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Sektionen för Anestesiologi och Intensivvård

Local Infiltration Analgesia in knee and hip arthroplasty: Efficacy and Safety

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Fatin Affas
M.D

Huvudhandledare:
Docent Carl-Olav Stiller
Karolinska Institutet
Institutionen för Medicin-Solna
Enheten för klinisk farmakologi

Bihandledare:
Docent Nina Olofsson
Karolinska Institutet
Institutionen för Fysiologi och Farmakologi
Sektionen för Anestesiologi och Intensivvård

Bihandledare:
Professor Per Wretenberg
Karolinska Institutet
Institutionen för Molekylär medicin och Kirurgi
Sektionen för Ortopedi

Fakultetsopponent:
Professor Harald Breivik
Rikshospitalet, Oslo Universitet Norge
Anestesiologi och intensivvård

Betygsnämnd:
Professor Torsten Gordh
Uppsala Universitet
Institutionen för kirurgiska vetenskaper,
Anestesiologi och intensivvård

Professor Edward Högestätt
Lund Universitet
Avdelningen för klinisk kemi och farmakologi

Docent Paul Ackermann
Karolinska institutet
Institutionen för Molekylär medicin och kirurgi
Sektionen för Ortopedi

Stockholm 2014

From the Department of Physiology and Pharmacology
Section for Anesthesiology and Intensive Care Medicine
Karolinska Institutet, Stockholm, Sweden

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Fatin Affas
M.D.

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This thesis is dedicated

to

My husband **NABIL**

and to

my children **REEM**, **KARAM and RAMY**

ABSTRACT

Local infiltration analgesia (LIA) is a new multimodal wound infiltration method. It has attracted growing interest in recent years and is widely used all over the world for treating postoperative pain after knee and hip arthroplasty. This method is based on systematic infiltration of a mixture of ropivacaine, a long acting local anesthetic, ketorolac, a cyclooxygenase inhibitor (NSAID), and adrenalin around all structures subject to surgical trauma in knee and hip arthroplasty.

Two patient cohorts of 40 patients scheduled for elective total knee arthroplasty (TKA) and 15 patients scheduled for total hip arthroplasty (THA) contributed to the work presented in this thesis. In a randomized trial the efficacy of LIA in TKA with regard to pain at rest and upon movement was compared to femoral block. Both methods result in a high quality pain relief and similar morphine consumption, but fewer patients in the LIA group reported pain of 7/10 on any occasion during the 24 h monitoring period (paper I).

In the same patient cohort the maximal total plasma concentration of ropivacaine was below the established toxic threshold for most patients although a few reached potentially toxic concentrations of 1.4-1.7 mg/L. The time to maximal detected plasma concentration was around 4-6 h after release of tourniquet in TKA (paper II).

All patients in the THA cohort were subjected to the routine LIA protocol. In these patients both the total and unbound plasma concentration of ropivacaine was determined. The concentration was below the established toxic threshold. As ropivacaine binds to α-1 acid glycoprotein(AAG) we assessed the possibility that increased AAG may decrease the unbound concentration of ropivacaine. A40 % increase in AAG was detected during the first 24 h after surgery, however the fraction of unbound ropivacaine remained the same. There was a trend towards increased C_{max} of ropivacaine with increasing age and decreasing creatinine clearance but the statistical power was too low to draw any conclusion (paper III).

Administration of 30mg ketorolac according to the LIA protocol both in TKA and THA resulted in a similar C_{max} as previously reported after 10 mg intramuscular ketorolac (paper II, paper IV). Neither age, nor body weight or BMI, nor creatinine clearance, correlates to maximal ketorolac plasma concentration or total exposure to ketorolac (AUC) (paper IV).

In conclusion, LIA provides good postoperative analgesia which is similar to femoral block after total knee arthroplasty. The plasma concentration of ropivacaine seems to be below toxic levels in most TKA patients. The unbound plasma concentration of ropivcaine in THA seems to be below the toxic level.

The use of ketorolac in LIA may not be safer than other routes of administration, and similar restrictions should be applied in patients at risk of developing side effects.

PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Affas F, Nygårds EB, Stiller CO, Wretenberg P, Olofsson C.
Pain control after total knee arthroplasty: a randomized trial comparing local infiltration anesthesia and continuous femoral block.
Acta Orthop. 2011; Aug;82(4):441-7

II. Affas F, Stiller CO, Nygårds EB, Stephanson N ,Wretenberg P, Olofsson C.
A randomized study comparing plasma concentration of ropivacaine after local infiltration analgesia and femoral block in primary total knee arthroplasty.
Scandinavian Journal of Pain 3(2012) 46-51

III. Affas F, Eksborg S,Wretenberg P, Olofsson C, Stiller CO
Ropivacaine pharmacokinetics after local infiltration analgesia in hip arthroplasty.
Anesthesia and Analgesia accepted for publication

IV. Affas F, Eksborg S, Wretenberg P, Olofsson C, Stephanson N, Stiller CO
Plasma concentration of ketorolac after local infiltration analgesia in hip arthroplasty.
Submitted for publication

ABBREVIATIONS

AAG	α-1 acid glygoprotein
ACEI	angiotensin-converting enzyme inhibitors
ARB	angiotensin receptor blockers
ASA	American Society of Anesthesiologists classification
ATP	adenosine triphosphate
AUC	area under the curve
BMI	body mass index
Ca^{+}	calcium ion
CFU	colony-forming unit
CI	confidence interval
CNS	central nervous system
COX	cyclooxygenase
CRF	cause report form
CV	cardiovascular
ECG	electrocardiogram
FDA	Food and Drug Administration
IV	intravenous
K^{+}	potassium
LAST	local anesthetic systemic toxicity
LIA	local infiltration analgesia
Na^{+}	sodium ion
NRS	numeric rating scale
NSAID	non-steroidal anti-inflammatory drug
PCA	patient controlled analgesia
RCT	randomized controlled trial
PG	prostaglandin
THA	total hip arthroplasty
TKA	total knee arthroplasty

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Introduction

Osteoarthritic pain

In common with other joints, the knee and hip joints are covered with cartilage. The touching surfaces are covered with a lubricating synovial membrane that prevents friction and pain. Progressive arthritis, trauma, or destructive diseases of the joint may lead to cartilage wear and joint damage, resulting in progressively increasing pain and stiffness, and decreasing daily function (1). At a certain point total knee or hip replacement may be the only option to regain function and get rid of pain. Patients with severe radiographic changes report the best relief of pain upon movement after total knee arthroplasty. However, neither radiographic nor histological findings seem to predict pain intensity in patients scheduled for total knee arthroplasty (2).

Total knee and hip arthroplasties are considered to be one of the most cost-effective interventions available in modern surgery in terms of increased quality-adjusted life expectancy (3-5).

Knee and hip arthroplasty

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are very common procedures at orthopedic clinics in developed countries. These highly successful surgical procedures alleviate pain, correct leg deformity and help patients with debilitating arthritis to restore function and resume normal activities (6). During knee and hip replacement surgery, damaged bone and cartilage are replaced with components made of metal alloys, high molecular-weight polyethylene. In Sweden more than12 000 knee arthroplasties (7) and more than 14 000 hip arthroplasties(8) are performed every year. This number is expected to increase over the next twenty years, because of increasing life expectancy and a high prevalence of osteoarthritis in elderly people.

Pain after knee and hip arthroplasty

Postoperative pain is common after total joint arthroplasty and effective pain relief may be hard to achieve (9,10). Pain compromises the early outcome of knee and hip arthroplasty by affecting patient ambulation and compliance with physical therapy. Inadequate pain control increases the length of hospital stay, escalates the cost of care, and is associated with venous thromboembolism, coronary ischemia, myocardial infarction, pneumonia, insomnia, cognitive dysfunction, poor wound-healing, and slowed overall recovery (11). Further, the experience of severe pain during the postoperative period increases the risk of patient demoralization, dissatisfaction and chronic pain syndrome (12-15). Thus the aim of pain relief after joint replacement surgery is not only to prevent or reduce pain, but also to speed up the healing process (16).

Methods of pain relief after knee and hip arthroplasty

The most effective pain treatment after knee and hip arthroplasty has traditionally been opioid analgesics and epidural analgesia (17,18).

Parenteral opioids

Opioid drugs produce their pharmacological effects, including analgesia, by acting on receptors located on neuronal cell membranes. The presynaptic action of opioids to inhibit neurotransmitter release is considered to be their major effect in the nervous system. Opioids act supraspinally, spinally, and peripherally to produce analgesia, thereby reducing sensitization both centrally and peripherally (19,20).

While opioid analgesic drugs are very effective analgesics for postoperative pain management, adequate pain relief is not always achieved. Possible causes may be the use of less-than-optimal doses to avoid adverse effects like respiratory depression, nausea, vomiting, constipation, urinary retention, excessive somnolence, confusion and pruritus (21,22). A previous study at our hospital demonstrated that patient-controlled analgesia with intravenous morphine either with or without parenteral tramadol is insufficient to achieve sufficient pain relief after TKA (23).

In addition, opioid analgesics are suboptimal for relieving pain, particularly during physiotherapy and rehabilitation (24) .

Epidural analgesia

Epidural analgesia may be useful for postoperative pain relief following major lower-limb joint replacement (25). Common adverse effects of epidural analgesia are hypotension, urinary retention, motor block limiting ambulation, and spinal hematoma secondary to anticoagulant therapy. The introduction of low-molecular-weight heparin for the prevention of postoperative deep-vein thrombosis and pulmonary emboli might have increased the risk of spinal hematoma after epidural analgesia (26-29). Since similar pain relief may be obtained with methods with a lower risk of serious adverse events, a recent review concluded that epidural analgesia may no longer be considered the gold standard in this context (30).

Femoral nerve block

Femoral nerve block is another modality of pain management after TKA that has received recognition because of its ability to provide superior analgesia with fewer side-effects than intravenous opioids or epidural analgesia (31-37). Femoral block is technically demanding, and requires additional anesthetic time (38). Single-injection femoral nerve block improves analgesia and reduces postoperative morphine requirement (39-41). A disadvantage is the decreased muscle tone of the quadriceps muscles, which counteracts effective rehabilitation and increases the risk of patient falls (42-45). In addition, nerve injury (46-50) and local infections (51-53) have been reported. An overall complication rate of 1.5%, and a risk of permanent nerve injury of 0.2% have been reported after continuous femoral nerve block with indwelling catheter in 1190 patients undergoing knee arthroplasty (54,55).

Local infiltration analgesia (LIA)

The limitations of the previously-mentioned methods of postoperative analgesia might have inspired Drs. Kerr and Kohan in Sydney, Australia to develop a multimodal wound infiltration technique for control of acute postoperative pain following knee and hip replacement surgery (56). Known as local infiltration analgesia (LIA), this method is based on systematic infiltration of a mixture of ropivacaine, ketorolac and adrenaline around all the structures subjected to surgical trauma. In contrast to epidural analgesia and peripheral nerve blocks, multimodal infiltration is cheap and requires only limited technical skills.

LIA reduces postoperative pain at its origin without loss of muscle strength, decreases opioid consumption, improves lower-limb function, limits postoperative complications, decreases operating room time and shortens hospital stay (5,57-64).

Some studies have compared LIA after TKA with other methods of postoperative pain treatment, such as systemic analgesia and placebo (65-67). However data about its efficacy in comparison with other methods with proven analgesic effect, such as femoral block (68), was sparse prior to the present project**.** Information on safety margins and the plasma concentration of ropivacaine after LIA was incomplete (66,69,70). Regarding ketorolac, no information on plasma concentration after LIA was available.

Components of the LIA mixture

The mixture of local infiltration analgesia consists of three components with different mechanisms of action: **ropivacaine**, a local anesthetic, **ketorolac** a cyclooxygenase inhibitor or non-steroidal anti-inflammatory drug (NSAID), and **adrenaline**.

Ropivacaine

Ropivacaine is a long-acting amide local anesthetic agent of the pipecoloxylidide group, structurally related to bupivacaine (71,72) .Compared to bupivacaine, ropivacaine is less lipophilic and less likely to penetrate large myelinated motor fibers. In isolated animal nerve studies, ropivacaine was more selective for Aδ and C (pain) than Aβ (motor) nerve fibers and produced significantly less depression in motor fibers as compared to bupivacaine (73-75) . The mechanism of action of ropivacaine, as for all local anesthetics, is the reversible inhibition of Na^+ channels in neurons, blocking the propagation of the action potential along nerve fibers (76) . Several other properties of ropivacaine which may be of importance for its use in the context of LIA in joint replacement surgery have been described:

Vasoconstriction

Ropivacaine, at a concentration of 0.2-0.25 %, decreases cutaneous blood flow upon direct application in healthy male volunteers (77-80). Similar observations have been reported in preclinical animal studies (81).

Anti-inflammatory effects

Peripheral nerve blocks with ropivacaine after total knee arthroplasty inhibit clinical inflammation without detectable changes in cytokine concentrations in tissue and plasma (82). In animal studies intravenous ropivacaine exerts anti-inflammatory activity by inhibiting both leukocyte rolling and adhesion in ulcerative colitis, and decreasing inflammatory mediators in acute lung injury (83,84). Retrospective analysis of patients undergoing colon, prostate or breast cancer surgery indicates a better long-term outcome after epidural anesthesia/analgesia than after patient-controlled analgesia (85-87) .

A recent experimental study suggests that this effect is independent of their known role as sodium-channel blockers. Anti-inflammatory properties associated with inhibition of tumor necrosis factor have been suggested to be important (88).

Antibacterial activity

Ropivacaine may possess antimicrobial activity. Disruption of microbial cell membrane permeability leading to leakage of cellular components and subsequent cell lysis has been suggested as the mechanism of action (89). *Staphylococcus aureus* does not multiply in ropivacaine 2 mg/mL at room temperature, and at 37°C the colony-forming unit (cfu) is reduced. Incubation in ropivacaine 10 mg/mL for six hours killed *Staphylococcus aureus* (90). *E. coli* grows in ropivacaine 2 mg/mL, but its cfu is reduced after six hours in 10 mg/mL at 37°C. Ropivacaine 0.1% also inhibits the growth of *Pseudomonas aeruginosa* (91).

Safety aspects of ropivacaine

Despite more than a century of use, and substantial achievements in local anesthetic development and modifications in clinical practice, systemic toxicity has remained a significant and potentially lethal problem (92). Although many anesthesiologists may occasionally see mild manifestations of local anesthetic toxicity, serious intoxication is rare (93). However, signs of toxicity may be unnoticed in most cases.

Systemic toxicity of local anesthetics is usually the result of accidental intravasal injection or of secondary plasma absorption of a large volume of local anesthetics (94-96). Information regarding local anesthetic systemic toxicity (LAST) is based mainly on case reports and case series (97). Information regarding the mechanisms of LAST is extrapolated from animal studies, since it is unethical to perform human randomized controlled trials of local anesthetic toxicity (98).

CNS toxicity

The central nervous system (CNS) is more sensitive to local anesthetic toxicity than the cardiovascular system (76). Unspecific signs of CNS toxicity (dizziness, tinnitus, circumoral paresthesia, taste perversion, shivering, muscle twitching and tremors) may progress to tonic-clonic seizures due to the blocking of inhibitory cortical neurons. With increasing plasma levels, both inhibitory and excitatory pathways are blocked, which results in generalized CNS depression with hypoventilation and coma (99). Data obtained from healthy volunteers indicates a significantly higher threshold for CNS toxicity and less cardiotoxicity with intravenous ropivacaine than with bupivacaine (100-102).

Cardiovascular toxicity

Cardiovascular toxicity of local anesthetics is also characterized by a biphasic order of events. Initially, tachycardia and hypertension dominate due to an activation of the sympathetic nervous system. This phase is followed by direct myocardial depression, arrhythmia and prolonged conduction, which may progress to total cardiovascular collapse (103).

Mechanisms of local anesthetic cardiac toxicity are still not completely understood. The potential cellular sites of local-anesthetic-induced cardiotoxicity include the sodium, potassium, and calcium channels, β_2-receptors and mitochondrial metabolism, and decreased adenosine triphosphate (ATP) synthesis in the cell (102,104-106). Also, Ca^{2+} dysfunction is associated with cardiotoxicity (92,107-109).

Mechanisms of cardiac toxicity of local anesthetics

1. Inhibition of Na^+ channels (110)
2. Inhibition of K^+-channels (111)
3. Inhibition of the β_2-adrenergic receptor (112)
4. Dysregulation of Ca^{2+} release from the sarcoplasmic reticulum (113)
5. Inhibition of Ca^{2+} uptake by the sarcoplasmic reticulum(107)
6. Inhibition of cyclic –adenosine monophosphate production (114)
7. Inhibition of mitochondrial energy metabolism by decrease in adenosine triphosphate ATP (115)

Tissue concentrations of local anesthetic drug in the myocardium can be two-to-three times greater than the concurrent arterial blood concentrations (93) and displacement of drugs bound to plasma proteins occurs in acidosis (116) or in the presence of drugs such as β-blockers and calcium-channel antagonists.

α-1 acid glycoprotein

α-1 acid glycoprotein (AAG) or orosomucoid, an acute-phase protein, is synthesized by the liver (117-119). Plasma AAG levels in healthy young adults are reportedly in the range of 55-140mg/L (120). Ropivacaine is highly bound (94%) in plasma to AAG, and changes in the plasma concentration of this acute-phase protein affect the plasma concentration of the unbound fraction of ropivacaine. Increased levels of AAG decrease the free concentration and toxicity of ropivacaine (121,122).

A two- to fivefold increase in the plasma concentration of AAG occurs in response to various stressful stimuli including physical trauma such as surgery, tissue injury, inflammation or infection. After surgery the AAG level increases, peaking at 3-4 days postoperatively (118). No information has been presented about the ropivacaine plasma concentration after LIA in THA and its relation to AAG.

Ketorolac

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID), which blocks the cyclooxygenase (COX) enzymatic pathway and ultimately inhibiting two individual prostaglandin pathways (123). The COX-1 pathway is involved in prostaglandin-E_2-mediated gastric mucosal protection and in thromboxane effects on coagulation. The inducible COX-2 pathway is involved primarily in the generation of prostaglandins included in the modulation of pain and fever, but has no effect on platelet function or the coagulation system.

Both COX-1 and COX-2 may be involved in pain signaling by increasing the synthesis of prostaglandin E_2 (123,124). COX-1 selective drugs may increase the risk of bleeding and COX -2 selective drugs increase the risk of cardiovascular events. Intramuscular ketorolac induces pain relief comparable with morphine in a wide variety of surgical procedures (125-128).Intra-articular ketorolac produces analgesia (129). Decreased prostaglandin E_2 concentrations in synovial tissue correlate with decreased pain experienced by the patient (130,131). According to a recent study ketorolac seems to be more efficient when given locally in the LIA mixture than via the intravenous route (132) . Compared to LIA without ketorolac, LIA with ketorolac reduces morphine consumption and pain intensity (133). Earlier readiness for hospital discharge has also been reported (133,134).

Safety of ketorolac

Bleeding

All COX-1 inhibitors may carry an increased risk of bleeding due to inhibition of thromboxane synthesis in platelets. Ketorolac has high selectivity for COX-1. However, ketorolac has been administered to patients with intracranial hemorrhage requiring craniotomy. These patients had no higher risk of bleeding than controls did (135). An increased risk of gastrointestinal bleeding has been reported after the use of ketorolac for more than five days (136,137).

Cardiovascular risk

All cyclooxygenase inhibitors/NSAIDS have been linked to increased cardiovascular morbidity. The American Food and Drug Administration (FDA) has concluded that an increased risk of serious adverse cardiovascular (CV) events may be a class effect for NSAIDs (excluding aspirin).

However, the risk seems to be higher with COX-2 selective inhibitors (138-141). COX-2 selective inhibitors block the synthesis of prostacyclin, an endogenous antithrombotic prostaglandin (142) and increase the risk of myocardial infarction (143). In a meta-analysis of a randomized controlled study of COX-inhibitors, the risk of myocardial infarction was higher with COX-2 selective inhibitors than with placebo or naproxen (144). Large epidemiological studies in relatively healthy individuals (145), patients with heart failure (146), and patients with a history of myocardial infarction found that the risk of myocardial infarction and death increased with COX-2 inhibitors and diclofenac but not with naproxen (145-147).

Ketorolac has a higher selectivity for COX-1 than naproxen does (148) which may indicate a low risk of ischemic cardiovascular events. But data from randomized clinical studies is insufficient to prove this hypothesis. However, epidemiological studies point towards a lower risk of myocardial infarction with ketorolac than with opioids (149). A recent report on 1300 patients scheduled for cardiac surgery concluded that ketorolac carries no increased risk of cardiac events (150). In contrast, a recent observational study from Taiwan indicates an increased risk with ketorolac (151).

Renal side effects

All COX-inhibitors/NSAIDS may decrease renal function by inhibiting the synthesis of PGE_2, which maintains glomerular filtration (152-154). This effect seems to be less important in healthy individuals without renal problems (155). However, elderly patients or those with hypovolemia, dehydration, cirrhosis, or heart failure are more prone to renal impairment by COX-inhibitors (156,157).

Despite the wide use of ketorolac, nephrotoxicity remains a concern (158). Numerous case reports have linked ketorolac treatment to renal failure (159-161), and even a single dose may induce renal toxicity (162). Ketorolac, as other NSAIDs, inhibits prostaglandin-mediated renal function (159,163) Prostaglandins regulate a variety of renal functions such as vascular tone, salt and water balance,

and renin release (164). Prostaglandins are synthesized in the kidney, and the principal prostaglandins PG E_2, -D_2 and ,-I_2 (prostacyclin) are powerful vasodilators (165). This effect does not appear to compromise renal hemodynamics in patients with normal renal function.

The mechanism of renal failure induced by NSAID is the inhibition of prostaglandin-induced vasodilatation of the afferent arteriole in conditions of reduced renal perfusion, which reduces glomerular perfusion. In addition, concomitant use of angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor antagonists and diuretics, especially in elderly or dehydrated subjects, may precipitate acute renal failure, hyponatremia, or hyperkalemia (166-168).

The risk of acute renal failure with parenteral ketorolac has been assessed in a large observational study including 10 000 patients (169). The risk with ketorolac administered for less than five days was similar to that with opioids.

However, several case reports of renal failure after ketorolac have been published (170-173). At our department we have observed at least two cases of severe renal impairment after ketorolac in joint arthroplasty (174) .

Adrenaline

Adrenaline is a potent agonist at both α- and β-adrenoceptors. It is one of the most common additives used to modify the pharmacodynamic and pharmacokinetic properties of local anesthetics. Vasoconstriction and less bleeding are the main reasons for adding adrenaline to local anesthetics (175,176).

The addition of adrenaline delays systemic absorption and reduces the peak plasma concentration of ropivacaine after thoracic paravertebral block (177,178). Adrenaline may have some analgesic effect through α_2-agonists, and adrenoceptors can modify certain K^+-channels in the axons of peripheral nerves, potentiating the impulse-blocking actions of any Na^+-channel inhibitor (i.e. local anesthetics) (179-181).

Aims

This PhD thesis presents studies on the efficacy and safety of LIA using ropivacaine and ketorolac for post-operative pain management after total knee and hip arthroplasty.

The aims were to assess

1. whether pain relief after LIA in knee arthroplasty is as effective as femoral block,

2. whether the plasma concentration of ropivacaine after LIA in knee arthroplasty is higher than after femoral block,

3. whether the plasma concentration of ketorolac after LIA in knee arthroplasty reaches levels linked to toxicity,

4. whether the maximal dose adjusted concentration of ropivacaine after LIA is higher in THA as compared to TKA,

5. whether the plasma concentration of unbound ropivacaine after LIA in hip arthroplasty reaches levels linked to toxicity,

6. whether an increase in AAG after hip arthroplasty decreases the unbound concentration of ropivacaine,

7. whether the plasma concentration of ketorolac after LIA in hip arthroplasty reaches levels linked to toxicity,

8. whether local administration of ketorolac in LIA may be safer as compared to the intramuscular route

Patients and Methods

All the studies were conducted in accordance with the Declaration of Helsinki and according to good clinical practice. They were approved by the Regional Research Ethics Committee at the Karolinska Institutet in Stockholm, Sweden and by the Swedish Medical Products Agency. Oral and written informed consent was obtained.

Two patient cohorts were included (table 1):

1) Forty patients with TKA (Papers I, II).

2) Fifteen patients with THA (Papers III, IV).

Table 1 Patient demographics

	TKA (n=40) Papers I, II	THA (n=15) Papers III, IV#
Sex (M/F)	19/21	8/7
Age (mean; range)	68 (29-88)	64 (32-85)
Weight (kg) (mean)	80	88
BMI (mean)	27	29
ASA I / II / III	5 /15 /20	4 /4 /7

TKA= total knee arthroplasty, THA= total hip arthroplasty, M=male, F= female, BMI= body mass index, ASA= American Society of Anesthesiologists classification.

In two patients ketorolac was not quantified

Inclusion criteria: patients older than 18 years, American Society of Anesthesiologists (ASA) classification I-III, with osteoarthritis or rheumatoid arthritis.

Exclusion criteria*:* allergy to or intolerance of one of the study drugs, renal insufficiency, epilepsy, patients unable to understand the written patient information and informed consent form, mental illness, dementia, QT interval on electrocardiogram (ECG) > 450 msec before start.

Anesthesia

All surgical procedures (TKA, THA) were performed under spinal anesthesia at the level of L2-L3 or L3-L4 intervertebral space. Isobaric bupivacaine 5 mg/mL at a volume of 3 ml was injected with the patient lying with the operating side upwards. Before induction of spinal anesthesia, monitoring of oxygen saturation, blood pressure and electrocardiogram (ECG) was started. Sedation was induced with midazolam 1-2mg IV or propofol 10-30mg IV.

Study Design

The clinical trial reported in Papers I and II was a prospective randomized open trial.
The clinical trial reported in Papers III and IV was an open study with no comparative treatment. Both studies were performed at the orthopedic clinic at the Karolinska University Hospital in Solna between January 2007 and June 2011.
This project was not supported by the drug industry.

Total Knee arthroplasty (Paper I, II)

The patients were assigned at random to one group of 20 patients receiving femoral nerve block (F) and one group of 20 receiving LIA.

Group F

The group F patients received a femoral block with catheter under sterile conditions with the patient supine after induction of spinal anesthesia.
Using the "*Winnie approach*" (182) and a nerve stimulator connected first to the needle and then to the catheter to identify the femoral nerve, ropivacaine 30mL(2mg/ml) was injected followed by 15 mL of the same concentration every 4 hours for 24 h (total dose 240mg/24h). In addition this group received IV ketorolac 10mg eight-hourly for the first 24 h.

LIA in Total Knee arthroplasty

Patients in the LIA group received peri- and intra-articular infiltration of 156 mL solution containing150 mL ropivacaine (2mg/mL), 1ml ketorolac (30mg/mL) and 5mL adrenaline (0.1mg/mL).This solution was prepared by the operation nurse prior to start of the surgical procedure.

The surgeon infiltrated the LIA solution sequentially:

1) 30 mL was injected intracutaneously at the start of the operation,
2) 80 mL was injected into the posterior part of the capsule, close to the incision line, in the *vastus intermedius* and *lateralis* and around the collateral ligaments before cementation,
3) 46 mL was instilled through an intra-articular catheter (epidural catheter) inserted at the end of the surgical procedure.

In the recovery room all patients were provided with a patient-controlled-analgesia (PCA) morphine pump programmed to give an intravenous bolus of morphine 2 mg/dose on demand with a lock-out time of 6 min and maximum dose of 35 mg/4 hours. All patients were introduced to the PCA technique and encouraged to use it as often as needed. After 24 hours PCA pump use was verified with a printout of all doses of morphine and their time of administration.

In addition to PCA all patients received paracetamol (1 g x 4) started in the morning of the operation day. All patients were instructed preoperatively by the nurse about pain assessment using a numeric rating scale (NRS), no pain = 0, worst imaginable pain =10. Pain intensity at rest and upon movement was recorded hourly during the first 24 hours by the patient (if awake). ECG was performed preoperatively, two hours after the end of surgery in the recovery room and 24 hours postoperatively on the ward.

Blood samples in TKA

Blood sampling for ropivacaine and ketorolac plasma concentration was started 20 minutes after injecting ropivacaine in the femoral catheter in group F (Time zero "0" in the femoral group). In the LIA group the release of the tourniquet was time zero "0". Additional samples were taken at 40 and 60 minutes and at 2, 4, 6, 12, and 24 hours. The 12-hour samples were taken only in four patients due to the inconvenient sampling time. The blood samples were centrifuged directly, plasma-separated and immediately frozen and stored at -20^0 C until assayed.

LIA in Total Hip Arthroplasty

Fifteen patients undergoing THA received peri-articular infiltration with a mixture of 100 ml ropivacaine (2 mg/ml), 1 ml ketorolac (30 mg/ml), and 5 ml adrenaline (0,5mg). The total volume was 106 ml.

Blood samples in THA

Blood samples (5ml x 2) for plasma concentration of ropivacaine and ketorolac were taken at 10, 20, 30, 45 minutes and 1h, 2h, 3h, 4h, 6h, 8h, 12 h, 24h and 30h after completing LIA. The samples were centrifuged directly, plasma-separated, immediately frozen and stored at -20^{o} C until assayed. Blood samples for serum albumin and creatinine were collected preoperatively. Blood samples for analysis of AAG were collected prior to moving the patient to the operating room and 1h, 4h, 12h and 24 h post-surgery.

Quantification of total and unbound ropivacaine

Ropivacaine was quantified with liquid chromatography mass spectrometry (LC–MS) following ultrafiltration and liquid-liquid extraction at the Department of Clinical Pharmacology, Karolinska Laboratory, Karolinska University Hospital, Huddinge. The limit of quantification was 0.0053 mg/L (20 nmol/L), maximal calibration point 2.66 mg/L (10000 nmol/L). Doxepine (Sigma-Aldrich, St. Louis, MD) was used as internal standard. The unbound ropivacaine concentration was determined following centrifugation of 300 µL plasma at 5500 g for 10 min at 37 ºC with an angle-head centrifuge using an Amicon ULTRA centrifugal filter (the Ultracel-10K membrane contained regenerated cellulose 10000 MWCO, Millipore, Billerica, MA).

Quantification of AAG

AAG was analyzed with nephelometry at the Department of Clinical Chemistry at the Karolinska Laboratory, Karolinska University Hospital, Solna. The range for quantification was 0.35-108 g/L.

Quantification of Ketorolac

Ketorolac was quantified with liquid chromatography mass spectrometry LC-MS/MS using Waters Acquity Ultra-performance liquid chromatograph with a vacuum degasser, binary pump, and sample manager connected to a Quattro Premier XE tandem mass spectrometer with MassLynx™/Target Lynx™ Software version 4.1 (Waters Co, Milford, MA, USA). The reference material ketorolac trometamol was obtained from USP, Rockville, MD, USA and the internal standard ketobemidon-d4 was a gift from Professor Ulf Bondesson (Swedish University of Agricultural Sciences, Uppsala, Sweden). The quantification limit was 0.01 mg/L for each compound and the calibrated range was up to 10 mg/L.

Statistical analysis

Sample size: A sample size of 20 in each group has an 80% power to detect a difference between means of 1.0 on the NRS with a significance level (alpha) of 0.05 (two-tailed) using the unpaired Student *t*- test (paper I).

A sample of 13-15 patients (papers III and IV) was considered to be sufficient for a hypothesis generating study.

Since we wanted to determine whether the plasma concentration of ropivacaine and ketorolac after LIA reached toxic or near-toxic levels, mainly descriptive statistics with focus on maximal plasma concentration are presented. The maximal concentration of ropivacaine of each patient in the LIA group was compared to that of each patient in the femoral block group with an unpaired *t* test. Graphpad Prizm 5.02 for Windows www.graphpad.com was used for the statistical analysis and the graphs. $P < 0.05$ was considered as statistically significant.

Statistica 12, (Statsoft Oklahoma, USA) was used to calculate linear correlation and estimate the statistical power. A power of at least 80 % was required to draw any conclusion on correlation.

Specific aims

Paper 1

Primary aim

- To assess differences in average pain intensity at rest and upon movement during the first 24 hours after TKA in patients with femoral block and LIA.

Secondary aim

- To determine total morphine use via i.v. PCA pump during the 24 hours after TKA in patients with femoral block and LIA.

Ancillary analyses

- Average pain intensity during 24 hours at rest and upon movement,
- Average pain following imputation of missing data by "0" if the patient was asleep and by last observation carried forward if data was missing for other reasons.
- The fractions of patients who reported pain intensity < 5 at rest and during movement, i.e. mild pain intensity (Jensen et al. 2003; 183) in the two study groups were compared using Fisher's exact test.
- The fractions of patients who reported pain intensity > 7 at rest and during movement, i.e. severe pain (Jensen et al. 2003, 183) in the two study groups were also compared with Fisher's exact test.
- Safety monitoring including indications of cardiac arrhythmias and incidence of reported adverse events.

Paper II

Primary aim

- To compare the maximal plasma concentration of ropivacaine during the first 24 hours after LIA and femoral block in TKA.
- To assess the maximal plasma concentration of ketorolac during the first 24 hours after LIA in TKA.

Paper III

Primary aim

- To assess the maximal plasma concentration and the area under the curve (AUC) of unbound ropivacaine during 30 hours after LIA in THA. .

Secondary aim

- To analyze whether patient age, weight, BMI and creatinine clearance correlates to the maximal concentration or AUC of unbound ropivacaine after LIA in THA.
- To analyze the contribution of AAG in binding ropivacaine after LIA in THA.

Paper IV

Primary aim

- To document the maximal plasma concentration and the area under the curve (AUC) of ketorolac during 30 hours after LIA in THA.

Secondary aim

- To analyzed whether patient age, weight, BMI and creatinine clearance correlates to the maximal concentration or AUC of ketorolac after LIA in THA.

Results

Part 1: Pain

Pain at rest and upon movement after TKA with LIA or with femoral block

The average pain intensity during the first postoperative day was low in both groups. The average pain intensity at rest (**Fig 1**) and upon movement (**Fig 2**) was similar. During the first 12 hours at some time points marginally higher average pain intensity at rest was detected in the femoral block group as compared to the LIA group. From 12-24 h the average pain intensity was similar in both groups (**Fig 1**). With regard to pain upon movement from 6 h to 12 hours lightly higher average pain was reported in the femoral block group, but from 12-24 h the average pain intensity was slightly lower in the femoral block group (**Fig 2**).

The average NRS without imputation of missing NRS registration points due to the patients being asleep or unable to fill in the CRF due to other activities is presented in **table 2.**

Table 2.

Primary Outcome

	Femoral block n = 20	LIA n = 20
Average pain NRS *at rest*	2.1 (1.4 – 2.9)	1.6 (1.0 – 2.3)
Average pain NRS *upon movement*	2.4 (1.5 – 3.2)	2.4 (1.7 – 3.0)

Reported data only. Missing NRS registration due to the patients being asleep or unable to fill in the CRF due to other activities were not imputed. Data expressed as mean (95 % confidence interval).

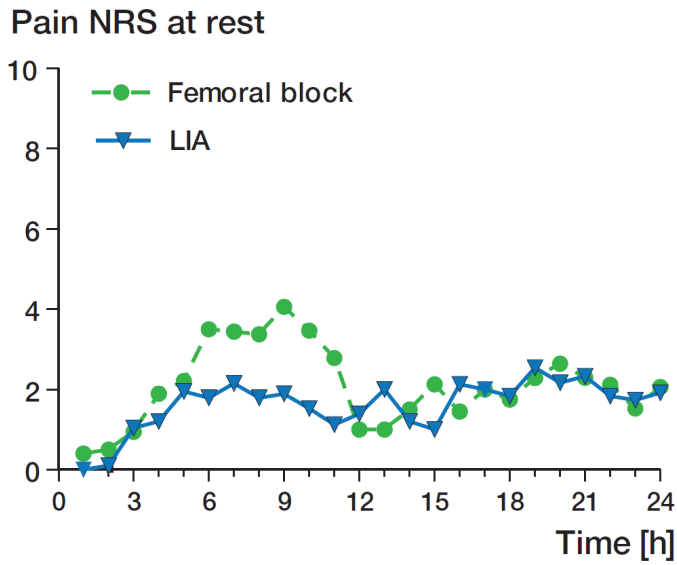

Figure 1. Average pain score (NRS) at rest during 24h after surgery. No data recorded for sleeping patients . (n=20 in each group)

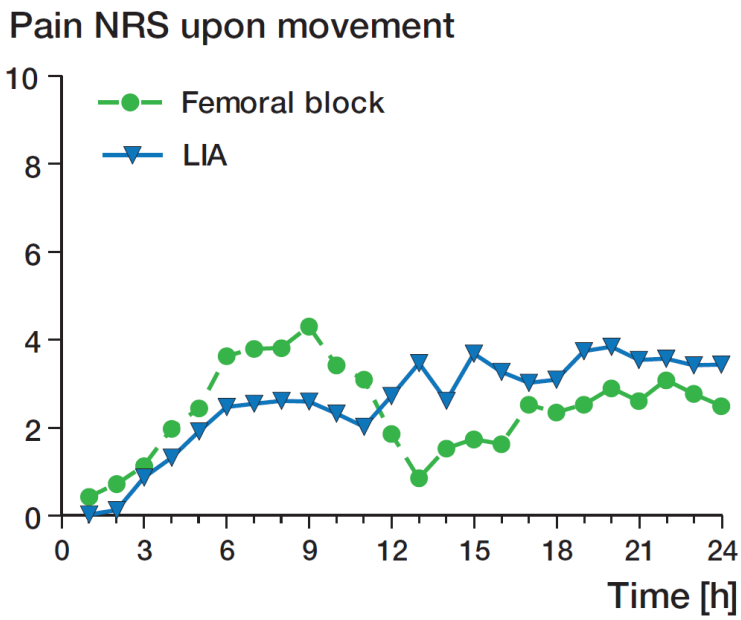

Figure 2. Average pain score (NRS) upon movement during 24h after surgery. No data recorded for sleeping patients. (n=20 in each group)

Incidence of "acceptable pain relief" after TKA

The incidence of NRS < 5, suggested by Jenssen *et al*. (183) to be indicative of acceptable pain relief throughout the 24-hour observation period at rest and on movement was twice as high in the LIA group as in the femoral block group (Table 3).

Incidence of "unacceptable pain relief" after TKA

The incidence of NRS pain intensity > 7, at rest on one or more occasions during the 24 hour observation period was five times higher in the femoral block group than in the LIA group (Table 3). NRS > 7 upon movement was reported only by 1/20 patients in the LIA group as compared to 7/19 patients in the femoral block group. This difference was statistically significant (Fisher's exact test p=0.044).

Table 3

Ancillary analysis pain intensity after TKA

	Femoral block (n=19)	LIA (n=20)
NRS < 5 at rest	7/20	12/20
NRS < 5 upon movement	5/20	8/20
NRS > 7 at rest	5/20	1/20
NRS > 7 upon movement	7/20	1/20

NRS< 5 refers to the number of patients who reported pain intensity lower than 5 throughout the 24 h of observation. NRS>7 refers to the number of patients who reported pain intensity greater than 7 once or more often during the 24 h of observation.

Morphine use after LIA or femoral block in TKA

The average total morphine use via the i.v. PCA pump during the first postoperative day was 10 mg higher in the femoral block group than in the LIA group (Figure 3). However, the morphine dose per kg was almost identical in both groups (Table 4).

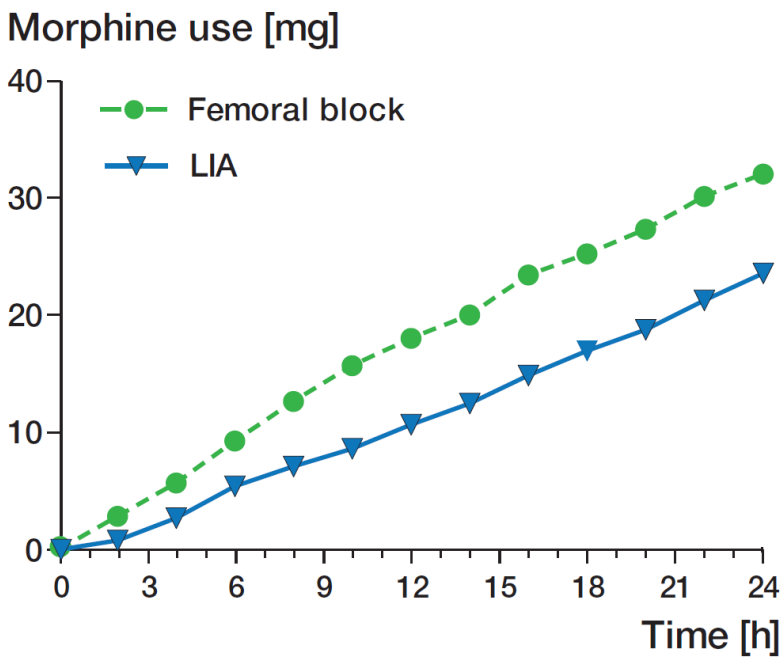

Figure 3. Average morphine use (PCA) mg for the two groups during the first 24 h after surgery. (n=20 in each group)

Table 4.

	Femoral block	LIA
Total morphine (mg)	32 (23 – 41)	24 (16 – 31)
Total morphine (mg /kg)	0.4 (0.3 – 0.5)	0.3 (0.2 - 0.4)

Total morphine refers to intravenous morphine administered via a PCA during 24 hours. Data expressed as mean (95 % CI).

Results part 2: Ropivacaine

Ropivacaine concentration after LIA or femoral block in TKA

The individual pattern of ropivacaine after LIA and during femoral block is shown in **figure 4** and the maximal detected concentration in **figure 5**. Maximal plasma concentrations in the LIA group were detected at four or six hours after injection. In the femoral block group, the highest levels were often detected at 24 hours (Figure 4).

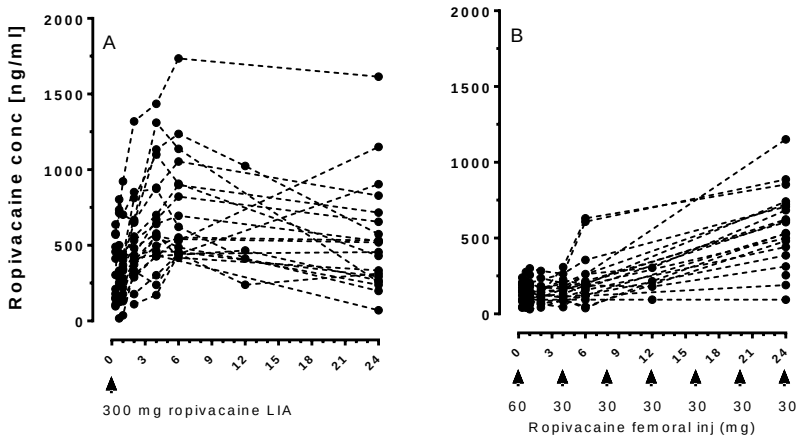

Fig 4. Total plasma concentration of ropivacaine during 24 h. (A) LIA group (n = 20). In this group zero "0" refers to release of the tourniquet. The LIA group received 300 mg ropivacaine. (B) Femoral block group (n = 19). In this group time zero "0" refers to completion of the first injection for femoral block (60 mg), the subsequent doses (30 mg every 4 h) are indicated in the figure.

Maximal ropivacaine concentration after TKA

Similar maximal plasma concentrations of ropivacaine were detected in the LIA group and in the femoral block group during the first 24 hours (Figure 5, Table 5). No statistical difference was detected between the LIA group and the femoral block group.

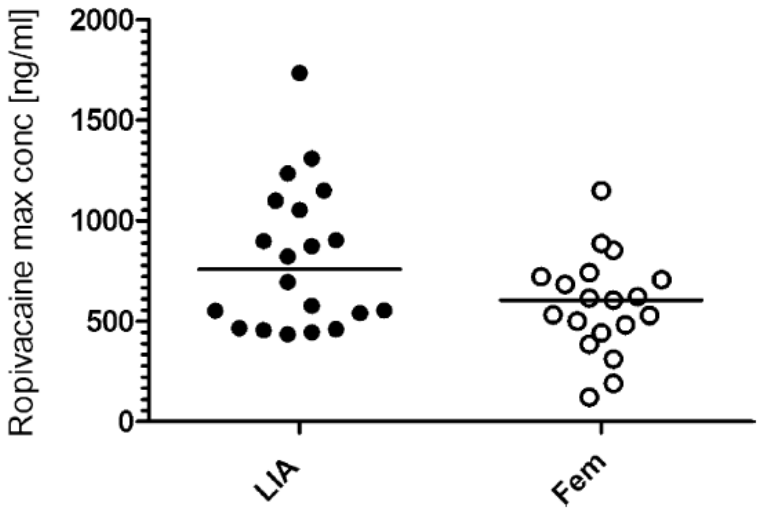

Fig 5. Maximal detected concentration of ropivacaine during 24 h. Data expressed as maximal concentration for each patient. The line indicates the median.

Table 5.

Maximal ropivacaine plasma concentration during 24 h [ng/ml].

	Range	Mean (95% CI)
LIA, $n = 20$	435–1735	813 (644–982)
Femoral block, $n = 19$	122–1151	567 (450–684)

Ropivacaine concentration after LIA in THA

Ropivacaine was analyzed in all patients, but two blood samples at 10 and 20 minutes are missing from one patient. AAG was analyzed in 14 patients. The 24-hour sample of one patient is missing. The range of serum albumin was 33-44 g/L.

Demographic data and plasma concentration for each patient are shown in **Table 6.**

The time to maximum unbound plasma concentration was 4-8 h in 12 of 15 patients. A 35-year-old patient with normal weight reached the peak unbound concentration after 1 hour. A 58-year-old patient with normal weight reached this concentration after 2 hours, and a 75-year-old with a BMI of 32 kg/m^2 did so after 12 hours.

The maximal detected concentration of total ropivacaine ranged between 0.443 and 1.356 mg/L.

Table 6

Patient demographics and results for ropivacaine

Patient number sex	ASA	Age years	Weight kg	BMI kg x m^2	CC mL/min	Cmax Unbound mg/L	Cmax Total mg/L	AUC unbound (0-30h) h x mg /L	Tmax Unbound hours
1 M	I	65	89	29	82	0.016	0.578	-	4
2 F	I	58	63	24	106	0.013	0.769	0.180	2
3 M	II	54	90	28	134	0.022	0.672	0.317	4
4 M	II	85	75	27	58	0.018	0.995	0.229	4
5 F	I	32	62	24	143	0.015	0.443	0.268	8
6 F	I	35	74	26	150	0.004	0.505	0.075	1
7 F	III	75	100	32	75	0.018	0.872	0.328	12
8 M	III	61	105	36	140	0.023	0.877	0.316	6
9 M	III	79	90	28	62	0.018	1.356	0.290	4
10 M	II	72	83	25	108	0.021	0.754	0.327	4
11 F	III	76	106	40	69	0.026	0.686	0.272	8
12 F	III	71	107	35	98	0.018	0.576	0.313	6
13 F	III	58	106	38	101	0.016	0.548	0.320	6
14 M	III	70	71	24	66	0.031	1.333	0.335	6
15 M	II	65	95	24	159	0.012	0.448	-	4

CC: Creatinine clearance was calculated according to Cockroft Gould
AUC: Area under the curve, M: male, F: female

The pharmacokinetic profiles for total and unbound ropivacaine after LIA in THA are shown in **Fig. 6**.

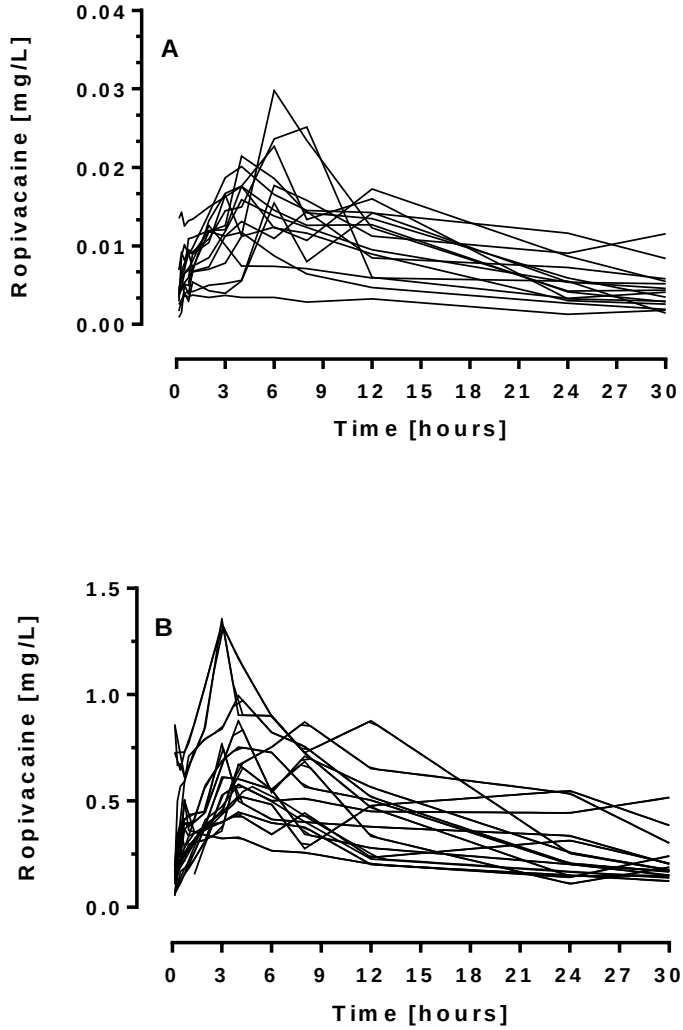

Fig. 6. Individual data of unbound (A) and total (B) plasma concentrations of ropivacaine versus time during 30 hours after LIA.

Ropivacaine concentration after LIA in TKA compared to THA

Division of the median maximal concentration ropivacaine with dose administered after TKA and THA reveals that a higher relative concentration was achieved after THA. These results seem to support the use of lower doses of ropivacaine in THA (200 mg) as compared the TKA (300 mg). The relative maximal ropivacaine concentration in THA is 36 % higher as compared to TKA. **Table 7**

Table 7
Comparison of total plasma concentration of ropivacaine after LIA

	Range (mg/L)	**Mean (95 % CI) mg/L**
TKA LIA, n=20	0.435-1.735	0.813 (0.644-0.982)
Median concentration / dose: 0.758 mg/L **/ 300** mg **= 0.00253** 1/L ***300 mg ropivacaine in TKA***		
THA LIA, n=15	0.443- 1.356	0.686 (0.602-0.920)
Median concentration / dose: 0.686 mg/L **/ 200** mg **= 0.00343** 1/L ***200 mg ropivacaine in THA***		
Relative maximal ropivacaine concentration THA/TKA		**0.00343/0.00253 = 1.36**

Correlation of C_{max} of ropivacaine after LIA in THA versus age, creatinine clearance, weight and BMI

A trend towards correlation of Cmax and increasing age and decreasing creatinine clearance was detected (**Fig 7**). However, the statistical power of the linear correlation of C_{max} versus age or creatinine clearance was 53% and 50% respectively. Using a two-sided test based on our data at least 29 individuals are needed to get a power of 80 % to test the hypotheses that the maximal unbound ropivacaine concentration correlates with age and creatinine clearance.

Neither patient weight nor BMI correlated to the maximal unbound ropivacaine concentration (**Fig. 7**)

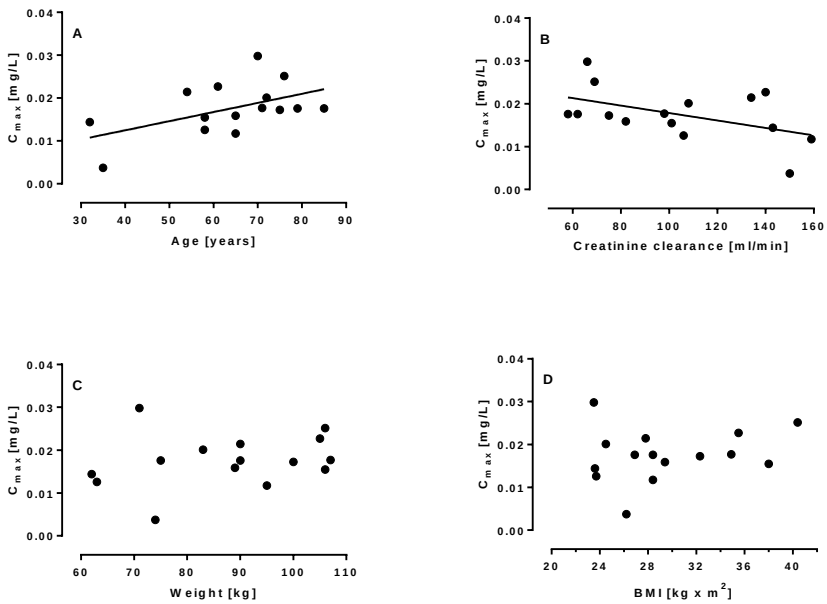

Fig. 7. Maximum concentration (Cmax) of unbound ropivacaine in relation to age (A), creatinine clearance (B), body weight (C) and BMI (D).

Correlation of AUC of ropivacaine and age, creatinine clearance, weight and BMI

Neither patient age, nor creatinine clearance, nor weight nor BMI correlated to the AUC of unbound ropivacaine (**Fig. 8**).

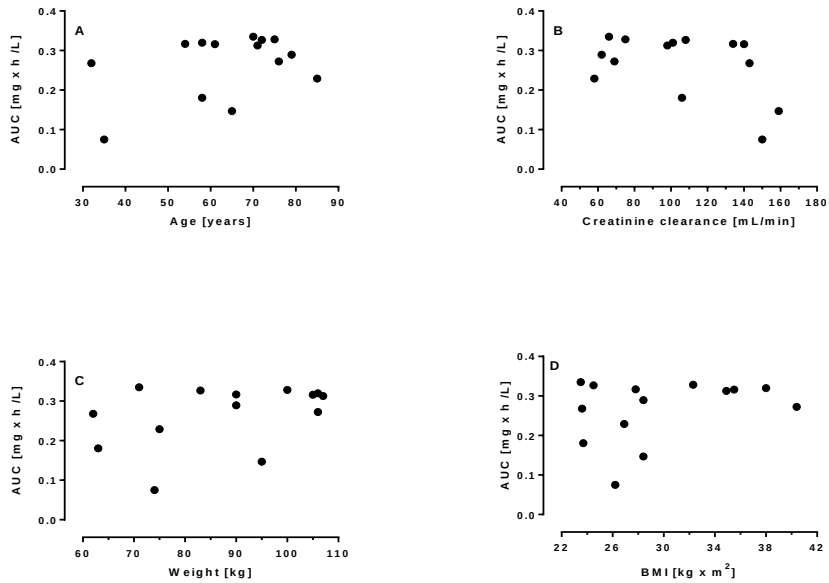

Fig. 8. Total exposure of ropivacaine expressed as area under the curve (AUC) in correlation to patient age (A), creatinine clearance (B), body weight (C) and BMI (D).

AAG at different time points after THA

The AAG concentration increased during the first 24 h by a median of 20 percent (range 12-37). A small early decrease in AAG was observed within the first four hours (**Fig. 9**).

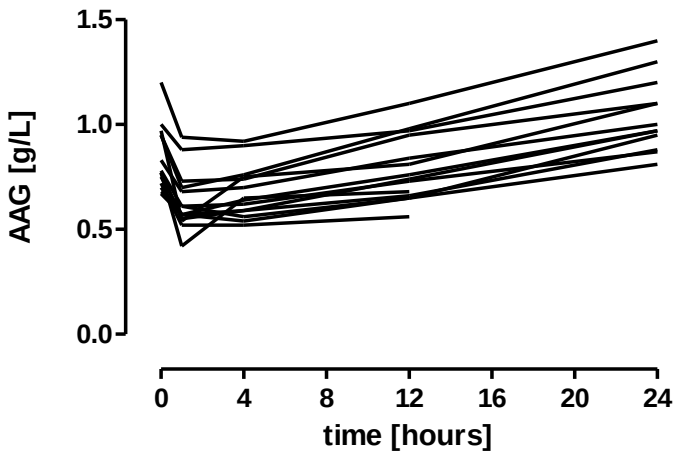

Fig. 9. Individual plasma concentrations of α-1 acid glycoprotein versus time profile (24 h) in 14 patients. Time zero "0" indicates a baseline sample prior to surgery.

Correlation of AAG and the percentage of unbound ropivacaine after LIA in THA

As illustrated in **Fig. 9** the concentration of AAG did not increase during the first 24 hours after THA. The unbound percentage of total ropivacaine did not correlate to the plasma concentration of AAG at 1, 4, 12 or 24 hours (**Fig 10**).

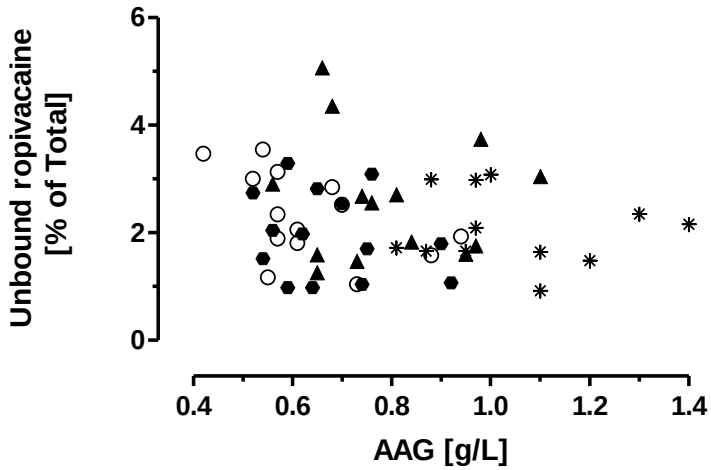

Figure 10.Unbound fraction of ropivacaine expressed as percentage of total at different concentrations of AAG (α-1 acid glycoprotein) at 1 h after surgery (open circle), at 4 h after surgery (●), at 12 h (▲) and 24 h (*) versus plasma concentration during 24 h after LIA in 14 patients.

Results part 3: Ketorolac

Ketorolac concentration after LIA in TKA

The individual pattern of the ketorolac plasma concentration is shown in **Fig.11**
The range of the maximal plasma concentrations of ketorolac one hour or two hours after tourniquet release in the LIA group was 152-958 ng/ml (95 % percent, confidence interval 303-512 ng/ml) (n=19).

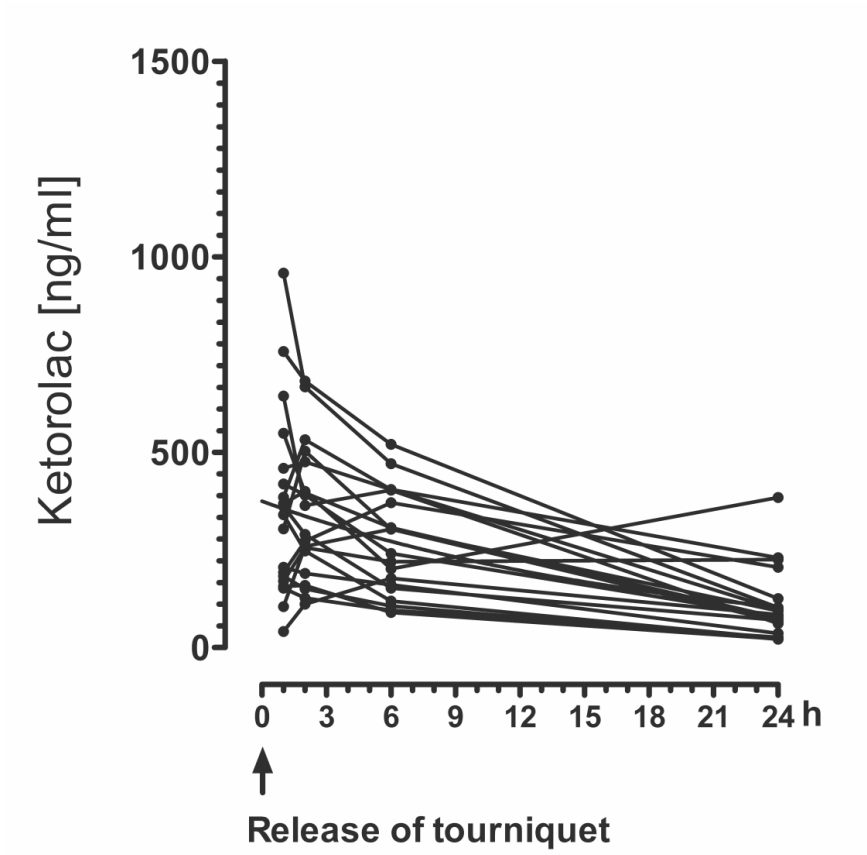

Fig. 11. Total plasma concentration of ketorolac in the LIA group, which received 30mg ketorolac. In this group zero "0" refers to release of the tourniquet.

Ketorolac concentration after LIA in THA

The median of the peak (maximal detected concentration) ketorolac plasma concentrations was 0.82 mg/L (range: 0.31-2.16 mg/L). One patient (No 2, table 8) had a peak concentration and AUC almost twice as high as the other patients.

The individual pharmacokinetic profiles for ketorolac during the 30 post-operative hours are shown in **Fig. 12**. Patient demographics and PK results of ketorolac after LIA in THA are presented in **table 8**

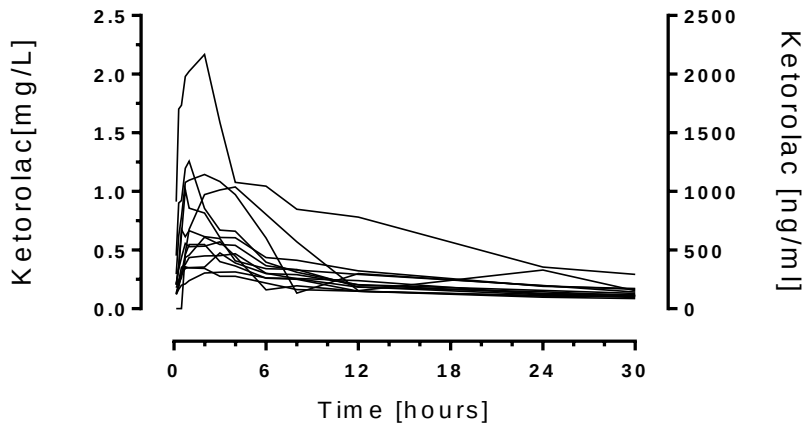

Fig. 12. Individual total plasma concentrations of ketorolac expressed as mg/L (left Y-axis) and as ng/ml (right Y-axis) versus time during 30 hours after LIA (n=13).

Table 8
Patient demographics and PK results of ketorolac after LIA in THA

Patient number	Sex	Age [years]	Creatinine clearance mL/ min	Weight [kg]	BMI kg/m^2	AUC 0-30 h [mg x h /L]	Cmax [mg/L]	Tmax [hours]
1	Male	65	82	89	29.4	NA	1.039	4
2	Female	58	106	63	23.7	22.847	2.167	2
3	Male	54	134	90	27.8	8.856	1.259	1
4	Male	85	58	75	26.9	11.212	1.146	2
5	Female	35	150	74	26.2	4.704	0.358	0.75
6	Female	75	75	100	32.3	6.740	0.474	3
7	Male	61	140	105	35.5	5.801	0.571	3
8	Male	79	62	90	28.4	5.878	0.547	1
9	Male	72	108	83	24.5	8.747	0.608	2
10	Female	76	69	106	40.4	7.156	0.675	0.5
11	Female	71	98	107	34.9	6.058	0.313	4
12	Female	58	101	106	38.0	10.258	1.016	0.75
13	Male	70	66	71	23.5	6.600	0.470	4

Correlation of C_{max} of ketorolac after LIA in THA versus age, creatinine clearance, weight and BMI

Apart from the outlier described above not even a trend towards a correlation between age, creatinine clearance, patient weight or BMI and C_{max} could be identified (**Fig. 13**).

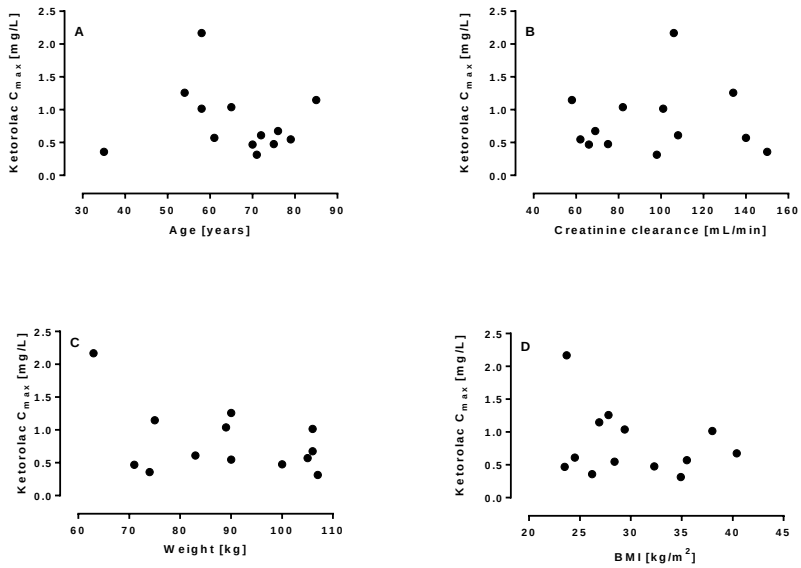

Fig. 13. Maximum detected concentration (C_{max}) of total ketorolac in relation to age (A), creatinine clearance (B), body weight (C) and BMI (D) (n=13).

Correlation of AUC of ketorolac after LIA in THA versus age, creatinine clearance, weight and BMI

Neither age, nor creatinine clearance, nor patient weight nor BMI displayed any correlation to the AUC of ketorolac (Fig 14).

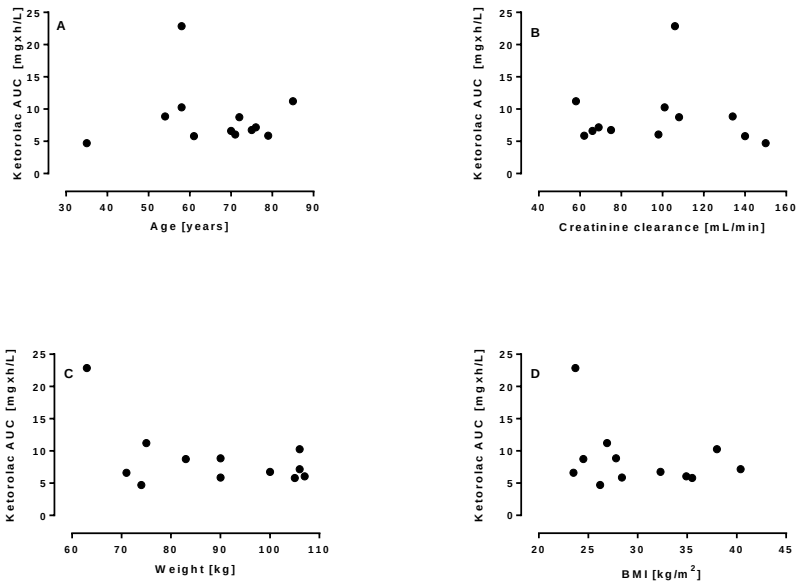

Fig. 14. Total exposure to ketorolac expressed as area under the curve AUC (0-30h) correlated to patient age (A), creatinine clearance (B), body weight (C) and BMI (D) (n=12).

Adverse effects after LIA in TKA and THA with ropivacaine and ketorolac

Neither tachycardia, nor arrhythmias on ECG, nor neurological signs of local anesthetic toxicity (circum oral paresthesia, tinnitus, muscle twitch or seizure) were detected. ECG recording two hours after surgery did not show any prolongation of the QT interval >450 msec compared to preoperative ECG in any patient included in the present studies on TKA and THA.

Discussion

Pain intensity and morphine consumption after total knee and hip arthroplasty with LIA

Effective pain relief after knee and hip replacement surgery is crucial not only for patient satisfaction but for early mobilization and faster rehabilitation and better outcome. Both LIA and femoral block resulted in low average pain intensity during the first post-operative day (Paper I). Similar results have been obtained in a recent randomized study comparing pain intensity at rest and during movement in 60 patients with total knee arthroplasty (184).

However, only 1/20 (5 %) of patients in the LIA group reported pain intensity greater than 7/10 on NRS upon movement as compared to 7/19 (37 %) after femoral block. No difference between LIA and femoral block was observed with regard to pain at rest. These findings are in line with the observation that differences in efficacy between treatment modalities may appear only when pain is assessed during function, not at rest (185). Low pain intensity upon movement may be crucial for rapid rehabilitation, particularly after joint replacement.

Femoral nerve block does not cover the posterior part of the knee, which is innervated by the sciatic nerve. Some authors recommend a supplementary sciatic nerve block to achieve better pain relief after TKA (186,187). However, sciatic nerve block may weaken muscles needed for mobilization after surgery (188).

In addition, femoral nerve block usually produces a partial motor block of the *quadriceps femoris* muscle, which could delay early postoperative mobilization. This effect is avoided with LIA (5,24,184).

With regard to the analgesic efficacy of LIA in total hip arthroplasty (THA) we did not compare this to any other method of post-operative pain relief. However, we asked all our patients for a general assessment of their satisfaction with the postoperative pain management. Eighty-six percent of the patients with THA included in studies III/IV, reported good (73 %) or excellent (13 %) pain relief after LIA.

Our data do not permit to draw a conclusion on the exact contribution of Ketorolac to analgesia induced by LIA. However, we have observed less efficient postoperative analgesia in patients who received local infiltration analgesia without ketorolac in the mixture. In addition, ketorolac is more effective when given intra-articularly and in LIA compared to other routes of administration (132-134).

Ropivacaine plasma concentration after LIA in TKA and THA

The maximal ropivacaine concentrations observed in knee arthroplasty (Paper II) were below the established toxic threshold for most of our patients although two individuals reached concentrations of 1.4 – 1.7 µg/mL.

Similar concentrations have been linked to signs and symptoms of toxicity after i.v. administration in healthy volunteers (100,101). In addition, the maximal plasma concentration of ropivacaine using the LIA protocol seems to be higher than after femoral block during the first 24h. However, studies on peripheral and central block have reported even higher plasma concentrations (2 - 4.2 µg/mL) without adverse reactions (189,190).

Very few investigators have studied safety aspects of LIA or assessed plasma concentrations of ropivacaine after LIA in TKA and THA. Bianconi et al (70) reported total plasma concentrations of ropivacine in patients subjected to elective hip/knee arthroplasty. The range of maximum plasma concentration (C_{max}) was 0.30-1.28 µg/mL, which is comparable to our study (Papers II, III). However, the dose used in that study was 200 mg ropivacaine plus a continuous infusion of 10 mg/h for 55h. The maximal concentration was detected 24h after LIA. Vendittoli et al (66) reported a plasma concentration of ropivacaine in the range of 0.65-1.35 µg/mL after LIA with 275 mg. However, the plasma concentration was monitored during 90 minutes only and a higher plasma concentration later than 90 minute could not be detected.

The maximal detected concentration of ropivacaine in our studies was reached around four to six hours after LIA. By that time most of the patients had been moved from the post-anesthetic recovery room to the ward and minor signs and symptom of toxicity may have passed unnoticed.

To avoid plasma levels higher than those after a single dose, a reduced bolus dose may be considered prior to removal of the peri-articular catheter at 24 h.

Since only the unbound fraction of ropivacaine is pharmacologically active, we assessed both unbound and total plasma concentration of ropivacaine after LIA in THA (paper III). The range of the maximal detected unbound plasma concentration during 30 hours after LIA with 200 mg ropivacaine was 0.004 – 0.03 µg/mL. The upper limit of this range is close to the maximal unbound levels of ropivacaine (0.038 µg/mL) reported after the same dose of ropivacaine (200 mg) in LIA without

epinephrine (191). During four hours after LIA with 400 mg ropivacaine in THA, a maximal concentration of unbound ropivacaine of 0.06 µg/mL was reported in five patients (192) .The same dose of ropivacaine in LIA for TKA resulted in a maximal unbound concentration of 0.032-0.12 µg/mL in 8 patients (193).

Our results indicate that higher age and lower creatinine clearance may correlate to the maximal unbound ropivacaine concentration. However, a statistical power of 66 % for age and 50 % for creatinine clearance was insufficient. At least 29 individuals are needed to test these hypotheses with 80 % power based on our patient cohort without severe renal impairment. In our cohort, neither creatinine clearance, nor age, nor body weight correlated with the AUC of unbound ropivacaine. Renal function may be of greater importance for the AUC during continuous infusion than after a single infiltration as used in our protocol.

Safety aspects of ropivacaine

Knowledge of the potential risks of cardiac or central-nervous-system side-effects at different concentrations of ropivacaine is based on data obtained from early studies with healthy volunteers who received intravenous infusion of ropivacaine (101).

Side-effects sufficient to stop the intravenous infusion were reported at arterial concentrations of 0.34-0.85 µg/mL. This range has been considered to represent a relevant safety limit or neurological toxicity range for venous plasma concentration of unbound ropivacaine (194). However, the clinical relevance of this range may be questioned. Considerably higher unbound concentrations without adverse reactions have been reported during epidural or local infusion (195-197).

We did not detect any signs or symptoms of ropivacaine toxicity after LIA in the patients included in the present studies. A potential risk of local anesthetic toxicity during arthroscopic knee surgery is illustrated by case reports of healthy patients subjected to synovial surgery with local administration of bupivacaine (75 mg and 150 mg) (198,199).

Regarding the effect of tourniquet use, a previous study suggests that a longer duration of tourniquet ischemia may lead to a faster absorption of local anesthetics and higher peak plasma level due to enhanced post-ischemic reperfusion. In contrast, the longer duration of tourniquet inflation after local anesthetics injection increases tissue binding, and decreases peak serum levels (200).

Regarding THA, the tourniquet does not apply but the surgical wound is large and the possibility of absorption of local anesthetics is greater. A lower dose of ropivacaine (200 mg instead of 300 mg) may decrease the risk of high plasma concentration. The maximal total concentration after LIA with 300 mg in TKA was 0.81µg/mL, and after LIA with 200 mg in THA was 0.78µg/mL. Thus, the absorption of ropivacaine is greater after LIA in THA than in TKA.

Ropivacaine binding to α-1 acid glycoprotein (AAG)

Ropivacaine binds mainly to AAG (201,202). This protein increases in stress conditions like surgical trauma. We detected AAG levels similar to those in young healthy adults (120). After 24 hours the AAG level in our study had increased by less than 40 percent, which did not result in any significant change in the unbound concentration of ropivacaine. AAG increases after 24 hours, as shown in several studies of prolonged infusion of ropivacaine (195,203,204). AAG levels may double around 4 days postoperatively and seem to reach a maximal concentration at the sixth to twelfth postoperative day (205,206).

Ketorolac

Information on ketorolac plasma concentration after LIA in knee or hip arthroplasty has not been presented yet (March 2014). In paper II the range of the maximal detected plasma concentration of ketorolac after LIA in knee arthroplasty was 0.15 – 0.96 mg/L. In hip arthroplasty (paper IV) the maximum plasma concentration of ketorolac after LIA was 0.82 mg/L (0.31-2.16). This is comparable to the maximal plasma concentrations after 10 mg ketorolac given intramuscularly in healthy volunteers 0.77 mg/L (207).

We could not find any correlation between peak concentration or C_{max} and the patient age within our cohort. These results are line with the reported similar range after an intramuscular injection of 30 mg ketorolac in young adults (mean age 30 years) and healthy elderly (mean age 72 years) (207).

We could not demonstrate any effect of creatinine clearance on the peak concentration of ketorolac within the range present in our cohort 58-150 ml/min. Renal function is more important for total exposure or AUC than the peak concentration after a single dose. However, we could not find any correlation between creatinine clearance and AUC either. A tendency towards higher AUC after intramuscular injection of 30 mg ketorolac to elderly as compared to younger adults

has been reported (207). We could presume that individuals with creatinine clearance lower than 50 ml/min may have higher AUC. But due to safety concern of ketorolac in patients with reduced renal function a clinical trial on this issue may be ethically questionable.

Our data on ketorolac after LIA do not seem to help identify patients with a higher risk of potential adverse events. Instead it seems reasonable to avoid ketorolac in patients with congestive heart failure treated with ACE inhibitors or ARB and in patients with low creatinine clearance. The optimal cutoff level of creatinine clearance remains to be established.

Adrenaline

The dose of adrenaline in LIA is 0.5 mg. Its presence in the LIA mixture may be advantageous as a cardiovascular marker to detect intravascular injection.

However, the optimal dose of epinephrine in the LIA mixture based on a risk / benefit analysis has not been established. Adrenaline increases pulse and blood pressure and exposes the patient to an increased risk of cardiac ischemia. So far the benefit of adrenaline in the LIA protocol seems to be based on tradition and assumptions rather than solid scientific evidence.

General discussion

Systemic toxicity from local anesthetics is relatively rare. However, local anesthetic toxicity can be catastrophic to the individual when it does occur.

Although many anesthesiologists may occasionally see mild manifestations, most never encounter serious intoxication.

In most of our patients the plasma concentration of ropivacaine after LIA in knee and hip arthroplasty did not reach levels linked to toxicity. However, patients undergoing knee and hip arthroplasty are usually old with various medical diseases. Slow incremental and frequent aspiration during LIA mixture infiltration is advisable. Lipid emulsion should be available for use in case of toxicity, since this therapy is effective for treating local anesthetic toxicity (208). However, the mechanism of the reversal of toxic effects of local anesthetics by lipid emulsion is still unclear. One theory is that it creates a lipid plasma phase that essentially extracts the high lipid-soluble local anesthetic molecules from the aqueous plasma phase (209-211).

An important question still not answered is how much local anesthetic is required in the LIA mixture to produce the optimal therapeutic effect.

The manufacturer Astra Zeneca recommends a maximal dose of 225mg. Higher doses of ropivacaine are used in various institutions both in knee and hip arthroplasty. It may be difficult to recommend a safe maximal dose of local anesthetics because individuals vary in their sensitivity to local anesthetics toxicity, as has already been observed in a ropivacaine toxicity study in healthy volunteers (101). The correlation between blood levels and signs of toxicity is considered multifactorial as physiological, anatomical and pharmacokinetic factors all contribute (212).

Although we could not find any previously reported case of ropivacaine toxicity after LIA in knee and hip arthroplasty, this does not mean that the possibility of its occurrence is negligible, especially in severely ill patients with renal and hepatic impairment.

It seems that single doses may carry a lower risk of toxicity than continued infusion; but scientific proof for this assumption is at least weak.

Older patients may have a higher peak of unbound ropivacaine than younger ones. We found a trend towards a correlation between age and unbound maximal ropivacaine, at least 29 individuals are needed to get sufficient power based on our data. It may be advisable to use lower doses of ropivacaine in patients at higher risk

of developing adverse events. However, our data are insufficient to provide an exact dose recommendation for these patients.

Intuitively, the ”one size fits all” approach using the same dose of ropivacaine for a patient weighing a hundred kilos and one weighing fifty may seem inappropriate. However, our data do not indicate that dosage-per-kilo carries a lower risk of peak concentrations of ropivacaine.

Ketorolac plasma concentration after LIA infiltration in both knee and hip arthroplasty is not negligible, and the risk of renal side-effects should be kept in mind. Age 80 years or older is an independent risk factor for NSAID nephrotoxicity, since 50% of 80-year-old patients have already lost half their glomerular filtration rate (31). Patients with congestive heart failure, hepatic cirrhosis, hypovolemia or underlying renal disease are more susceptible to ketorolac-induced nephrotoxicity (213,214). Heart failure is increasingly diagnosed in the elderly and 30–50% of these patients with heart failure suffer from some degree of renal insufficiency, making their kidneys even more vulnerable to renal adverse events.

Increasing life expectancy, with a growing geriatric population, produces a new cohort of elderly surgical candidates extremely vulnerable to potential nephrotoxic effects of combinations of drugs, in particular in clinical conditions where renal perfusion is reduced.

In our department we had two cases of renal failure after hip and knee arthroplasty after local infiltration analgesia with ketorolac. Both patients were elderly (80 and 89 years) with concomitant treatment with ACE inhibitors or ARB. One required renal dialysis treatment (174).

Based on these observations we now avoid ketorolac in LIA in patients with renal impairment treated with ACE inhibitors or ARB.

Conclusion

1. Pain relief after LIA in knee arthroplasty is as effective as femoral block.

2. The plasma concentration of ropivacaine after LIA in knee arthroplasty is slightly higher than after femoral block.

3. The plasma concentration of ketorolac after LIA in knee arthroplasty does not reach levels linked to toxicity.

4. The maximal dose adjusted concentration of ropivacaine after LIA may be 36 % higher in THA as compared to TKA.

5. The plasma concentration of unbound ropivacaine after LIA in hip arthroplasty does not reach levels linked to toxicity.

6. An increase in AAG by 40 percent after 24 hours has no effect on the unbound concentration of ropivacaine after hip arthroplasty.

7. The plasma concentration of ketorolac after LIA in hip arthroplasty did not reach levels linked to toxicity.

8. The same safety considerations as for intravenous or intramuscular ketorolac should be applied for ketorolac in LIA.

In 1943, the first amino-amide local anesthetic was developed in Sweden by Löfgren and Lundquist, and this xylidine derivative, which they called lidocaine, was first marketed in 1948. Lidocaine has been in clinical use for more than 60 years. It is the most widely used local anesthetic worldwide and remains one of the safest and most efficacious local anesthetic agents ever manufactured (Lofgren NL. Studies on local anesthetics: II Svensk Kem Tidskr 1946; 58: 206-17).

It is worth mentioning that *xylocaine* was introduced for the first time clinically at the Karolinska Hospital, in 1944, by Professor Torsten Gordh. Professor Gordh was the first anesthetist in our department and in Sweden.

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I

Pain control after total knee arthroplasty: a randomized trial comparing local infiltration anesthesia and continuous femoral block

Fatin Affas[1], Eva-Britt Nygårds[1], Carl-Olav Stiller[2], Per Wretenberg[3], and Christina Olofsson[1]

[1]Department of Anesthesiology and Intensive Care, [2]Department of Medicine, Clinical Pharmacology Unit, and [3]Department of Molecular Medicine, Section of Orthopaedics, Karolinska Institute and Karolinska University Hospital, Solna, Sweden
Correspondence: per.wretenberg@karolinska.se
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Background and purpose **Pain after total knee arthroplasty (TKA) is usually severe, and epidural analgesia or femoral nerve block has been considered to be an effective pain treatment. Recently, local infiltration analgesia (LIA) has become increasingly popular but the outcome of this method regarding the analgesic effect has not been fully evaluated. We compared local infiltration analgesia and femoral block with regard to analgesia and morphine demand during the first 24 h after TKA.**

Methods **40 patients undergoing TKA under spinal anesthesia were randomized to receive femoral nerve block (group F) or peri- and intraarticular infiltration analgesia (group LIA) with a mixture containing ropivacaine, ketorolac, and epinephrine. All patients had access to intravenous patient-controlled analgesia (PCA) with morphine postoperatively. Pain intensity at rest and upon movement was assessed on a numeric rating scale (0–10) on an hourly basis over 24 h if the patients were awake.**

Results **The average pain at rest was marginally lower with LIA (1.6) than with femoral block (2.2). Total morphine consumption per kg was similar between the 2 groups. Ancillary analysis revealed that 1 of 20 patients in the LIA group reported a pain intensity of > 7 upon movement, as compared to 7 out of 19 in the femoral block group (p = 0.04).**

Interpretation **Both LIA and femoral block provide good analgesia after TKA. LIA may be considered to be superior to femoral block since it is cheaper and easier to perform.**

Pain after total knee arthroplasty (TKA) is usually severe and difficult to manage, and insufficient pain relief may delay recovery. The most effective pain treatment has traditionally been epidural analgesia or femoral nerve block (Singelyn et al. 1998, Ganapathy et al. 1999, Chelly et al. 2001, Davies et al. 2004, Ilfeld et al. 2006) in combination with opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs, cyclooxygenase (cox) inhibitors). Each of these methods has its specific side effects. Urinary retention and muscular weakness are often reported after epidural analgesia. Unpleasant numbness of a large part of the lower extremity is common after femoral block. Opioid analgesics often cause sedation, nausea and vomiting, and also urinary retention. Non-selective cox inhibitors may cause gastrointestinal bleeding, renal complications, and epidural hematoma, especially in combination with anti-thrombotic prophylaxis with low-molecular-weight heparin (Afzal et al. 2006).

An alternative method for postoperative pain relief after TKA, which has attracted growing interest in recent years, is multimodal wound infiltration analgesic technique consisting of peri- and intraarticular infiltration of local anesthetics and NSAID in the knee (LIA) (Andersen et al. 2008a, b, Kerr and Kohan 2008). This technique appears to offer several advantages over traditional methods, since the analgesia affects only the surgical area with limited interference of the muscle strength. Thus, easier rehabilitation of the operated extremity and earlier discharge from the hospital can be expected (Reilly et al. 2005, Essving et al. 2009). Furthermore, recent studies have shown that the LIA technique reduces the requirement for postoperative analgesia with opioids (Tanaka et al. 2001, Busch et al. 2006, Vendittoli et al. 2006).

Only a few investigators have randomly compared LIA with other methods with proven analgesic effect, such as femoral block or epidural analgesia (Parvataneni et al. 2007, Toftdahl et al 2007). Parvatanemi and collaborators (2007) have shown that a combination of a femoral block and local administration of bupivacaine, morphine, and epinephrine results in better pain relief and patient satisfaction than femoral block. Toftdahl and collaborators (2007) presented data suggesting that LIA with ropivacaine, ketorolac, and epinephrine results

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in faster postoperative activation, as indicated by being better able to walk more than 3 m on the first postoperative day as compared to femoral block. A retrospective comparison (DeWeese et al. 2001) indicated that epidural anesthesia with fentanyl and bupivacaine resulted in better pain relief and less use of other analgesics than did continuous infiltration of the knee with bupivacaine.

Femoral block is known to be an effective pain treatment after TKA (Szczukowski et al. 2004, Navas et al. 2005, Duarte et al. 2006). We compared the LIA technique with femoral block regarding efficacy of pain management at rest and upon movement after TKA. We also investigated whether LIA reduced the demand for intravenous morphine, administered via a patient-controlled analgesia (PCA) pump during the first 24 h postoperatively.

Patients

This randomized parallel clinical 1:1 trial was used to compare two protocols of postoperative pain relief after total knee arthroplasty. The inclusion criteria were as follows: patients with osteoarthritis or rheumatoid arthritis scheduled for primary unilateral elective total knee arthroplasty under spinal anesthesia, American Society of Anaesthesiologists (ASA) classification I–III, and more than 18 years old. Exclusion criteria were allergy or intolerance to one of the study drugs, renal insufficiency, epilepsy, language difficulty, mental illness, dementia, QT interval on ECG > 450 msec before start. After giving oral and written informed consent, 40 patients scheduled for primary unilateral total knee arthroplasty were randomly assigned to 2 groups of postoperative pain management immediately before the surgical procedure.

The setting of this single-site academic trial was the orthopedics clinic at Karolinska University Hospital in Solna. The first patient was included on January 15, 2007 and the final patient was included on March 25, 2008.

Randomization

The randomization sequence was determined by mixing 40 tickets, 20 labeled "F" and 20 labeled "LIA" in sealed opaque envelopes, and drawing one envelope at a time. The anesthesiologist performing the spinal anesthesia and femoral block or supervising the LIA technique did not participate in the randomization procedure.

Interventions

Group F received a femoral block with ropivacaine (Narop; Astra Zeneca) and group LIA received peri- and intraarticular infiltration with ropivacaine + ketorolac (Toradol; Roche) and epinephrine (Adrenalin; NM Pharma).

Preparation

Before induction of spinal anesthesia, monitoring of oxygen saturation, blood pressure, and electrocardiogram (ECG) was started. Sedation was induced with midazolam (Midazolam; Alpharma), 1–2 mg intravenously. The level of spinal anesthesia was L2-L3 or L3-L4. Isobaric bupivacaine (Marcain Spinal; Astra Zeneca), 5 mg/mL at a volume of 3 mL, was injected with the patient lying with the operating side upwards.

Before the start of the operation, all patients were sedated with midazolam or propofol (Propofol; Abbot), maintaining spontaneous ventilation. All patients received 2 g dicloxacillin intravenously before surgery. Antithrombotic therapy with low-molecular-weight heparin (LMWH), enoxaparinnatrium (Klexane; Aventis Pharma) 40 mg, started the day before surgery and was given for at least 5 days. The TKA procedure was performed following application of a thigh tourniquet, which was inflated just before skin incision and released after wound closure.

Group F

These patients received a femoral nerve block directly after spinal anesthesia. They were placed in the supine position. Under sterile conditions, the pulse of the femoral artery was identified, the needle (Plexolong Nanolin cannula facette 19G × 50 mm; Pajunk) connected to a nerve stimulator (Simplex B, serial no 17002; Braun) set up to deliver 1.2 mA was inserted cephalad, 45 degrees to skin and at the level of femoral crease, 1–1.5 cm lateral to the femoral artery pulse (Winnie et al. 1973). The femoral nerve was identified by eliciting quadriceps muscle contractions ("dancing patella"). The current was gradually reduced to achieve twitches of the quadriceps muscle at 0.2–0.4 mA and the catheter (StimuLong Sono; Pajunk) was advanced through the needle.

The connection of the nerve stimulator was changed from needle to catheter, and stimulation intensity was started at 1.2 mA until the desired motor response was obtained. Thereafter, the intensity was reduced to 0.2–0.4 mA. The catheter was secured in place with transparent dressing. After negative blood aspiration, 30 mL ropivacaine (2 mg/mL) was injected followed by 15 mL of the same concentration every 4 hours for 24 h (total dose 240 mg/24 h). All patients had a urinary bladder catheter, inserted after spinal anesthesia and removed on the day after surgery. Group F received ketorolac (10 mg intravenously) in the post-anesthetic care unit, and again after 8 h and 16 h. The total dose of ketorolac was 30 mg.

Group LIA

These patients received peri- and intraarticular infiltration of a solution containing 150 mL ropivacaine (2 mg/mL), 1 ml ketorolac (30 mg/mL), and 5 ml epinephrine (0.1 mg/mL). This solution was prepared by the operation nurse before the start of the surgical procedure. The solution was given sequentially: 30 mL was injected intracutaneously at the start of the operation, 80 mL was injected into the posterior part of the capsule, close to the incision line, in the vastus intermedius and lateralis and around the collateral ligaments before

cementation, and 46 mL was instilled through an intraarticular catheter (epidural catheter gauge 16) inserted at the end of the surgical procedure. The total dose of ropivacaine during the first 24 h postoperatively was 300 mg and the total dose of ketorolac was 30 mg.

Recovery

In the recovery room, all patients were provided with a patient-controlled analgesia (PCA) morphine pump (Abott Pain Manager; Abbot Laboratories) programmed to give an intravenous bolus of morphine (2 mg/dose) on demand with a lock-out time of 6 min and maximum dose of 35 mg over 4 h. All patients were introduced to the PCA technique and encouraged to use it as often as needed. After 24 hours, PCA pump use was verified with a printout of all doses of morphine and their time of administration. In addition to PCA, all patients received paracetamol (1 g × 4), either orally or intravenously.

All patients were informed preoperatively by the nurse about pain assessment using a numeric rating scale (NRS): 0 = no pain and 10 = worst imaginable pain, based on the visual analog scale. NRS score at rest or upon movement during the first 24 h was recorded on an hourly basis by the patients, if awake.

ECG was performed preoperatively, 2 h after the end of surgery in the recovery room and 24 h postoperatively in the ward. All patients received postoperative physiotherapy, which started on the morning after operation.

Statistics

Power analysis was performed using average VAS/NRS score during 24 h as the primary variable. A previous study of patients undergoing knee arthroplasty treated with a femoral nerve block reported a mean visual analog scale score of 3.6 (SD 1.1) upon movement, at 24 h (Singelyn et al. 1998). We wanted to be able to detect a difference of 1 unit between LIA and femoral block. A sample size of 20 in each group would have 80% power to detect a difference between means of 1.0 with a significance level (alpha) of 0.05 (two-tailed) using the unpaired Student's t-test (GraphPad StatMate 1.0; GraphPad, San Diego, CA).

Outcomes

Primary outcome. Differences in average pain intensity at rest and upon movement during the first 24 h after TKA were analyzed with the Mann-Whitney U-test. As we had 2 primary efficacy outcomes, a significance level of $p < 0.02$ was chosen for each analysis. No data were imputed for the primary outcome if the patient was asleep or unable to record NRS.

Secondary outcome. Total morphine use via the intravenous PCA pump during the 24-h period in the 2 study arms were analyzed with the Mann-Whitney U-test. Descriptive statistics were used to describe the morphine dose per kg in each study arm.

Ancillary analyses

These were as follows. 1. Average pain intensity in 24 hours following imputation of missing data. Missing data was replaced by "0" if the patient was asleep. The most recent NRS score obtained was used to replace missing if pain rating was not provided due to other reasons. 2. The fraction of patients who reported a degree of pain intensity of < 5 at rest and during movement, i.e. mild pain intensity (Jensen et al. 2003) in the 2 study groups was compared with Fisher's exact test. 3. The fraction of patients who reported a pain intensity of > 7 at rest and during movement, i.e. severe pain (Jensen et al. 2003) in the two study groups was compared with Fisher's exact test.

Safety monitoring

We monitored indications of cardiac arrhythmias and incidence of reported adverse events.

Ethics

This trial (protocol no. 4773 KCR S2006-011) was conducted according to the Helsinki declaration and was approved by the regional ethics committee of the Karolinska Institute (EPN 151:2006/34610) and the Swedish Medical Product Agency (EudraCT 2006-002581-19). The trial was monitored by the Karolinska Trial Alliance. This trial was not registered in the FDA database of clinical trials.

Results

40 patients participated in this trial, which was conducted. 20 patients were randomized to LIA and 20 to femoral block. All patients completed the study. Data were analyzed according to strict intention-to-treat (sITT) analysis according to Herman et al. (2009). One patient in the F group had a history of insensitivity to pain. He did not demand any morphine by PCA and pain was assessed as 0 on the NRS at all time points. The most recent NRS score obtained was used to replace missing if pain rating was not provided due to other reasons The most recent NRS score obtained was used to replace missing if pain rating was not provided due to other reasons and there was no use of morphine by PCA and 0 on the NRS at all times. This rare condition was not detected by the screening physician at inclusion in the trial. Exclusion of the data obtained from this patient and analysis according to modified intention-to-treat method (mITT) (Herman et al. 2009) did not affect the outcome data (data not shown). The baseline characteristics and the demographic data of the patients were similar in both groups—except for the average weight, which was higher in the femoral block group (Table 1). On average, 6 hourly time points of 24 were missing due to the patients being asleep or unable to fill in the CRF due to activities outside the ward.

Table 1. Baseline patient demographics

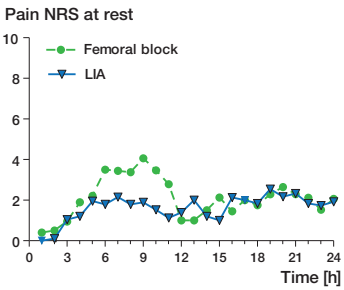
	Femoral block	LIA
Sex (M/F)	8 / 12	11 / 9
Age, mean (range)	69 (53–88)	67 (29–85)
Weight in kg, mean (SD)	83 (13)	78 (18)
Length in cm, mean (SD)	168 (9)	171 (11)
BMI (mean)	27	27
ASA I / II / III	2 / 8 / 10	3 / 7 / 10
RA / OA	3 / 17	6 / 14

M: male; F: female; RA: rheumatoid arthritis; OA: osteoarthritis; ASA: American Society of Anaesthesiologists classification.

Table 2. Primary outcome

	Femoral block n = 20	LIA n = 20
Average pain NRS at rest [a]	2.1 (1.4–2.9)	1.6 (1.0–2.3)
Average pain NRS upon movement [a]	2.4 (1.5–3.2)	2.4 (1.7–3.0)

[a] Reported data only. Missing NRS registrations due to the patients being asleep or unable to fill in the CRF due to other activities were not imputed. Data are expressed as mean (95% CI).



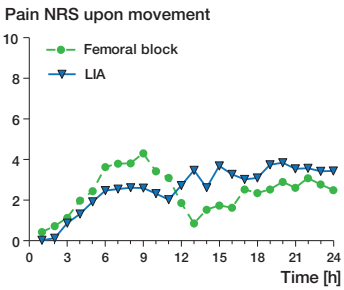


Figure 1. Average pain score (NRS) at rest and upon movement over 24 h after surgery. If the patient was sleeping, no data were recorded (n = 20 in each group).

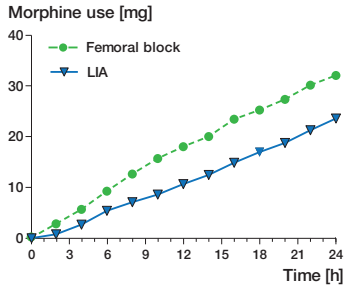


Figure 2. Average morphine use (PCA) in mg for the 2 groups during the first 24 h after surgery (n = 20 in each group).

Primary outcome

The average degree of pain intensity during the first postoperative day was low in both groups. The average degree of pain intensity at rest and upon movement was similar (Table 2 and Figure 1).

Secondary outcomes

The average total morphine use via the intravenous PCA pump during the first postoperative day was 10 mg higher in the femoral block group than in the LIA group, but this difference was not statistically significant (Figure 2). However, the morphine dose per kg was almost identical in both groups (Table 3).

Ancillary analysis

1. Imputation of missing data by "0" if the patients was asleep, and using the most recent NRS score to replae missing data if pain rating was not provided due to other reasons resulted in a mean NRS at rest of 2.2 (95% CI: 1.4–3.1) in the femoral block group and of 1.5 (CI: 0.8–2.1) in the LIA group. The average pain score upon movement, following imputation of missing observations, was 2.2 (CI: 1.5–3.0) in the femoral block group and 2.1 (CI: 1.5–2.8) in the LIA group. 2. Incidence of NRS less than 5 throughout the 24-h observation period (probably acceptable pain relief) at rest and upon movement was twice as high in the LIA group than in the femoral block group (Table 4). 3. The incidence of NRS pain intensity greater than 7 at rest on one or more occasions during the 24-h observation period was 5 times higher in the femoral block group than in the LIA group (Table 4). NRS greater than 7 upon movement was only reported by 1 of 20 patients in the LIA group and 7 of 19 patients in the femoral block group (p = 0.04, Fisher's exact test).

Table 3. Secondary outcome

	Femoral block	LIA
Total morphine (mg)	32 (23–41)	24 (16–31)
Total morphine (mg/kg)	0.4 (0.3–0.5)	0.3 (0.2–0.4)

Total morphine refers to intravenous morphine administered via a PCA in 24 h. Data are expressed as mean (95% CI).

Safety analysis

None of the patients had prolonged QT interval at the ECG 2 hours and 24 hours postoperatively. No adverse events were reported during the 24-h study period.

Table 4. Ancillary analysis

	Femoral block (n = 19)	LIA (n = 20)
NRS < 5 at rest	7	12
NRS < 5 upon movement	5	8
NRS > 7 at rest	5	1
NRS > 7 upon movement	7	1 [a]

NRS < 5 refers to the number of patients who reported a NRS lower than 5 throughout the 24 h of observation. NRS > 7 refers to the number of patients who reported pain intensity greater than 7 once or more often during the 24 h of observation.
[a] p< 0.05 (Fisher's exact test).

Discussion

Our data indicate that the 2 analgesic regimens gave similar quality of pain relief during the first 24 h. Some studies have compared LIA with other pain treatments after TKA, such as systemic analgesia and placebo, and have reported superior outcome with LIA regarding postoperative analgesia and opioid consumption. The positive results in those studies are not surprising, since the analgesic treatment in the control groups mainly consisted of less effective methods of postoperative pain treatment (Lombardi et al. 2004, Vendittoli et al. 2006, Parvataneni et al. 2007, Rostlund and Kehlet 2007, Andersen et al. 2008, Kerr and Kohan 2008, Essving et al. 2009).

Both femoral block and LIA resulted in low average pain intensity during the first postoperative day. The average degree of pain intensity at rest, but not upon movement, was slightly lower in the LIA group. This small difference is probably without clinical significance. The access to PCA-administered morphine until pain was acceptably low, NRS < 4, would be expected to result in a similar degree of pain relief. The total use of morphine per kg was similar in both groups, which indicates that the pain relief of both methods was comparable. Using ancillary analysis, we found that a pain intensity of greater than 7 on NRS with movement was less common in the LIA group, a difference that reached statistical significance. This result must be regarded as hypothesis generating, and should be confirmed by a separate study.

We compared 2 routinely used methods that are both effective for postoperative pain relief in TKA. None of the patients in this study were given an analgesic other than intravenous morphine, administered through a PCA pump, and paracetamol (4 g in 24 h).

Femoral block and LIA after TKA have been compared previously (Parvataneni et al. 2007, Toftdahl et al. 2007). However, in the study by Toftdahl et al., the femoral block group also received intraarticular injection of morphine (4 mg) and bupivacain (50 mg), and in the study by Parvateneni et al. a variable dose of morphine (4–10 mg) and methylprednisolone (40 mg) was given to the LIA group. In both trials, reduced opioid consumption was found with LIA. Pain relief at rest was good, but was similar in the 2 groups during the first 24 h. In accordance with our findings (with fewer patients reporting high-intensity pain on movement in the LIA group), a previous study has found better pain relief during physiotherapy after LIA (Toftdahl et al. 2007).

The tendency of lower efficacy with femoral block may be due to the fact that the posterior part of the knee is innervated by the sciatic nerve. Thus, a femoral block does not cover this area and supplementary treatment with systemic analgesics such as opioids and NSAIDs is needed. In our study, all the patients in the femoral group received ketorolac in a total dose of 30 mg intravenously during the first 24 h—the same amount as administered locally in the LIA group.

One explanation as to why LIA is so effective might be that there is evidence for a clinically relevant peripheral analgesic action of intraarticular NSAIDs (Romsing et al. 2000). The analgesic effect of NSAIDs may be better after intraarticular administration than after systemic administration (Day et al. 1999). Furthermore, in a study comparing the analgesic effect of NSAIDs after wound infiltration with that after systemic administration, the result was in favor of local infiltration (Ben-David et al. 1995). Our study groups received NSAID either intravenously (group F) or via peri- and intraarticular infiltration (group LIA), but the study design was not set up to answer the question of the most effective route of administration of NSAID. Furthermore, a clear relationship between the dose of NSAIDs and their analgesic effect has been established (Collins et al. 1998). Thus, the systemic dose of NSAIDs used may have been too low for full analgesic effect in the femoral group.

The high quality of the femoral blocks in this study might be one explanation for the small difference in analgesic efficacy between the two methods. It is well known that the quality of a peripheral blockade might depend on the experience of the anesthesiologist, and all but 2 blocks were performed by an experienced anaesthesiologist (FA).

Experience is also of importance for perioperative local infiltration. When we introduced the LIA method at our institution, we noticed that surgeons also have a learning curve in doing effective local infiltration. The more experienced the surgeon is, the more effective is the postoperative pain relief. This may also be due to less tissue trauma being produced by experienced surgeons.

Limitations of the study

Open labeled studies have a disadvantage compared to blinded studies, due the interference of expectancy of the patient and the staff in interpretation of the outcome. The patients in group F received an initial femoral nerve block followed by bolus doses of ropivacaine every 4 h during the first 24 h, and not continuous infusion of local anesthetic, which might have been more effective due to a steady concentration of ropivacaine over time and probably better pain control. The randomization procedure was simple and did not use block design, which

could be a disadvantage. Furthermore, stratification according to to sex and osteoarthritis or rheumatoid arthritis might have resulted in 2 groups with less difference.

Since the number of patients with rheumatoid arthritis was higher in the LIA group, we cannot rule out that LIA or femoral block may be more effective in this patient category. The observation period of 24 h may be too short, especially with regard to adverse events. Furthermore, it would have been good to investigate whether there were differences regarding ease of rehabilitation or physical therapy.

In summary, in this randomized study we could not confirm that there was any clear superiority of perioperative infiltration of local anaesthetic (LIA) over femoral block in combination with i.v. ketorolac in total knee arthroplasty, since the two analgesic regimens gave similar quality of pain treatment during the first 24 h. However, LIA may be considered the preferred option since it is cheaper and easier to perform than femoral block. In addition, LIA involves the surgeon in alleviating postoperative pain.

FA: Conducted the femoral block and supervised the LIA procedure and participated in the trial application. EBN: Participated in the planning of the trial and acted as anaesthesiologist of some of the patients in this trial. COS: Participated in the planning and supervising of the trial and finalizing the manuscript. PW: Performed most of the TKA in this trial. Participated in organizing the trial. CO: Responsible for the planning and application of the trial to the medical product agency. Participated in writing the manuscript.

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No competing interests declared.

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Clinical pain research

A randomized study comparing plasma concentration of ropivacaine after local infiltration analgesia and femoral block in primary total knee arthroplasty

Fatin Affas[a], Carl-Olav Stiller[b,*], Eva-Britt Nygårds[a], Niclas Stephanson[b], Per Wretenberg[c], Christina Olofsson[a]

[a] Department of Anaesthesiology and Intensive Care, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden
[b] Department of Medicine, Clinical Pharmacology Unit, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden
[c] Department Molecular Medicine, Section of Orthopaedics, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden

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ABSTRACT

Pain after total knee arthroplasty (TKA) is difficult to control. A recently developed and increasingly popular method for postoperative analgesia following knee and hip arthroplasty is Local Infiltration Analgesia (LIA) with ropivacaine, ketorolac and epinephrine. This method is considered to have certain advantages, which include administration at the site of traumatized tissue, minimal systemic side effects, faster postoperative mobilization, earlier postoperative discharge from hospital and less opioid consumption. One limitation, which may prevent the widespread use of LIA is the lack of information regarding plasma concentrations of ropivacaine and ketorolac.

The aim of this academically initiated study was to detect any toxic or near-toxic plasma concentrations of ropivacaine and ketorolac following LIA after TKA.

Methods: Forty patients scheduled for primary total knee arthroplasty under spinal anaesthesia, were randomized to receive either local infiltration analgesia with a mixture of ropivacaine 300 mg, ketorolac 30 mg and epinephrine or repeated femoral nerve block with ropivacaine in combination with three doses of 10 mg intravenous ketorolac according to clinical routine. Plasma concentration of ropivacaine and ketorolac were quantified by liquid chromatography–mass spectrometry (LC–MS).

Results: The maximal detected ropivacaine plasma level in the LIA group was not statistically higher than in the femoral block group using the Mann–Whitney *U*-test ($p = 0.08$). However, the median concentration in the LIA group was significantly higher than in the femoral block group ($p < 0.0001$; Mann–Whitney *U*-test).

The maximal plasma concentrations of ketorolac following administration of 30 mg according to the LIA protocol were detected 1 h or 2 h after release of the tourniquet in the LIA group: 152–958 ng/ml (95% CI: 303–512 ng/ml; $n = 20$). The range of the plasma concentration of ketorolac 2–3 h after injection of a single dose of 10 mg was 57–1216 ng/ml (95% CI: 162–420 ng/ml; $n = 20$).

Conclusion: During the first 24 h plasma concentration of ropivacaine seems to be lower after repeated femoral block than after LIA. Since the maximal ropivacaine level following LIA is detected around 4–6 h after release of the tourniquet, cardiac monitoring should cover this interval. Regarding ketorolac, our preliminary data indicate that the risk for concentration dependent side effects may be highest during the first hours after release of the tourniquet.

Implication: Femoral block may be the preferred method for postoperative analgesia in patients with increased risk for cardiac side effects from ropivacaine. Administration of a booster dose of ketorolac shortly after termination of the surgical procedure if LIA was used may result in an increased risk for toxicity.

1. Introduction

Pain after TKA is difficult to control. A recently developed and increasingly popular method for postoperative analgesia following knee and hip arthroplasty is Local Infiltration Analgesia (LIA) with ropivacaine, ketorolac and epinephrine [1]. This method is considered to have certain advantages, which include administration

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* Corresponding author at: Clinical Pharmacology Unit L7:03, Department of Medicine-Solna, Karolinska University Hospital, Solna, SE-171 76 Stockholm, Sweden. Tel.: +46 8 5177 3261.
E-mail address: Carl-Olav.Stiller@ki.se (C.-O. Stiller).

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at the site of traumatized tissue, minimal systemic side effects, faster postoperative mobilization, earlier postoperative discharge from hospital and less opioid consumption [1–5]. One limitation, which may prevent the widespread use of LIA is lack of knowledge regarding potential toxicity resulting from excessive plasma concentrations of ropivacaine. Although the manufacturer (AstraZeneca) recommends 300 mg ropivacaine as a maximum dose for infiltration, much larger doses are often used [2–6]. Ropivacaine is a long-acting local anaesthetic agent similar to bupivacaine [7]. It is considered to be less toxic to the central nervous system and the cardiovascular system [7,8]. The risk of cardiac arrhythmia is shared with all local anaesthetics and depends on the plasma concentration. Signs of toxicity may be observed at 1500 ng/ml [7]. Intra-articular doses of 150 mg ropivacaine in the knee joint result in a maximal total plasma concentration of 1175 ng/ml [9]. The typical dose of ropivacaine in LIA is 300 mg administered over 30 min. Thus, the plasma concentration of ropivacaine following LIA may reach the threshold for neural and cardiovascular toxicity.

Maximum tolerated doses of local anaesthetics in combination with epinephrine administered by infiltration have not yet been established [10].

Ketorolac is a non-selective cyclooxygenase inhibitor, which has been used for postoperative analgesia during almost twenty years [11]. Local administration affords similar or better pain relief than systemic administration [12]. However, especially postoperatively, there is a dose- and plasma-concentration-dependent risk of renal side effects with decreased glomerular filtration in addition to an increased risk of peptic ulcer and bleeding. The peak plasma concentration of ropivacaine and ketorolac following intra- and peri-articular infiltration is presumably reached later than that following i.v. administration. However, extensive surgical trauma and soft-tissue dissection may increase systemic absorption during major orthopedic surgery. This effect may be delayed by the use of a thigh tourniquet during surgery [13].

The aim of the present randomized, single-site clinical trial was to collect data on the plasma concentration of ropivacaine and ketorolac during two different routine protocols of post operative pain relief in patients scheduled for primary knee arthroplasty in order to detect any toxic or near-toxic plasma concentrations. One group (LIA) received intra- and peri-articular injection of ropivacaine, ketorolac and epinephrine and the other a femoral block with ropivacaine and i.v. injection of ketorolac according to clinical routine.

2. Patients and methods

The present academically initiated randomized trial was conducted in accordance with the Helsinki Declaration II and approved by the Regional Research Ethics Committee at the Karolinska Institutet in Stockholm (2006/397-31/4) and by the Swedish Medical Products Agency. The enrolment period started in December 2006 and lasted until February 2008.

Inclusion criteria: Adult patients (older than 18 years) with osteoarthritis or rheumatoid arthritis scheduled for primary unilateral elective total knee arthroplasty, American Society of Anesthesiologists (ASA) classification I–III.

Exclusion criteria: Allergy or intolerance to one of the study drugs, renal insufficiency, epilepsy, language difficulty, mental illness, dementia, QT-interval on Electro Cardio Graph (ECG) > 450 ms before start.

After oral and written informed consent, 40 patients scheduled for primary unilateral total knee arthroplasty under spinal anaesthesia were randomly assigned into two groups of postoperative pain management immediately prior to the surgical procedure:

Femoral block (*Group F*) received ropivacaine (Narop®, AstraZeneca) av i.v. ketorolac (Toradol®, Roche) at the PACU and *group LIA* received peri- and intraarticular infiltration with ropivacaine + ketorolac (Toradol®, Roche) and epinephrine (Adrenalin®, NM Pharma).

2.1. Randomization

The randomization sequence was determined by mixing 40 tickets, 20 labelled "F" and 20 labelled "LIA" in sealed opaque envelopes and drawing one envelop at a time. The envelopes were consecutively numbered from 1 to 40 (Christina Olofsson and Eva-Britt Nygårds). Information of the procedure for postoperative pain relief for the first patient was found in envelop 1 and for the second patient in envelop 2 and so on.

2.2. Procedure

Antithrombotic therapy with low molecular weight heparin, enoxaparinnatrium (Klexane®, Aventis Pharma) 40 mg started 12 h before spinal anaesthesia and was given for at least 5 days. Before induction of spinal anaesthesia monitoring of oxygen saturation, blood pressure and electrocardiogram (ECG) was started. Sedation was induced with midazolam (Midazolam®, Alpharma) 1–2 mg i.v. or propofol (Propofol®, Abbot). Puncture for spinal anaesthesia was at level L2–3 or L3–4. Isobaric bupivacaine (Marcain Spinal®, AstraZeneca) 5 mg/ml at a volume of 3 ml was injected with the patient lying with the operating side upwards. All patients had a urinary bladder catheter, inserted after spinal anaesthesia and removed the day after surgery. All patients received 2 g dicloxacillin i.v. before surgery.

The TKA-procedure was performed following inflation of a thigh tourniquet, which was inflated just before skin incision and released after wound closure. The release of the tourniquet is time zero "0" in the LIA group.

Group F received a femoral nerve block directly after spinal anaesthesia.

Patients were placed in the supine position. Under sterile condition, the pulse of the femoral artery was identified, the needle (Plexolong Nanolin cannula facette 19G × 50 mm®, Pajunk) connected to a nerve stimulator (Simplex B®, Braun: serial no. 17002) set up to deliver 1.2 mA was inserted cephalad 45 angle to skin at the level of femoral crease 1–1.5 cm lateral to the femoral artery pulse [14]. The femoral nerve was identified by eliciting quadriceps muscle contractions ("dancing patella"). The current was gradually reduced to achieve twitches of the quadriceps muscle at 0.2–0.4 mA and the catheter (StimuLong Sono®, Pajunk) was advanced through the needle.

The connection of the nerve stimulator was changed from needle to catheter and stimulation intensity was started at 1.2 mA until the desired motor response was obtained. Thereafter, the intensity was reduced to 0.2–0.4 mA. The catheter was secured in place with transparent dressing (Tegaderm®, 3 M). After negative blood aspiration 30 ml ropivacaine 2 mg/ml (Narop) was injected followed by 15 ml ropivacaine 2 mg/ml 4 hourly for 24 h (total dose ropivacaine 240 mg/24 h). Group F received ketorolac (Toradol) 10 mg intravenously in the Post Anaesthetic Care Unit (PACU), and again after 8 h and 16 h. The total dose of ropivacaine during 24 h was 240 mg and the total dose of ketorolac was 30 mg.

Group LIA received peri- and intra-articular infiltration with a mixture of 150 ml ropivacaine (2 mg/ml), 1 ml ketorolac (30 mg/ml), and 5 ml epinephrine (0.1 mg/ml) (total volume 156 ml). This solution was prepared by the operation nurse prior to the start of the surgical procedure. The solution was given sequentially; 30 ml was injected intracutaneously at the start of the

operation, 80 ml was injected into the posterior part of the capsule, close to the incision line, in the vastus intermedius and lateralis and around the collateral ligaments before cementation, and 46 ml was instilled through an intraarticular catheter (epidural catheter gauge 16) inserted at the end of the surgical procedure. The total dose of ropivacaine during the first postoperative 24 h was 300 mg and the total dose of ketorolac was 30 mg.

In the recovery room all patients were provided with a patient controlled analgesia (PCA) morphine pump (Abbott Pain Manager®, Abbott Laboratories) programmed to give an intravenous bolus of morphine 2 mg/dose on demand with a lock-out time of 6 min and maximum dose of 35 mg/4 h. All patients were introduced to the PCA-technique and encouraged to use it as often as needed. After 24 h PCA pump use was verified by a print out of all doses of morphine and their time of administration. In addition to PCA all patients received paracetamol (1 g × 4), either orally (Alvedon®, Astra Zeneca) or i.v. (Perfalgan®, Bristol-Myer Squibb).

Electro Cardio Graph (ECG) was performed preoperatively, 2 h after the end of surgery in the recovery room and 24 h postoperatively in the ward.

All patients received postoperative physiotherapy, which started the morning after operation.

2.3. Blood samples

Blood samples for ropivacaine and ketorolac plasma concentration were drawn from a vein in the arm not used for i.v. infusions, or from a radial-artery cannula used for patient monitoring. Blood sampling was started 20 min after injecting ropivacaine in the femoral catheter in group F (Time zero "0" in femoral group). In the LIA group the release of the tourniquet was time zero "0". The first sample was taken at 20 min. Additional samples were taken at 40 and 60 min and 2, 4, 6, 12, 24 h. The 12-h samples were taken only in four patients due to the inconvenient sampling time. The blood samples were centrifuged directly, plasma-separated and immediately frozen and stored at −20 °C until assayed.

Table 1
Patient demographics.

	Femoral block	LIA
Sex (M/F)[a]	8/11	11/9
Age mean (range)	69 (53–88)	67 (29–85)
Weight (kg)	83 ± 13	78 ± 18
Height (cm)	168 ± 9	171 ± 11
BMI	27	27
ASA I/II/III	2/8/9	3/7/10
RA/OA[b]	3/16	6/14

Values are expressed as mean (range) or mean ± SD.
[a] M: male, F: female.
[b] RA: rheumatoid arthritis, OA: osteoarthritis.

2.4. Quantification of ropivacaine and ketorolac

The reference materials ropivacaine and the internal standard bupivacaine were obtained from AstraZeneca, Södertälje, Sweden. The reference material ketorolac trometamol was obtained from USP, Rockville, MD, USA and the internal standard ketobemidon-d4 was a gift from Prof. Ulf Bondesson (Swedish University of Agricultural Sciences, Uppsala, Sweden).

Ropivacaine was quantified by LC–MS using Agilent 1100 MSD (Agilent Technologies, CA, USA). Ketorolac was quantified by LC–MS/MS consisting of a Waters Acquity UPLC (Ultra-performance liquid chromatograph) connected to a Quattro Premier XE tandem mass spectrometer. The limit of quantification was 10 ng/ml for each compound and the maximal calibrated range was 10,000 ng/ml. Analytical details are provided by the corresponding author upon request.

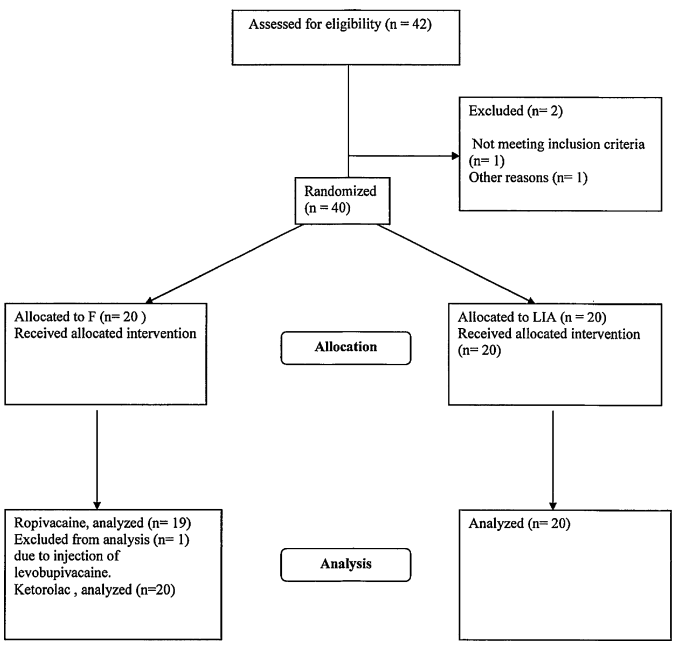

Fig. 1. Consort flow chart.

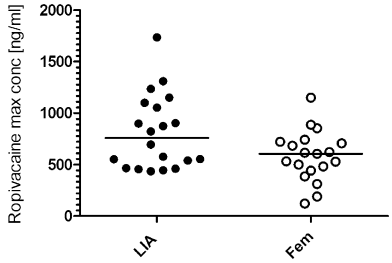

Fig. 2. Maximal detected concentration of ropivacaine during 24 h. Data expressed as maximal concentration for each patient. The line indicates the median. No statistical difference was detected between the LIA and femoral block group.

2.5. Statistical analysis

The sample size of this study was based on the power for detection of a significant difference in pain intensity published as a separate article [15]. A sample size of 20 in each group has an 80% power to detect a difference between means of 1.0 with a significance level (α) of 0.05 (two-tailed) using the unpaired Student's *t*-test.

The aim of the study was to determine if the plasma concentration of ropivacaine and ketorolac after LIA reaches toxic or near-toxic levels. Thus, mainly descriptive statistics with focus on maximal plasma concentration are presented. The maximal concentration of ropivacaine of each patient in the LIA group was compared to the maximal concentration of each patient in the femoral block group by unpaired *t*-test.

Graphpad Prizm 5.02 for Windows www.graphpad.com was used for statistical analysis and the graphs.

3. Results

The demographic characteristics were similar in both groups (Table 1). Plasma concentration of ropivacaine and ketorolac from one patient in the femoral group was excluded from the study since levobupivacaine was injected instead of ropivacaine due to a misunderstanding. Data on the ketorolac concentration of one patient in the LIA group is not available (Fig. 1).

Table 2
Maximal ropivacaine plasma concentration during 24 h [ng/ml].

	Range	Mean (95% CI)
LIA, $n = 20$	435–1735	813 (644–982)
Femoral block, $n = 19$	122–1151	567 (450–684)

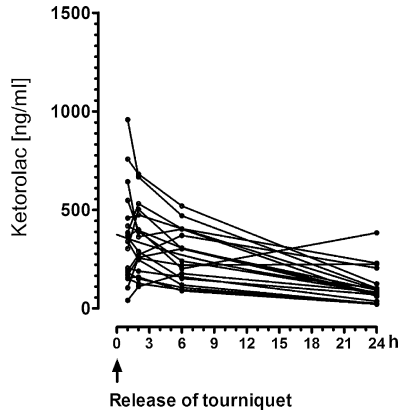

Fig. 4. Total plasma concentration of ketorolac in the LIA group. The LIA group received 30 mg ketorolac. In this group zero "0" refers to release of the tourniquet.

Similar maximal plasma concentrations of ropivacaine were detected in the LIA group and in the femoral block group during the first 24 h (Fig. 2, Table 2). Maximal plasma concentrations in the LIA group were detected at 4 or 6 h after injection (Fig. 3A). In the femoral block group, the highest levels were often detected at 24 h (Fig. 3B).

The maximal detected ropivacaine plasma level in the LIA group was not statistically higher than in the femoral block group using Mann–Whitney *U*-test ($p = 0.08$). However, the median concentration in the LIA group (95% CI: 376–611 ng/ml) was significantly higher than in the femoral block group (95% CI: 124–183 ng/ml) (<0.0001; Mann–Whitney *U*-test).

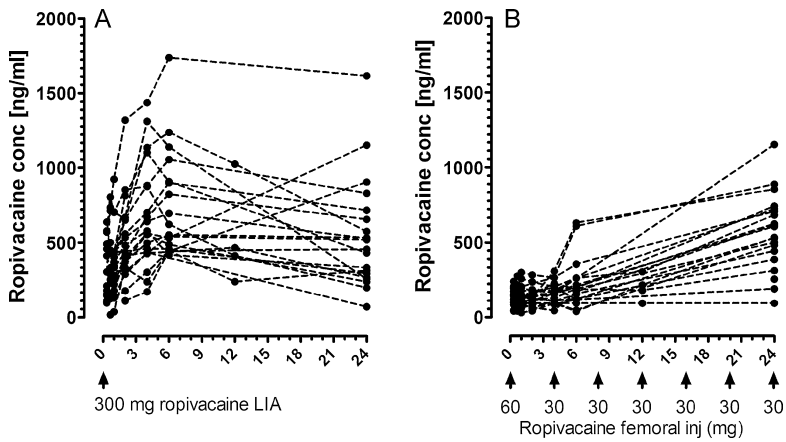

Figure 3. Total plasma concentration of ropivacaine during 24 h. (A) LIA group ($n = 20$). In this group zero "0" refers to release of the tourniquet. The LIA group received 300 mg ropivacaine. (B) Femoral block group ($n = 19$). In this group time zero "0" refers to completion of the first injection for femoral block (60 mg), the following doses (30 mg every 4 h) are indicated in the figure.

The range of the maximal plasma concentrations of ketorolac 1 h or 2 h after release of the tourniquet in the LIA group was 152–958 ng/ml (95% CI: 303–512 ng/ml; $n = 20$) (Fig. 4). The femoral block group received three doses of i.v. ketorolac 10 mg. Due to the fact that the i.v. injection of ketorolac at the PACU was performed at different time points depending on the arrival of the patient, we cannot present a proper concentration curve for ketorolac. The range of the plasma concentration of ketorolac 2–3 h after injection of a single dose of 10 mg was 57–1216 ng/ml (95% CI: 162–420 ng/ml; $n = 20$). At 24 h, 2–3 h after injection of the third dose of ketorolac 10 mg the range of the plasma concentration was 10–529 ng/ml (95% CI: 145–285 ng/ml).

4. Discussion

The maximal plasma concentration of ropivacaine using the LIA protocol seems to be higher than after femoral block.

Plasma levels of ropivacaine following peri-and intraarticular injection according to the LIA protocol may approach toxic levels during the first 4–6 h. However, since we did not analyze the plasma concentration between 6 and 12, and 12 and 24 h, we cannot exclude the possibility that some individuals displayed maximal levels later than 6 h after induction of LIA. This delayed peak was not expected and despite insufficient data on the exact time of maximal plasma concentration from the present study, it may be wise to consider cardiac monitoring for at least 6 h after surgery—a timepoint when most patients are transferred to ordinary wards without routine cardiac monitoring.

The plasma concentration of ropivacaine after repeated femoral block was higher than expected and in contrast to a common belief, the ropivacaine plasma level tended to accumulate during the first 24 postoperative hours using the present protocol. Since the plasma level of ropivacaine after femoral block had not started to decline at 24 h we cannot exclude the possibility of higher ropivacaine levels after 24 h.

The range of maximal plasma levels following LIA and following repeated femoral block displayed a considerable overlap. However, approximately one-third of the LIA group displayed ropivacaine levels higher than 1 μg/ml, as compared to only one individual following repeated femoral block.

Despite the finding of higher plasma concentrations of ropivacaine following LIA, we got no indication of adverse cardiac or CNS events. ECG monitoring two hours after ending the infiltration of local anaesthetic showed no arrhythmic effect of ropivacaine. Unfortunately we did not monitor the ECG around 4–6 h after LIA during the highest detected ropivacaine levels. Central nervous and cardiovascular ropivacaine toxicity has been detected in healthy volunteers at plasma concentrations of 1–2 μg/ml following intravenous infusion [7,8]. However, studies on peripheral and central blocks have reported higher plasma concentrations (2–4.2 μg/ml) without adverse reactions [16,17]. The ropivacaine concentrations observed in the present study were below the established toxic threshold for most of our patients although a few reached a plasma concentration of 1.4–1.7 μg/ml.

We are aware of a growing popularity of bolus doses or continuous infusions to top up preoperative wound infiltration of local anaesthetic after total knee arthroplasty [1,2,18,19]. Since the maximum concentration of ropivacaine was reached around four to six hours after giving the total dose, adding a bolus dose of local anaesthetic early in the postoperative period may result in potentially hazardous concentrations.

Periarticular administration of 30 mg ketorolac according to the LIA procedure seems to lead to a plasma concentration similar to that three hours following either a single intravenous injection of 10 mg or three hours after three injections of 10 mg separated by 8 h. Thus, our data may indicate that both routes result in similar exposure to ketorolac or at least similar maximal levels of ketorolac. However, since the data points are sparse our present study cannot determine whether higher plasma levels of ketorolac are reached with local infiltration anaesthesia or with repeated intravenous administration.

Our data indicate that the common clinical routine of adding oral or intravenous NSAIDs a few hours after terminating the surgical procedure if LIA was used may increase the risk of concentration-dependent side effects of ketorolac.

4.1. Study limitations

One obvious limitation of the present study is that the data collected on the plasma concentration of ropivacaine and ketorolac following administration with LIA did not cover the peak plasma concentration in most patients, and the data are insufficient to permit proper pharmacokinetic analysis. Thus our data are hypothesis generating rather than hypothesis testing. Unfortunately we did not analyze the free concentration of ropivacaine, nor plasma α_1-acid glycoprotein. The latter is increased after surgery and binds to ropivacaine and bupivacaine [19] and may prevent the rise of the free and pharmacologically active fraction of the local anaesthetic. These aspects are the focus of ongoing studies.

Plasma concentrations of ketorolac appeared to be similar regardless of route of administration.

However, the plasma samples were not optimized to cover peak concentration after repeated intravenous administration in the femoral block group.

Unselective cyclooxygenase inhibitors (NSAIDs) may decrease renal function and inhibit platelet function and cannot be used for all patients [20]. In the present study we did not detect increased bleeding or decreased renal function using routine clinical monitoring. Thus we cannot exclude a minor increase of postoperative bleeding. However, a previous study also in patients with TKA has assessed the risk for postoperative bleeding with ketorolac [21]. Four intravenous doses of ketorolac 30 mg every 6 h (total 120 mg/24 h) did not result in a marked increase of postoperative bleeding monitored as decreased hematocrite.

Possible renal side effects of ketorolac have been assessed in healthy, well hydrated patients anaesthetized with sevoflurane. Neither renal glomerular nor tubular dysfunction was detected [22]. However, elderly patients are at greater risk for renal side effects and in order to address this issue in depth, a randomised trial with a control group not treated with unselective COX-inhibitors would be needed.

The present experimental protocol using different dosing intervals and doses was not designed to determine whether ketorolac carries a higher risk for adverse effects after peripheral administration or after intravenous administration.

The LIA technique has been shown to result in a long lasting pain relief and reduced need for opioid analgesics [1,2,23]. The average pain intensity in the LIA group and the femoral block group was around 2 on a VAS scale in both groups, details are presented in a separate publication [15].

The direct analgesic effect in the surgical field and the addition of epinephrine, which prolongs the action of the local anaesthetic agent are obvious reasons. Our findings also raise the possibility of a prolonged action due to considerable systemic concentrations of the local anaesthetic 24 h after the administration of ropivacaine. During the past thirty years preclinical and clinical studies have reported analgesic effects of intravenously administered sodium channel blockers. It is still unclear whether intravenously administered sodium channel blockers can affect acute postoperative pain. Conflicting results after perioperative intravenous infusion of lidocaine have been presented [24–26]. Lidocaine is the most

commonly used local anaesthetic for intravenous infusion in clinical studies, due to its lower cardio toxicity compared with long-acting sodium channel blockers. It has a brief effect and most trials terminate the infusion shortly after the end of the operation, which prevents accumulation. Ropivacaine has a similar mechanism of action as lidocaine and it seems reasonable to assume that also ropivacaine may have systemic effects as well. We are not aware of the use of lidocaine in LIA after total knee or hip arthroplasty.

We did not investigate the effect of compression bandage [13] on the distribution of ropivacaine and ketorolac and it is hard to predict how compression of the lower limb would affect the systemic distribution of ropivacaine and ketorolac. A lower blood flow may slow down the time to reach concentration equilibrium between the leg and the systemic circulation. However, a lower volume of the leg may increase the systemic concentration slightly.

5. Conclusion

The risk for concentration dependent side effects of ropivacaine may be higher after local administration according to the LIA protocol than using repeated femoral block. Since the maximal ropivacaine level following LIA is detected around 4–6 h after release of the tourniquet, cardiac monitoring should during this period be considered. Regarding ketorolac, our preliminary data indicate that the risk for concentration dependent side effects may be highest during the first hours after release of the tourniquet. The common routine of administration of a booster dose of ketorolac shortly after termination of the surgical procedure, if LIA was used, may result in an increased risk for toxicity. Our data do not indicate that local administration of ketorolac is a safer alternative than repeated intravenous injection and similar restrictions should be applied for both routes.

Conflict of interest

None.

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III

Ropivacaine pharmacokinetics after local infiltration analgesia in hip arthroplasty

Fatin Affas M.D.
Department of Physiology and Pharmacology, section of anesthesia and intensive care, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden.
Staffan Eksborg Ph.D. (Professor)
Department of Women's and Children's Health; Childhood Cancer Research Unit, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden.
Per Wretenberg M.D., Ph.D., (Professor)
Section of Orthopaedics, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden.
Christina Olofsson M.D., Ph.D., (Associate Professor)
Department of Physiology and Pharmacology section of anesthesia and intensive care, Karolinska Institutet, Solna, Sweden.
Carl-Olav Stiller M.D., Ph.D., (Associate Professor)
Department of Medicine, Clinical Pharmacology Unit Karolinska Institutet and Karolinska University Hospital, Solna, Sweden.

Corresponding author: **Fatin Affas MD**
Dept of Physiology and Pharmacology / Karolinska Institutet
Anesthesia and intensive care unit F:2
Karolinska University Hospital, Solna,
SE-17176 Stockholm
Sweden

Tel+ 46-8-51772066 Fax+ 46-8-307795 e-mail: fatin.affas@ki.se

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Abbreviated title: Ropivacaine Plasma Concentration after LIA
Conflict of interest: None

Abstract

This study determined the plasma concentration of ropivacaine by liquid chromatography-mass spectrometry (LC-MS) during 30 h following Local Infiltration Analgesia (LIA) in 15 patients with elective hip arthroplasty. The 95 % upper prediction bound of maximal unbound plasma concentration or ropivacaine was 0.032 mg/L. Alpha 1 acid glycoprotein did not correlate to the fraction of unbound ropivacaine during the first 24 h after LIA. No signs or symptoms of systemic local anesthetic toxicity were observed. The Clopper Pearson 95 % upper confidence limit for adverse signs was 0.218.

Introduction

Local infiltration analgesia (LIA) with ropivacaine, ketorolac and epinephrine is a technically simple method for postoperative pain management after knee and hip replacement (1), which has gained popularity in many countries (7). LIA not only improves postoperative pain, but reduces the need for opioid analgesic drugs, and leads to faster rehabilitation and earlier discharge from hospital (2-6). Information regarding the pharmacokinetics and safety margin of ropivacaine and area under the curve (AUC) after LIA is still sparse. Ropivacaine binds mainly to alpha$_1$-acid glycoprotein (AAG) (8), a plasma protein, which increases upon trauma (8-14).

Local anesthetic toxicity has been reported with doses considered to be safe and without proven intravascular placement (15). Large surgical incisions and soft-tissue dissection, typical of major orthopedic surgery may lead to peak plasma levels of local anesthetics (16) with increased risk for central nervous system and cardiovascular toxicity (17).

The aim of this study was to determine the maximal plasma concentration of unbound ropivacaine during 30 hours following elective primary total hip arthroplasty using LIA for postoperative analgesia. In addition, we assessed whether the level of AAG during the first postoperative day after LIA correlates to the fraction of unbound ropivacaine.

Materials and Methods

This study, conducted between 2010 and 2011, was approved by the IRB and the medical product agency of Sweden. We included adult patients, ASA I-III, without allergy to any one of the study drugs, creatinine plasma concentration < 100 mmol/L, QT-interval < 450 msec. Access to research staff limited inclusion of patients. No eligible patient refused participation. All patients had spinal anesthesia at L2-L3 or L3-L4 with isobaric bupivacaine (Marcain Spinal®, AstraZeneca). LIA consisted of peri- and intra-articular infiltration with a mixture of 100 ml ropivacaine (2 mg/ml; Narop®, AstraZeneca), 1 ml ketorolac (30 mg/ml; Toradol®, Roche), and 5 ml epinephrine (0,1mg/ml; Adrenalin®, NM Pharma): 20 ml were injected subcutaneously at the start of the operation and the remaining 86 ml in the capsula, the resutured short outward rotators and the gluteus maximus.

Quantification of total and unbound ropivacaine

Sampling started 10 minutes after completing LIA at 10, 20, 30, 45 minutes and 1h, 2h, 3h, 4h, 6h, 8h, 12 h, 24h and 30h respectively. LC-MS (Agilent 1100 MSD; Agilent Technologies, CA) was used. Limits of quantification: 0.0053 mg/L- 2.66 mg/L. Internal standard: Doxepine (Sigma-Aldrich, St.Louis, MD). The unbound ropivacaine concentration was determined following centrifugation at 5500 g for 10 min at 37 ºC using an Amicon ULTRA centrifugal filter.

Quantification of AAG

Plasma AAG, collected prior to moving the patient to the operating room and 1h, 4h, 12h and 24 h post-surgery, was analyzed with nephelometry (Immage by Beckman Coulter).

Objective

The primary aim of this pilot study was to document the maximal plasma concentration and the area under the curve (AUC) of unbound ropivacaine during 30 hours after LIA. ECG-changes and neurological symptoms of local anesthetic toxicity were monitored according to clinical routine.

Statistics

This pilot study without prior power calculation used a sample size of 15, based on previous experience (18). Prizm 6.0 software (Graphpad Software, San Diego, California) was used to calculate AUC. The upper prediction bound for maximal unbound ropivacaine was 2.22 SD based on normal distribution. Since zero adverse events were observed, we calculated the Clopper Pearson exact value (McCracken CE and Looney SW, "A comparison of methods for finding the upper confidence limit for a binomial proportion when zero successes are observed," JSM 2011.). Statistica 12, Statsoft OK, was used to calculate linear correlation and estimate the statistical power. $P < 0.05$ and a power of at least 80 % were required to draw any conclusion on correlation.

Results

No patient dropped out. Demographic data and individual results are presented in table 1, pharmacokinetic profile for ropivacaine in Fig. 1, AAG profile over time in Fig 2 and percentage unbound ropivacaine versus AAG in Fig 3 respectively. The 95 % upper prediction bound for unbound ropivacaine was 0.032 mg/L. The statistical power of the linear correlation of C_{max} versus age or creatinine clearance was 53% and 50% respectively.

Neither tachycardia, nor arrhythmias on ECG, nor neurological signs of local anesthetic toxicity (circumoral paresthesia, tinnitus, muscle twitch or seizure) were detected. The Clopper-Pearson 95 % upper confidence limit for adverse signs was 0.218.

Two hours after surgery no prolongation of QT-interval >450 msec was observed in any patient.

Discussion

The 95 % upper prediction bound for maximal unbound plasma concentration after injection of 200 mg ropivacaine in LIA was 0.032 mg/L. This level is comparable to levels observed after LIA without epinephrine (19), and half as high as after 400 mg (20). Plasma concentrations within the same range (21-26), or considerably higher (27,28), without adverse reactions have been reported during epidural infusion or peripheral nerve block with ropivacaine. Side-effects sufficient to stop an intravenous infusion were reported at arterial concentrations of 0.34-0.85 mg/L (33). This range has been considered to represent a relevant safety limit in studies reporting the venous plasma concentration of unbound ropivacaine (25, 28). Using a two-sided test based on our data at least 29 individuals are needed to get a power of 80 % to test the hypotheses that the maximal unbound ropivacaine concentration correlates with age and creatinine clearance.

Ropivacaine binds mainly to AAG (12,14) , but previous studies on ropivacaine after LIA (16,20,30) do not report the plasma level of AAG. We detected AAG levels similar to those in young healthy adults (31). After 24 hours AAG had increased by less than 40 percent. However, we did not find any correlation between the plasma concentration of AAG and the percentage of unbound plasma concentration of ropivacaine during the first 24 h after LIA infiltration. AAG levels may double around 4 days postoperatively and seem to reach a maximal concentration at the sixth to twelfth postoperative day (11, 13). An increase of AAG, sufficient to decrease the unbound concentration of ropivacaine has been observed later than 24 hours after surgical trauma (8,21,27,32). An obvious limitation of this hypothesis-generating pilot study was the small size. Not only the unbound plasma concentration, but also physiological, anatomical and pharmacokinetic factors contribute to toxicity of LA (29).

Inclusion of more elderly patients with decreased renal function is needed to determine cutoff levels for decreased doses of ropivacaine in LIA required for safety concerns.

Conclusions

Since the unbound ropivacaine concentration after 200 mg of ropivacaine administered during LIA is below plasma concentrations linked to adverse cardiac or neurological reactions we continue with the same dose of ropivacaine in patients similar to those included in this study. AAG levels are of minor importance for unbound ropivacaine plasma concentration during the first 24 h after THA with LIA. Larger studies are needed to test the hypothesis that the unbound ropivacaine concentration correlates with age and creatinine clearance.

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Table 1. Patient demographics and results

15 M	II	65	95	24	159	0.012	0.448	-	4
Patient number sex	**ASA**	**Age years**	**Weight kg**	**BMI kg x m^2**	**CC mL/min**	**Cmax Unbound mg/L**	**Cmax Total mg/L**	**AUC unbound (0-30h) h x mg /L**	**Tmax Unbound hours**
1 M	I	65	89	29	82	0.016	0.578	-	4
2 F	I	58	63	24	106	0.013	0.769	0.180	2
3 M	II	54	90	28	134	0.022	0.672	0.317	4
4 M	II	85	75	27	58	0.018	0.995	0.229	4
5 F	I	32	62	24	143	0.015	0.443	0.268	8
6 F	I	35	74	26	150	0.005	0.505	0.075	1
7 F	III	75	100	32	75	0.018	0.872	0.328	12
8 M	III	61	105	36	140	0.023	0.877	0.316	6
9 M	III	79	90	28	62	0.018	1.356	0.290	4
10 M	II	72	83	25	108	0.021	0.754	0.327	4
11 F	III	76	106	40	69	0.026	0.686	0.272	8
12 F	III	71	107	35	98	0.018	0.576	0.313	6
13 F	III	58	106	38	101	0.016	0.548	0.320	6
14 M	III	70	71	24	66	0.031	1.333	0.335	6
15 M	II	65	95	24	159	0.012	0.448	-	4

CC: Creatinine clearance was calculated according to Cockroft Gould
AUC: Area under the curve, M: male, F: female

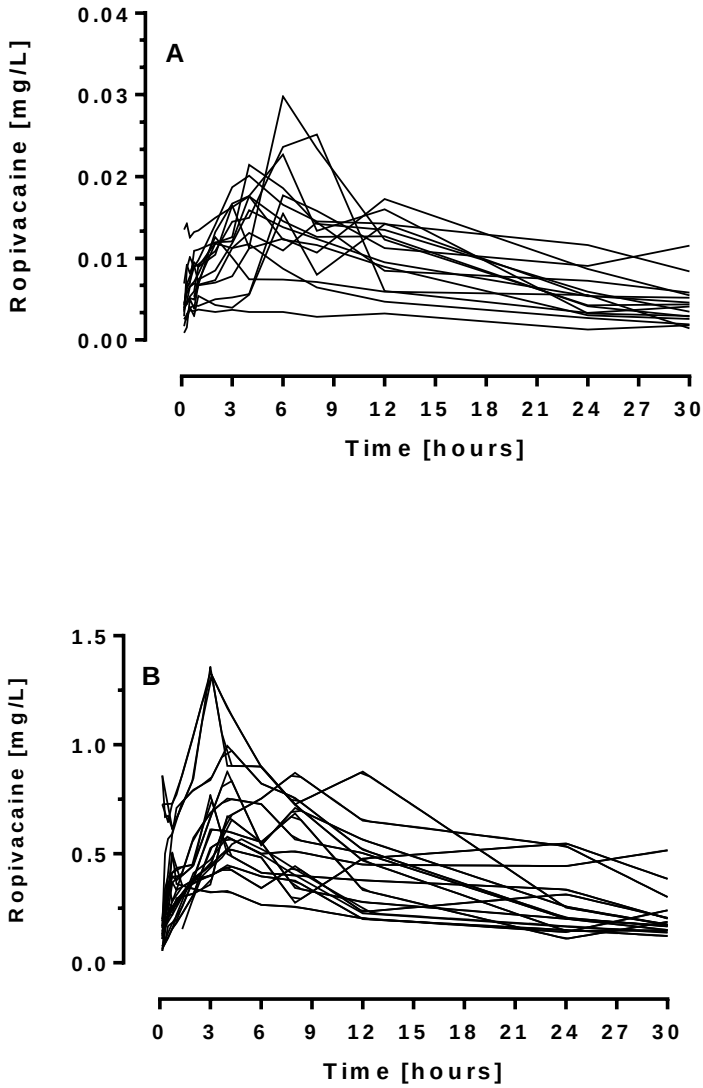

Figure 1. Individual data of unbound [A] and total (bound and unbound) [B] plasma concentrations versus time during 30 hours after LIA. The lower limit of the maximal tolerated arterial concentration of ropivacaine at the end of an infusion of 10 mg/min in healthy volunteers is 0.34 mg/L (33).

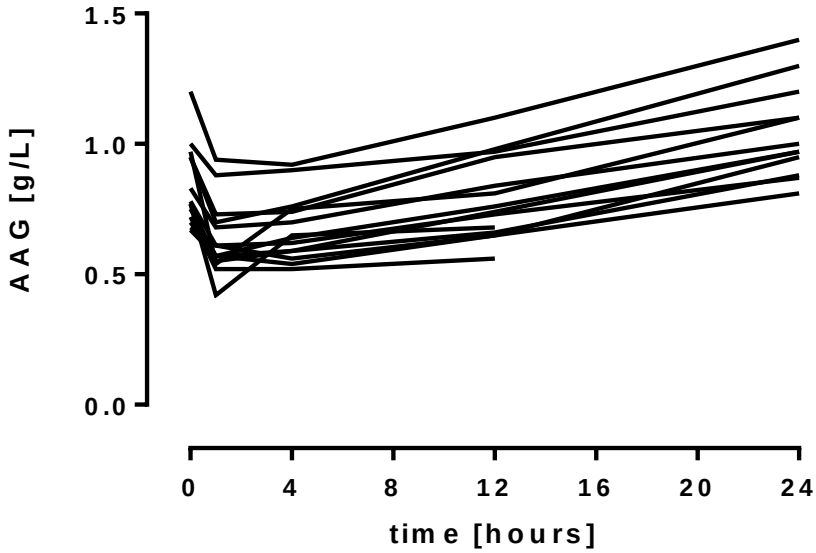

Figure 2. Individual plasma concentrations of α-1 acid glycoprotein versus time profile (24 h) in 14 patients. Time zero "0" indicates a baseline sample prior to surgery.

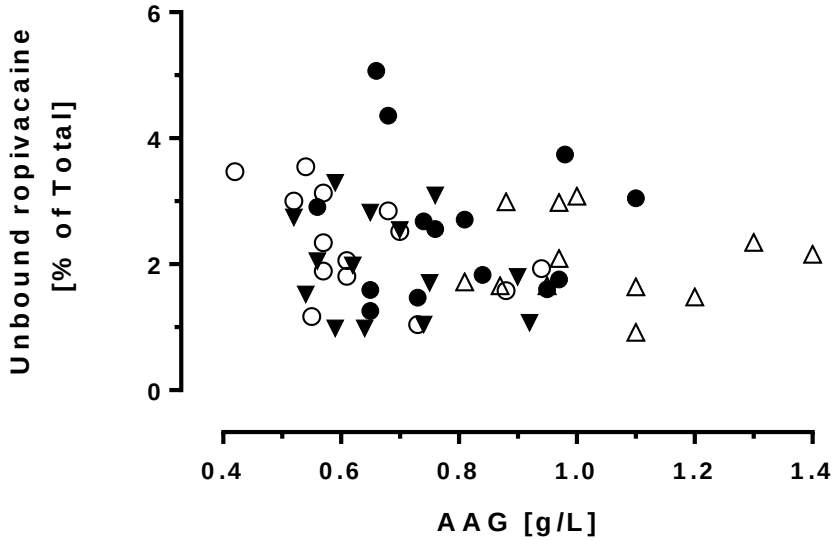

Figure 3.Unbound fraction of ropivacaine at different concentrations of AAG (α-1 acid glycoprotein) at 1 h after surgery (open circle), at 4 h after surgery (filled circle), at 12 h (open triangle) and 24 h (filled triangle) in 14 patients.

IV

Plasma concentration of ketorolac after Local infiltration analgesia in hip arthroplasty

Fatin Affas M.D.
Department of Physiology and Pharmacology, section of anesthesia and intensive care, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden.
Staffan Eksborg Pharm.D. (Professor)
Department of Women's and Children's Health; Childhood Cancer Research Unit, Department of Molecular Medicine, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden.
Per Wretenberg M.D., Ph.D., (Professor)
Section of Orthopaedics, Karolinska Institutet and Karolinska University Hospital, Solna, Sweden.
Christina Olofsson M.D., Ph.D., (Associate Professor)
Department of Physiology and Pharmacology section of anesthesia and intensive care, Karolinska Institutet, Solna, Sweden.
Niclas Stephanson Ph.D.
Department of Medicine, Clinical Pharmacology Unit Karolinska Institutet and Karolinska University Hospital, Solna, Sweden.
Carl-Olav Stiller M.D., Ph.D., (Associate Professor)
Department of Medicine, Clinical Pharmacology Unit Karolinska Institutet and Karolinska University Hospital, Solna, Sweden.

Corresponding author: **Fatin Affas MD**
Dept of Physiology and Pharmacology / Karolinska Institutet
Anesthesia and intensive care unit F:2
Karolinska University Hospital, Solna,
SE-17176 Stockholm
Sweden

Tel+ 46-8-51772066 Fax+ 46-8-307795 e-mail: fatin.affas@ki.se

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Abbreviated title: Ketorolac plasma concentration after LIA

Abstract

Background: Local Infiltration Analgesia (LIA) with local anaesthetic (ropivacaine), a non-steroidal anti-inflammatory drug (Ketorolac), and epinephrine after lower extremity arthroplasty has gained increasing popularity during the last decade. This method has certain advantages, which include minimal systemic side effects, faster postoperative mobilization, earlier postoperative discharge from hospital and less opioid consumption. However, information regarding plasma concentrations of ketorolac after LIA mixture is insufficient to predict the risk of renal impairment in patients subjected to arthroplasty.

Aim: To determine the maximal plasma concentration and the exposure of ketorolac during the first 30 h following LIA in hip arthroplasty.

Methods: Thirteen patients scheduled for primary total hip arthroplasty with LIA (ropivacaine 200 mg, ketorolac 30 mg and epinephrine 0.5 mg in a volume of 106 ml) were included. Plasma concentration of ketorolac was quantified by liquid chromatography- mass spectrometry (LC-MS). In addition we assessed the effect of increasing age and decreasing glomerular filtration rate on the maximal plasma concentration and the total exposure to ketorolac during 30 h.

Results: The range of the maximal plasma concentration 0.3 – 2.2 mg/L, was detected 30 minutes – 4 hours after completing the infiltration. Similar plasma levels have been reported after intramuscular injection of the same dose of ketorolac to healthy elderly volunteers**.**

Conclusion: Exposure to ketorolac after LIA may be comparable to an intramuscular injection of the same dose. Decision of dose reduction should be based on clinical assessment of risk factors.

Introduction

Ketorolac tromethamine is a non-specific cyclooxygenase inhibitor (nonsteroidal anti-inflammatory drug; NSAID) of the pyrrolizine carboxylic acid class, with analgesic, anti-inflammatory, and antipyretic properties[1-3]. Ketorolac decreases acute musculoskeletal and post-surgical pain [4] and reduces postoperative opioid consumption[5-7].

Ketorolac in combination with ropivacaine and epinephrine is used for Local infiltration analgesia (LIA) in total knee and hip arthroplasty. This method for postoperative pain management has gained popularity in recent years, due to reduced need for opioid analgesic drugs, faster rehabilitation and earlier discharge from hospital[8-12]. However, the important role of NSAID in LIA has been disputed[13].

Ketorolac as other NSAIDs /cyclooxygenase inhibitors carry a well-known risk for acute and chronic renal impairment[14-16]. Increasing age and decreasing glomerular filtration rate as well as treatment with diuretics, angiotensin converting enzyme inhibitors or angiotensin II-receptor blocking agents have been identified as risk factors for renal impairment[17].

The objective of this clinical trial was to determine the maximal plasma concentration and the total exposure to ketorolac after local injection of 30 mg ketorolac according to the LIA protocol in total hip arthroplasty. In addition we determined if increasing age and decreasing GFR may lead to increased plasma levels of ketorolac.

Method

The present single-center, open trial was conducted at the Karolinska University Hospital in Solna, Sweden in accordance with the Helsinki Declaration II. It was approved by the Regional Research Ethics Committee at the Karolinska Institutet in Stockholm (2008/1370-31) and by the Swedish Medical Products Agency (EudraCT nr 2008-005471-10 protocol number 4745). Oral and written informed consent was obtained. The enrolment period was from June 2010 to June 2011. Limited access to research staff affected the speed of inclusion.

Inclusion criteria: Adult patients (older than 18 years), American Society of Anaesthesiologists (ASA) classification I-III, with osteoarthritis or rheumatoid arthritis scheduled for primary, unilateral, elective total hip arthroplasty.

Exclusion criteria: Allergy or intolerance to one of the study drugs, renal insufficiency (creatinine clearance < 50 ml/min), epilepsy, unable to understand the Swedish patient information and informed consent document, mental illness, dementia, QT-interval on electrocardiograph (ECG) > 450 msec before start.

Interventions

All patients had spinal anesthesia at L2-L3 or L3-L4 according to clinical routine with isobaric bupivacaine (Marcain Spinal®, AstraZeneca) 5mg/ml at a volume of 3 ml injected with the patient lying with the operating side upwards. Sedation was induced with midazolam (Midazolam®, Alpharma) 1-2 mg i.v. or propofol (Propofol®, Abbot). Antithrombotic prophylaxis with low-molecular-weight heparin, dalteparin natrium (Fragmin®,Pfizer) 5000IU was started 12 hours before spinal anesthesia and was given for at least 5 days. All patients received 2 g dicloxacillin i.v before surgery. Before induction of spinal anesthesia, monitoring of oxygen saturation, blood pressure and electrocardiogram (ECG) was started

according to clinical routine. In addition, ECG (12-lead) was recorded in all patients preoperatively, and 2 h post-surgery in the recovery room.

Local infiltration analgesia (LIA)

All patients received peri-articular infiltration with a mixture of 100 ml ropivacaine (2 mg/ml; Narop®, AstraZeneca), 1 ml ketorolac (30 mg/ml; Toradol®, Roche), and 5 ml epinephrine (0,1mg/ml; Adrenalin®, NM Pharma). The total volume was 106 ml. This solution was prepared before the surgical procedure started. The solution was given sequentially: 20 ml subcutaneously at the start of the operation and the remaining 86 ml in the capsula, the resutured short outward rotators and the gluteus maximus.

Blood sampling

Blood samples for ketorolac plasma concentration (5ml) were collected from a vein in the arm not used for i.v. infusions. Blood sampling was started 10 minutes after completing LIA at 10, 20, 30, 45 minutes and 1h, 2h, 3h, 4h, 6h, 8h, 12 h, 24h and 30h respectively. The blood samples were centrifuged directly, plasma-separated, immediately frozen and stored at -20^{o} C until assayed. Blood samples for serum albumin and creatinine were collected preoperatively.

Quantification

Ketorolac was quantified by LC-MS/MS (Waters Acquity Ultra-performance liquid chromatograph with a vacuum degasser, binary pump, and sample manager connected to a Quattro Premier XE tandem mass spectrometer with MassLynx™/Target Lynx™ Software version 4.1 (Waters Co, Milford, MA, USA). The reference material ketorolac trometamol was obtained from USP, Rockville, MD, USA and the internal standard ketobemidon-d4 was

a gift from Prof. Ulf Bondesson (Swedish University of Agricultural Sciences, Uppsala, Sweden). The limit of quantification was 0.01 mg/L for each compound and the calibrated range was up to 10 mg/L. Methodological details can be provided upon request.

Aim

The primary aim of this study was to determine the maximal plasma concentration as well as the area under the curve (AUC) of ketorolac during 30 h after LIA.

The secondary aim was to analyze if the patient age, creatinine clearance, weight, or body mass index (BMI) correlated to the maximal concentration or AUC of ketorolac.

Pharmacokinetic and Statistical Analysis

For this pilot study without power calculation a sample size of 13 was regarded as sufficient based on previous experience[18]. Descriptive statistics was used. Statistical analysis including correlation (Pearson) and the AUC were performed with Prizm 6.0 software (Graphpad Software, San Diego, California). Significance was defined as $p < 0.05$.

Results

A total of 13 patients were enrolled in the study. These patients were operated by the same surgeon (P.W.) duration time of surgery was 1.12-1.25 h. The range of serum albumin was 33-44 g/L. Patient demographics are presented in Table 1.

The median of the peak (maximal detected concentration) ketorolac plasma concentrations was 0.82 mg/L (range: 0.31-2.16 mg/L). The 95 % confidence interval was: 0.51-1.13 mg/L. One patient (No 2) displayed a peak concentration and AUC almost twice as high compared to the other patients. Individual data on the maximal detected ketorolac concentration and the total exposure to ketorolac expressed as AUC are shown in Table 1. The 95 % confidence interval for age, creatinine clearance, weight and BMI were 58-74 years, 77-115 ml/min, 80-98 kg and 27-34 kg/m^2 respectively.

The pharmacokinetic profiles for ketorolac concentrations during the 30 post-operative hours are shown in Fig. 1. Neither age, nor creatinine clearance, nor patient weight nor BMI displayed a significant correlation to the peak ketorolac concentration (Fig 2.) or to the AUC (Fig 3).

Discussion

To the best of our knowledge this is the first study to investigate ketorolac plasma concentration and pharmacokinetics after LIA in hip arthroplasty. The range of the maximal detected plasma concentration of ketorolac after LIA was 0.31-2.16 mg/L. We had one outlier with a maximal concentration twice as high as the other patients (pat # 2). Our range seems to overlap with the range reported after intramuscular injection of the same dose (30 mg) to healthy elderly volunteers (1.45-3.82 mg/L)[18]. Time to peak concentration was 30 min to 4 hours in our patients, who received epinephrine in LIA as compared to 30 min to 2 hours after intramuscular injection[18]. We could not find any correlation between peak concentration or C_{max} and the patient age within our cohort. These results are in line with the results after an intramuscular injection of 30 mg ketorolac in young adults (mean age 30 years) and healthy elderly (mean age 72 years)[18].

Decreasing creatinine clearance did not increase the peak concentration of ketorolac within the range present in our cohort 58-150 ml/min. Renal function is more important for total exposure or AUC than the peak concentration after a single dose. However, we could not find any correlation between creatinine clearance and AUC either. In contrast, a tendency towards higher AUC after intramuscular injection of 30 mg ketorolac to elderly as compared to younger adults has been reported[18] . We cannot exclude the possibility that individuals with creatinine clearance lower than 50 ml/min may have higher AUC. But due to safety concern of ketorolac in patients with reduced renal function a clinical trial on this issue may be ethically questionable.

In patient #2, the peak plasma concentration was at least 70 percent higher and the AUC was at least 100 percent higher than all other patients in this study. A possible explanation for this outlier could be an undetected partial intravascular injection during infiltration or infiltration in proximity to a larger blood vessel in combination with relatively low body weight and female sex.

Neither weight nor BMI had any significant effect on the peak plasma concentration or total exposure of ketorolac. Our cohort was rather homogenous, but we could not even detect any trend. The volume of distribution of ketorolac is 0.1- 0.3 L/kg[19]. Thus, the amount of total body water seems to be more important for the pharmacokinetic profile than body weight.

In summary our study may suggest that the peak concentration of ketorolac and the total exposure to ketorolac after LIA shows small inter individual variation within a small patient cohort for elective orthopedic surgery. However, these data cannot be used to assess the potential risk for adverse events with ketorolac, since other factors than peak plasma level or AUC may be more important to predict the risk for renal side effects. A concentration that may be safe in one individual may cause renal impairment in another individual. Renal prostaglandins do not appear to play a significant role in the maintenance and regulation of renal blood flow under normal conditions in healthy individuals. However, in patient with decreased renal function and in the presence of risk factors the response of the kidney to NSAIDs will be different, since the production of local renal prostaglandins [20] is crucial for the maintenance of renal function in the face of hemodynamic compromise.

Risk factors that make patients more susceptible to the renal side effects of NSAIDs drugs include advanced age, preexisting mild renal dysfunction, volume depletion, congestive heart

failure, cirrhosis and gastrointestinal bleeding [21]. Combination of NSAIDs and drugs used for treatment of hypertension and heart failure (diuretics and angiotensin converting enzyme inhibitors ACE-inhibitors) may impair renal function further[17].

Acute and chronic impairment of renal function have been reported as complications of treatment with NSAIDs. Although toxicity has been associated with repeated use for several days, renal failure can occur after a single dose[20-22]. During the last two years our department had two cases of renal failure in patients treated with ketorolac in the LIA mixture after hip and knee arthroplasty. Both patients were older than 70 years and were on treatment with ACE-inhibitors. One patient required dialysis treatment[23] .

The focus of this study was quantification of the plasma concentration of ketorolac after LIA. Limitations of this study were the lack sufficient previous data that could be used to calculate an adequate power. A control group treated with the same dose of ketorolac as used in LIA, but via the intramuscular route would be the ultimate test to determine if the exposure to ketorolac is lower or higher using the LIA protocol.

Thus, this study is hypothesis generating rather than hypothesis testing. Our data did not indicate a correlation between age, creatinine clearance and body weight or BMI and the maximal ketorolac plasma concentration or total exposure to ketorolac (AUC). Our patient cohort could have been too small to detect a correlation. In addition, a patient cohort with a wider confidence interval of age, creatinine clearance, weight and BMI should be studied to address the issue of correlation.

No clinical signs of decreased renal function were observed during the course of this study. However, minor effects might have escaped detection in clinical routine. In order to test the hypothesis if ketorolac in LIA decreases renal function, a more specific marker of glomerular

filtration, such as cystatin C prior to LIA and after LIA should be monitored. Another limitation of this study was the determination of total and not unbound concentration of ketorolac. However, ketorolac is highly protein bound (more than 99 %) and our patients had normal plasma albumin.

Conclusions

Within our patient cohort of relatively healthy elderly patients with normal renal function increasing age and decreasing renal function did not seem to increase exposure to ketorolac. Decision of dose reduction should be based on clinical assessment of risk factors.

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Table 1.

Patient number	Sex	Age [years]	Creatinine clearance mL/ min	Weight [kg]	BMI kg/m^2	AUC 0-30 h [mg x h /L]	Cmax [mg/L]	Tmax [hours]
1	Male	65	82	89	29.4	NA	1.039	4
2	Female	58	106	63	23.7	22.847	2.167	2
3	Male	54	134	90	27.8	8.856	1.259	1
4	Male	85	58	75	26.9	11.212	1.146	2
5	Female	35	150	74	26.2	4.704	0.358	0.75
6	Female	75	75	100	32.3	6.740	0.474	3
7	Male	61	140	105	35.5	5.801	0.571	3
8	Male	79	62	90	28.4	5.878	0.547	1
9	Male	72	108	83	24.5	8.747	0.608	2
10	Female	76	69	106	40.4	7.156	0.675	0.5
11	Female	71	98	107	34.9	6.058	0.313	4
12	Female	58	101	106	38.0	10.258	1.016	0.75
13	Male	70	66	71	23.5	6.600	0.470	4

Figure 1

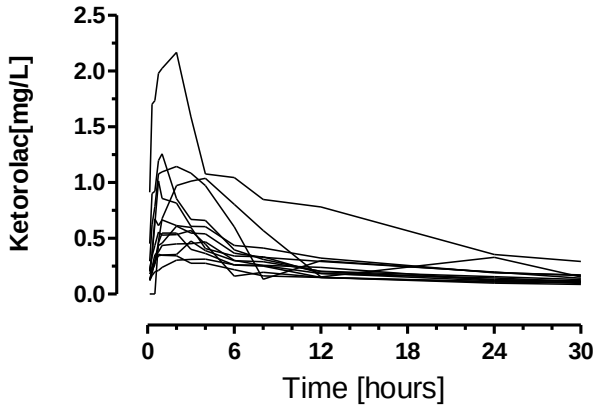

Figure 1. Individual data of total plasma concentration of ketorolac versus time during 30 hours after LIA (n=13).

Figure 2

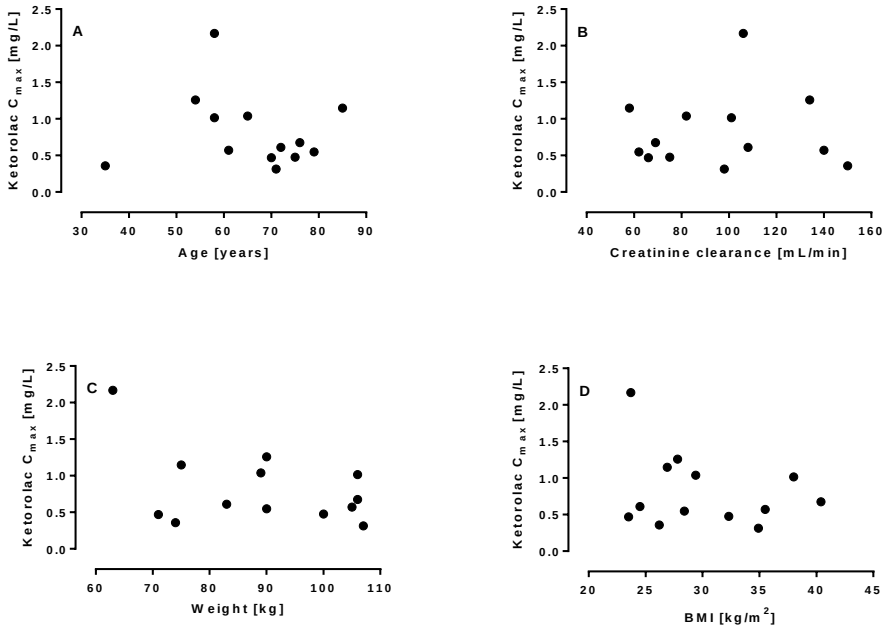

Figure 2. Maximum detected concentration (C_{max}) of total ketorolac in relation to age (A), creatinine clearance (B), body weight (C) and BMI (D) (n=13).

Figure 3

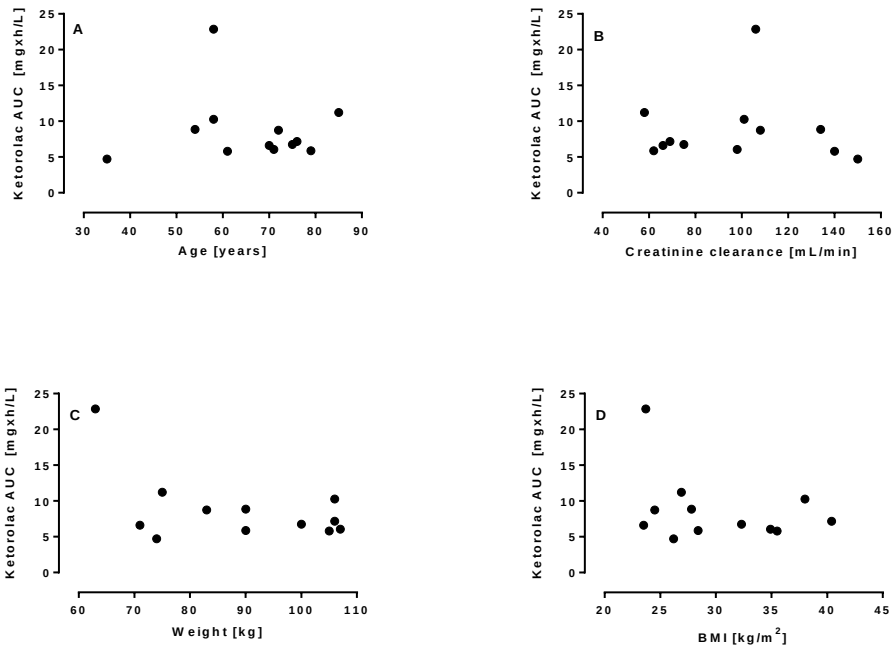

Figure 3. Total exposure of ketorolac expressed as area under the curve AUC (0-30h) in correlation to patient age (A), creatinine clearance (B), body weight (C) and BMI (D) (n=12).