript{30} it may have some protective effect against chronicification of postoperative pain.\textsuperscript{26} Ketamine is another drug that may be part of some fast-track protocols, but because of its psychotomimetic side effects\textsuperscript{30} its use is controversial.

**Regional anesthetic techniques to reduce opioid use**

In enhanced recovery protocols, patients are encouraged to start mobilizing on the day of surgery. This is a challenge for anesthesiologists in treating postoperative pain while side effects such as drowsiness or muscle weakness impeding the possibility of safe mobilization, should be minimal or preferably absent.

**Nerve blocks**

Peripheral nerve blocks anesthetize a particular area of the body by blocking specific nerves to the part of the body that is to be operated. Compared to epidural analgesia, peripheral nerve blocks allow the possibility of targeted analgesia limited to the operated limb, without unwanted, bilateral or sympathetic side effects.\textsuperscript{26} Femoral nerve blocks (FNB), or previously the 3-in-1 blocks, are considered to be the golden standard for optimal analgesia after total knee arthroplasty.\textsuperscript{21,25} (Fig. 2)

Mostly, nerve blocks are performed under ultrasound guidance, alone or accompanied by nerve stimulation. With the introduction and development of ultrasound machines tailored to regional anesthesia, the success rate of nerve blocks has improved, the onset time and dose of local anesthetic necessary to establish a block have decreased and the chance of incidental vascular punctures is reduced.\textsuperscript{20,31} Recent functional developments in catheter systems
have made it easy to place a perineural catheter and provide a continuous peripheral nerve
block. A catheter next to the femoral nerve for example provides the option of continuous or
intermittent bolus administration of local anesthetic to extend postoperative analgesia. In
general, with the use of a perineural catheter analgesia can be prolonged for several days; as
a result, opioid consumption can be reduced as compared to single shot blocks and adverse
effects related to systemic analgesic medication will be less frequently.39–41

Figure 2. The femoral nerve

Figure 3. Innervation of the knee joint

When a femoral nerve block is used to provide postoperative analgesia, pain in the popliteal
fossa is not covered by this block, since this area is innervated by the tibial and peroneal nerve,
both deriving from the sciatic nerve. (Fig. 3) The majority of patients are not hindered by pain
in the popliteal fossa. However, up to 20% of the patients who undergo total knee arthroplasty,
experience severe postoperative pain in this area.40 To relieve pain in the popliteal fossa, the
sciatic nerve can be blocked or the posterior capsule of the knee joint can be infiltrated with a
long acting local anesthetic.

Local infiltration analgesia (LIA)
Femoral nerve block provides sufficient analgesia in most patients undergoing total knee
arthroplasty, however motor function may also be affected, impeding (independent)
mobilization if and as long as the motor function is diminished. To provide analgesia after
total knee arthroplasty and allow for early mobilization without impaired motor function, a
novel technique has been developed. This easy and straightforward technique is called local
infiltration analgesia.41,42 Local infiltration analgesia is based on the infiltration of a long
acting local anesthetic in the tissues surrounding the knee. Local infiltration analgesia exerts
its analgesic effect directly at the site of injection, providing analgesia without systemic side
effects such as drowsiness or nausea associated with high-dose opioids, or quadriceps muscle
weakness as a side effect of femoral nerve block.

Ropivacaine
Femoral nerve blocks or local infiltration analgesia for total knee arthroplasty are usually
performed with a long-acting local anesthetic such as bupivacaine, levobupivacaine or
ropivacaine. Because of its systemic toxic potential and the high dose of local anesthetic needed
for local infiltration analgesia, bupivacaine is not a logical choice. Both levobupivacaine and
ropivacaine have a more favourable safety profile and both drugs are used in LIA protocols. Of
the two, ropivacaine is the preferred drug, since its cardio and neurotoxic potential reduced
compared to levobupivacaine.43,44

Structure and mechanism of action
Ropivacaine, like all amide-type local anesthetics, contains a lipophilic benzene ring, a
hydrophilic aminogroup and an amide bond connecting these two structures. (Fig. 4)

Figure 4. Structure of Ropivacaine

Ropivacaine exerts its therapeutic effect at the site of injection by blocking voltage-gated
sodium channels in the axons. Only ionized ropivacaine is capable of blocking voltage-gated
sodium channels, impeding membrane depolarisation, which in turn prevents the conduction
of electric impulses through the nerve.

Pharmacokinetics
Immediately after injection, ropivacaine starts to be absorbed into the central compartment.
The vascularity of the infiltrated tissue is one of the main factors determining the resorption
speed.45 Blood flow is fundamental to systemic absorption; the higher the blood flow, the more
rapid the rise in plasma concentration. After systemic absorption, ropivacaine is distributed
through the whole body and can be taken up by virtually all organs. Microsomal cytochrome
P-450 enzymes in the liver metabolize ropivacaine, and subsequently the metabolites are
primarily excreted by the kidneys.46

Toxicity
Once absorbed into the bloodstream, approximately 95% of ropivacaine is protein-bound
in plasma, mainly to α1-glycoprotein.47 Only the unbound, unionized fraction is able to cross
cell membranes and distribute to other tissues. If the plasma concentration of unbound,
unionized ropivacaine exceeds the toxic threshold, symptoms of systemic toxicity may occur
in the central nervous system (CNS) or the heart. Exceeding the toxic threshold may occur
extremely rapid, for instance in case of inadvertent intravascular injection. In such cases, toxic
symptoms typically occur within minutes after injection. Systemic toxicity may also develop
gradually after a delay of tens of minutes to hours; this can happen when the total dose of
local anesthetic is too large, or when elimination is delayed.
Although the incidence of systemic toxicity after local anesthetic use is very low when standard safety precautions are observed, the consequences can be severe. The mild toxic effects are perioral numbness or metallic taste. However, symptoms can rapidly develop from mild into serious and potentially disastrous complications, such as seizures, respiratory depression and arrhythmias or cardiac arrest. In the central nervous system, local anesthetics affect the balance between inhibitory and excitatory pathways. Although CNS toxicity can present immediately with seizures or CNS depression, a more gradual increase in symptoms is usually seen. Before seizures develop, patients may experience a variety of other symptoms. Early symptoms can include dizziness, and visual or auditory disturbances such as tinnitus. When local anesthetic concentration in the CNS continues to increase, muscle twitching, shivering and tremors can be observed. Ultimately grand-mal seizures and CNS depression including the vasomotor center can occur.

The cardiovascular symptoms are usually less pronounced, since the cardiovascular system is more resistant to local anesthetic toxicity than the CNS. Higher doses of the same drug are required to provoke cardiotoxic symptoms as compared to CNS symptoms. The cardiac toxicity of local anesthetics is caused by several mechanisms. Interference with sodium and potassium channels results in rhythm disturbances and may initially be characterized by sympathetic activation presenting with hypertension and tachycardia. Next, blocking of the cardiac conduction system will result in brady-arrhythmia and ventricular ectopy, and blocking of calcium channels may cause myocardial depression. Local anesthetics also interfere with mitochondrial respiration, inhibiting the production of ATP by oxidative phosphorylation. This is particularly important in high-energy tissues such as the heart, where rapid depletion of ATP stores may contribute to the loss of contractility and aggravate myocardial depression. Ultimately, the combination of the cardiac (myocardial depression and brady-arrhythmia) and CNS (depression of the vasomotor center) toxic effects of local anesthetics may cause cardiovascular collapse.

Non-pharmacological reduction of postoperative pain

Physicians, and anesthesiologists in particular, are used to relieve postoperative pain with drugs. Our armoury includes several classes of drugs, which can be administered orally or parenterally, preemptively or as escape medication. Additionally, we try to decrease the demand for these drugs by applying regional or local anesthetic techniques to relieve postoperative pain.

However, there are more ways to reduce the need for escape medication. Patients can benefit from every day, drug related and non-drug related, choices we make in clinical practice. The perioperative use of a tourniquet in total knee arthroplasty has long been subject to discussion. For decades, tourniquets were used to facilitate a dry surgical field and reduce intraoperative blood loss. However, the first concerns of an altered risk on thrombotic events when a tourniquet is used for knee replacement surgery date back to the nineties. Tourniquet use is not only associated with a higher risk of thrombotic events, the risk of wound infection is also higher, the risk for nerve damage is increased and postoperative rehabilitation may be hindered. Paradoxically, when using a tourniquet total (i.e. both intra- and postoperative) blood loss is not decreased as compared to surgery without tourniquet and the fixation of the arthroplasty is not improved. Furthermore, the use of a tourniquet is associated with thigh pain. Despite these considerations there still is a low threshold for perioperative tourniquet use, since orthopedic surgeon experience that perioperative tourniquet use contributes to a drier surgical field, which facilitates the surgical procedure.

Clinical outcomes of patients undergoing any kind of treatment are not only determined by guidelines and protocols. Physicians’ individual performances or choices in treatment may also have an influence. To improve one’s behaviour, insight in one’s own performance and the influence on clinical outcome is essential. Differences in technique between physicians and the effect on outcome for individual patients may be very subtle. However, monitoring and comparing of individual performances in groups of patients might reveal differences in clinical outcome between physicians. If properly managed, this can be used as an instrument for inter-collegial discussion with the aim of improving both individual and collective performance.

Until now, evaluation of individual performance to improve collective outcomes and inter-colleague comparison of objective parameters are not widely accepted in our healthcare system. Moreover, still little is known about comparing individual performance, and what effect, if any, it has on the quality of care. These reservations notwithstanding, tools to improve individual and collective performance in terms of outcome are worth investigating.

Rationale and outline of this thesis

Recently developed enhanced recovery protocols aim for shorter hospital length of stay and better functional recovery. Prompt mobilization, preferably starting on the day of surgery, is one of the main pillars of enhanced recovery protocols. A substantial part of the patients undergoing total knee arthroplasty experience severe postoperative pain, which may impede early mobilization, slow rehabilitation and predispose to the development of persistent pain. Therefore adequate postoperative analgesia is a cornerstone in total knee arthroplasty rehabilitation.

Local infiltration analgesia and femoral nerve block are widely accepted techniques to relieve pain and reduce opioid consumption after total knee arthroplasty, both with their own benefits and disadvantages. The femoral nerve block has replaced the use of an epidural in many centers, but this technique is still associated with unilateral motor weakness, which may hamper mobilization. Local infiltration analgesia aims to provide an equal analgesic efficacy, while avoiding additional motor impairment. In these terms local infiltration analgesia may be the optimal technique to cover pain after total knee arthroplasty. However, the analgesic duration of single shot local infiltration analgesia may be shorter than that of a continuous femoral nerve block. The use of a catheter in the surgical field to provide continuous ropivacaine administration (continuous local infiltration analgesia) is still controversial, since it may alter the infection risk.

The optimal analgesic regimen for total knee arthroplasty has to strike a balance between adequate pain relief and minimal interference with the Fast-Track principles of early mobilization. To compare the benefits and disadvantages of a femoral nerve block with the LIA-technique we designed the study described in Chapter 2.
posterior knee capsule in combination with a femoral nerve catheter in terms of pain and functional recovery until one year after surgery in patients undergoing primary total knee arthroplasty.

To ensure sufficient analgesia with LIA, a high dose of ropivacaine is infiltrated in the tissues surrounding the knee. Often this dose exceeds the maximum recommended dose of 3-4 mg/kg. When the LIA-technique was introduced in our institution, its safety track record was still relatively short. After a sudden case of systemic toxicity, we carried out the pharmacokinetic study described in Chapter 3, to gain more insight in the maximum plasma concentrations and the timeframe in which patients are most at risk to develop a possible systemic toxic reaction.

Recently, performing total knee arthroplasty without the use of a tourniquet is gaining popularity. Since local blood flow is one of the main determinants of systemic absorption, the presence or absence of a tourniquet may affect the concentration-time curve. In Chapter 4 we describe the pharmacokinetic profile of the same mixture of ropivacaine and epinephrine as used in Chapter 3, however in this cohort no tourniquet was used at the time of infiltration.

Subsequently Chapter 5 describes the effect of a tourniquet on concomitant opioid use when local infiltration analgesia is used to provide postoperative analgesia.

Chapter 6 discusses the introduction and development of a monitoring system for the collective and individual success rates of peripheral nerve blocks and the effect this monitoring system has on postoperative pain scores.

In Chapter 7 the main results of this thesis are summarized and discussed together with the recommendations and directions for future research.

References


Femoral Nerve Catheter versus Local Infiltration Analgesia in Fast Track Total Knee Arthroplasty: Short-Term and Long-Term Outcome

Chapter 2

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Introduction
Abstract

Background
The aim of this study was to compare the effects on short-term and long-term pain and functional outcome of periarticular local anesthetic infiltration (LIA) with LIA of the posterior knee capsule in combination with a femoral nerve block (FNB) catheter in patients undergoing total knee arthroplasty.

Methods
Eighty patients were randomised to one of two groups: Subjects in group LIA received periarticular LIA with ropivacaine 0.2% for postoperative analgesia; subjects in group FNB received LIA of the posterior capsule and a FNB catheter. The primary outcome parameter was functional capacity of the knee one year after surgery. Secondary parameters included mobility as determined by accelerometer data, pain, satisfaction with the analgesic regimen, hospital length of stay, and use of pain medication three and twelve months after surgery.

Results
There were no differences between groups in long-term functional capacity, patient satisfaction and hospital length of stay. In the first two days, subjects in group FNB had slightly lower pain scores and used less opioids, and subjects in group LIA had a higher level of accelerometer activity. Three and twelve months after surgery, subjects in group FNB had lower maximum pain scores and were less likely to use any pain medication one year after surgery.

Conclusions
Both techniques were similar regarding long-term functional outcome. Subjects in group FNB had slightly lower pain scores and lower opioid consumption after operation, lower maximum pain scores at three and twelve months, and were less likely to use any pain medication one year after surgery.

Trial Registration
NCT01966263

Introduction

Total knee arthroplasty (TKA) reduces knee pain and improves knee joint function in patients with knee osteoarthritis. TKA may be associated with severe postoperative pain, which in turn may slow rehabilitation and predispose to the development of persistent pain. Perioperative pain protocols therefore focus on achieving optimal pain relief with a minimum of side effects; however, these goals may conflict with changing surgical perspectives with emphasis on early mobilization and reduced length of hospital stay. Recently developed fast track protocols (enhanced recovery protocols) aim for shorter hospital length of stay and better functional recovery. Fast track protocols that incorporate early mobilization have been shown to improve functional recovery and patient satisfaction, and are associated with a lower incidence of thromboembolic adverse events.

FNB provides good analgesia and is considered the standard of care by many. However, the use of a FNB has become disputable because like epidural analgesia, it may hamper early mobilization. Recent developments such as local infiltration analgesia (LIA) aim at providing adequate analgesia while avoiding motor impairment. Several RCTs comparing LIA with FNB have been conducted, and three meta-analyses show no differences in the two techniques regarding postoperative analgesia and complication rates. Although LIA may provide acceptable perioperative analgesia, there are no data on long-term functional recovery and persistent pain.

We performed a blinded randomized controlled trial comparing periarticular LIA of the knee with LIA of the posterior knee capsule in combination with a FNB catheter in terms of functional outcome and pain in patients undergoing primary TKA. Primary outcome measure was knee function, tested with functional tests. Secondary outcomes were perioperative and long-term knee pain, use of analgesics, length of hospital stay and patient-reported functional outcome by questionnaires.

Methods

This blinded randomized study was approved by the Independent Review Board Nijmegen (IRBN2013005) and was registered with an international clinical trials registry (www.clinicaltrials.gov, number NCT01966263) before onset of participant enrolment. Patients undergoing primary unilateral TKA were assessed for eligibility during preoperative screening visit. Patients were informed about the study and written informed consent was obtained from all patients. The study was conducted between November 2013 and November 2015 at the Sint Maartenskliniek Nijmegen, The Netherlands, according to the Declaration of Helsinki and later revisions thereof and in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for Good Clinical Practice.

Patients

Eligible participants were all adults aged 50-80 years with ASA physical health classification I, II or III. Patients presented with non-inflammatory knee osteoarthritis and were scheduled for fast track, primary, unilateral total knee arthroplasty under spinal anesthesia. Exclusion
criteria were defined as: any contra-indication for locoregional or spinal anesthesia, traumatic osteoarthritis or rheumatoid arthritis requiring TKA, an active local or systemic infection, known intolerance or contraindication for local anesthetics, paracetamol, NSAIDs or opioids, body mass index more than 40 kg/m², inability to walk independently (inability to walk at least 10 meters without a walking aid), scheduled for contra-lateral TKA within a year, or scheduled for another surgery within three months, use of opioids or anti-neuropathic pain medication for more than one year, or physical, emotional or neurological conditions that would compromise compliance with postoperative rehabilitation and follow-up.

Study procedure
Using a computer-generated sequence of random numbers in eight blocks of 10 and a sealed envelope technique, patients were randomized to one of two groups: group FNB or group LIA. The envelopes were opened just before surgery, when the patient arrived in the anesthetic room. Patient, anesthesiologist and orthopaedic surgeon were informed about the study allocation. The physical therapists and research assistants who assessed the outcome variables were blinded for treatment allocation and the patient was instructed not to discuss the analgesic regimen with anyone.

Anesthesia and surgical procedure
All surgeries were performed according to standard hospital protocol. In the anesthetic room, standard monitoring (pulse oximeter, non-invasive blood pressure and electrocardiogram) was applied to all patients and intravenous access was established. Before spinal anesthesia, patients in group FNB received a femoral catheter (Contiplex, BBraun, Melsungen, Germany) with dual guidance (ultrasound and nerve stimulation). A correct position of the needle and catheter tip was verified by the spread 5-10 mL of NaCl 0.9% injected under ultrasound guidance. The catheter was secured with a transparent dressing with an antimicrobial gel pad. In patients in group LIA a sham femoral catheter was taped to the skin in a similar fashion as with patients in group FNB.

All patients received spinal anesthesia with 10 mg hyperbaric bupivacaine 0.5% in the sitting position. Upon completion of the subarachnoid injection patients were turned to the lateral decubitus position, the side of surgery being dependent. The lateral decubitus position was maintained for twenty minutes to achieve a predominantly unilateral block, after which the patients were turned to the supine horizontal position.

During surgery, patients received conscious sedation with propofol upon request. A pneumatic tourniquet was placed around the patient’s thigh and inflated to 50 mmHg above systolic blood pressure with a maximum of 250 mmHg. The knee was approached through a medial parapatellar arthrotomy, all patients received a Genesis II posterior-stabilized (PS) TKA (Smith & Nephew, Memphis, TN, USA) with patellar resurfacing.

Study interventions
After placement of the prosthetic components and before wound closure, patients in both groups received local infiltration of the posterior knee capsule with 50 mL ropivacaine 0.2% plus epinephrine 1:200.000 and of the subcutaneous tissue with 50 mL ropivacaine 0.2% without epinephrine. Patients in group FNB received three additional boluses of ropivacaine 0.2% via the femoral catheter at 6 hour intervals up to 18 hours after the initial bolus injection.

Multimodal analgesia
All patients received oral multimodal analgesia consisting of paracetamol 1000 mg q.i.d., etoricoxib 50 mg once daily, and gabapentin 600 mg b.i.d. or 300 mg if patients were older than 60 years.

Breakthrough pain [numeric rating scale (NRS > 3)] in the recovery room was treated with intravenous morphine. At the orthopaedic ward, breakthrough pain (NRS > 3) was treated with oxycodone 5-10 mg ad libitum.

Rehabilitation and discharge criteria
Rehabilitation was according to the standard hospital fast track protocol. The protocol includes preoperative explanation of the protocol and instruction of the patients to ensure maximum involvement, short acting spinal anesthesia, mobilization within 4 hours after operation, physical therapy twice daily and evaluation of reaching the discharge criteria twice daily. Weight bearing mobilization was started as soon as spinal anesthesia had worn off and patients were encouraged to exercise. Patients were discharged when a set of discharge criteria was met (Table 1).

Table 1. Hospital discharge criteria

- Making independent transfers
- Walking independently and safely with walking aid
- Climbing stairs independently and safely (if necessary for home situation)
- Active knee flexion ≥ 60 degrees, passive knee extension 0 degrees
- Quadriceps muscle force ≥ 3 on Medical Research Council Scale for muscle strength

Outcome measurements
Data collection, including conducting all functional tests, was done by blinded physical therapists and research assistants. Functional capacity of the knee was assessed before operation, at hospital discharge, at three and at twelve months after surgery using the Timed Up and Go Test (TUG), Stair Climbing Test (SCT) and the Six Minute Walking test (6MWT). The TUG and SCT measure the time in seconds to perform predefined tests, the 6MWT the distance in meters. These tests have been validated for detection of improvement or deterioration in hip or knee function following surgery.13 The functional tests were conducted by three blinded physical therapists, all tests were conducted in the same manner, in the same hall, using the same stairs and chair. At three and twelve months the patients performed the functional tests just before their postsurgical follow up visit to the orthopaedic surgeon at the outpatient clinic.

In addition, knee function was evaluated using the Lower Extremity Functional Scale (LEFS) and the Oxford Knee Score (OKS) preoperatively, at six weeks and at three and twelve months
after surgery. At the same time intervals, fear of movement was measured using the Tampa Scale for Kinesiophobia (TSK), and quality of life was assessed using the EQ5D-3L and a Visual Analogue Scale (VASQL).

During hospital admission, a research assistant blinded for group allocation visited the patient twice daily at 8 am and 8 pm to assess postoperative pain by NRS (0 = no pain, 10 = worst possible pain). At each time point, patients were asked to rate their average pain during the previous 12-hour period. In the morning of the first two days after surgery, an accelerometer was attached to the non-operated thigh and in the evening, it was taken off. Accelerometers were used to assess the level of activity: an accelerometer can detect body movements by measuring orientation and acceleration in three orthogonal planes; anteroposterior, mediolateral and vertical. Hereby the intensity of activity over time can be estimated and postures and transfers can be calculated by using the orientation of the meter in relation to the body.14 The patients were instructed to continue their normal routine whilst wearing the accelerometer. Accelerometer data were either classified as ‘active’, which meant the accelerometer was in the upright position and moving; or ‘resting’; which was all other positions.

Twice daily the patients were visited by the physical therapist, who was blinded for group allocation, and who recorded the ability of the patient to mobilize.

At discharge, patients rated their satisfaction with the analgesic regimens on an NRS scale (0 = very dissatisfied, 10 – very satisfied), and range of motion (ROM) was calculated by the sum of knee flexion and extension as measured with a long-arm goniometer.

Pain and the use of analgesic medication for knee pain were assessed before operation, and at three and twelve months after surgery. Patients were asked to rate their average and their maximum pain in the two weeks preceding the contact moment on an 11-point numeric rating scale (NRS), ranging from no pain (0) to worst imaginable pain (10).

Sample size and statistical analysis

The null hypothesis of our study was that differences in anesthetic technique for TKA do not affect long-term functional outcome. Of the three tests we used to evaluate functional capacity, the SCT has the largest variance.15,16 To reduce the risk of insufficient power, we defined functional capacity of the knee one year after surgery as determined by SCT as the primary outcome parameter. Based on two studies,15,16 the sample size necessary to detect at least a 30% difference with a 90% probability and \( \alpha < 0.05 \) was 37 patients per group. Allowing for patient withdrawal during the study period, we included 40 patients per group.

Data were analysed using Stata version 13.1 (Stata Corporation, College Station, TX, USA) and are presented as mean (SD). Knee function outcome scores were analysed using multiple regression models. Linear regression was used to investigate the effect of the analgesic technique on the use of pain medication. A multilevel regression model was used to investigate the effect of analgesic technique on pain scores after operation, during the first 2 postoperative days. Time, time squared and baseline pain score were used as covariates in this model. The model used a random intercept, to allow for the clustering of the first four pain scores recorded after operation at 8 p.m. and 8 a.m. within each patient. For this specific analysis R version 3.4.3 was used as statistical software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Recruitment and flow of the patients is shown in a Consolidated Standards of Reporting Trials (CONSORT) flow diagram (Figure 1). All enrolled subjects received the allocated intervention. Patients in both groups had similar demographic and surgical characteristics. Distribution of baseline characteristics across the treatment groups is shown in Table 2, adverse events in Table 3.

![Figure 1. CONSORT Flow diagram](image)

Table 2. Baseline characteristics. Displayed as mean (SD) or number of patients.

<table>
<thead>
<tr>
<th>Group FNB (n=40)</th>
<th>Group LIA (n=40)</th>
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<td>Sex, no. M/ no. F</td>
<td>20 / 20</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 (6.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.0 (4.9)</td>
</tr>
<tr>
<td>ASA classification, no. I / no. II / no. III</td>
<td>8 / 24 / 8</td>
</tr>
<tr>
<td>Side of surgery, no. left / no. right</td>
<td>22 / 18</td>
</tr>
<tr>
<td>Duration of surgery (minutes)</td>
<td>72 (16)</td>
</tr>
<tr>
<td>Tourniquet time (minutes)</td>
<td>55 (11)</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>3.2 (1.1)</td>
</tr>
</tbody>
</table>
### Table 3. Adverse events

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount of AE</th>
<th>Treatment</th>
<th>Sequelae</th>
<th>Post-study interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wounds, Bleedings and Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Infected haematoma</td>
<td>1</td>
<td>Surgical cleaning, antibiotics</td>
<td>n.a.</td>
<td>Revision of arthroplasty</td>
</tr>
<tr>
<td>• Wound infection</td>
<td>1</td>
<td>Wound cleaning, change of insert during debridement</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>• Postoperative bleeding</td>
<td>1</td>
<td>Compression bandage and 2 days immobilization</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>• Wound dehiscence after fall on POD1</td>
<td>1</td>
<td>Surgical cleaning, antibiotics, 2 days immobilization</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Group LIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Wound infection</td>
<td>1</td>
<td>Surgical cleaning, antibiotics</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>• Wound dehiscence after removing stitches</td>
<td>1</td>
<td>2 weeks immobilization</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Acute pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Severe pain until 30 days after TKA</td>
<td>1</td>
<td>Prolonged hospitalisation for analgesic treatment</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Limited Range of Motion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB</td>
<td></td>
<td></td>
<td></td>
<td>Both with good function after inlay replacement</td>
</tr>
<tr>
<td>• Manipulation under anesthesia</td>
<td>2</td>
<td>Manipulation under anesthesia</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Group LIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Manipulation under anesthesia</td>
<td>2</td>
<td>Manipulation under anesthesia</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>• Manipulation under anesthesia</td>
<td>1</td>
<td>Manipulation under anesthesia</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Chronic pain</td>
<td></td>
<td></td>
<td></td>
<td>Pain resolved after resection of lateral facet patella</td>
</tr>
<tr>
<td>Group FNB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Neuropathic pain</td>
<td>1</td>
<td>Cryoablation</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>• Neuropathic pain</td>
<td>1</td>
<td>Cryoablation and trigger point injections</td>
<td>Yes</td>
<td>Pain resolved after resection of lateral facet patella</td>
</tr>
<tr>
<td>Group LIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Severe pain of unknown origin</td>
<td>2</td>
<td>No treatment</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Contralateral TKA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB</td>
<td>1</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group LIA</td>
<td>3</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Missing values

**Average pain scores during hospitalization**

During the first two days, average pain scores were missed in one to three patients because of absence during the regular visit. This concerned different patients every day. Missing average pain scores on the second day after surgery were due to patients being already discharged from the hospital.

Accelerometer data could not be obtained in all patients due to technical failure. This concerned different patients every day.

**Functional capacity**

Four patients (two in each group) were discharged before the functional capacity tests could be performed and one patient in group LIA was unable to perform the SCT on the day of discharge.

At three months, one patient from group FNB was excluded from continued data collection due to revision surgery of the knee; one patient from group FNB withdrew from follow up due to the development of a malignancy. One patient in group FNB and two in group LIA missed the appointment at three months. None of these patients had missed the functional capacity tests at discharge.

At twelve months, a third patient from group FNB and three patients from group LIA were excluded from continued data collection due to TKA of the contralateral knee between three and twelve months. In group LIA, one patient withdrew from follow up at twelve months due to the development of a severe eye disorder requiring intensive treatment. One patient from group FNB was unable to perform the 6MWT due to severe backache. These patients were other patients than those with missing values at discharge and three months.

**Average and maximum pain scores at three and twelve months**

The missing values for average and maximum pain scores at three and twelve months concern the patients who missed the three-month appointment, withdrew from follow up or were excluded from continued data collection for reasons mentioned earlier.

All missing values were classified as completely at random, except for missing pain scores on postoperative day 2 due to hospital discharge.
Long-term outcome variables

Functional capacity
Patients in both groups showed a major improvement in performance of functional knee capacity over time (Table 4).

Table 4. Functional performances displayed as mean (SD) and adjusted differences for baseline performance.

<table>
<thead>
<tr>
<th>Group</th>
<th>SCT (sec)</th>
<th>TUG (sec)</th>
<th>6MWT (meters)</th>
<th>ROM (º)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB N</td>
<td>21.8 (11.3)</td>
<td>10.1 (2.9)</td>
<td>394 (97)</td>
<td>107 (17)</td>
</tr>
<tr>
<td>Group LIA N</td>
<td>17.1 (6.8)</td>
<td>9.0 (2.3)</td>
<td>432 (99)</td>
<td>111 (13)</td>
</tr>
<tr>
<td>Adjusted diff between means (95% CI)</td>
<td>-8.2 (-19.8 to 3.5)</td>
<td>-1.6 (-2.1 to 2.0)</td>
<td>8 (-22 to 38)</td>
<td>-2 (-9 to 5)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.166</td>
<td>0.380</td>
<td>0.603</td>
<td>0.157</td>
</tr>
<tr>
<td><strong>Discharge</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB N</td>
<td>66.3 (25.9)</td>
<td>21.7 (8.1)</td>
<td>203 (69)</td>
<td>74 (15)</td>
</tr>
<tr>
<td>Group LIA N</td>
<td>54.2 (24.7)</td>
<td>19.6 (7.3)</td>
<td>219 (66)</td>
<td>72 (17)</td>
</tr>
<tr>
<td>Adjusted diff between means (95% CI)</td>
<td>2.4 (-1.5 to 6.3)</td>
<td>-0.4 (-0.5 to 1.3)</td>
<td>4 (-44 to 16)</td>
<td>-2 (-9 to 5)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.222</td>
<td>0.356</td>
<td>0.368</td>
<td>0.569</td>
</tr>
<tr>
<td><strong>3 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB N</td>
<td>16.8 (6.4)</td>
<td>8.3 (1.5)</td>
<td>440 (81)</td>
<td>106 (13)</td>
</tr>
<tr>
<td>Group LIA N</td>
<td>17.4 (10.4)</td>
<td>8.5 (2.4)</td>
<td>447 (72)</td>
<td>102 (13)</td>
</tr>
<tr>
<td>Adjusted diff between means (95% CI)</td>
<td>1.9 (-0.7 to 4.5)</td>
<td>0.4 (-0.5 to 1.3)</td>
<td>-13 (-44 to 16)</td>
<td>-5 (-11 to 1)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.153</td>
<td>0.047</td>
<td>0.078</td>
<td>0.106</td>
</tr>
<tr>
<td><strong>12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB N</td>
<td>13.8 (4.7)</td>
<td>7.6 (1.2)</td>
<td>505 (84)</td>
<td>112 (17)</td>
</tr>
<tr>
<td>Group LIA N</td>
<td>14.3 (7.1)</td>
<td>7.8 (1.9)</td>
<td>489 (71)</td>
<td>112 (12)</td>
</tr>
<tr>
<td>Adjusted diff between means (95% CI)</td>
<td>1.9 (-0.7 to 4.5)</td>
<td>0.2 (-0.2 to 1.1)</td>
<td>-32 (-64 to -0.4)</td>
<td>-1 (-8 to 5)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.153</td>
<td>0.047</td>
<td>0.078</td>
<td>0.106</td>
</tr>
</tbody>
</table>

SCT: stair climbing test (primary outcome measure), TUG: timed up and go test, 6MWT: 6 minute walk test, ROM: range of motion, FNB: femoral nerve block, LIA: local infiltration analgesia, CI: confidence interval.

Knee function and quality of life
Knee function as measured by LEFS and OKS improved over time in both groups. Knee function was comparable between the groups and there were no statistically significant differences at any of the time intervals. The same trend was found regarding quality of life as evaluated by EQ5D-3L and VASQL, as well as fear of movement as measured by TSK.

Pain
Average and maximum pain scores decreased over time in both groups. Maximum pain scores, but not average pain scores, were slightly lower in group FNB at three and twelve months after surgery; p=0.047 and p=0.021 respectively (Table 5 and Figure 2).

Table 5. NRS Pain scores at 3 and 12 months, displayed as mean (SD) and differences between mean adjusted for baseline pain score.

<table>
<thead>
<tr>
<th>Group</th>
<th>NRS average pain</th>
<th>NRS maximum pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB N</td>
<td>4.7 (2.3)</td>
<td>7.2 (4.5)</td>
</tr>
<tr>
<td>Group LIA N</td>
<td>3.9 (2.2)</td>
<td>6.7 (2.2)</td>
</tr>
<tr>
<td>Adjusted diff between means (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.047</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>3 Months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB N</td>
<td>2.4 (2.1)</td>
<td>3.8 (2.8)</td>
</tr>
<tr>
<td>Group LIA N</td>
<td>2.8 (1.7)</td>
<td>4.6 (2.2)</td>
</tr>
<tr>
<td>Adjusted diff between means (95% CI)</td>
<td>0.7 (-0.1 to 1.5)</td>
<td>1.2 (0.0 to 2.4)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.380</td>
<td>0.197</td>
</tr>
<tr>
<td><strong>12 Months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group FNB N</td>
<td>1.1 (1.8)</td>
<td>1.8 (2.4)</td>
</tr>
<tr>
<td>Group LIA N</td>
<td>1.5 (2.0)</td>
<td>3.0 (2.6)</td>
</tr>
<tr>
<td>Adjusted diff between means (95% CI)</td>
<td>0.5 (-0.4 to 1.4)</td>
<td>1.4 (0.2 to 2.6)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.037</td>
<td>0.167</td>
</tr>
</tbody>
</table>

NRS: numeric rating scale, FNB: femoral nerve block, LIA: local infiltration analgesia, CI: confidence interval.

Use of analgesics.
Three months after surgery, there was no difference between the groups in the use of analgesics. Twelve months after surgery, patients in group LIA were almost six times more likely to use analgesic medication for pain in the operated knee as compared to patients in group FNB (Odds ratio 5.9; 95% CI 1.1-31.7; p=0.037) (Table 6).
Table 6. Rescue analgesic use during hospitalisation and analgesic use at 3 and 12 months follow up. In hospital oxycodone used was added up per patient for each day. Data are expressed as mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Group FNB N</th>
<th>Group LIA N</th>
<th>Adjusted difference between means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative, in hospital, oxycodone use (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of surgery</td>
<td>61 (8.9)</td>
<td>10.9 (10.3)</td>
<td>4.8 (0.5 – 9.0)</td>
</tr>
<tr>
<td>Day after surgery</td>
<td>15.9 (12.4)</td>
<td>28.6 (20.2)</td>
<td>12.8 (5.3 – 20.2)</td>
</tr>
<tr>
<td>Day 2 after surgery</td>
<td>15.1 (16.3)</td>
<td>13.0 (15.6)</td>
<td>2.1 (−5.3 – 5.6)</td>
</tr>
<tr>
<td>Analgesic use at 3 months (no / yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracetamol</td>
<td>29/9</td>
<td>25/13</td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>37/2</td>
<td>32/6</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>35/3</td>
<td>33/5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>37/1</td>
<td>37/1</td>
<td></td>
</tr>
<tr>
<td>Overall use of pain medication at 3 months (no / yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>28/10</td>
<td>22/16</td>
<td></td>
</tr>
<tr>
<td>Analgesic use at 12 months (no / yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracetamol</td>
<td>36 / 1</td>
<td>32 / 7</td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>37 / 0</td>
<td>35 / 4</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>35 / 2</td>
<td>38 / 1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>36 / 1</td>
<td>39 / 0</td>
<td></td>
</tr>
<tr>
<td>Overall use of pain medication at 12 months (no / yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35 / 2</td>
<td>30 / 9</td>
<td></td>
</tr>
</tbody>
</table>

FNB, femoral nerve block; LIA, local infiltration analgesia, CI: confidence interval.

Short-term outcome variables

Postoperative pain and opioid use
Group FNB showed lower mean pain scores during the first two postoperative days, multilevel analysis revealed a difference of 0.95 (95% CI 0.39 – 1.51, p = 0.001) (Figure 3). Similarly, a difference in favour of the FNB group was found for maximum pain scores (difference 1.22; 95% CI 0.41 – 2.02; p = 0.003).

Also, group FNB showed lower opioid consumption on the day of surgery and the day after surgery. Table 6 displays data on postoperative analgesic use. Oxycodone consumption on the day of surgery was 6.1 (8.9) mg in group FNB vs 10.9 (10.3) mg in group LIA (adjusted difference between means 4.8; 95% CI 0.5 – 9.0). Oxycodone consumption on the day after surgery was 15.9 (12.4) mg in group FNB vs 28.6 (20.2) mg in group LIA (adjusted difference between means 12.8, 95% CI 5.3 – 20.2). There was no difference in patient satisfaction with the analgesic regimen (8.5 (1.8) in group FNB vs. 8.1 (1.3) in group LIA).

Postoperative activity
Group FNB showed lower activity levels on the day of the surgery and the first postoperative day as measured by accelerometry. Time spent active on the day of surgery was 2.3 (2.4) minutes in group FNB vs 4.4 (2.9) minutes in group LIA (adjusted difference between means 2.2, 95% CI 0.9 – 3.4). Time spent active on the day after surgery was 20.5 (14.9) minutes in group FNB vs 27.7 (14.1) minutes in group LIA (adjusted difference between means 7.2, 95% CI 0.5 – 13.9).

Mobilization
There was no difference between the groups in the ability to mobilize. ROM on the day of discharge was equal between groups FNB and LIA (74 (15) degrees and 72 (16) respectively), and there was no difference in hospital length of stay (Table 2).

Serious adverse events
None of the patients showed any sign of local anesthetic systemic toxicity (LAST). One falling incident was recorded. A patient in the FNB group mobilized unattended shortly after her return to the ward. The effects of spinal anesthesia may not have been fully resolved at this time and may have contributed to the fall.

Figure 3. Postoperative pain scores during hospitalization. Postoperative pain scores were assessed twice daily by a blinded research assistant. Data are plotted as means with standard deviation (SD). Multilevel analyses on presented pain scores, corrected for baseline pain scores showed a significant pain reduction in group FNB (p = 0.001). FNB, femoral nerve block; LIA, local infiltration analgesia; NRS, numeric rating scale.
Discussion

We found no differences in functional recovery of the knee at six weeks, three months and one year after surgery between the FNB and LIA group. These results agree with several other studies, although differences in methodology and the time of follow-up exist. 10,16

We found that the maximum pain scores at three months and a year after surgery were slightly but significantly higher in group LIA, and the odds of taking any pain medication for knee pain one year after surgery was almost six times higher in the LIA group. Patients in group FNB also had lower pain scores and less opioid consumption in the immediate postoperative period. As postoperative pain is a possible risk factor for the development of chronic pain, 12,18 the possibility of a causal relation is intriguing and should be kept in mind. However, since our study was neither powered nor designed to detect the influence of anesthetic technique on postoperative pain and chronicization of pain after TKA, further study will be necessary to elucidate this.

Studies analysing the effect of analgesic technique on long-term recovery after TKA are scarce; most studies comparing FNB and LIA focus mainly on differences in the early postoperative period. Although pain and opioid consumption in the immediate postoperative period are important issues from a perspective of patient comfort and satisfaction, the effect of an analgesic technique on long-term parameters such as functional recovery and pain is equally essential.

Regarding short-term outcome, we found that patients in group FNB had lower pain scores and less oxycodone use on the first day and night after operation, as well as on the day after surgery. The issue of the optimal analgesic regimen for fast track TKA is controversial. Our results agree with Carl10 and Kovalak11, who report less opioid use and lower pain scores in the first two days after surgery when comparing femoral nerve catheter combined with LIA of the posterior part of the knee, compared to LIA of both the posterior and anterior area of the knee. However, other studies reported better analgesia with LIA compared to FNB alone. 12,13,19-21 A possible explanation for this difference is the combination of FNB with local infiltration of the posterior capsule. Different branches of the femoral, obturator, and sciatic nerve contribute to the innervation of the knee14 and FNB alone does not provide analgesia of the sciatic part of the knee. The addition of a sciatic nerve block has been shown to provide better analgesia than FNB alone15 and local infiltration of the posterior capsule likely has a comparable effect.

Although the difference between the groups in pain scores and opioid use is statistically significant, the clinical relevance in the immediate postoperative period may be argued. Pain scores were low in both groups, and patient satisfaction with the analgesic technique was equally high.

Subjects in group FNB showed less activity as measured with the accelerometer on the first two days, but ROM at hospital discharge was similar between groups, as well as length of hospital stay and functional test scores. Early mobilization is believed to promote recovery after TKA and is one of the key features of fast track rehabilitation protocols. In our study we measured the time patients spent active (standing, walking) using accelerometry, an objective way to measure physical activity.16 Our data show that patients in group FNB were less active during the first day was short in both groups, on average 20 and 28 minutes during a twelve-hour interval (8 am until 8 pm). Since there was no difference between the groups on hospital length of stay, the clinical relevance of this difference in mobility is questionable.

Because of the potential of FNB to interfere with muscle strength, there is concern that the risk of falling is increased. We observed one falling incident in group FNB. This happened when the patient, contrary to instructions, mobilized unattended at a time that spinal anesthesia may not have been fully resolved. We did not observe any other falling incidents.

The dose of 400 mg ropivacaine we use for LIA is high, and well above the maximum recommended dose of 3-4 mg/kg for most patients. Although pharmacokinetic studies involving LIA with 400 mg ropivacaine for TKA found free ropivacaine concentrations to remain below the toxic threshold16,17 and we observed no signs of LAST in any of our patients, it may be prudent to consider reducing the dose of ropivacaine in patients with a low body weight, or in patients who are otherwise at an increased risk for LAST.

Our study has several limitations. We used a combination of ropivacaine and epinephrine for LIA, but around the world LIA mixtures vary in composition, additives, and dose of local anesthetic; also, we opted for an intermittent bolus technique in the FNB group, whereas others may favour a continuous infusion. Our results therefore are not necessarily representative for different LIA mixtures and different modes of application.

Although the total dose of ropivacaine in both groups is comparable, the systematic difference between the two methods of pain relief may favour the FNB group because these patients received three additional boluses with local anesthetic up to 18 hours after surgery, whereas patients in group LIA only received “single shot” infiltration at the end of surgery. To counteract this difference, an intra-articular catheter allowing similar top-ups would have been necessary in the LIA group. However, intra-articular catheters are controversial because of fear of an increased risk of infection, and for that reason not used in many orthopaedic centres, including ours. Therefore, despite this systematic difference between the two techniques, a comparison is still relevant from a clinical perspective.

For ethical reasons, we refrained from inserting femoral catheters in patients randomized to group LIA, tapping a sham catheter to the skin instead. Although an in–vivo placebo catheter would have been a better option with respect to blinding, it is our opinion that the risk of an invasive sham catheter would not justify the benefits. Thus the subjects were not blinded to group allocation. The treating anesthetists and surgeons were also not blinded. Given the study design, blinding of the anesthetists was not possible. Blinding the operating room personnel, including the surgeons, would have necessitated sham infiltration of the anterior capsule and subcutaneous tissue with normal saline in the FNB group, causing unnecessary swelling. In addition, it would have made the LIA procedure more complicated with different injectates for the anterior part of the knee for the two groups, increasing the risk of unintentional protocol violation. However, because the physical therapists and the research assistants collecting the data were blinded and none of the anesthetists, surgeons, or operating room personnel were involved in outcome measurements or data collection, we believe these limitations have not affected our results. Furthermore, performance on physical tests such as the 6MWT, SCT and TUG is not only determined by knee function per se, but also by factors such as age, sex,
This study was supported entirely by internal funds of the department of Anesthesiology, Susan, research nurse, and Jolanda Rubrech, research assistant, for managing the logistics of consultant, for his advice and assistance in the statistical analyses. Also, we thank Saskia conducting the functional tests and Ewald Bronkhorst, statistical and methodological

We would like to thank Tim Janssen, physical therapist, for his advice and assistance in conducting the functional tests and Ewald Bronkhorst, statistical and methodological consultant, for his advice and assistance in the statistical analyses. Also, we thank Saskia Susan, research nurse, and Jolanda Rubrech, research assistant, for managing the logistics of this study.

Acknowledgements

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References


Abstract

Background
Although considered safe, no pharmacokinetic data of high-dose, high-volume local infiltration analgesia (LIA) with ropivacaine without the use of a surgical drain or intra-articular catheter have been described. The purpose of this study is to describe the maximum total and unbound ropivacaine concentrations (C_{max}, C_{u max}) and corresponding maximum times (T_{max}, T_{u max}) of a single-shot ropivacaine (200ml 0.2%) and 0.75 mg epinephrine (1000µg/mL) when used for LIA in patients for total knee arthroplasty.

Methods
In this prospective cohort study, twenty patients were treated with LIA of the knee for primary total knee arthroplasty. Plasma samples were taken at 20, 40, 60, 90, 120, 240, 360 minutes and at 24 hours after tourniquet release, in which total and unbound ropivacaine concentrations were determined.

Results
Results are given as median [IQR]. Highest ropivacaine concentration (C_{max}) was 1.06 µg/mL [0.34]; highest unbound ropivacaine concentration (C_{u max}) was 0.09 µg/mL [0.05]. The corresponding time to reach the maximum concentration for total ropivacaine was 312 minutes [120] after tourniquet release, and for the unbound fraction 265 [110] minutes after tourniquet release.

Conclusion
Although great inter-individual variability was found between the maximum ropivacaine concentrations, both maximum total and unbound serum concentrations of ropivacaine remained well below the assumed systemic toxic thresholds of 4.3 and 0.56 µg/mL.

Trial Registration
NL4653 (NTR4796)

Introduction

Over the past few years, enhanced rehabilitation protocols (fast-track surgery protocols) were introduced for numerous surgical procedures to improve short- and long-term functional recovery, reduce morbidity, decrease length of convalescence and increase patient satisfaction – resulting in reduced hospital costs as a secondary gain.\(^{1,2}\) To facilitate enhanced rehabilitation protocols, optimal analgesia with minimal side effects should be provided. Postoperative pain treatment is an integrated part of the fast-track protocol, usually including pre-emptive and multimodal analgesia but also locoregional and local infiltration techniques are commonly incorporated.

In total knee arthroplasty (TKA), local infiltration analgesia (LIA) of the knee allows immediate postoperative mobilization without side effects such as drowsiness (opioids) or impaired motor function (femoral nerve block) that impedes rehabilitation.\(^{3,4}\) The LIA technique is based on local infiltration of the soft tissues surrounding the knee with a long-acting local anesthetic (LA). LIA is a straightforward and effective technique, which provides effective analgesia in the initial postoperative period after TKA and is adopted by orthopedic surgeons around the globe.\(^{3}\)

Local anesthetics exert their therapeutic effect directly at the site of injection. In a continuous manner, the LA is absorbed from tissue into the central compartment and is then eliminated from the plasma. Absorption speed and peak plasma concentration vary with the site of injection and type of LA used.\(^{6}\) The commonly used local anesthetic for LIA is ropivacaine, chosen for its long-acting profile, reduced cardiotoxicity in comparison to bupivacaine and its intrinsic vasoconstrictor properties. In plasma on average 95% of ropivacaine is bound to α₁-glycoprotein and approximately 5% of the total plasma concentration of ropivacaine is in the free form. Only unbound, unionized ropivacaine is able to cross the cell membrane of the nerve cell, exerting its pharmacological effect by blocking voltage-gated sodium channels from inside the nerve cell and preventing depolarization.

The plasma levels of ropivacaine are determined by absorption from the injection site, distribution and metabolization by cytochrome P450 enzymes in the liver and subsequent primarily urinary excretion. Plasma levels of unbound ropivacaine are, instead of bound ropivacaine, pharmacologically active and determine if, and to what extent, systemic effects of ropivacaine occur. When the plasma concentration of unionized ropivacaine exceeds the toxic threshold in the central nervous system (CNS) or heart, symptoms of systemic toxicity occur.

Doses of ropivacaine used for LIA or peripheral nerve blocks often exceed the recommended maximum dose of 3-4mg/kg.\(^{10}\) Concerns have been raised about the high doses of ropivacaine used for LIA with regard to LAST (local anesthetic systemic toxicity).\(^{11}\) Since LIA has only recently gained popularity, its safety track record is relatively short and so far little is known about the pharmacokinetic profile of ropivacaine applied for single-shot LIA of the knee. Thousands of patients have received LIA for TKA and to our knowledge, only one case of LAST after LIA has been described,\(^{12}\) suggesting that the technique is safe. Knowledge about plasma concentrations of ropivacaine and time to reach the highest plasma concentration will help determine safe doses of ropivacaine for LIA and provide a time frame for close monitoring of patients postoperatively.
The purpose of the present study is to describe the maximum total (C_{max}) and unbound (C_{u,max}), ropivacaine concentration, corresponding maximum times (T_{max}, resp. T_{u max}) and proximity to the toxic threshold, when a solution of 400 mg ropivacaine (200 ml, 0.2%) and 0.75 mg epinephrine (1000 µg/mL) is used as a single-shot LIA in TKA.

Methods

Patients

Before onset of participant enrolment, this prospective cohort study was approved by the Medical Research Ethics Committee Slotervaart Hospital and Reade and registered at the Netherlands Trial Registry (http://wwwtrialregister.nl, NTR4796). All patients who were scheduled for enhanced rehabilitation protocol for primary TKA under spinal anesthesia were assessed for eligibility. Eligible patients were those aged between 50-80 years with ASA physical health classification I or II, body mass index less than 40 kg/m², and hemoglobin 7.5 mmol/L or greater. Exclusion criteria were placement of a surgical drain, known hypersensitivity to amide-type local anesthetics, known history of hepatic or renal insufficiency and use of any medications that affect the clearance of ropivacaine.8

All eligible patients were informed verbally and in writing about the study and written informed consent was obtained from all participating patients. The study was conducted at the Sint Maartenskliniek Nijmegen, The Netherlands between January and May 2015 according to the Declaration of Helsinki and later revisions thereof and in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for Good Clinical Practice.

Anesthetic and Surgical procedure

All patients were treated according to the standard hospital enhanced rehabilitation protocol. Basic oral pain treatment was started preoperatively at the day of the surgery: paracetamol 1000 mg four times daily, etoricoxib 90 mg once daily and gabapentin 300 mg and 600 mg both once daily or 300 mg twice daily if patients were older than 70 years. Premedication consisted of 10 mg oxazepam orally. Additional pain therapy was started when the postoperative pain score (Numerical rating scale, NRS) was 2-4.

Surgery was performed under spinal anesthesia and upon patient request supplemented with sedation using propofol. Before placement of spinal anesthesia intravenous access and routine monitoring (electrocardiogram, non-invasive blood pressure and peripheral oxygen saturation) was established in all patients. Spinal anesthesia was performed with the patient in the sitting position at the third or fourth lumbar interspace. After obtaining a free flow of cerebrospinal fluid, 10 mg hyperbaric bupivacaine was administered and the patient was placed in the lateral decubitus position with the operative side dependent. The lateral decubitus position was maintained for twenty minutes with the aim of obtaining a preferential sensory and motor block on the operative side. A pneumatic tourniquet, inflated to 100 mmHg above normal systolic pressure, with a maximum of 300 mmHg, was used on the patient's thigh to diminish blood loss. Cemented posterior-stabilized total knee replacement with patella resurfacing, was performed according to standard hospital procedure.

After cementing, the knee was infiltrated by the orthopedic surgeon. 300 mg ropivacaine 0.2% (300 mL) was mixed with 0.75 mL epinephrine (1000 µg/mL). Two thirds of this solution was injected in the posterior and one third in the anterior capsule. After closure of the parapatellar arthrotomy another 100 mg of ropivacaine 0.2% (50 mL) without epinephrine was infiltrated in the subcutaneous tissues. Just before tourniquet release, patients received an i.v. bolus of 10 mg/kg tranexamic acid with a maximum of 1000 mg. All patients received a compression bandage before transfer to the recovery room.

Blood sampling and assays

Pre-operatively, before any intravenous fluids were administered to the patient, a baseline blood sample was taken. Before start of the surgery, all patients received two peripheral intravenous catheters (PIVC). One of the PIVCs, at least 16-gauge in size, was placed in the antecubital vein or great saphenous vein and was only used for blood sampling. No intravenous fluids were administered through this PIVC. Venous blood samples were taken at 20, 40, 60, 90, 120, 240, 360 minutes and at 24 hours after release of the tourniquet. At each collection moment, two samples of 5 mL blood were drawn. The first sample was drawn and discarded, as this sample was diluted with NaCl 0.9%. The second (undiluted) 5 mL was kept in an EDTA tube, centrifuged within one hour after collection and stored at -80ºC until assay of the whole batch. Total ropivacaine concentrations were determined in all serum samples. After determining the sample with the highest total concentration per patient, the unbound ropivacaine levels were determined in ultra filtrates of these samples as well as in the samples taken immediately before and after this time point. Ropivacaine levels were detected by a validated liquid chromatography – tandem mass spectrometry (LCMSMS) method as previously described.11

Sample size and statistics

The study was designed to describe the pharmacokinetic profile of 400 mg ropivacaine with epinephrine, when used for LIA of the knee. Because a sample size calculation is not possible in a descriptive study, we based the chosen sample size on experience and common sense. In case of small inter-individual variation and a homogenous study group, a sample size of six subjects is well accepted for pharmacokinetic studies. Since the study subjects in our study are heterogenic and more than one variable is measured, a larger sample size is required. We assumed that a sample size of 18 subjects would be appropriate, allowing for subjects to withdraw during the study period we chose to include 20 subjects. Analysis was conducted using GraphPad Prism 6 software (GraphPad Software Inc., San Diego, CA, USA). Frequency distribution was tested using Kolmogorov-Smirnov test for normality. Normally distributed data are presented as mean (SD) and non-normal distributed data are presented as median [IQR]. Primary end points were peak serum concentration of total ropivacaine in plasma (C_{max}) and unbound ropivacaine in ultra-filtrate (C_{u,max}) and the corresponding times to reach peak concentrations in serum (T_{max} and T_{u max}, respectively).
Results

All patients completed the study protocol. None of the patients showed any sign of LAST. Patient characteristics are shown in Table 1.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (mean ± SD)</th>
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<tr>
<td>Sex (M/F)</td>
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<tr>
<td>Age (years)</td>
<td>58.5 ± 6.7</td>
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<tr>
<td>Weight (kg)</td>
<td>89 ± 14</td>
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<td>Height (m)</td>
<td>1.73 ± 0.10</td>
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<td>BMI (kg/m²)</td>
<td>30 ± 4</td>
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</table>

Values are proportions or mean ± SD.

Table 2. Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
<td>C_{max} (µg/mL)</td>
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</tr>
<tr>
<td>T_{max} (min)</td>
<td>240 [120]</td>
</tr>
<tr>
<td>C_{u max} (µg/mL)</td>
<td>0.09 [0.05]</td>
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<td>T_{u max} (min)</td>
<td>300 [110]</td>
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</table>

C_{max} = maximum total ropivacaine concentration; T_{max} = time to C_{max}; C_{u max} = maximum free ropivacaine concentration; T_{u max} = time to C_{u max}.

Pharmacokinetic data

A summary of the pharmacokinetic data is given in Table 2. In eight samples the unbound ropivacaine concentration was below the lower limit of quantitation (0.05 µg/mL). For further calculations these samples were classified as 0.05 µg/mL to prevent underestimation of mean C_{u max}.

Median peak plasma concentration of total ropivacaine (C_{max}) was 1.06 µg/mL [0.34], median time to reach maximum plasma concentration (T_{max}) was 240 minutes [120]. Figure 1 shows the pharmacokinetic data; Figure 2 shows total ropivacaine plasma concentrations for all individual patients. Median peak plasma concentration of unbound ropivacaine (C_{u max}) was 0.09 µg/mL [0.05], median T_{u max} was 300 minutes [110].

Raw data of total and unbound ropivacaine are presented in Table 3.

Figure 1. Median total ropivacaine concentrations. Data are presented as median with first and third quartiles, whiskers represent data in 1.5 interquartile range with outliers plotted as individual points (Tukey boxplot).

Figure 2. Individual datapoints of total ropivacaine plasma concentrations.
Discussion

This is the first study that describes the pharmacokinetic profile of ropivacaine after high-dose, high-volume, single-shot LIA of the knee with epinephrine, without the use of a periarticular catheter or surgical drain. We found a great inter-individual variation in the plasma concentration of ropivacaine, but even the highest measured Cmax (2.26 µg/mL) and Cmax,Cu (0.13 µg/mL) are well below the toxic threshold described by Knudsen et al. in 1997, which were 4.3 and 0.56 µg/mL, respectively.12

In the literature many different procedures of LIA for knee surgery are described with varying doses of ropivacaine and additives such as epinephrine or analgesics. Some authors use an intra- or periarticular catheter for continuous postoperative ropivacaine infusion, and sometimes a surgical drain is left at the operative site. These variations in technique may influence the efficacy of the LIA in terms of pain relief, but they may affect ropivacaine plasma concentrations as well.

The first to describe the pharmacokinetic profile of ropivacaine LIA after TKA was Affas et al. in 2012.13 They studied pharmacokinetics of 300 mg ropivacaine, epinephrine and additional ketorolac by taking blood samples at 40 and 60 minutes, and at 2, 4, 6, 12, 24 hours after tourniquet release. Slightly lower mean maximum ropivacaine concentrations (mean: 0.813 µg/mL, range: 0.435-1.735 µg/mL) were found compared to our study. They found the Tmax between 4-6 hours after tourniquet release and, also similar to our study, some of the patients showed the highest plasma concentrations at 24 hours after tourniquet release. They found slightly lower peak plasma concentrations, which can be explained by the 25% lower dose compared to our study.

The cause of the great inter-individual variety of plasma concentrations and time to peak plasma concentrations is unclear. Patient characteristics such as protein binding capacity and speed of elimination through cytochrome P450 enzymes may be a factor. Also, the adding of epinephrine to the ropivacaine could be of influence, slowing the uptake of ropivacaine by its vasoconstrictive properties, and possibly the injection technique may also contribute to plasma absorption of ropivacaine.

Brydone et al.14 used 400mg ropivacaine for LIA, a similar dose as in our study, without added epinephrine and they found a more rapid rise in plasma concentration, with a peak concentration at 20 minutes after tourniquet release. A maximum peak concentration of 3.093 µg/mL was found, 37% higher than our maximum. In contrast to our protocol, an intra-articular catheter was placed infusing 20 mg ropivacaine per hour, therefore making it unclear whether the rapid rise in plasma concentration and higher peak plasma concentration is due to the intra-articular catheter or to the absence of epinephrine. In their study, potential toxic concentrations of total ropivacaine were reached in 2 patients. However, their highest mean free ropivacaine concentration was 0.041µg/mL (SD 0.023) at t<20 minutes, overall sample concentrations varied from 0.001 µg/mL to 0.104 µg/mL and thus stayed far below the toxic threshold.

Another study combined 375 mg ropivacaine with epinephrine as LIA with two infusion catheters, both infusing 40 mg/hour.15 Patients reached the maximum unbound ropivacaine concentration 20 minutes after tourniquet release. Maximum peak concentration was 2.26 µg/mL, well below the toxic threshold.

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<th>% free</th>
<th>Time before peak concentration (min)</th>
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Table 3. Individual ropivacaine concentrations.

Total ropivacaine serum concentrations (µg/mL) and corresponding unbound ropivacaine ultra-filtrate concentrations (µg/mL). Na = not applicable. * Sample drawn 10 minutes later than scheduled due to logistic reason.
concentration 6 hours after ropivacaine injection, however maximum total plasma concentrations were reached 24 hours after the end of surgery. Despite the additional 192 mg administrated via both catheters, maximum total and unbound ropivacaine concentrations were slightly lower (0.888 µg/mL (0.539-1689) and 0.050 µg/mL (0.025-0.105), respectively) as compared to our study, which could be explained by the surgical drain. An average volume of 600 mL shed blood with high ropivacaine concentrations was collected via the surgical drain in the first 6 hours after surgery. Like in our study, free fractions were here highly variable; with a range of 2.7-12.6% and an average free fraction of 4.8%.

A limitation of our study is the scarcity of samples between 6 and 24 hours, just after the peak concentration. Based on the literature available when we designed the study, we had expected a much faster uptake of ropivacaine. Brydone et al. and Ng et al. found a T_max of 30 minutes after LIA resp. intra-articular administration of ropivacaine without epinephrine, while Thomassen et al. and Affas et al. found the T_max 4-6 hours after the administration of LIA with added epinephrine. These two latter studies encountered the same problem of 'missing' peak plasma concentrations in the sampling scheme. Unfortunately both these studies were yet to be published when we designed our study and we used the sampling scheme of the two first studies, expecting an earlier rise in plasma concentrations.

One of our patients had unexpected early peak plasma concentrations. Peak concentrations were found in the first hour after tourniquet release, while C_max was comparable with other patients (Table 3, patient 3). In this patient the analgesia was already insufficient from 1.5 hour after tourniquet release. This patient was successfully titrated with intravenous morphine and clonidine. The early rise of plasma ropivacaine and insufficient analgesia may be explained by rapid intravenous absorption of ropivacaine, the cause of which is unknown.

In our study, we used 150 mL ropivacaine 0.2% with-, and without epinephrine. The ropivacaine with epinephrine was injected in the periarticular tissue. After closure of the knee capsule, the subcutaneous tissue of the knee was infiltrated with 50 mL of ropivacaine without epinephrine in order to prevent blistering of the skin. Compared with ropivacaine with epinephrine, the portion of ropivacaine without epinephrine will be absorbed more rapidly with an expected C_max of 20 minutes after tourniquet release. From a theoretical perspective, this portion may be expected to contribute to the rise in the plasma concentration of ropivacaine especially during the first 20-40 minutes. However, since the plasma concentration continued to rise well beyond 40 minutes, we do not believe that the portion of ropivacaine without epinephrine affected the C_max and T_max found in our study.

We cannot exclude the possibility that the true maximum plasma concentration lies between 4 and 6 hours or even 6 and 24 hours in some patients. This T_max, which appears to be at least later than four hours after tourniquet release, makes monitoring the patients until beyond this point logistically and financially challenging. In addition, prolonged monitoring would also interfere with the principles of fast track recovery. Although actual maximum plasma concentrations may be missed in our study, maximum plasma levels of unbound ropivacaine remain so far below toxic concentrations that LIA with high-dose ropivacaine and added epinephrine can be considered safe. Prolonged monitoring is in our opinion therefore not necessary.

This pharmacokinetic study was not powered to investigate the incidence of LAST, however, based on current data there are no indications that the use of 400mg ropivacaine combined with epinephrine in TKA yields a high risk of LAST. Knudsen et al. defined the unbound ropivacaine toxic threshold in arterial samples to be 0.56 (range: 0.34-0.85) µg/mL. With a maximum unbound ropivacaine concentration of 0.13 µg/mL when ropivacaine is used for LIA, the peak concentration remains far below the toxic threshold.

In conclusion, a single shot of 400 mg ropivacaine with added epinephrine for LIA after TKA appears to be safe, the maximum plasma concentrations of ropivacaine stay far below the toxic threshold of 0.56 µg/mL free ropivacaine. However, because of great inter-individual variety in the absorption of local anesthetics and in the threshold of local anesthetic toxicity, sporadic cases of LAST may still occur. The time to reach C_max might be several hours after tourniquet release, this slow absorption is contributing to the safety profile of high-dose ropivacaine for LIA.

Financial support and sponsorship
This study was supported entirely by internal funds of the department of Anesthesiology, Sint Maartenskliniek, Nijmegen, The Netherlands.
References

Abstract

Background

Local infiltration analgesia (LIA) with ropivacaine for Total Knee Arthroplasty (TKA) is increasingly used. Despite the high doses of ropivacaine, LIA is considered safe and this perception is sustained by pharmacokinetic data demonstrating that maximum concentrations of ropivacaine stay well below the toxic threshold in plasma. These pharmacokinetic studies all involve TKA procedures with the use of a tourniquet. Recently, performing TKA without the use of a tourniquet is gaining popularity, but no pharmacokinetic data exist when LIA is administered for TKA without the use of a tourniquet. The purpose of this study is to describe the pharmacokinetic profile of a single-shot ropivacaine (200ml 0.2%) and 0.75 mg epinephrine (1000µg/mL) when used for LIA in patients for TKA without a tourniquet.

Methods

In this prospective cohort study twenty patients treated with LIA for TKA without a tourniquet were studied. Plasma samples were taken at 20, 40, 60, 90, 120, 240, 360, 480, 600, 720 and 1440 minutes after local anesthetic infiltration, in which total and unbound ropivacaine concentrations were determined.

Results

Results are given as median [IQR]. Median peak ropivacaine concentration was 1.16 µg/mL [0.46]; median peak unbound ropivacaine concentration was 0.05 µg/mL [0.02]. The corresponding times to reach the maximum concentration for total and unbound ropivacaine were 360 [240] and 360 [360] minutes respectively.

Conclusion

Although great inter-individual variability in ropivacaine concentration was found, both total and unbound maximum serum concentrations remained below the assumed systemic toxic thresholds in all samples.

Trial registration
NL6159 (NTR6306).

Introduction

Total knee arthroplasty (TKA) is commonly used to treat severe knee osteoarthritis. During the last decades, the prevalence of TKA has been increasing worldwide, and this increase is expected to continue in the next decades.1 Thus, TKA is at present a frequently performed procedure, claiming an increasing part of the orthopedic surgical capacity. In recent years, research has focused on improving outcome and reducing length of hospital stay by developing fast-track surgery protocols.2,3

TKA is associated with severe postoperative pain that is not only uncomfortable for the patient, but may also hinder early mobilization, recovery and hospital discharge; adequate treatment of postoperative pain is therefore mandatory. A multimodal pain treatment including local infiltration analgesia (LIA) is often used to provide analgesia. LIA is considered to be a simple and low-invasive technique4 that is characterized by the infiltration of a long acting local anesthetic in the soft tissues surrounding the knee joint,5,6 providing effective analgesia in the early postoperative period without side effects such as nausea (opioids) or m. quadriceps femoris weakness (femoral nerve block).

LIA is usually performed with ropivacaine in relatively high doses exceeding the maximum recommended dose of 3-4 mg/kg,7,8 and therefore local anesthetic systemic toxicity (LAST) is a concern. Nevertheless, worldwide thousands of patients have received LIA for knee surgery with no apparent signs of systemic toxicity and pharmacokinetic studies9–11 have confirmed the safety of high doses of ropivacaine for LIA, the concentration of unbound ropivacaine in plasma staying well below the toxic threshold.12,13 The pharmacokinetic studies mentioned above concerned patients who had surgery under tourniquet-induced exsanguination with the tourniquet still inflated at the time of local infiltration. However, because of an increased awareness of the disadvantages of a tourniquet, total knee arthroplasty without the use of a tourniquet is gaining popularity.14

It is undetermined if the absence of circulation at the site of infiltration caused by an inflated tourniquet and the hyperperfusion following deflation affect the systemic absorption of ropivacaine and to what extent. The aim of the present study is to describe the pharmacokinetic profile of ropivacaine after LIA in TKA surgery without the use of a tourniquet.

Methods

Patients

This prospective cohort study was approved by the Medical Research Ethics Committee Slotervaart Hospital and Reade (NL60548.048.17, date of approval February 10th, 2017) before onset of participant recruitment. The study was registered at the Netherlands Trial Registry (http://www.trialregister.nl) with trial ID NTR6306 on January 16th, 2017.

Patients scheduled for primary TKA under spinal anesthesia without the use of a tourniquet were assessed for eligibility. Criteria for inclusion were ASA physical status classification I or II, age 50-80 years, body mass index less than 40kg/m², and hemoglobin 7.5 mmol/L or greater. Exclusion criteria were the (expected) use of a tourniquet, placement of a surgical drain,
known hypersensitivity to amide-type local anesthetics, hepatic or renal insufficiency and use of medications that are known to affect the clearance of ropivacaine. Eligible patients were informed verbally and in writing, and written informed consent was obtained from all participants before the start of the study.

The study was conducted at the Sint Maartenskliniek Nijmegen, The Netherlands between February and May 2017 according to the Declaration of Helsinki and later revisions thereof and in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for Good Clinical Practice.

Anesthetic and Surgical procedure

The anesthetic and surgical procedures have been described in a previous study conducted in our institution and are identical except for the absence of a tourniquet during surgery. Briefly, all patients received standard multimodal analgesia with paracetamol 1000 mg q.i.d., etoricoxib 90 mg once daily and gabapentin gabapentin 300 mg and 600 mg both once daily or 300 mg twice daily if patients were older than 70 years. This analgesic regimen was started preoperatively on the day of surgery. Postoperative pain was evaluated with a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain possible). In case of an NRS score ≥ 4 patients received oxycodone 5 to 10 mg orally.

Surgery was performed under standard monitoring (electrocardiogram, non-invasive blood pressure and peripheral oxygen saturation). The anesthetic technique was unilateral spinal anesthesia with 10 mg hyperbaric bupivacaine 0.5%. During surgery patients were either awake or sedated with propofol upon request.

After implanting and cementing a Genesis II Total Knee System with patellar resurfacing (Smith & Nephew, Memphis, TN, USA), LIA was performed by the orthopedic surgeon using 300 mg ropivacaine 0.2% (150 mL) with epinephrine 5 µg/mL for the posterior and anterior capsules; a further 100 mg ropivacaine 0.2% (50 mL) without epinephrine was infiltrated subcutaneously, the total dose of ropivacaine being 400 mg. Upon conclusion of the subcutaneous ropivacaine infiltration the time was designated T=0.

Blood sampling and assays

Before anesthesia, all patients received a peripheral intravenous catheter for the administration of fluids and medication. Blood samples for the assessment of ropivacaine concentrations were drawn from a separate 16-gauge peripheral intravenous catheter placed in the antecubital vein of the contralateral arm. No intravenous fluids were administered through this sampling catheter, except flushing with 1-2 mL NaCl 0.9% following each sampling to prevent clotting in the catheter. A baseline sample was taken immediately after placement of the sampling catheter; consecutive samples were obtained at T = 20, 40, 60, 90, 120, 240, 360, 480, 600, 720 and 1440 minutes by one of the investigators. Based on the results of our previous study, we added the 480-, 600-, and 720-minute samples to the sampling schedule. To avoid saline-diluted samples, two samples of 5 mL each were drawn at all time intervals. The first sample was discarded; the second sample was drawn in an EDTA tube, centrifuged and stored at -80°C within one hour after collection. The samples were kept in storage until the last patient had been completed so that all samples could be assayed in one batch.

The analysis of the ropivacaine concentrations was performed by the Laboratory for Toxicology, Therapeutic Drug Monitoring and Pharmaceutical analysis of the Department of Clinical Pharmacy and Pharmacology at the University Medical Center Groningen, Groningen, the Netherlands, using Liquid chromatography-tandem mass spectrometry as described previously. Total ropivacaine concentrations were measured in all samples. The concentration of unbound ropivacaine of each patient was assessed in ultrafiltrate of the sample with the highest total ropivacaine concentration, as well as in those of the preceding and following time point samples. Thus, from each patient three unbound ropivacaine concentrations were obtained; the highest value of these three concentrations was taken as the individual maximum unbound ropivacaine concentration (C u,max) and used for calculating the average C u,max. To calculate the average unbound ropivacaine fraction, we used all free concentrations and the corresponding total ropivacaine concentrations.

Sample size and statistics

The purpose of this study was to describe the pharmacokinetic profile of ropivacaine 400 mg ropivacaine when used for LIA in TKA surgery without the use of a tourniquet. Since this is primarily a descriptive study, the sample size was not calculated but based on choice. Because the methodology of this study is identical to our previous study but for the absence of a tourniquet, we decided to study the same number of subjects (n=20).

Data were analyzed using Stata version 13.1 (Stata Corporation, College Station, TX, USA). Data were tested for normality using the Shapiro-Wilk test. Data are presented as mean (SD) or median [IQR], as appropriate. Peak concentrations of total and unbound ropivacaine (C max and C u,max respectively) and the times to reach these peak concentrations (T max and T u,max respectively) are reported.

Results

The study protocol was completed by all patients. The flow of patient recruitment and study participation is shown in Figure 1. No signs or symptoms of LAST were observed in any of the patients. Patient characteristics are displayed in Table 1.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>9/11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.3 ± 5.7</td>
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<tr>
<td>Weight (kg)</td>
<td>88 ± 14</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.71 ± 0.08</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>30 ± 5</td>
</tr>
</tbody>
</table>

Values displayed as number of patients or mean ± SD
Pharmacokinetic data

Median peak plasma concentration of total ropivacaine ($C_{\text{max}}$) was 1.16 [0.46] µg/mL; median time to reach maximum plasma concentration ($T_{\text{max}}$) was 360 [240] minutes. Median peak unbound ropivacaine concentration ($C_{u\text{max}}$) was 0.05 [0.02] µg/mL, median $T_{u\text{max}}$ was 360 [360] minutes. The highest individual $C_{u\text{max}}$ was 0.082 µg/mL. Mean unbound ropivacaine fraction was 3.7% (1.3).

Figure 2 shows total ropivacaine plasma concentrations for all individual patients. In Table 2 and Figure 3 we have combined the results of the present study with those of our previous study. The raw data of total and unbound ropivacaine concentrations are presented in Table 3.

Table 2. Pharmacokinetic data.

<table>
<thead>
<tr>
<th></th>
<th>No Tourniquet cohort (n=20)</th>
<th>Tourniquet cohort (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>1.16 [0.46] (0.78; 2.34)</td>
<td>1.00 [0.34] (0.61; 2.28)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (min)</td>
<td>360 [240] (240; 600)</td>
<td>240 [120] (40; 360)</td>
</tr>
<tr>
<td>$C_{u\text{max}}$ (µg/mL)</td>
<td>0.05 [0.02] (0.014; 0.093)</td>
<td>0.09 [0.05] (0.05; 0.13)</td>
</tr>
<tr>
<td>$T_{u\text{max}}$ (min)</td>
<td>360 [360] (240; 720)</td>
<td>300 [110] (60; 370)</td>
</tr>
</tbody>
</table>

Data displayed as median [IQR] (minimum value; maximum value). $C_{\text{max}}$ = maximum total ropivacaine concentration; $T_{\text{max}}$ = time to $C_{\text{max}}$; $C_{u\text{max}}$ = maximum free ropivacaine concentration; $T_{u\text{max}}$ = time to $C_{u\text{max}}$.
### Table 3: Individual ropivacaine concentrations.

<table>
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<tr>
<th>Patient</th>
<th>Time (min)</th>
<th>Total conc. (mg/mL)</th>
<th>Free conc. (mg/mL)</th>
<th>% free</th>
<th>Time (min)</th>
<th>Total conc. (mg/mL)</th>
<th>Free conc. (mg/mL)</th>
<th>% free</th>
<th>Time (min)</th>
<th>Total conc. (mg/mL)</th>
<th>Free conc. (mg/mL)</th>
<th>% free</th>
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</thead>
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<td>0.056</td>
<td>4.5%</td>
<td>500*</td>
<td>1.19</td>
<td>0.055</td>
<td>4.6%</td>
<td>720</td>
<td>1.15</td>
<td>0.068</td>
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<tr>
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<td>600</td>
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<td>6.4%</td>
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<td>480</td>
<td>1.24</td>
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<td>1.73</td>
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<td>1.01</td>
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<td>480</td>
<td>1.79</td>
<td>0.093</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

**Discussion**

This study describes the pharmacokinetic profile of ropivacaine after a single-shot, high-dose LIA in TKA without the use of a tourniquet. Although the variation in ropivacaine concentrations is large, all total and unbound concentrations are well below the toxic threshold as described by Knudsen (4.3 µg/mL for total ropivacaine and 0.56 µg/mL for unbound ropivacaine).  

Many different procedures of LIA for knee surgery have been published with varying administration techniques, post-operative drain use, additives, and differences in doses of ropivacaine. Although these technical differences may affect the pharmacokinetic profile, and differences in ropivacaine dose make a comparison of maximum concentrations problematic, the available pharmacokinetic data have shown that ropivacaine concentrations do not reach toxic levels.

We found a $T_{max}$ of 360 minutes in the present study and 240 minutes in our previous study. This agrees with the results of Affas et al. who reported a $T_{max}$ of 240 – 360 min in a study using a LIA mixture of 300 mg ropivacaine with epinephrine and ketorolac for TKA, and a $T_{max}$ of 240 minutes using a LIA mixture of 200 mg ropivacaine with epinephrine and ketorolac for total hip arthroplasty. This $T_{max}$ of 240 – 360 minutes seen with LIA is much later than the $T_{max}$ associated with peripheral nerve blocks. In a study using 450 mg ropivacaine with epinephrine 5 µg/mL for combined sciatic/femoral nerve block the mean $T_{max}$ was 100 minutes, and others have reported a mean $T_{max}$ of 80 minutes for lumbar plexus block and 38 minutes for combined lumbar plexus/sciatic nerve block using ropivacaine with epinephrine 2.5 µg/mL. $T_{max}$ is largely determined by absorption from the site of injection and elimination; since differences in the elimination of ropivacaine between LIA and peripheral nerve blocks are unlikely, the most likely explanation for the difference in $T_{max}$ is that absorption with LIA is considerably slower than with peripheral nerve block. A possible explanation is that in case of LIA local blood flow may be reduced by postoperative swelling.

Tourniquets are used to create a bloodless surgical field, with the purpose of facilitating the surgical procedure and limiting intra-operative blood loss. However, these advantages come with a price; the use of a tourniquet may be associated with complications such as venous thrombosis, wound infections and delayed functional recovery or uncomfortable thigh pain at the level of the tourniquet. Because it was demonstrated that the use of a tourniquet might reduce intraoperative blood loss but has little, if any, effect on total (intraoperative plus postoperative) blood loss, awareness of the disadvantages of a tourniquet has increased and caused a shift in the balance towards surgery without a tourniquet.

The purpose of our present study was to investigate if the absence of a tourniquet affects the pharmacokinetics of ropivacaine. With Bier block, it has been shown that after tourniquet release a significant portion of the local anesthetic remains in the operated limb for a prolonged time. When performing surgery with a tourniquet there is a 10- to 15-minute timeframe between ropivacaine infiltration and restoration of the blood flow. During this period, systemic absorption is absent and postponed until the time of deflation. In analogy with the observed pharmacokinetics with Bier block, it is conceivable that this delay in absorption affects the pharmacokinetic profile of ropivacaine compared with the situation without the use of a tourniquet, when systemic absorption starts simultaneously with local
anesthetic infiltration. Specifically, we wanted to know if the absence of a tourniquet would result in a more rapid uptake of local anesthetic and a higher $C_{max}$, with possible implications for patient safety in terms of the risk of LAST. Comparing the data of the present study with those of our previous study, it is obvious that the presence or absence of a tourniquet during infiltration has no major impact on the pharmacokinetic profile of ropivacaine. Maximum concentrations are comparable, and the difference in $T_{max}$ is marginal with considerable overlap and most likely explained by the absence of samples between 360 and 1440 minutes in the study with tourniquet (Table 3 and Figure 3). To what extent the intrinsic vasoconstrictive properties of ropivacaine itself, the addition of epinephrine to the local anesthetic, or the phase of hyperaemia following tourniquet deflation affect systemic absorption remains speculative.

In the present study, the unbound fraction of ropivacaine was 3.7%, whereas in our previous study, this fraction was considerably higher (8.3% (SD 2.0), calculated from all free concentrations and corresponding total concentrations). In different pharmacokinetic studies, the unbound fraction of ropivacaine varies widely, the two main reasons being differences in analytical methods, or differences in alpha-1-acid glycoprotein. Because we used the same analytical method and ultrafiltration technique in both studies and differences in alpha-1-acid glycoprotein between the two study populations seem unlikely, we have no explanation for this difference in the unbound fraction of ropivacaine.

A limitation of our previous study was the scarcity of samples between 6 and 24 hours. Based on the literature available at that time, we expected $T_{max}$ in the range between 1 and 6 hours. To avoid missing actual peak concentrations beyond six hours, we extended the sampling schedule in the present study with additional samples at 8, 10 and 12 hours after ropivacaine infiltration. Indeed, in the present study we found $T_{max}$ to be later than 6 hours in 35 % of the patients.

The finding that with or without tourniquet $T_{max}$ occurs at 4-6 hours after infiltration may be disturbing from a safety perspective; patients have been discharged from the recovery and are no longer frequently monitored for signs of LAST at the time ropivacaine concentrations reach their maximum. On the other hand, the $C_{max}$ and $C_{max}$ reported by others and by us are far below the toxic threshold, and worldwide, large numbers of patients have been treated with LIA without signs of LAST. Based on these observations the conclusion that LIA with or without tourniquet is a safe technique seems warranted. However, it should always be kept in mind that local anesthetic concentration per se is not the only determinant of LAST: Individual patient factors such as comorbidities, co-medication, blood flow at the site of infiltration, and general condition play an equally important role.

In conclusion, this study demonstrates that the absence of a tourniquet does not affect the maximum plasma concentrations or the time to reach maximum plasma concentrations of ropivacaine when used as LIA for TKA. Maximum plasma concentrations of unbound ropivacaine stay far below the toxic threshold of 0.56 μg/mL.

**Financial support and sponsorship**
This study was supported entirely by internal funds of the department of Anesthesiology, Sint Maartenskliniek, Nijmegen, The Netherlands.

**References**


Chapter 5

Influence of a Tourniquet on Opioid Consumption after Local Infiltration Analgesia for Total Knee Arthroplasty

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Abstract

Background
To provide postoperative analgesia after total knee arthroplasty (TKA), local infiltration analgesia (LIA) with ropivacaine is increasingly used. TKA may be performed with or without the use of a tourniquet. The absence of local blood flow when infiltrating local anesthetic below an inflated tourniquet may affect the rate of systemic absorption, and this may have an effect on the duration and intensity of analgesia as compared to LIA without the use of a tourniquet. The aim of this study was to investigate the influence of tourniquet use during surgery on the time to first request (TTFR) of opioids, and opioid consumption.

Methods
Two historical time-based cohorts (one with and one without tourniquet during surgery) of 300 patients underwent primary TKA under spinal anesthesia and received LIA to provide postoperative analgesia. The cohorts were compared for TTFR of opioids and opioid consumption.

Results
TTFR did not significantly differ between the tourniquet and non-tourniquet group with a median [25th-75th percentile] of respectively 240 [102-651] and 282 [100-720] minutes. Median [25th-75th percentile] oxycodone use was higher in the tourniquet group with 50 [20-90] vs. 40 [10-77.5] mg (p=0.01).

Conclusion
There was no difference in the time to first opioid consumption, suggesting that the presence of an inflated tourniquet during local anesthetic injection does not alter systemic absorption sufficiently to affect the duration of analgesia. However, the use of a tourniquet was associated with a higher opioid consumption, which is most likely caused by pain resulting from the tourniquet itself.

Introduction

Total knee arthroplasty (TKA) is usually performed in the setting of an enhanced recovery protocol. TKA may be associated with severe postoperative pain that may hamper early mobilization. Adequate pain relief is therefore an essential part of enhanced recovery. In many centers, local infiltration analgesia (LIA) in combination with oral analgesics has been introduced as the preferred method of postoperative analgesia because it combines adequate analgesia with a minimum of side effects. LIA protocols may vary in terms of dose and additives, but are characterized by local infiltration of the tissues surrounding the knee joint with a long acting local anesthetic (LA) such as ropivacaine.

TKA can be performed with or without the use of a tourniquet. When the LIA mixture is infiltrated in the absence of a tourniquet, systemic absorption will commence immediately. By contrast, in case of an inflated tourniquet systemic absorption will be delayed until the tourniquet is deflated and local blood flow restored. On the other hand, after deflation of a tourniquet there will be a period of hyperemia with a concomitant increase in systemic absorption. It is not known if these differences in systemic absorption with or without tourniquet alter the pharmacokinetic profile of LIA sufficiently to affect the duration of analgesia.

Until recently, TKA in our hospital was performed with the use of a tourniquet and LIA for postoperative pain relief. Perceived advantages of a tourniquet are a dry surgical field and reduced intraoperative blood loss. However, the use of a tourniquet has become subject to discussion. In two meta-analyses, Zhang3 and Tai4 showed that total blood loss is not affected by tourniquet use, but it does increase the risk of thromboembolic events and might even hinder early postoperative rehabilitation. Based on these results, our standard practice has recently changed to performing TKA without the use of a tourniquet. The purpose of this cohort study was to investigate if the presence or absence of an intraoperative tourniquet affects the duration of LIA.

Methods
The protocol of this study was approved by the hospital's investigational review board. The Medical research and Ethics Committee ’Slotervaart Hospital and Reade, Amsterdam, The Netherlands’ reviewed the study on June 7th 2017 and determined, based on the Dutch Medical Research Involving Human Subjects Act (Dutch acronym: WMO), that the research activities described meet the requirements for exemption from Ethical Committee review.

Patient demographics, procedure characteristics, opioids consumption and use of analgesics from 600 patients were extracted from the patient data management system. Medico 2016 our standard surgical procedure for primary TKA changed from perioperative tourniquet use, to surgery without the use of a tourniquet. The tourniquet cohort (Group T) comprised the last 300 patients who underwent primary TKA with perioperative tourniquet use before protocol change. The non-tourniquet cohort (Group NT) included the first 300 patients who underwent primary TKA after protocol change. Patients who were not treated according to the standard surgical procedure and perioperative protocol for the time-period in which they underwent surgery, were excluded.
In our hospital, TKA is performed according to a standard protocol, detailing the anesthetic and surgical procedure, perioperative pain treatment and rehabilitation, and discharge criteria. All patients receive spinal anesthesia with 10 mg hyperbaric bupivacaine 0.5% in the sitting position. After bupivacaine injection patients are turned into the lateral decubitus position for 20 minutes with the side of surgery dependent to achieve a predominantly unilateral block. Upon request patients receive conscious sedation with propofol (1-4 mg/kg/h) during surgery. In Group T, a pneumatic tourniquet is placed on the patient’s thigh and automatically inflated to 50 mmHg above systolic blood pressure; in group NT, no tourniquet is used. After placement of the implants and before wound closure, all patients receive LIA: The posterior and anterior knee capsules are infiltrated with 100 mL and 50 mL ropivacaine 0.2% + epinephrine 5 µg/mL respectively; the subcutaneous tissue is infiltrated with 50 mL ropivacaine 0.2% without epinephrine. All patients receive an i.v. bolus of 10 mg/kg tranexamic acid with a maximum of 1000 mg. This dose is administered just before tourniquet release in group T; in group NT, tranexamic acid is administered in the anesthetic room before the start of surgery. After wound closure, all patients receive a compression bandage before transfer to the recovery room.

Standard oral multimodal analgesia includes paracetamol 1000 mg q.i.d., etoricoxib 90 mg once daily and gabapentin 600 mg b.i.d. or 300 mg if age is > 60 years. Pain is evaluated with a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable). On the orthopedic ward, NRS scores are recorded by a nurse at least once during each 8-hour shift. In addition, patients are instructed to contact the nurses when pain exceeds NRS 3 and these scores are recorded as well. In the recovery room, NRS scores are recorded and in case of an NRS > 3, pain relief is titrated with intravenous increments of morphine 1-2 mg or piritramide 1.5-3 mg until the NRS is ≤ 3. At the orthopedic ward, breakthrough pain (NRS > 3) is treated with oxycodone 5-10 mg ad libitum or i.m./i.s.c. opioids if oxycodone alone is not sufficient. Sporadically, tramadol is used when other opioids are not well tolerated. The distribution of opioids on the recovery and orthopedic ward is standardized: Opioids are checked, signed and registered in the patient data management system by two nurses at the time of distribution. According to our standard TKA protocol, patients are encouraged to mobilize starting on the day of surgery. Patients must fulfill functional criteria before discharge (Table 1).

Table 1. Functional discharge criteria

| Active knee flexion ≥ 60 degrees, passive knee extension 0 degrees |
| Quadriceps muscle force ≥ 3 on Medical Research Council Scale for muscle strength |
| Making independent transfers |
| Walking independently and safely with walking aid |
| Climbing stairs independently and safely (if necessary for home situation) |

Outcome measurements

The primary outcome parameter was the time to first request (TTFR) of postoperative pain relief, defined as the time (in minutes) between ropivacaine infiltration and the first gift of any opioid. Secondary outcomes included hospital length of stay, transfusion requirements and the amount of opioids administered during hospitalization. Total opioid consumption was converted to intravenous morphine equivalent, using conversion factors of 0.67 for oral oxycodone, 0.7 for intravenous piritramide, and 0.05 for oral tramadol. An average NRS pain score at rest and during activity was calculated for each patient from all NRS scores recorded during hospitalization; average pain scores per group are based on these individual scores.

Sample size calculation and statistical analysis

Our null hypothesis was that the presence or absence of a tourniquet would not result in differences in the TTFR. A difference of 180 min was chosen as clinically relevant. Data gathered in our hospital for quality monitoring of primary TKA without the use of a tourniquet showed a standard deviation of 561 minutes in the TTFR. Based on these data, the sample size required to identify a difference in TTFR of at least 180 min with a power of 80% was 300 patients per group (two-sided, level of significance 0.05). Data analysis was performed using Stata version 13.1 (Stata Corporation, College Station, TX, USA). Data were tested for normality using the Shapiro-Wilk test. Descriptive statistics of patient and operation characteristics are presented as percentage (95% confidence interval), mean ± SD or median and IQR [25th-75th percentile], as appropriate. Differences between the cohorts were tested for significance using the Mann-Whitney and Chi-square test for numerical and categorical variables respectively. A P-value < 0.05 was considered statistically significant.

Results

All patients underwent surgery between December 2015 and March 2017. In this period 108 patients underwent TKA under general anesthesia. These patients are not included in the cohorts. Patients in both cohorts had similar demographic and surgical characteristics (Table 2). In the tourniquet and non-tourniquet cohort respectively 31 and 27 patients did not use a NSAID because of an allergy or kidney insufficiency. All patients received paracetamol and gabapentin. There was no statistically significant difference in the TTFR between the two groups with a median [IQR] of 240 [102-652] minutes for Group T versus 282 [200-700] minutes for Group NT (p=0.482).

There was no difference in blood transfusion requirements between the groups (Table 2). Total opioid consumption (median [IQR]) was significantly higher in group T: 37.5 [17-67] mg, as compared to group NT 27 [10-60] mg (p=0.014). This difference was caused by a higher oxycodone consumption of patients in group T. There were no differences in parenteral opioid and tramadol consumption, nor were there differences in the percentage of patients using opioids. Data on opioid consumption are summarized in Tables 3A and B.

There were no differences between the groups in the average NRS pain scores at rest (median [IQR] 1.9 [1.4-2.5] for group T and 1.9 [1.3-2.5] for group NT) and during activity (median [IQR] 3.1 [2.4-3.7] for group T and 2.5 [2.3-3.3] for group NT).

There was no difference between Group T and Group NT in median hospital length of stay (median [IQR] 2 [2-3] and 2 [2-3] days respectively).
Influence of a tourniquet on opioid consumption

The purpose of this study was to investigate the influence of an intra-operative tourniquet on the duration of LIA as determined by the TTFR of opioids. There was no difference in the TTFR between the two cohorts and thus our null hypothesis is retained. We found that the total opioid consumption was higher in patients in the tourniquet group. There was no difference in hospital length of stay.

The rationale for the use of a pneumatic tourniquet during TKA is twofold: To limit intraoperative blood loss and to facilitate a bloodless surgical field. However, tourniquets are associated with several complications such as deep venous thrombosis, wound infections, and delayed functional recovery caused by tissue ischemia underneath and distal to the tourniquet. Tourniquet use is also associated with increased postoperative pain: The first report describing the influence of a tourniquet on postoperative pain after TKA dates from 1995. Several RCTs followed after this first study, most of them reaching the same conclusion: Use of a tourniquet increases postoperative pain after TKA.

When using LIA, it stands to reason that the duration of analgesia will be affected by absorption of the local anesthetic from the site of injection. Local blood flow is one of the main determinants of systemic absorption. Studies investigating lidocaine plasma levels after intravenous regional anesthesia demonstrate that prolonging the tourniquet time after injection slows down peak systemic absorption and lowers peak concentration. Likewise, compared to performing LIA without a tourniquet, the absence of circulation at the site of injection when performing LIA with an inflated tourniquet will delay the initial absorption. Whether this delay alters the pharmacokinetic profile sufficiently to exert an effect on the duration of LIA is speculative; a delay in systemic absorption might result in an increased presence of local anesthetic at the site of injection, which might lengthen the duration of analgesia. However, in the absence of pharmacokinetic data these contemplations remain hypothetical. We were unable to demonstrate an increased duration of analgesia in group T as determined by the TTFR and under the conditions of this study we conclude that the presence or absence of a tourniquet does not affect the duration of LIA.

Although the average NRS scores were similar, total opioid consumption was significantly higher in group T. Since there was no difference in the TTFR, it seems that in group T postoperative pain was more intense, requiring more opioids after the effect of LIA had worn off. The most likely explanation for this observation is pain resulting from the tourniquet itself. The most likely explanation for this observation is pain resulting from the tourniquet itself.

Our findings are in agreement with the study from Ejaz’s et al., in which patients underwent TKA without LIA. In that study, patients in the tourniquet group had a higher opioid consumption as compared to the non-tourniquet group. Similar results were described by Abdel et al. who reported an extended interval between opioid injections in the first 24 hours after surgery in patients who underwent surgery without the use of a tourniquet.

Although a femoral nerve block is still considered the golden standard by many, LIA is increasingly used for postoperative analgesia after TKA. LIA was introduced in 2008 as a multimodal opioid-sparing technique for knee and hip surgery with the aim to achieve adequate analgesia without motor impairment and with reduced opioid-related side effects.

### Table 2. Group characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group T (n=300)</th>
<th>Group NT (n=300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. M/ no. F</td>
<td>107 / 193</td>
<td>125 / 175</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65 (6.7)</td>
<td>65 (9.3)</td>
</tr>
<tr>
<td>Number patients with age &gt; 60 years</td>
<td>212/300</td>
<td>221/300</td>
</tr>
<tr>
<td>Number of patients not receiving etoricoxib*</td>
<td>32/300</td>
<td>27/300</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86 (17.3)</td>
<td>87 (12.7)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (10)</td>
<td>170 (13)</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>28.9 (5.4)</td>
<td>29.2 (5.4)</td>
</tr>
<tr>
<td>Duration of surgery, minutes</td>
<td>67 (15)</td>
<td>71 (13)</td>
</tr>
<tr>
<td>Tourniquet Time</td>
<td>50 [44-60]</td>
<td>n/a</td>
</tr>
<tr>
<td>Time from LIA to tourniquet deflation</td>
<td>13 [10-16]</td>
<td>n/a</td>
</tr>
<tr>
<td>Number of patients requiring RBC transfusion</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total units of RBC transfused</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

Data are displayed as number of patients, mean (SD), median [25th-75th percentile]. BMI = body mass index. RBC = red blood cells. *Due to allergy or kidney insufficiency. **RBC = red blood cells.

### Table 3A. Opioid consumption I

<table>
<thead>
<tr>
<th></th>
<th>Group T (n=300)</th>
<th>Group NT (n=300)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total opioid consumption (mg in se)</td>
<td>240 [102-651]</td>
<td>282 [100-720]</td>
<td>0.482</td>
</tr>
<tr>
<td>Opioid consumption (mg in se)</td>
<td>28 [17-67]</td>
<td>27 [10-60]</td>
<td>0.014</td>
</tr>
<tr>
<td>Oxycodone consumption (mg in se)</td>
<td>26.8 [6.7-51.9]</td>
<td>26.8 [6.7-51.9]</td>
<td>0.012</td>
</tr>
<tr>
<td>Oxycodone consumption (mg)</td>
<td>50 [20-90]</td>
<td>40 [20-77.5]</td>
<td></td>
</tr>
</tbody>
</table>

Data are displayed as median [25th-75th percentile]. Total opioid consumption is the sum of oxycodone and tramadol consumption, and i.v., i.m. and s.c. opioids administered intravenously as morphine standard equivalent (mg in se).

### Table 3B. Opioid consumption II

<table>
<thead>
<tr>
<th></th>
<th>Group T (n=300)</th>
<th>Group NT (n=300)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of any opioid (%)</td>
<td>91.0 (87.2 to 93.7)</td>
<td>90.0 (86.0 to 92.9)</td>
<td>0.676</td>
</tr>
<tr>
<td>Oxycodone use (%)</td>
<td>90.0 (86.0 to 92.9)</td>
<td>88.3 (84.1 to 91.5)</td>
<td>0.511</td>
</tr>
<tr>
<td>Use of parenteral opioids total (%)</td>
<td>24.0 (19.5 to 29.2)</td>
<td>23.3 (18.9 to 28.5)</td>
<td>0.848</td>
</tr>
<tr>
<td>Tramadol use (%)</td>
<td>3.0 (1.6 to 5.7)</td>
<td>3.3 (1.8 to 6.1)</td>
<td>0.816</td>
</tr>
</tbody>
</table>

Data are displayed as percentage (95% CI) of patients using postoperative opioids.
resulting in rapid recovery and reduced length of hospital stay. Although in different studies mixtures used for LIA vary in composition and in volume, two systematic reviews and meta-analyses have concluded that there are no significant differences in postoperative pain scores at rest and opioid consumption between LIA and femoral nerve block. Thus, in terms of postoperative pain relief, LIA appears to be an acceptable alternative for femoral nerve block.

Our study has several limitations. Although measuring postoperative pain scores is part of our perioperative protocol and NRS scores are recorded regularly, the exact timing of taking these scores is not standardized, and the number of pain scores recorded per patient may vary. The average pain scores per group are less solid when compared to a prospective analysis and should therefore be interpreted with caution. However, because our patients are instructed to ask for pain relief and our perioperative protocol ensures that patients are treated with opioids when the NRS pain score exceeds 3, we believe that the difference in total opioid consumption combined with similar average pain scores reliably reflects a difference in the intensity of postoperative pain between the two groups and that patients in group T need more opioids to establish adequate pain relief.

A second limitation of our study is that we did not evaluate the influence of a tourniquet on possible differences in short-term functional recovery between the two groups. However, since patients must meet a defined set of functional criteria before discharge and we found no difference in hospital length of stay, we conclude that under the conditions of this retrospective analysis, the use of a tourniquet does not interfere with short-term functional recovery.

Conclusions
We found no difference in the TTFR after LIA for TKA with or without tourniquet, suggesting that the effect of an inflated tourniquet during local anesthetic infiltration does not alter systemic absorption sufficiently to affect the duration of analgesia. The use of a tourniquet was associated with a higher total opioid consumption, which is most likely caused by pain resulting from the tourniquet itself.

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This study was supported entirely by internal funds of the department of Anesthesiology, Sint Maartenskliniek, Nijmegen, The Netherlands.

References
Chapter 6

Improving Performance by Monitoring the Success Rate of Peripheral Nerve Blocks

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Abstract

In our hospital, we introduced a system to measure the collective and individual efficacy of brachial plexus and popliteal nerve blocks with the objective to create transparency as an instrument for monitoring and improvement. Initially, individual results were anonymous, but after one year anonymity was lifted within the team of anesthesiologists and results are now discussed quarterly.

Collective performance of interscalene, supraclavicular and popliteal blocks improved significantly over time. Sharing and discussing collective and individual performance has resulted in critical self-appraisal and increased willingness to learn from each other, and strengthened the team's ambition for further improvement.

Introduction

Increasing attention is being paid to multimodal performance evaluation of medical professionals and benchmarking health care outcomes. Both objective criteria such as clinical outcomes and more subjective aspects such as evaluation of patient satisfaction may be part of a physician's appraisal. To guarantee a certain level of education, continuous medical education (CME) is mandatory for board-certified specialists.

Attending refresher courses or congresses enhances knowledge and familiarity with recent developments. However, the effect size is considered to be small for physicians' performances and patient outcome, and the true impact of CME is usually not examined.

Recertification programs suggest a certain level of knowledge, but as far as we know, none of the recertification programs require proof of technical skills. This is in sharp contrast with e.g. aviation, where all pilots – regardless of their experience- are trained and examined several times a year on knowledge, crew resource management and technical skills.

We believe that besides CME and training stressful situations, "continuous performance evaluation" may contribute to maintain and improve both cognitive and technical skills. A critical condition for improvement is transparency. We decided to evaluate our efficacy regarding peripheral nerve blocks (PNBs) with the objective to establish a benchmark for our collective performance and transparency in individual performance, as well as a monitoring system for future changes in policy.

Methods

In accordance with Dutch law (Dutch Medical Research Involving Human Subjects Act [WMO]), this survey meets the requirements for exemption from Research Ethics Committee review under the WMO. A statement to this effect was obtained from the Research Ethics Committee Slotervaart Hospital and Reade, Amsterdam, The Netherlands. All anesthesiologists involved were asked for permission to publish these data.

Assessing postoperative pain intensity in the recovery or post anesthesia care unit with the Numerical Rating Scale (NRS) is standard procedure in our practice; pain relief is considered adequate with NRS scores ≤ 3. Accordingly, we defined a PNB as successful when the first postoperative NRS score was ≤ 3 in the surgical area. All pain scores are obtained by qualified recovery room nurses, who are instructed to wait with the first measurement until the patient is awake and fully responsive.

For practical reasons, we limited this survey to patients receiving an upper extremity block (interscalene, supraclavicular, infraclavicular or axillary) or a popliteal block. To cover pain at the medial part of the lower leg and discomfort from a tourniquet, popliteal blocks in our practice are always combined with either a saphenous nerve block or a block of the femoral and lateral cutaneous femoral nerve. All blocks are placed with dual guidance (ultrasound and nerve stimulation) using ropivacaine 0.75% or mepivacaine 1.5%, without additives. All procedures are performed with the ultrasound probe in short axis view. An in-plane approach...
is used for all upper extremity blocks and for the vast majority of popliteal blocks. Depending on the kind of surgery and the patient's and surgeon's preference surgery is performed either awake, with additional sedation or general anesthesia. Sedation is provided with propofol alone or in combination with remifentanil, general anesthesia is performed with propofol/ remifentanil.

From July 1st, 2014 we started extracting data from the Patient Data Monitoring System (Chipsoft, Amsterdam, the Netherlands) into Excel spreadsheets to calculate individual and collective success rates for each type of block. After the first six months, the individual performance was discussed in one-on-one dialogs between the individual anesthesiologist and the department head, at this time individual data were not shared within the department's staff. The collective performance was published in the hospital's Quality & Safety department's three-monthly performance report.

One year after the introduction, lifting the anonymity of the individual performance scores was discussed and unanimously agreed on. From that moment on, individual scores are shared internally between the anesthesiology staff and the results are discussed every three months. Anonymity is maintained in external communications.

We did not distinguish between patients receiving a single shot or a continuous PNB. The collective data are presented as six-month averages and include all blocks, i.e. blocks placed by staff, residents and fellows. Analysis was conducted using Prism 7 software (GraphPad Software Inc., San Diego, CA, USA). Statistical analysis of the collective performance over time used the \( \chi^2 \) test for trend, Pearson's \( r \) was calculated to assess a possible correlation between the individual number of blocks and success rate; \( P<0.05 \) was considered significant.

### Results

All anesthesiologists involved agreed to publication of these data and have given written consent.

The data from 10 patients were excluded from evaluation because of lacking NRS scores. The number of blocks and collective performance per six-month period are summarized in Table 1. Figure 1 shows a graphical representation of the upper extremity blocks.

<table>
<thead>
<tr>
<th>Type of PNB</th>
<th>jul-14</th>
<th>jan-15</th>
<th>jul-15</th>
<th>jan-16</th>
<th>jul-16</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interscalene (N)</td>
<td>359</td>
<td>383</td>
<td>323</td>
<td>400</td>
<td>348</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Success Rate</td>
<td>88.0%</td>
<td>87.2%</td>
<td>92.9%</td>
<td>93.0%</td>
<td>94.3%</td>
<td></td>
</tr>
<tr>
<td>Supraclavicular (N)</td>
<td>43</td>
<td>57</td>
<td>33</td>
<td>29</td>
<td>11</td>
<td>0.0127*</td>
</tr>
<tr>
<td>Success Rate</td>
<td>81.4%</td>
<td>91.2%</td>
<td>93.9%</td>
<td>96.6%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Infraclavicular (N)</td>
<td>34</td>
<td>28</td>
<td>50</td>
<td>47</td>
<td>37</td>
<td>0.78</td>
</tr>
<tr>
<td>Success Rate</td>
<td>94.1%</td>
<td>96.4%</td>
<td>96.0%</td>
<td>97.9%</td>
<td>94.6%</td>
<td></td>
</tr>
<tr>
<td>Axillary (N)</td>
<td>89</td>
<td>74</td>
<td>61</td>
<td>85</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Success Rate</td>
<td>98.9%</td>
<td>100%</td>
<td>98.4%</td>
<td>100%</td>
<td>97.6%</td>
<td>0.50</td>
</tr>
<tr>
<td>Popliteal (N)</td>
<td>415</td>
<td>360</td>
<td>383</td>
<td>344</td>
<td>455</td>
<td></td>
</tr>
<tr>
<td>Success Rate</td>
<td>93.3%</td>
<td>93.3%</td>
<td>93.5%</td>
<td>96.5%</td>
<td>96.9%</td>
<td>0.0027*</td>
</tr>
</tbody>
</table>

The columns show six-month average success rates; data are numbers or percentages. P-value: \( \chi^2 \) test for trend of success rates. * = Statistically significant.

Trend analysis shows a significant increase of the success rate over time for interscalene (\( P = 0.0001 \)), supraclavicular (\( P = 0.0127 \)) and popliteal blocks (\( P = 0.0027 \)), whereas the changes in infraclavicular and axillary blocks are not significant.
We found no correlation between the individual number of blocks and performance: Pearson’s $r = 0.08$, 95 % CI = −0.39 – 0.5 (Figure 2).

Discussion

One goal of our monitoring system was to provide transparency in individual and collective success rates of PNBs as a starting point for continuous performance evaluation and improvement. The results show that the collective performance of interscalene, supraclavicular and popliteal blocks improved significantly over time; the success rates of axillary and infraclavicular blocks did not change significantly. A possible explanation is that these latter blocks already had a high success rate to start with.

We have been able to set a benchmark that can be used to monitor personal fluctuations. In addition, the system can be used to monitor the effect of changes in e.g. dose and concentration of local anesthetic, adjuvants, concomitant medication and/or equipment.

Our study has several limitations. Most importantly, we did not attempt to control for possible confounders, and we have no control group with which to compare our data. Therefore, our results are subject to confounder bias. While there has been no change in patient characteristics or surgical techniques, we cannot exclude the possibility of other factors influencing the outcome and therefore the statistical results of our study should be interpreted with caution. The number of blocks was not equally divided between the staff anesthesiologists, residents and fellows. However, we found no correlation between the individual number of the different blocks performed, and the corresponding success rates (Figure 2); we therefore believe that differences in the individual number of performed blocks is not a factor affecting the individual or collective results. We defined a block as being successful when the first postoperative NRS of local anesthetic, adjuvants, concomitant medication and/or equipment.

Although evaluation of individual performance can improve collective outcomes, inter-colleague equation of objective parameters is not yet widely accepted, and still little is known about comparing individual performance and the effect on the quality of care. Introducing a monitoring system that reveals personal performance is a challenge when people are not used to it, because it can be perceived as external or punitive. A key element for successful implementation is mutual trust. To overcome initial anxiety and avoid skepticism, the matter was first discussed extensively within the team of anesthesiologists. Emphasis was placed on nonjudgmental registration, a safe environment, and anonymity of the individual scores. It was emphasized that only the collective performance data would be shared externally, and that sharing personal scores with fellow anesthesiologists was an individual choice. Individual scores and position on the ranking would be shared only face-to-face between the individual and the head of the department with the guarantee that they solely would be used as personal evaluation tool and there would be no disciplinary consequences.

Lifting the anonymity obviously poses a new challenge for the safe environment. It was agreed beforehand that the decision to lift the anonymity had to be unanimous and that if one or more staff members would not agree, anonymity would be maintained. Each staff member was approached individually by mail and asked for his opinion with emphasis on privacy and the right to oppose without explanation. The entire staff turned out to be in favor, and thus anonymity was lifted.

A notable but welcome spin-off from our registration system was the development of an open atmosphere in which it is possible to evaluate techniques and personal opinions and exchange experiences without judgment, but with the purpose of improving performance. Not unexpectedly, awareness of personal performance works as an incentive for self-appraisal and, when appropriate, for improvement. While anesthesiologists usually perform their PNBs without fellow anesthesiologists watching, we have observed an increase in asking a second opinion from a colleague, especially in situations where the ultrasound picture is ambiguous. We have seen that the introduction of the performance monitoring system has resulted in a reduced threshold to ask each other’s opinion or to seek each other’s advice, and we have noticed individual adaptations in technique, in particular local anesthetic volume. After the internal anonymity was lifted we started with three monthly meetings where both collective and individual performance are analyzed and discussed with the purpose of further improvement in terms of increasing collective scores and reducing inter-individual variation.

When discussing individual performance, it is paramount to keep reminding each other that the focus should not be on individuals, but rather on the performance as a group and on identifying possible causes for unsuccessful blocks and developing strategies for improvement. To emphasize this we have recently changed the format of the meeting,
sending each participant a personal list of his own unsuccessful blocks during the previous three months with a request to scrutinize these blocks for possible explanations, which are then discussed during the meeting.

Our monitoring system has been in place for 2 ½ years, and it seems that after an initial period of increase in success rates, the results are leveling off (the most recent rise in the success rate of supraclavicular blocks should be interpreted with caution, since it is based on only 11 procedures). We believe that given all the variables, a 100% success rate for all procedures is unattainable and that future efforts should focus on maintaining the present high success rates and minimizing inter-individual variation.

In conclusion, we have introduced a monitoring system for the collective and individual success rates of PNBs of the upper extremity and for popliteal blocks. Despite its limitations, it has provided us with an objective measure of our performance, resulted in an increase in the success rates of interscalene, supraclavicular, and popliteal blocks, and has opened the possibility of monitoring the effect of changes in the department's policy regarding the different aspects of PNB.

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References
Chapter 7

General discussion
General discussion

Total knee arthroplasty (TKA) is a frequently performed surgery to improve chronic refractory joint pain and improve mobility, in patients suffering from severe osteoarthrosis. Although TKA is performed to improve pain and function in the long term, the first days after surgery are notorious for the risk of severe postoperative pain. Severe postoperative pain is not only uncomfortable for the patient, it can delay rehabilitation and is assumed to be a prognostic factor for the development of chronic pain. Therefore adequate postoperative analgesia, preferably without impeding mobilization, is a cornerstone in rehabilitation after TKA.

Different strategies exist to alleviate postoperative pain after TKA. Postoperative regimens including continuous epidural infusion of local anesthetic provide excellent analgesia, but have become less attractive because of the concomitant motor weakness, hampering early mobilization. Opioid analgesia is associated with systematic side effects such as nausea and drowsiness.

Local infiltration analgesia (LIA) and femoral nerve blocks (FNB) are two other methods to reduce postoperative pain after TKA while diminishing opioid requirements. To gain more insight and knowledge on these two methods, we performed several studies that make up the core of this thesis. This concluding chapter summarizes and discusses the main findings in relation to the current literature, the clinical implications arising from these studies and proposes future directions. Finally, the conclusions of this thesis are presented.

Discussion of main findings

The study described in Chapter 2 was designed to compare periarticular LIA of the knee with LIA of the posterior knee capsule in combination with a FNB catheter in terms of pain and functional outcome in patients undergoing primary TKA. In this randomized controlled trial, short and long-term outcome was assessed in terms of pain, activity levels and functional recovery.

In this study, Group FNB had lower pain scores and lower opioid consumption until the first postoperative day. This benefit of continuous FNB on pain and opioid consumption was not reported in two meta-analyses. However, in these analyses no distinction was made between single-shot and continuous femoral nerve block. Furthermore, in these meta-analyses the effect of popliteal fossa infiltration or sciatic nerve block as an addition to FNB was not included in the assessment. The sciatic nerve plays a substantial role in the innervation of the knee joint and blocking the sciatic nerve contributes to better analgesia after TKA. Popliteal fossa infiltration likely has a comparable effect. Omitting a sciatic nerve block or posterior fossa infiltration as variable in models in these meta-analyses, may have underestimated the positive effect of a continuous FNB compared to local infiltration of the anterior capsule of the knee.

Pain and opioid consumption in the early postoperative period may be important issues from the patient’s perspective, however optimal functional recovery in the long term is the main goal of TKA. Studies focussing on the influence of analgesic technique on functional recovery
Femoral nerve block is associated with the possibility of quadriceps motor weakness. Since walking time is associated with a better functional outcome, the LIA technique is used in order to provide postoperative pain relief without affecting motor function. Indeed, in our study group FNB showed a clinically small, but statistically significant lower activity level until the first postoperative day. However, since there was no difference in the functional recovery one year after TKA, the clinical relevance of this diminished postoperative mobility in group FNB is questionable. The absence of differences in functional recovery one year after surgery is in agreement with another study with a crossover design. Nevertheless, walking time after hospitalisation and functional recovery six weeks after surgery were slightly more favourable in group FNB in the study by Carli.

Finally, a remarkable finding is the higher maximum pain score and analgesics consumption in group LIA one year after total knee arthroplasty. Although the pathophysiology of persistent postoperative pain is not completely understood, significant lower pain scores until a month after surgery are also reported by patients treated with continuous regional anesthetic techniques in a prospective observational registry. In summary, the fear that FNB hampers functional recovery after TKA is not supported by clinical evidence; FNB may have a beneficial effect in preventing chronic postoperative pain.

Chapter 3 is the first study describing the pharmacokinetic profile of ropivacaine after high-dose, high-volume, single-shot LIA of the knee with epinephrine, without a draining system such as a periarticular catheter or surgical drain. A phenomenon often seen in both pharmacodynamic and pharmacokinetic studies is a high inter-individual variability. Likewise, we also found a large variation in the plasma concentrations, however even the maximum total (C_{max} 2.26 µg/ml) and unbound (C_{u, max} 0.13 µg/ml) ropivacaine concentration in our study remained well below the assumed toxic thresholds of 4.3 and 0.56 µg/ml, respectively.

During TKA a tourniquet is often used to create a dry surgical field and reduce intraoperative blood loss. However, the use of a tourniquet is associated with an increased risk of thromboembolic events, wound infections and prolonged thigh pain. These findings have raised important questions about the necessity of perioperative tourniquet use. Therefore the standard practice in several centers has recently been changed to performing TKA without the use of a tourniquet. Chapter 4 describes the pharmacokinetic profile of a high-dose, single-shot LIA when no tourniquet was used at the moment of infiltration. In analogy with our study in which a tourniquet was used (Chapter 3), the maximum total (C_{max} 2.34 µg/mL) and unbound (C_{u, max} 0.093 µg/mL) ropivacaine concentration remained below the toxic threshold. Comparing these two pharmacokinetic studies, we did not observe a clinically relevant difference in C_{max} or T_{max} between ropivacaine infiltration with or without tourniquet.

In our study with tourniquet a number of patients showed an early C_{max} (T_{max} ≤ 240 minutes in 11/20 patients), whereas in the study without tourniquet none of the patients had a T_{max} < 240 minutes. This is in contrast with the theory underlying the pharmacokinetic principles of locally infiltrated medication. Vascularity is a main determinant of systemic absorption speed. When using a tourniquet an artificial decrease in vascularity is created. Studies investigating lidocaine plasma levels after intravenous administration demonstrate that prolonging the tourniquet time after infiltration slows down peak systemic absorption and limits peak concentration. Therefore the early peaks found in a number of patients in our tourniquet study are surprising. In general, the hyperaemic period after tourniquet release might contribute to this phenomenon. Immediately after tourniquet release the blood flow through the ischemic limb is restored and can increase to almost 5 times above baseline. An increased blood flow increases the concentration gradient governing passive diffusion of ropivacaine into the systemic circulation. Other possible explanations for very early peaks (40 minutes) found in the study described in Chapter 3 are an accidental omission of adrenaline in the LIA mixture, or difficulty to identify the veins and arteries when a tourniquet is used. An inflated tourniquet causes the collapse of arteries and veins and may hamper the identification of the blood vessels when aspirating before infiltrating ropivacaine. Possibly, the risk of accidental intravascular ropivacaine injection is increased when a tourniquet disables the ability to identify the blood vessels.

In Chapter 5 we investigated the influence of perioperative tourniquet use on the time to first request (TTFR) of opioids and total opioid consumption when local infiltration analgesia is used to reduce postoperative pain. We found no statistically significant difference in median TTFR between the two groups, however, there was a difference in total opioid consumption. Patients in the Tourniquet group consumed significantly more opioids as compared to patients who underwent total knee arthroplasty without perioperative tourniquet use. The observation that patients in the tourniquet group used more opioids is most likely caused by the pain resulting from the tourniquet itself, be it due to compression, ischemia, or both. This is in accordance with other studies investigating tourniquet influence on pain or opioid consumption after total knee arthroplasty.

Combining the findings described in Chapter 4 and Chapter 5 we conclude that the use of a tourniquet does not delay systemic absorption of ropivacaine to the extent that it affects the duration or intensity of analgesia after local infiltration analgesia. On the contrary, looking at the data on total opioid consumption it seems that postoperative pain is reduced when no tourniquet is used.

In Chapter 6 we discussed a monitoring system to evaluate the collective and individual performance with regard to the efficacy of peripheral nerve blocks. In healthcare increasing attention is being payed to multimodal performance evaluation of medical professionals and benchmarking of health care outcomes. However, in contrast to another high-risk branch, e.g. aviation, there are hardly any objective measurements to guarantee a physician’s skills. The tool we introduced in this study helped us to evaluate and improve our performance regarding peripheral nerve blocks. We found an improvement of maximum 6.3 % in success rate of peripheral nerve blocks, without any other intervention except discussing the different techniques in a group of anesthesiologists.

There is not much known about comparing individual performance and the effect on the quality of care. A paper by St. Jacques discusses a monitoring system to evaluate and stimulate the punctuality of individual anesthesiologists and its effect on maximizing the productivity of the group of anesthesiologists as a whole. To stimulate the change in behaviour the anesthesiologists were publicly ranked and a financial reward was offered, depending...
on the physician's performance in relation to the others. At the end of the study period it turned out that the combination of public profiling and a financial incentive can change a physician’s behaviour and improve his productivity. However, some serious objections may be raised against this method to improve productivity. Firstly, only productivity was measured without any attention to actual skills or quality of care. Healthcare institutions have to be economical, but this should never subrogate their main goal: providing high quality health care. Furthermore, it is not unlikely that public ranking and financial rewarding for the high performers will enhance rivalry between colleagues.

Another study described a system focused on cost-effectiveness, evolving from a personal scoring system to a well accepted benchmark system, similar to our monitoring system. In accordance with our experience, this report suggests that with a performance and benchmarking system it is possible to change specialist behaviour without rewarding.

Since individual performance monitoring is still unfamiliar in the healthcare sector, mutual trust is of great importance before introducing individual monitoring systems.

Our performance monitoring focused on upper extremity and popliteal nerve blocks and not on the regional anesthetic techniques for TKA such as LIA or femoral nerve blocks. Although our monitoring system was thus not aimed at improving postoperative pain scores for TKA patients, we expect the improved success rate demonstrated for upper extremity and popliteal nerve blocks to apply equally for other block procedures.

Clinical implications

In our pharmacokinetic studies we demonstrated that after the administration of high dose locally infiltrated ropivacaine, total and unbound ropivacaine plasma concentrations remain far below the assumed toxic threshold of 4.3 and 0.56 µg/mL. The results of our studies suggest that in routine surgery, total knee arthroplasty can be safely performed without the use of a tourniquet, reducing postoperative opioid consumption without increasing the risk of systemic toxicity.

A femoral nerve catheter provides better analgesia in the early postoperative period than LIA of the anterior aspect of the knee, with both postoperative pain scores and opioid consumption being lower. Also considering the lower maximum pain scores and lower analgesic consumption in group FNB one year after surgery, these results suggest that there might be an association between the type of regional anesthesia and the risk to develop chronic pain. However, it should be kept in mind that the success rate of a peripheral nerve block also depends on the individual skills of the performer.

Finally, we consider individual performance monitoring to be a valuable first step in self-assessment and skills monitoring, which can contribute to the quality of care.

Potential limitations and future perspectives

Despite careful designing of the studies described in this thesis, several limitations and directions for future research can be designated.

The study described in Chapter 2 has some small but unavoidable limitations. Firstly, patients participating in this study were not blinded for ethical reasons. However, we believe this limitation has not affected our results, since the physical therapists assessing the ability to mobilize and the research assistants collecting the pain scores were blinded. Furthermore, performance on physical tests such as the 6MWT, SCT and TUG is not only determined by knee function, but also by factors such as age, sex, body mass index; also, possible health issues might adversely affect the performance on these tasks. We assume that by using randomisation these confounding factors were equally divided between the two groups, and therefore did not exert a significant bias.

A notable finding of this study is the slightly but significantly higher maximum pain scores in group LIA. The number of patients reporting high mean pain scores (Numeric rating scale [NRS] >3) one year after surgery was similar in both groups (10%). However, remarkable is the high rate of patients in group LIA (42%) reporting high maximum pain scores (NRS >3) one year after surgery compared to FNB (26%) and to the literature (30%). Additionally, the odds of using analgesics for knee pain a year after total knee arthroplasty was almost 6 times greater in the LIA group. This relation may be spurious and clinical relevance of this difference can be argued; still, patients in group FNB also had lower pain scores and less opioid consumption in the immediate postoperative period. Since early postoperative pain is a possible risk factor for the development of chronic pain, the possibility of a causal relation is intriguing. Further studies, which should include a larger number of patients, will be necessary to elucidate this.

Chronic postoperative pain or persistent postsurgical pain (PPSP) is defined as pain that lasts beyond the healing of injured tissue and the related inflammatory processes. PPSP is hard to treat, therefore is has serious consequences for both society and individual patients, since chronic pain affects all dimensions of quality of life. Younger age, female gender, obesity, psychological distress, preoperative and acute postoperative pain have so far been identified as predictors of chronic postsurgical pain after total knee arthroplasty. However, effective preoperative and individual identification of patients prone to develop chronic postoperative pain is, yet, not possible. Future research should focus on factors predicting chronic post-surgical pain and strategies to reduce the impact of these factors when possible.

Recently, it has been hypothesized that central sensitisation may be predictive for the development of persistent postoperative pain. Quantitative sensory testing (QST) might be an instrument to assess pain processing and the degree of central sensitisation prior to surgery. QST contains a broad spectrum of test batteries to assess sensitisation. However, preoperative QST does not show consistent results. Although several studies have identified possible promising predictors for chronic pain, more exploration in this discipline is necessary to determine the possible role of QST in clinical practice. Because of the huge impact of chronic pain on both the individual patient as well as society as a whole, the possibility to identify patients at risk preoperatively and strategies to reduce or prevent the development of chronic pain would be a great achievement.
Femoral nerve blocks may be associated with weakness of the quadriceps muscle, which may hamper early mobilization. Although there is no evidence that impaired motor function, as a result of femoral nerve blocks, adversely affects recovery after TKA, there might be a future for motor function sparing techniques. Recent studies have shown that a single shot adductor canal block provides similar analgesia but limited quadriceps weakness compared to femoral nerve block, allowing for easier mobilization.\textsuperscript{37,38} However, this benefit is less pronounced or absent when comparing continuous femoral with continuous adductor canal blocks.\textsuperscript{39–41} Future research should determine which role is provided for adductor canal blocks in enhanced recovery protocols after TKA.

The study discussed in Chapter 3 has one main limitation; the scarcity of samples between 6 and 24 hours after ropivacaine infiltration, made it impossible to determine the $C_{\text{max}}$ and $T_{\text{max}}$ in some of the patients. To overcome this hiatus, we extended the sampling schedule until 12 hours after ropivacaine infiltration in the subsequent study (Chapter 4). Future research should also focus on prolonging the analgesic duration of locally infiltrated ropivacaine. There may be an role for multivesicular liposomes containing a local anesthetic, however proof of these multivesicular liposomes extending the duration of a single-shot local anesthetic is not yet irrefutable.\textsuperscript{42}

Lastly, when extracting data or monitoring healthcare quality via the hospital information system, a certain amount of bias will slip into a dataset. However, this bias represents the daily practice probably can become a valuable source to monitor and improve quality of care.

References

Chapter 8

Conclusions
Conclusions

The main conclusions that can be drawn from the work described in this thesis are:

- The choice of anesthetic technique, femoral nerve block or local infiltration analgesia, does not influence functional recovery after total knee arthroplasty. (Chapter 2)

- Patients treated with a femoral nerve block have lower postoperative pain scores and opioid consumption compared to patients treated with local infiltration analgesia. (Chapter 2)

- Patients treated with local infiltration have higher maximum pain scores at 3 and 12 months after total knee arthroplasty and are almost six times more likely to use analgesic medication 1 year after surgery. (Chapter 2)

- Total and free ropivacaine concentrations after a high-dose, single-shot ropivacaine with epinephrine remain below the assumed toxic threshold for local anesthetic systemic toxicity. (Chapters 3 and 4)

- Perioperative tourniquet use does not substantially decrease systemic absorption of locally infiltrated ropivacaine. (Chapters 3 and 4)

- Perioperative tourniquet use does increase postoperative opioid consumption. (Chapter 5)

- Individual and collective performance monitoring have the ability to contribute to improving physicians' practical skills and quality of health care. (Chapter 6)
Summary

In patients suffering from severe osteoarthritis, total knee arthroplasty is a frequently performed surgery to improve chronic refractory joint pain and improve mobility. Total knee arthroplasty is well known for its chance on severe postoperative pain. Chapter 1 provides a general introduction to the different kinds of anesthesia for total knee arthroplasty, including regional anesthesia techniques. Multimodal analgesia as well as several aspects of the local anesthetic ropivacaine are discussed and an outline of this thesis is described. In the subsequent chapters the results of our studies investigating these methods and factors are further presented and discussed.

Methods to provide postoperative analgesia after total knee arthroplasty

Two currently popular methods to provide postoperative analgesia after total knee arthroplasty are a continuous femoral nerve block and local infiltration analgesia. Nerve blocks usually offer sufficient analgesia in most of the patients, however motor function is also affected. This might impede (independent) mobilisation as long as motor function is diminished. Because local infiltration analgesia provides analgesia without affecting motor function, virtually immediate postoperative mobilization is possible and it is hypothesized that this might enhance rehabilitation after total knee arthroplasty. In Chapter 2 the influence of these techniques on early and late functional recovery and pain relief are extensively discussed.

Apart from functional outcome and medication use one year after surgery, the quality of short-term postoperative pain relief is discussed. It was found that patients receiving a femoral nerve block had slightly lower pain scores and reduced analgesic consumption, both in the immediate postoperative period as well as 12 months after surgery. Clinically relevant differences in knee function were not found between the groups.

Pharmacokinetics of high dose locally infiltrated ropivacaine

Local infiltration analgesia is an easy and straightforward technique to provide postoperative pain relief after total knee arthroplasty. Since this technique has only been introduced a little more than a decade ago its safety track is still relatively short. To gain more insight in the pharmacokinetics of the high dose of ropivacaine used for local infiltration analgesia, Chapters 3 and 4 describe the pharmacokinetic profile of ropivacaine when used for local infiltration analgesia in total knee arthroplasty with (Chapter 3) or without (Chapter 4) tourniquet.

Similar to most pharmacokinetic studies, we found a high inter-individual variation in the plasma concentrations in both studies, but even the highest measured ropivacaine C_{max} (2.34 µg/ml) and C_{max} (0.13 µg/ml) remained well below the assumed toxic thresholds.

Factors affecting postoperative pain and opioid consumption

Since postoperative pain may have an influence on the development of chronic pain, identifying non pharmacological factors to decrease postoperative pain and opioids consumption are another field worth exploring.

Chapter 5 describes the influence of perioperative tourniquet use on the time to first request (TTFR) of opioids and total opioid consumption when local infiltration analgesia is used to reduce postoperative pain. We found no statistically significant difference in median TTFR between the Tourniquet and non-Tourniquet group. However, opioid consumption was higher in the Tourniquet group 37.5 (17-67) mg as compared to patients who underwent total knee
arthroplasty without perioperative tourniquet use, 27 (10-60) mg. Possible explanations for the effect of a tourniquet on local anesthetic uptake and on postoperative pain are discussed.

Chapter 6 describes the influence of monitoring immediate postoperative pain on the success rate of peripheral nerve blocks. Improvement of individual and collective performance is demonstrated and discussed, as well as the strategy and risks of introducing a monitoring system in anesthesia practice.

In Chapter 7 the main finding of this thesis of this discussed in a broader perspective, addressing the clinical implications, potential limitations and future perspectives.

Finally, Chapter 8 sums up the conclusions that can be drawn from this thesis.
Samenvatting

Patiënten die lijden aan ernstige slijtage van het kniegewricht (gonartrose) kunnen gebaat zijn bij een totale knieprothese (totale knie arthroplastiek). Een knieprothese wordt geplaatst met het doel de mobiliteit te verbeteren en om op den duur pijnklachten te verminderen. Echter, de eerste dagen na totale knie vervangende chirurgie zijn geassocieerd met ernstige postoperatieve pijn.

Hoofdstuk 1 omvat een algemene introductie op dit proefschrift waarin een achtergrond en aanleiding tot de onderzoeken worden geschetst. Eveneens worden verschillende vormen van anesthesie (verdoving) en analgesie (pijnbestrijding), welke routinematig voor totale knie vervangende chirurgie toegepast worden, uiteengezet. In de hierop volgende hoofdstukken worden de resultaten van de uitgevoerde onderzoeken gepresenteerd en besproken.

Methoden van postoperatieve pijnbestrijding na totale knie prothese chirurgie

Lokale infiltratie analgesie en het nervus femoralis blok zijn momenteel populaire postoperatieve pijnbestrijdingstechnieken. Zenuwblokkades bieden meestal voldoende pijnstilling, maar gaan gepaard met motorische blokkade. De spierzwakte die hiervan het gevolg kan zijn (onafhankelijke) mobilisatie belemmeren en zolang de motorische functie is verminderd. Lokale infiltratie analgesie, waarbij een lokaal anestheticum direct in het weefsel rondom de knie wordt geïnfiltratied, verschaft pijnstilling zonder de motorische functie te beïnvloeden. Hierdoor is vrijwel onmiddellijk postoperatieve mobilisatie mogelijk. Er wordt verondersteld dat directe postoperatieve mobilisatie de revalidatie na een totale knie prothese kan verbeteren. In Hoofdstuk 2 wordt ingegaan op de invloed van deze twee technieken op vroeg en laat functioneel herstel, pijnverlichting en medicijngebruik. Patiënten die een blokkade van de nervus femoralis kregen hadden iets lagere pijnscores en een vermindere inname van pijnstillende medicatie, zowel in de onmiddellijke postoperatieve periode als 12 maanden na de operatie. Er werden geen klinisch relevante verschillen in kniefunctie gevonden tussen de groepen.

Farmacokinetiek van hoog gedoseerde lokaal geïnfiltrerde ropivacaïne

Lokale infiltratie analgesie is een eenvoudige, pragmatische en doelgerichte methode om in pijnstilling na een totale knie prothese te voorzien.

Aangezien deze techniek iets meer dan een decennium geleden is geïntroduceerd, zijn de gegevens over veilige toepassing nog relatief schaars. Om meer inzicht te krijgen in de farmacokinetiek van de hoge dosis ropivacaïne die wordt gebruikt voor lokale infiltratie analgesie, wordt in de hoofdstukken 3 en 4 het farmacokinetisch profiel van ropivacaïne, toegepast als lokale infiltratie analgesie bij totale knieprothese, met (Hoofdstuk 3) of zonder (Hoofdstuk 4) tourniquet op het moment van infiltratie, beschreven. Beide studies toonden, in overeenstemming met de meeste andere farmacokinetic studies, een hoge interindividuele variatie in de plasmaconcentraties, maar zelfs de hoogst gemeten ropivacaïne Cmax (2,34 μg / ml) en Cmin (0,13 μg / ml) bleven ruim onder de veronderstelde toxische drempels.

Niet medicamenteuze factoren die van invloed zijn op postoperatieve pijn en opiaat consumptie

Omdat postoperatieve pijn een rol kan spelen bij de chronificatie van pijn, is de identificatie
van niet-farmacologische factoren die postoperatieve pijn en opioid consumptie kunnen verminderen de moeite waard.

**Hoofdstuk 5** beschrijft de invloed van een perioperatieve tourniquet op de TTFR (Time To First Request, het tijdstip waarop voor het eerst om pijnstilling wordt gevraagd) en de totale opioid consumptie wanneer lokale infiltratie analgesie wordt toegepast als methode van postoperatieve pijnbestrijding bij patiënten die een totale knie arthroplastiek ondergingen. Er was geen statistisch significant verschil in de mediane TTFR tussen de groep met- en de groep zonder tourniquet. De totale opioid consumptie was in de Tourniquet groep echter hoger dan in de groep waarbij geen tourniquet werd gebruikt (37.5 (17-67) mg respectievelijk 27 (10-60) mg). Mogelijke verklaringen voor de invloed van een tourniquet op de absorptie van lokaal anestheticum en op de mate van postoperatieve pijn worden besproken.

**Hoofdstuk 6** beschrijft de invloed van routinematig monitoren van postoperatieve pijn op het succespercentage van perifere zenuw blokkades. Een individuele en collectieve verbetering van succespercentages wordt getoond en besproken.

Eveneens wordt verder ingegaan op de strategie en risico’s die gepaard gaan met het introduceren van een individueel monitoringsysteem.

In **Hoofdstuk 7** worden de belangrijkste bevindingen van dit proefschrift in breder perspectief getrokken. Verder worden de klinische implicaties, beperkingen en mogelijke toekomstperspectieven besproken.

Tenslotte presenteert **Hoofdstuk 8** de conclusies van dit proefschrift.
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The research on local and regional analgesia for total knee arthroplasty became the foundation of this thesis. Sietske is BROK® certified since September 2015 (BROK® ref. 25852). In 2018 she started her residency in anesthesiology at the Radboud University Medical Center (dr. Keijzer-Broeders).
Bibliography


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This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands or Medical Research Ethics Committee Slotervaart Hospital and Reade, Amsterdam, the Netherlands has given approval to conduct of these studies.

Individual projects are stored at Sint Maartenskliniek research server (V:) under research_archief (Chapters 2, 3, 4, and 5) or anesthesiology server H:\OK\ANAEST\Performance (Chapter 6). Hardcopies of the projects are stored at the Sint Maartenskliniek archive.

Privacy of the participants in Chapter 2, 3 and 4 is warranted by use of encrypted and unique individual subject codes. Informed consents and decryption keys of these chapters are stored and locked away separately from the anonymized questionnaires and CRFs.

Data of Chapters 5 and 6 is anonymously extracted from the patient data management system. On first arrival in the Sint Maartenskliniek all patients are informed about the use of anonymous patient data and the 'opt-out' arrangement to object to the use of anonymized data. None of the patients in these cohorts objected to the use of anonymous data.

Data management was performed in secured and locked Excel files. Before analysis a second investigator monitored all data. Data was converted from excel to STATA, Prism or R to perform statistical analysis.

The data will be saved for 15 years after termination of the individual studies. Using patient data in future research is only possible after a renewed permission by the patient as recorded in the informed consent. Datasets are available from the corresponding author on reasonable request.


