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EFFECTS OF ANAESTHESIA METHOD, TOURNIQUET USE AND ADIPOSITY STATUS ON OUTCOMES AFTER TOTAL KNEE ARTHROPLASTY

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ACADEMIC DISSERTATION

To be presented for public examination with the permission
of the Faculty of Medicine of the University of Helsinki in lecture hall 116 at
Unioninkatu 35, Helsinki, on 12 May 2023 at 12 o'clock.

Helsinki 2023

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ISBN 978-951-51-8987-5 (paperback)
ISBN 978-951-51-8988-2 (PDF)

Unigrafia Oy
Helsinki 2023

To my family

ABSTRACT

Background and aims

Total knee arthroplasty (TKA) is a very common and effective treatment for severe knee osteoarthritis. This operation is usually performed under spinal or general anaesthesia and with or without a surgical tourniquet. Owing to limited and partially conflicting data, this study aimed to investigate whether TKA performed under spinal or general anaesthesia and with or without a tourniquet is associated with different postoperative outcomes. Our study group also investigated the predictive performance of adiposity status on TKA-related outcomes and the applicability of a predictive risk index for persistent postsurgical pain (PPP) to TKA patients.

Methods

We conducted a longitudinal, parallel, single-centre, randomized controlled trial in which 404 patients referred for TKA were randomized into spinal versus general anaesthesia and no-tourniquet versus tourniquet groups. We included patients between 18 and 75 years old with Kellgren–Lawrence grade 3 to 4 knee arthritis unresponsive to conservative treatment, body mass index (BMI) ≤ 40 kg/m^2 and American Society of Anesthesiologists physical status classification < 4. The patients underwent unilateral primary TKA between October 2016 and December 2018 and were followed for up to 12 months after surgery.

In Study I, we investigated whether postoperative in-hospital outcomes differed between the spinal and general anaesthesia groups and between the no-tourniquet and tourniquet groups. Additionally, we compared combined study groups (spinal anaesthesia and no tourniquet versus spinal anaesthesia and tourniquet versus general anaesthesia and no tourniquet versus general anaesthesia and tourniquet). The primary outcome was the use of intravenous oxycodone with patient-controlled analgesia (PCA) device during the first 24 postoperative hours. Secondary outcomes included other pain management, pain, nausea, vomiting, use of antiemetics, adverse events, change in haemoglobin levels and length of hospital stay.

Studies II to IV were prespecified secondary analyses of the randomized trial. In Study II, we investigated possible differences between the spinal and general anaesthesia groups and between the no-tourniquet and tourniquet groups in the change in pain 3 and 12 months after TKA. Additionally, we conducted post hoc analyses concerning the prevalence of PPP 3 and 12 months after TKA and the number of patients who had received prescriptions for gabapentinoids or strong opioids during follow-up.

In Study III, we investigated the predictive performance of body fat percentage (BFP) on TKA-related outcomes. In-hospital outcomes included multiple variables such as operation time, pain management and adverse events. The follow-up outcomes included the measured knee range of motion (ROM) and patient-reported pain, knee function, health-related quality of life and satisfaction with TKA 3 and 12 months after surgery. Additional follow-up outcomes included thromboembolic events, surgical site infections, readmissions during the first 90 postoperative days and the incidence of manipulation under anaesthesia, revision surgery and mortality during the first postoperative year. Furthermore, we conducted a post hoc analysis in which we investigated the predictive performance of BMI on the respective outcomes.

In Study IV, we investigated whether a previously presented predictive risk index for PPP was applicable to patients who undergo TKA. We grouped patients into low- to moderate-risk and high-risk groups for PPP and investigated possible differences in pain scores between these groups at 3 and 12 months after TKA.

Results

In Studies I and II, 395 patients were included in the analyses. The cumulative doses of PCA-administered oxycodone during the first 24 postoperative hours were not significantly different between the spinal and general anaesthesia groups, the no-tourniquet and tourniquet groups, or the four combined anaesthesia and tourniquet groups. Similarly, the use of oral oxycodone, pregabalin and peripheral nerve blocks during hospital stay did not differ between the study groups. The spinal anaesthesia group reported more postoperative nausea and vomiting than the general anaesthesia group. The no-tourniquet group had greater decrease in haemoglobin levels than the tourniquet group; however, the incidence rates for blood transfusions did not differ between the groups. Differences in the incidence of adverse events and length of hospital stay were not significant in any comparison.

In Study II, the spinal anaesthesia group reported better improvements than the general anaesthesia group in three of six investigated pain variables at 12 months after TKA. The tourniquet group reported better improvements than the no-tourniquet group in all five pain severity variables at 12 months. However, differences in the improvements were not considered clinically important in either the anaesthesia or tourniquet comparisons. The proportions of patients who received prescriptions for strong opioids or gabapentinoids during follow-up also did not differ.

In Study III, the BFP cohort consisted of 294 patients. Of all the investigated variables, preoperative BFP was significantly associated only with knee ROM at 12 months after TKA. A 1-unit increase in BFP reduced ROM by 0.4 degrees (95% confidence interval [CI] −0.60 to −0.13). In post hoc analyses of 399 patients, a 1-unit increase in preoperative BMI increased surgery time by 0.6 minutes (95% CI

0.10 to 1.04) and reduced ROM by 0.5 degrees (95% CI −0.74 to −0.20) at 12 months after surgery. BFP and BMI were not significantly associated with other outcomes at 12 months after TKA.

In Study IV, 392 patients were included in the analyses. The low- to moderate-risk group reported less pain 3 and 12 months after TKA than the high-risk group. However, the threshold for minimal clinical importance between groups was reached in merely one of seven investigated pain variables at 12 months. Furthermore, the differences between the groups existed before the operation, and some pain scores improved slightly more in the high-risk than in the low- to moderate-risk group during the 12-month follow-up.

Conclusions

Whether TKA is performed under spinal or general anaesthesia and with or without a tourniquet appears to have no clinical impact on pain management, acute pain, in-hospital adverse events, length of hospital stay or PPP. Spinal anaesthesia may be associated with a higher risk for postoperative nausea and vomiting than general anaesthesia in TKA. For patients who are not morbidly obese, BFP and BMI appear to be poor predictors of TKA-related in-hospital results and patient-reported 12-month outcomes. The previously presented risk index does not appear to be applicable in predicting PPP at 12 months after TKA.

Keywords

acute postoperative pain, anaesthesia, analgesia, bioelectrical impedance analysis, Brief Pain Inventory–Short Form, body fat percentage, body mass index, general anaesthesia, health-related quality of life, obesity, Oxford Knee Score, patient-reported outcome, persistent postsurgical pain, postoperative nausea, randomized controlled trial, range of motion, risk index, spinal anaesthesia, total knee arthroplasty, tourniquet

TIIVISTELMÄ

Tutkimuksen tausta ja tavoitteet

Polven kokotekonivelleikkaus on hyvin yleinen ja tehokas polven vaikea-asteisen nivelrikon hoitomenetelmä. Leikkaus suoritetaan yleensä spinaalipuudutuksessa tai yleisanestesiassa. Verityhjiömansettia voidaan käyttää leikkauksen aikana. Aiemman tiedon rajallisuuden ja osittaisen ristiriitaisuuden vuoksi tämän tutkimuksen tavoitteena oli selvittää, ovatko spinaalipuudutuksen ja yleisanestesian käyttö sekä verityhjiömansetin käyttö tai käyttämättä jättäminen yhteydessä erilaisiin tuloksiin polven kokotekonivelleikkauksen jälkeen. Tutkimusryhmämme selvitti myös kehon rasvamäärän ennustearvoa polven tekonivelleikkauksen tuloksissa sekä pitkittyvää leikkauksenjälkeistä kipua ennustavan riski-indeksin soveltuvuutta polven tekonivelleikkauspotilaille.

Menetelmät

Toteutimme pitkittäisen ja rinnakkaisen satunnaistetun kontrolloidun yksikeskustutkimuksen, jossa 404 polven kokotekonivelleikkaukseen lähetettyä potilasta satunnaistettiin samanaikaisesti anestesiamuodon (spinaalipuudutus tai yleisanestesia) ja verityhjiömansetin käytön (kyllä tai ei) suhteen. Tutkimukseen hyväksyttiin 18–75-vuotiaat potilaat, joilla oli polvinivelessä Kellgren–Lawrence-luokituksen mukaan kolmannen tai neljännen asteen kulumamuutokset ja joiden oireisiin konservatiiviset hoitomenetelmät eivät olleet tehonneet. Lisäksi potilaiden painoindeksin tuli olla enintään 40 kg/m^2 ja anestesiariskiluokan (American Society of Anesthesiologists -luokitus) < 4. Potilaille tehtiin polven kokotekonivelleikkaus lokakuun 2016 ja joulukuun 2018 välisenä aikana ja heitä seurattiin 12 kuukautta leikkauksen jälkeen.

Tutkimuksessa I selvitimme, eroavatko spinaalipuudutus- ja yleisanestesiaryhmien sekä verityhjiön kanssa ja ilman sitä leikattujen ryhmien leikkauksenjälkeiset tulokset sairaalahoidon aikana. Vertasimme lisäksi yhdistettyjä tutkimusryhmiä (spinaalipuudutus ja ei verityhjiötä, spinaalipuudutus ja verityhjiö, yleisanestesia ja ei verityhjiötä sekä yleisanestesia ja verityhjiö). Ensisijainen tulosmuuttuja oli potilaiden itselleen kipupumpulla annosteleman suonensisäisen oksikodonin kokonaismäärä 24 tuntia leikkauksen jälkeen. Toissijaisia tulosmuuttujia olivat muu kivunhoito, kipu, pahoinvointi, oksentelu, pahoinvointilääkkeiden käyttö, haittatapahtumat, hemoglobiinipitoisuuden muutos ja sairaalahoidon kesto.

Tutkimukset II–IV olivat etukäteen suunniteltuja satunnaistetun tutkimuksen sekundaarisia analyysejä. Tutkimuksessa II selvitimme mahdollisia eroja spinaalipuudutus- ja yleisanestesiaryhmän sekä verityhjiöryhmien (kyllä tai ei) välillä kivun muutoksessa 3 ja 12 kuukautta polven kokotekonivelleikkauksen jälkeen. Tutkimme lisäksi post hoc -analyyseissä pitkittyneen kivun esiintyvyyttä 3

ja 12 kuukautta leikkauksen jälkeen ja reseptejä gabapentinoideista tai vahvoista opioideista seuranta-aikana saaneiden lukumääriä.

Tutkimuksessa III selvitimme, onko kehon rasvaprosentilla ennustevaikutusta polven kokotekonivelleikkauksen tuloksiin. Sairaalahoidon aikaisia tutkittuja muuttujia olivat muun muassa leikkausaika, kivun hoito ja haittatapahtumat. Seurantajakson aikaisia muuttujia olivat polven liikelaajuus sekä potilaan raportoima kipu, polven toiminta, terveyspainotteinen elämänlaatu ja tyytyväisyys leikkaukseen 3 ja 12 kuukautta leikkauksen jälkeen. Seurantajakson aikaisia muuttujia olivat myös laskimotukokset, keuhkoveritulpat, leikkausalueen infektiot ja leikkaukseen liittyvät takaisinotot sairaalaan 90 päivän sisällä leikkauksesta sekä polven narkoosimanipulaatioiden, uusintaleikkausten ja kuolleisuuden ilmaantuvuus ensimmäisenä leikkauksenjälkeisenä vuotena. Teimme lisäksi post hoc -analyysin, jossa tutkimme painoindeksin ennustevaikutusta samoihin muuttujiin.

Tutkimuksessa IV selvitimme, soveltuuko aikaisemmin esitetty pitkittynyttä leikkauksen jälkeistä kipua ennustava riski-indeksi polven kokotekonivelleikkauspotilaille. Jaoimme potilaat kahteen ryhmään: pienen–kohtalaisen sekä suuren riskin ryhmään. Tutkimme mahdollisia ryhmien välisiä eroja kipupisteissä 3 ja 12 kuukautta leikkauksen jälkeen.

Tulokset

Tutkimuksissa I ja II analysoitiin 395 potilaan tietoja. Kipupumpulla 24 ensimmäisen leikkauksen jälkeisen tunnin aikana otetussa oksikodonin kokonaismäärässä ei ollut merkittäviä eroja spinaalipuudutus- ja yleisanestesiaryhmien, ilman verityhjiötä ja verityhjiön kanssa leikattujen ryhmien eikä neljän yhdistetyn anestesia- ja verityhjiöryhmän välillä. Myöskään suun kautta otetun oksikodonin ja pregabaliinin sekä ääreishermopuudutusten käyttö ei eronnut tutkittujen ryhmien välillä. Spinaalipuudutusryhmä raportoi yleisanestesiaryhmää enemmän pahoinvointia ja oksentelua. Ilman verityhjiötä leikatussa ryhmässä hemoglobiinipitoisuus laski enemmän kuin verityhjiön kanssa leikatussa ryhmässä, mutta punasolusiirtojen ilmaantuvuudessa ei ollut merkittäviä eroja. Haittatapahtumien ilmaantuvuus tai sairaalahoidon kesto ei eronnut merkittävästi yhdessäkään vertailussa.

Tutkimuksessa II kuudesta tutkitusta kipumuuttujasta spinaalipuudutusryhmä raportoi kivun vähentyneen kolmessa enemmän kuin yleisanestesiaryhmä 12 kuukautta leikkauksen jälkeen. Erot tuloksissa olivat kuitenkin niin pieniä, että niitä ei pidetty kliinisesti merkittävinä. Verityhjiön kanssa leikattu ryhmä raportoi 12 kuukautta leikkauksen jälkeen kaikkien viiden kivun ankaruutta mittaavan tulosmuuttujan parantuneen enemmän kuin ilman verityhjiötä leikattu ryhmä. Näitäkään eroja ei kuitenkaan pidetty kliinisesti merkittävinä. Reseptin vahvasta opioidista tai gabapentinoidista seuranta-aikana saaneiden lukumäärät eivät eronneet kummassakaan vertailussa.

Tutkimuksessa III rasvaprosenttikohortti muodostui 294 potilaasta. Leikkausta ennen mitattu rasvaprosentti oli kaikista tutkituista tulosmuuttujista merkittävästi yhteydessä vain polven liikelaajuuteen 12 kuukautta polven kokotekonivelleikkauksen jälkeen: jokainen yhden prosentin lisäys rasvaprosentissa vähensi liikelaajuutta 0.4 astetta (95 %:n luottamusväli oli –0.60, –0.13). Painoindeksiä koskevissa post hoc -analyyseissä oli mukana 399 potilasta. Jokaista leikkausta edeltävän painoindeksin yhtä kg/m^2 lisäystä kohti leikkausaika piteni 0.6 minuuttia (95 %:n luottamusväli 0.10, 1.04) ja polven liikelaajuus 12 kuukautta leikkauksen jälkeen väheni 0.5 astetta (95 %:n luottamusväli –0.74, –0.20). Kehon rasvaprosentti tai painoindeksi eivät olleet merkittävästi yhteydessä muihin tulosmuuttujiin 12 kuukautta leikkauksen jälkeen.

Tutkimuksessa IV analysoitiin 392 potilaan tietoja. Pienen–kohtalaisen riskin ryhmä raportoi vähemmän kipua 3 ja 12 kuukautta polven kokotekonivelleikkauksen jälkeen kuin suuren riskin ryhmä. Seitsemästä tutkitusta kipumuuttujasta kliinisesti merkittävä ero havaittiin kuitenkin vain yhdessä vertailussa 12 kuukautta leikkauksen jälkeen. Erot pienen–kohtalaisen ja suuren riskin ryhmän kipupisteissä olivat olemassa jo ennen leikkausta ja 12 kuukauden seurannan aikana jotkin kipupisteet paranivat hieman enemmän suuren kuin pienen–kohtalaisen riskin ryhmässä.

Johtopäätökset

Sillä, suoritetaanko polven kokotekonivelleikkaus spinaalipuudutuksessa vai yleisanestesiassa ja verityhjiömansettia käyttämällä tai käyttämättä, ei vaikuta olevan kliinistä merkitystä leikkauksen jälkeiseen kivun hoitoon, sairaalahoidon aikaisiin haittatapahtumiin, sairaalahoidon kestoon tai akuuttiin tai pitkittyneeseen kipuun. Spinaalipuudutuksessa tehtyyn polven kokotekonivelleikkaukseen voi liittyä suurempi leikkauksen jälkeisen pahoinvoinnin ja oksentelun riski kuin yleisanestesiassa tehtyyn leikkaukseen. Kehon rasvaprosentti ja painoindeksi vaikuttavat ennustavan huonosti polven kokotekonivelleikkauksen sairaalahoidon aikaisia tuloksia ja potilaiden vuosi leikkauksen jälkeen raportoimia tuloksia niillä, jotka eivät ole sairaalloisen lihavia. Aikaisemmin esitetty riski-indeksi ei vaikuta soveltuvan 12 kuukautta polven kokotekonivelleikkauksen jälkeen esiintyvän kivun ennustamiseen.

Avainsanat

akuutti leikkauksen jälkeinen kipu, anestesia, biosähköinen impedanssi, Brief Pain Inventory -lyhyt versio, kiristysside, kivun hoito, leikkauksen jälkeinen pahoinvointi, lihavuus, liikelaajuus, Oxfod Knee Score, painoindeksi, pitkittynyt leikkauksen jälkeinen kipu, polven kokotekonivelleikkaus, potilaan raportoima tulos, rasvaprosentti, riski-indeksi, satunnaistettu kontrolloitu tutkimus, spinaalipuudutus, terveyspainotteinen elämänlaatu, verityhjiö, yleisanestesia

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Palanne RA, Rantasalo MT, Vakkuri AP, Madanat R, Olkkola KT, Lahtinen K, Reponen EM, Linko R, Vahlberg TJ, Skants NKA. Effects of anaesthesia method and tourniquet use on recovery following total knee arthroplasty: A randomised controlled study. *British Journal of Anaesthesia*. 2020 Nov; 125(5): 762–772.

II Palanne RA, Rantasalo MT, Vakkuri AP, Madanat R, Olkkola KT, Reponen EM, Linko R, Vahlberg TJ, Skants NKA. Anesthesia method, tourniquet use, and persistent postsurgical pain after total knee arthroplasty: A prespecified secondary analysis of a randomized trial. *Anesthesiology*. 2021 Oct 1; 135(4): 699–710.

III Palanne RA, Rantasalo MT, Vakkuri AP, Olkkola KT, Vahlberg TJ, Skants NKA. Fat tissue is a poor predictor of 1 year outcomes after total knee arthroplasty: A secondary analysis of a randomized clinical trial. *Scandinavian Journal of Surgery.* 2023 Mar; 112(1): 22–32.

IV Palanne RA, Rantasalo MT, Vakkuri AP, Olkkola KT, Vahlberg TJ, Skants NKA. Testing of a predictive risk index for persistent postsurgical pain on patients undergoing total knee arthroplasty: A prospective cohort study. Submitted 2023.

These publications are referred to in the text by their Roman numerals.

In addition to appearing in this thesis, Study I was used in Mikko Rantasalo's doctoral thesis.

ABBREVIATIONS

15D	15-dimension health-related quality of life questionnaire
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
BFP	Body fat percentage
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BPI-SF	Brief Pain Inventory–Short Form
CI	Confidence interval
ERAS	Enhanced recovery after surgery
IBW	Ideal body weight
IQR	Interquartile range
LIA	Local infiltration analgesia
LOS	Length of hospital stay
MCID	Minimal clinically important difference
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OKS	Oxford Knee Score
OR	Odds ratio
PCA	Patient-controlled analgesia
PONV	Postoperative nausea and vomiting
PPP	Persistent postsurgical pain
RCT	Randomized controlled trial
ROM	Range of motion
SD	Standard deviation
TKA	Total knee arthroplasty

1 INTRODUCTION

Total knee arthroplasty (TKA) aims at improving health-related quality of life by decreasing or removing pain and functional limitations of the knee. It is a very common procedure. In Finland, 13,500 primary TKAs were performed in 2019,[1] and the number of TKAs annually performed has been increasing worldwide for decades. In the United States, the estimated number of primary TKAs increased from approximately 274,000 to 680,000 per year (i.e., an increase of 148%) between 2000 and 2014,[2] and projections have suggested that the number of TKAs could increase a further 37% to 182% between 2014 and 2030.[2,3] Estimates concerning other developed countries also indicate increases in future TKA rates.[4-6]

Although TKA-related outcomes have been extensively investigated, the ongoing development of perioperative processes continues to challenge our knowledge of the best possible management of TKA. Thus, high-quality prospective studies that reflect current practices are warranted to keep us up to date.

This thesis was conceived due to the results of one such study, a randomized controlled trial (RCT) conducted by Harsten and colleagues and published by the *British Journal of Anaesthesia* in 2013.[7] In this trial, the effects of spinal and general anaesthesia on patients undergoing TKA were compared.[7] Harsten and colleagues reported that general anaesthesia was associated with less acute postoperative pain and opioid consumption than spinal anaesthesia.[7] In addition, patients in the general anaesthesia group were able to walk sooner and had less postoperative nausea and vomiting (PONV), less dizziness, and shorter length of hospital stay (LOS).[7]

These results were intriguing because we had regarded spinal anaesthesia as the optimal anaesthesia method for TKA in terms of clinical and patient-reported outcomes, and spinal anaesthesia was clearly the primary method for TKA in Finland. Consequently, we investigated the literature and found no other RCTs conducted in the era of fast-track surgery comparing the effects of spinal and general anaesthesia on TKA-related early outcomes. Furthermore, comparative data on the effects of these anaesthesia methods on persistent postsurgical pain (PPP) were extremely limited, and it appeared evident that recommendations to use spinal anaesthesia as the primary method in TKA were mainly based on retrospective and possibly partially outdated data. As a result, we decided to conduct a high-quality RCT concerning the effects of spinal and general anaesthesia on TKA outcomes.

During the planning of our RCT and this thesis, orthopaedic surgeons in our study group suggested that we should also investigate the effects of surgical tourniquet. Data concerning the use of tourniquet in TKA were controversial; it was associated

with both benefits and harms, and knowledge at the time was insufficient to indicate whether one approach outweighed the other. This controversy could also be seen in our own arthroplasty centre, as some orthopaedic surgeons performed TKAs with a tourniquet and some without. Thus, we decided to conduct a parallel RCT on the effects of tourniquet on TKA-related outcomes. In addition, we recognized the opportunity to investigate whether some combination of anaesthesia and tourniquet regimens would lead to better outcomes than others. We hypothesized that both anaesthesia and tourniquet regimens and their combinations would have similar effects on outcomes.

As the planning proceeded, we also decided to investigate other clinically interesting and insufficiently addressed issues by using the RCT sample as a single prospective cohort. The effects of obesity, defined by body mass index (BMI), on TKA-related outcomes had already been investigated. However, data concerning the possible association between body fat percentage (BFP) and TKA-related outcomes were extremely scant. Thus, we decided to measure participants' BFPs and include analyses concerning the predictive performance of BFP in this thesis. We hypothesized that an increase in BFP would be associated with increased risk for negative outcomes. Furthermore, as TKA is associated with a significant risk of PPP, we were interested in assessing whether PPP could be predicted by using a simple and clinically applicable prediction model. As a result, we decided to investigate whether a previously presented predictive risk index for PPP[8] was applicable to patients undergoing TKA. We hypothesized that it would be.

For this doctoral study, 2783 patients referred for TKA at Peijas Hospital of HUS Helsinki University Hospital between October 2016 and December 2018 were assessed. Of these patients, we recruited 413, of whom 404 were ultimately randomized into study groups. Patients underwent TKA under either spinal or general anaesthesia and with or without a surgical tourniquet, and their in-hospital treatments followed strict study protocols. Patients were followed for up to 12 months after surgery.

2 REVIEW OF THE LITERATURE

2.1 Knee osteoarthritis

Knee osteoarthritis (OA) is a progressive disease which causes structural damage to the knee joint.[9-11] The entire joint, including articular cartilage, ligaments, subchondral bone, synovium and periarticular muscles, is affected.[9-11] This causes pain and stiffness and reduces joint motion and muscle strength, which may lead to multiple negative long-term effects such as reduced physical activity, impaired sleep and disability.[9]

The risk of knee OA increases with age,[10,12] and the estimated global prevalence of knee OA in individuals aged ≥ 40 years is 23%.[13] In addition to age, several other risk factors for knee OA, such as female sex, overweight, obesity and previous knee injury, have been identified.[12]

The diagnosis of knee OA is based on symptoms and findings from physical and radiographical examination.[9-11] Severity of knee OA is usually assessed from antero-posterior radiograph according to the Kellgren–Lawrence classification (Table 1).[14] However, OA may manifest before radiographic findings become clear.[11] Thus, treatment should be commenced when the clinical presentation clearly fits OA.[11]

Table 1. *Kellgren–Lawrence classification for knee osteoarthritis*[14]

Grade	Findings in antero-posterior radiograph of the knee
0	No osteoarthritis findings
1	Doubtful narrowing of the knee joint space, possible formation of osteophytes
2	Possibly narrowed knee joint space, small osteophytes
3	Narrowed knee joint space, moderate sized osteophytes, sclerosis, possible deformity of bone ends
4	Severely narrowed knee joint space, large osteophytes, substantial sclerosis, deformity of bone ends

2.2 Conservative treatment of knee osteoarthritis

Conservative treatment of knee OA is divided into non-pharmacological and pharmacological therapies.[9,11]

The main non-pharmacological therapies are weight loss in case of overweight or obesity and exercise aimed at maintaining or increasing muscle strength, balance

and range of motion (ROM).[9-11,15,16] Other non-pharmacological methods include education about the nature and treatment of OA, self-management programs, gait aids, mind-body exercises, maintenance of physical activity and training of pain-coping skills.[9-11,15,17]

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as the first-line pharmacological therapy for knee OA.[11,15,18] Topical diclofenac in particular appears to be both safe and effective in reducing pain and improving function.[19,20] The use of pharmaceutical-grade crystalline glucosamine sulfate or chondroitin sulfate is also recommended as the first-line long-term therapy for pain, whereas other forms of glucosamine and chondroitin are not beneficial.[18] Oral NSAIDs are also effective; however, they are associated with increased risk of adverse events.[20] Duloxetine alone or combined with NSAIDs may also be used in OA, especially for patients who have pain from central sensitization.[15,17,18] In addition, intra-articular glucocorticoid injections are recommended, while recommendations concerning hyaluronic acid injections are controversial.[15,17]

Paracetamol appears to be largely ineffective in treating OA pain and has raised safety concerns.[18,20,21] Recommendations concerning its use for OA patients range from first-line treatment[22] to limited short-term requirements[18] and suggestions not to use it at all.[20,21] Opioids are also associated with adverse events that may outweigh the modest improvements in pain and function.[20,21] Thus, opioids are usually not recommended for OA patients[15,20,21] or are recommended only when other methods are unsuitable[17,22] or ineffective[22] or as a last attempt before surgery.[18]

If conservative treatment of knee OA fails or is insufficient, TKA should be considered.[9,18]

2.3 Total knee arthroplasty (TKA)

TKA is a cost-effective procedure[23,24] that usually reduces pain and improves knee function and health-related quality of life over the long term.[23,25-30] In addition, it is more effective than conservative treatment of knee OA.[25,26]

Although knee OA is the most common reason for primary TKA,[31-33] other conditions may also warrant this operation. In Finland, primary OA accounted for 94% of TKAs in 2020.[1] The next most common reasons for TKA were posttraumatic arthritis (2.5%) and inflammatory arthritis (rheumatoid, psoriatic or reactive; 2.1%).[1]

2.3.1 Incidence of TKA

Age and sex have particularly notable effects on the incidence of primary TKA.[1,2,33] In 2014, the estimated incidence per 100,000 inhabitants in the United States was 168 in the 45–54 age cohort and 909 to 1016 in the 65–74 age cohort.[2] The

incidence was 165 for males and 259 for females when all age groups were included.[2] In 2019 in Finland, the incidence of primary TKAs per 100,000 inhabitants was 115 in the 40–54 age cohort and 800 in the 65–74 cohort.[1] Incidence among those ≥ 40 years old was 389 for males and 577 for females.[1]

2.3.2 Surgery in TKA

TKA may be conducted with different instrumentations and techniques.[34] However, a standard starting incision is vertical and runs straight from over the femoral shaft and patella to the medial side of the tibial tubercle.[34] Most often, a medial parapatellar approach is used.[1] Subsequently, the patella is everted, the patellofemoral and anterior cruciate ligaments are released and the menisci removed.[34] Next, the femur and tibia are resected, and the components of the prosthesis are sized, tested and fixed.[34] Fixation is most often performed using bone cement.[1,33] The aim is a stable knee, usually without malalignments in mechanical axis or extension or flexion deficits. Patella may also be resected and surfaced. Suction drains may be inserted; however, their use has been declining significantly.[33,35] Finally, the wound is closed and dressed.[34]

Before surgery begins, patients receive prophylactic antibiotic.[1,33] Usually, tranexamic acid is given in order to reduce bleeding,[1,35] and antithrombotic prophylaxis is used postoperatively.[1,33,35]

2.3.3 Concept of fast-track TKA

Fast-track or Enhanced Recovery After Surgery (ERAS) protocols are a combination of standardized perioperative interventions or methods that are targeted to reduce LOS, complications and costs and to improve recovery after surgery.[36] The fast-track pathway begins with optimization of the patient's health status before admission.[36,37] During this phase, interventions like optimization of possible co-morbidities and nutritional status and renouncing smoking and misuse of alcohol are essential.[36,37] Perioperative methods include a wide range of practices, such as avoidance of unnecessarily long preoperative fasting, maintenance of normothermia, prophylaxis for PONV, infections, thrombosis and blood loss, along with early mobilization after surgery.[36,37]

The use of multimodal opioid-sparing analgesia, including the use of regional analgesia, is also important.[36,37] Current recommendations for analgesics after TKA include paracetamol and NSAIDs, which should be used routinely if no contraindications exist.[37,38] In addition, a single dose of intravenous dexamethasone ≥ 10 mg pre- or intraoperatively is recommended because it reduces both pain and PONV without any apparent safety concerns.[38] However, the use of intravenous glucocorticoids may increase blood glucose level, and data concerning the effects of this increase on patients with diabetes are limited.[39] Opioids may also be used

during the early postoperative period after TKA, especially as rescue analgesics.[37,38] Gabepentinoids appear to decrease pain and opioid use only minimally after TKA and have well known side effects.[38] Thus, current recommendations advise against using them.[37,38]

In the 2020 ERAS® Society recommendation, local infiltration analgesia (LIA) was recommended as the first-line regional analgesia method for patients undergoing TKA.[37] LIA was also recommended by the PROcedure SPEcific Postoperative Pain ManagemenT Working Group in 2022.[38] Adductor canal block is another recommended regional analgesia method; it appears to reduce pain as effectively as or even better than LIA.[38] Combining LIA with adductor canal block might be most advantageous and thus preferred.[38] Although femoral nerve block appears to reduce pain after TKA as effectively as LIA or adductor canal block, it is not recommended because it causes quadriceps muscle weakness, which may postpone postoperative mobilization.[38]

The implementation of fast-track protocols in TKA has significantly reduced LOS without increasing the risk of complications or readmissions.[40,41] In a Finnish centre, the median LOS was 5 days between 2009 and 2010; after the implementation of fast-track protocols, the median LOS fell to 3 days in 2012–2013.[40] Similar results were found in a Swedish multicentre study for the 2011–2015 period.[41] In another multicentre study of total knee and hip arthroplasty patients, median LOS was reduced from 3 days to 1 day between 2010 and 2017.[42] Additionally, the rate of complications leading to extended LOS decreased.[42] Currently, the LOS of a fast-track TKA ranges from 0 to 3 days.[37]

2.3.4 Risks of TKA

Although most patients benefit from TKA, the operation is not without risks. In 2013, a list of adverse events regarded as important in assessing TKA outcomes was published:[43] intraoperative vascular injury, intraoperative or early postoperative medial collateral ligament injury, postoperative bleeding and neural deficit, wound complication, symptomatic thromboembolic event, instability, malalignment, stiffness (reduced ROM), deep periprosthetic joint infection, periprosthetic fracture, disruption of the extensor mechanism, tibiofemoral and patellofemoral dislocation, wear of the bearing surface, osteolysis, implant loosening and fracture, dissociation of tibial insert, reoperation, revision, readmission within 90 days and death.[43]

The incidence of different adverse events varies. In a Swedish study, the 90-day readmission rate after fast-track TKA was 8.4%; however, only about half of these readmissions were related to an adverse event caused by surgery.[41] In an Australian registry study, the incidence of arthroplasty-related readmission during 6-month follow-up was 6.0%.[44] The incidence of prosthesis joint infection appears to be approximately 1.3%,[41] whereas 1.3% to 1.8% of TKA patients are diagnosed with

deep vein thrombosis[41,44] and 0.6% with pulmonary embolism.[41,44] In Finland in 2016, the 5-year rate for revision surgery after TKA was 3.7%.[1] In a German study, the relation between the number of revision operations performed and primary TKAs was 12.6% in 2018.[45] In an Australian registry study, the incidence rates for minor and major complications within 6 months after TKA were 46.6% and 14.4%, respectively.[44] The incidence of death within 30 days to 6 months after TKA appears to range from 0.1% to 0.2%.[41,44,46,47]

Multiple risk factors for complications after TKA have been presented. In a large retrospective study, male sex was associated with increased risk of many complications, such as pulmonary embolism and periprosthetic fracture.[48] Increasing age also appears to increase the risk of some complications, such as cardiovascular events and stroke,[48] while decreasing the risk of others, such as reoperation and surgical site infection.[44] The possible effects of surgical tourniquet, anaesthesia method and adiposity status on complications and other outcomes after TKA are addressed in the following chapters.

2.4 Surgical tourniquet in TKA

Surgical tourniquet is frequently used in TKA.[33,35] Reported benefits of its use include reduced bleeding during surgery, better visualization of the knee structures and improved component cementing.[49] However, tourniquet use may cause adverse events because of the mechanical pressure exerted on underlying tissues and ischaemia-reperfusion-related effects.[50]

Despite extensive research, data concerning the benefits and drawbacks of tourniquet use are conflicting to a certain extent. This appears to be reflected in practice; in Sweden in 2019, the use of tourniquet in different hospitals ranged from 0% to 100%.[33]

2.4.1 Tourniquet use and clinical outcomes after TKA

Multiple studies have confirmed that tourniquet use reduces intraoperative bleeding.[51-56] However, tourniquet and no-tourniquet groups do not appear to differ significantly in terms of total blood loss.[55-58] Furthermore, possible differences in blood transfusion rates between these groups do not appear significant.[52-56,59]

Tourniquet use appears to improve surgical visibility,[60] but this finding is not conclusive.[52] In terms of cement penetration and stability of fixation at 2 years after TKA, results suggest that there might not be a significant difference between tourniquet and no-tourniquet groups.[56,61-63]

The effects of tourniquet use on duration of surgery in TKA have been extensively examined. A systematic review and meta-analysis of 27 studies (with a total of 1070 patients) found that the use of a tourniquet reduced surgical time by approximately

4 minutes.[58] Yet, in the same meta-analysis, tourniquet use appeared to increase LOS by a mean of 0.34 days (*n* = 995).[58]

Pain management during hospital stay may be affected by tourniquet use. Small-scale RCTs have reported both increased need for opioids because of tourniquet use[52] and non-significant differences between the tourniquet and no-tourniquet groups.[57,61] Overall, however, data in this regard remain limited.

Results concerning the effect of tourniquet use on measured knee function after TKA are conflicting. Some data indicate that tourniquet use in TKA does not affect postoperative functional tests, such as those measuring muscle strength and walking, [51,54,60,64] but other data indicate that TKA without the use of tourniquet might improve these outcomes.[53,54,57] Conducting TKA without a tourniquet might also improve knee ROM.[52-54,56,59,61] Yet, depending on time point of measurement, results also suggest no difference in ROM after TKA, regardless of the use or non-use of tourniquet.[52-54,56,57,60]

Data concerning complications appear to favour TKA without tourniquet use. Extended use (more than 100–120 minutes) and high cuff pressure levels in particular have been associated with adverse events such as wound complications and nerve palsies.[65-67] In a systematic review and meta-analysis of RCTs published in 2012, the incidence of minor complications was higher in the tourniquet group.[49] Another meta-analysis published in 2014 reported that thromboembolic and non-thrombotic adverse events were higher in the tourniquet group.[55] Similarly, results from a meta-analysis published in 2021 indicated that tourniquet use was associated with a higher risk of combined severe adverse events.[58] However, when events concerning deep vein thromboses, pulmonary embolisms, infections, reoperations and mortality were analysed separately, only the risk for infections was significantly higher in the tourniquet group.[58]

In sum, results concerning clinical outcomes are either inconclusive or favour performing TKA without a surgical tourniquet.

2.4.2 Tourniquet use and patient-reported outcomes after TKA

Data concerning the effects of tourniquet use on acute postoperative pain after TKA are inconclusive. A recent meta-analysis reported that those who underwent surgery with a tourniquet had more pain on the first and third postoperative days than those whose operation did not involve a tourniquet.[58] These results were supported by a pair of RCTs that were not included in the meta-analysis.[53,54] Two additional studies have reported that the use of tourniquet was associated with higher acute pain.[56,59] However, some studies have found no differences in acute pain between tourniquet and no-tourniquet groups.[51,60] Furthermore, although some of the reported differences in pain scores between the groups were

statistically significant,[56,58,59] they may be regarded as clinically irrelevant; that is, they are less than 1.0 on a pain scale from 0 to 10.[68,69]

Data regarding the effect of tourniquet use on subacute and persistent postsurgical pain after TKA indicate that tourniquet use does not affect pain at 4 to 6 weeks,[59,60,64] 3 months,[53,57,59] 6 months,[52,53,59,64] 6 to 8 months[60] or 12 months[52] after surgery. However, pain appears to decrease up to 1 year after TKA.[70-72] At the same time, a recent systematic review concerning RCTs identified only a single study (n = 64)[52] that compared 1-year pain scores between patients whose TKAs were conducted with or without a tourniquet.[73] Thus, data concerning the long-term effects of tourniquet use on PPP after TKA are limited.

A recent meta-analysis found that patient-reported knee function at 3 months after TKA does not differ between those operated with and without a tourniquet.[58] Similarly, tourniquet use does not appear to affect patient-reported function at 6 to 8 months after TKA.[60] In addition, randomized trials using a questionnaire which combined measured functional outcomes and patient-reported pain and function (i.e., the Hospital for Special Surgery Knee Score), found no significant differences in the results between no-tourniquet and tourniquet groups at discharge,[53] 3 months,[53] 6 months,[53,59] 1 year[74] or 2 years[74] after TKA.

At 1 to 2 months after TKA, the reported quality of life in patients operated with a tourniquet might be better,[60] worse[52] or similar[64] when compared to patients operated without a tourniquet. However, the same reports indicate that there are no significant differences in quality of life at 6 to 12 months after TKA, regardless of whether a tourniquet was used.[52,60,64] Similarly, patient satisfaction does not appear to differ between tourniquet and no-tourniquet groups at 1 to 8 months after TKA.[59,60,64]

2.5 Anaesthesia methods in TKA

In a recent recommendation concerning anaesthesia in TKA, neuraxial anaesthesia (i.e., spinal, epidural or combined spinal-epidural anaesthesia) was recommended over general anaesthesia as the primary method.[75] This recommendation was based on a meta-analysis concerning postoperative adverse events. The results indicated that patients who had undergone TKA under neuraxial anaesthesia had lower odds for pulmonary and thromboembolic complications, pneumonia, acute kidney failure, urinary tract infections, all-cause infections, blood transfusions, critical care admissions and readmissions than patients who received general anaesthesia. Differences in mortality were not significant between the compared groups. However, the data in this meta-analysis were derived mostly from registry studies, and the level of evidence and thus the strength of recommendation were considered weak.[75] Currently, both neuraxial and general anaesthesia are regarded as suitable for TKA.[37]

Over time, the use of epidural anaesthesia in TKA has become rare. A meta-analysis concerning total knee and hip arthroplasties reported that between 1980 and 2003, epidural anaesthesia was most often compared with general anaesthesia, whereas from 2003 to 2015 only spinal and combined spinal-epidural anaesthesia were compared with general anaesthesia.[76]

In addition to epidural anaesthesia, the use of combined spinal-epidural anaesthesia in TKA appears to be declining. This is not surprising; the results of a retrospective register study comparing different neuraxial methods in total knee and hip arthroplasty cohorts indicated that those who underwent spinal anaesthesia had a lower rate of postoperative cardiac, pulmonary, gastrointestinal and thromboembolic complications and less prolonged LOS than those whose anaesthesia was epidural or combined spinal-epidural.[77] Similarly, the risk of severe neurological complications caused by neuraxial anaesthesia appears to be lower with spinal anaesthesia as opposed to epidural or combined spinal-epidural anaesthesia.[78-80] Furthermore, in a recent meta-analysis of RCTs, the use of LIA was shown to reduce acute postoperative pain after TKA better than epidural analgesia.[81] LIA was also associated with higher postoperative knee flexion and lower risk of nausea than epidural analgesia.[81] Finally, epidural analgesia is not recommended for routine use in TKA, owing to the risk of side effects like hypotension, reduced mobility and urinary retention, all of which may impede rapid recovery.[37,38] Thus, spinal and general anaesthesia are the most common anaesthesia methods in fast-track TKA.[33,82] The choice between these methods is usually based on a combination of individual risk assessment, guidelines and anaesthesiologist and patient preferences.

2.5.1 Spinal versus general anaesthesia and outcomes after TKA

Comparative data concerning the effects of spinal and general anaesthesia on the outcomes of TKA are limited. In a systematic review and meta-analysis of prospective studies published in 2016, neuraxial and general anaesthesia were compared in terms of major morbidity, mortality and patient-experienced outcomes.[76] Only six[7,83-87] of the included studies compared the effects of spinal and general anaesthesia in TKA, and two[86,87] of these studies were, in fact, retrospective.[76]

Two RCTs have compared cognitive and functional outcomes 3 months after surgery: one with 64 participants that investigated patients undergoing TKA[84] and another with 146 participants that investigated total knee and hip arthroplasty patients as a single cohort.[83] In the results, no significant differences between the spinal and general anaesthesia groups were detected except for reaction time, which was shorter in the general anaesthesia group of the mixed arthroplasty cohort.[83,84] Additionally, duration of surgery, LOS and improvement in satisfaction at 3 months after surgery did not differ significantly between the anaesthesia

groups.[83] However, both RCTs were published in 1990, and their perioperative management approaches differed significantly from current fast-track protocols.[83,84]

In a retrospective study published in 2014, surgical site infections during the first 30 postoperative days were not significantly associated with the type of anaesthesia (spinal or general), but this study investigated a cohort consisting of knee and hip arthroplasty patients and included patients who had undergone revision surgery.[86]

In a retrospective study of 147 patients published in 2018, postoperative mobilization, muscle strength and ROM did not differ significantly between spinal and general anaesthesia groups up to 7 days after TKA.[88] In another retrospective register study published in the same year, the odds of postoperative delirium were significantly higher in patients who underwent surgery under general rather than spinal anaesthesia.[89] However, this study included both total knee and hip arthroplasty patients.[89]

In the results of an RCT of 120 patients who underwent fast-track TKA, general anaesthesia resulted in less dizziness and PONV and shorter times to mobilize and reach hospital discharge criteria than spinal anaesthesia.[7] No differences in satisfaction with anaesthesia between the anaesthesia groups were noted at 6 months after surgery.[7]

2.5.1.1 Spinal versus general anaesthesia and acute pain after TKA

Comparative data concerning the effects of spinal and general anaesthesia on acute pain and pain management after TKA are conflicting. A small RCT reported that the general anaesthesia group experienced more pain upon arrival in the recovery room, where they also needed more analgesics than the spinal anaesthesia group.[85] However, this was hardly surprising given that spinal anaesthesia patients were most likely still under anaesthesia during recovery room admission and that general anaesthesia patients apparently did not receive any regional analgesia.[85] Furthermore, this RCT included both total hip and knee arthroplasty patients, and the sample size was only 40 patients, 18 of whom underwent TKA.[85]

In a retrospective study of 85 patients published in 2007, the general anaesthesia group reported more pain during the first 48 postoperative hours than the spinal anaesthesia group.[87] However, no information concerning surgery or management of spinal or general anaesthesia was presented,[87] and pain management approaches were not described in detail. In addition, patients in the general anaesthesia group were significantly younger than those in the spinal anaesthesia group.[87] In a recently published retrospective study, general anaesthesia was more often associated with moderate to severe acute postoperative pain (numerical rating scale [NRS] ≥4) on the first postoperative day than spinal anaesthesia.[90]

However, perioperative pain management in this multicentre study with 968 patients was variable, and LIA was used in only 16% of TKAs.[90]

In another recent retrospective study, 86 TKA patients received general anaesthesia and LIA, while 61 patients received spinal anaesthesia and LIA.[88] In the results, pain up to 4 days after surgery did not differ significantly between the groups.[88] More patients in the general anaesthesia group needed intravenous rescue opioids on the day of the operation, but there were no other differences in postoperative opioid consumption during the first 4 postoperative days.[88]

Two RCTs have reported that the amounts of postoperatively used opioids[84] or that "postoperative analgesia"[83] did not differ significantly between spinal and general anaesthesia groups. However, both RCTs[83,84] were published in 1990, before the fast-track era, and their results are thus most likely outdated. Furthermore, one of these studies investigated total hip and knee arthroplasty patients as a single cohort.[83]

Finally, in the results of an RCT of 120 patients that compared the effects of spinal and general anaesthesia on outcomes after fast-track TKA, the general anaesthesia group reported less pain from the sixth postoperative hour to the second postoperative day and used significantly less morphine via patient-controlled analgesia (PCA) device during the first 24 postoperative hours than the spinal anaesthesia group.[7]

In summary, previous data suggest that the use of spinal anaesthesia may result in lower, similar or higher acute postoperative pain after TKA when compared to the use of general anaesthesia. Only a single high-quality RCT on this topic has been published, the results of which supported the use of general over spinal anaesthesia.[7]

2.5.1.2 Spinal versus general anaesthesia and persistent pain after TKA

Data concerning the effects of spinal and general anaesthesia on PPP after TKA are also insufficient. It is especially unclear whether spinal and general anaesthesia have different effects on long-term analgesic requirements after fast-track TKA.

In an RCT that combined total hip and knee arthroplasty patients, improvement in overall pain at 3 months after surgery did not differ significantly between anaesthesia groups; however, this study was published in 1990.[83]

In a prospective cohort study, the type of anaesthesia – spinal and LIA, combined spinal-epidural, or other – was not significantly associated with the prevalence of moderate to severe PPP. However, the "other" anaesthesia was not defined in the study, and patients who underwent TKA under this undefined anaesthesia accounted only for 11% of 291 patients at 6-month follow-up and 7% of 288 patients at 12 months.[72]

In the results of a retrospective multicentre study which included both total knee and hip arthroplasty patients, general anaesthesia was associated with higher odds for severe PPP (pain score ≥ 5/10) than regional anaesthesia approximately 1 year after surgery.[91] However, no difference between anaesthesia methods was found when PPP was defined as any pain, and the significance of the results were limited by a low response rate (34%) and variations in regional anaesthesia and analgesia methods.[91]

A very recent randomized study comparing patients who underwent TKA under spinal or general anaesthesia reported that the spinal group had better function and less pain 3 months after surgery, but not at 6 months.[92] However, this study had some notable limitations. First, general anaesthesia patients received femoral nerve block, whereas spinal anaesthesia patients did not. Second, despite the presence of statistically significant differences, it is most likely that those differences did not attain a minimal clinically important difference (MCID) between groups. Third, 11 of 210 randomized patients were excluded before surgery due to protocol violations, and 47 patients did not receive the randomized anaesthesia. Fourth, the dropout rate at 6 months was 15%. Fifth, the use of intraoperative opioids, antiemetics, dexamethasone and tranexamic acid was not controlled.[92]

In summary, the scarce data concerning PPP after TKA that do exist appear either to favour the use of spinal over general anaesthesia or to indicate no difference in the effect of the methods.

2.6 Obesity and TKA-related outcomes

Adiposity or nutritional status is most commonly defined using BMI, which is obtained by dividing the patient's weight in kg with the square of the patient's height (m^2). The classification of nutritional status based on BMI as suggested by the World Health Organization is presented in Table 2;[93] the terms "overweight" and "morbid obesity" are commonly used instead of pre-obesity and obesity class 3, respectively.

Table 2. *Nutritional status according to body mass index*[93]

Category	**Body mass index (kg/m^2)**
Normal weight	18.5 to 24.9
Pre-obesity (overweight)	25.0 to 29.9
Obesity class 1	30.0 to 34.9
Obesity class 2	35.0 to 39.9
Obesity class 3 (morbid obesity)	≥ 40

Preoperative obesity appears to negatively impact some TKA-related outcomes. Increasing BMI increases the duration of surgery.[94-96] Additionally, obesity increases the risk for postsurgical infections and revision surgery.[97,98] Morbidly obese patients in particular appear to be at higher risk for surgical site infections after TKA than nonobese patients.[96,98,99] Furthermore, obesity may be associated with increased risk for pulmonary embolism[96] and deep vein thrombosis.[98] However, data indicating no association between increasing BMI and thromboembolic complications have also been presented,[97] and the odds of some complications, such as myocardial infarction and bleeding requiring transfusion, may be higher in the normal-weight group.[96] Nevertheless, there appears to be no difference in mortality between nonobese and obese TKA patients.[98]

A recent meta-analysis reported that obese patients had worse short-term (< 6 months) and long-term (≥ 6 months) pain outcomes after TKA than nonobese patients.[99] Only a single of nine studies included in this analysis reported that increased BMI was not associated with impaired long-term pain outcomes.[100] In addition, obese may experience more long-term disability than nonobese.[99]

However, a large registry study that was not included in the meta-analysis[99] found that BMI was not significantly associated with moderate to severe knee pain at 2 or 5 years after TKA.[101] Furthermore, although obese patients may report poorer scores concerning function, pain and general health at 6 or 12 months after TKA than nonobese patients, change scores – that is, the difference between preoperative and postoperative scores – of these variables at the respective time points might not be significantly associated with BMI.[102,103] Some studies even indicate that obese patients might have better improvements in ROM,[104] patient-reported function[105] and pain[106] than normal-weight patients. In addition, patient satisfaction with TKA does not appear to be directly associated with BMI classifications.[102]

2.6.1 Body fat percentage and TKA-related outcomes

Despite the common use of BMI in estimating body composition, it is not an accurate indicator.[93,107,108] BMI does not account for differences in adiposity levels caused by age, sex or ethnicity and does not differentiate adipose tissue from other tissues. Although BMI might have good specificity to identify excessive body fat, its sensitivity appears to be approximately 50%, indicating that patients who are not classified as obese may still have excessive body fat.[108]

BFP demonstrates adiposity status more accurately than BMI[107] and can be measured using dual-energy X-ray absorptiometry, air displacement plethysmography, hydrostatic weighing, computed tomography, magnetic resonance imaging and bioelectrical impedance analysis (BIA).[109] Of these methods, BIA is the most feasible in preoperative settings because measurement is fast, simple and non-invasive. In addition, many BIA devices are inexpensive and

portable and present BFP results that are comparable to dual-energy X-ray absorptiometry, which has often been used as a reference method.[110-113]

BIA is based on the measurement of a weak electric current which usually flows – depending on the device – from hand to foot, hand to hand or foot to foot.[114] Impedance refers to resistance to electrical current caused by total body water (extra- and intracellular fluid) and cell membranes.[115] Fat-free mass is considered a conductor of electrical charge, whereas fat mass is considered a non-conductor.[114] In BIA, equations are used to estimate fat-free mass based on total body water, which accounts for approximately 73% of fat-free mass.[114] Fat mass is then derived from the difference between measured body weight and fat-free mass, [114] and that result is used to calculate BFP.

The matter that BFP is a more precise indicator of adiposity status than BMI raises the question of whether BFP is also a better predictor of TKA-related outcomes. However, data concerning the association between BFP and TKA outcomes remain highly limited. Results from a pair of studies with combined total knee and hip arthroplasty cohorts indicated that BFP may predict PPP, function and adverse events better than BMI.[116,117] However, only a single one of these studies presented some of the results separately for TKA patients (*n* = 115).[117] Thus, the role of BFP as a predictor of TKA-related outcomes remains unclear.

2.7 Predicting persistent pain after TKA

Most patients (i.e., 81% to 88%) are satisfied with TKA at 1 year after surgery.[28,118-120] Yet, a significant proportion of patients remains dissatisfied, and this dissatisfaction is strongly associated with pain.

The prevalence of moderate to severe PPP after TKA appears to range from 7% to 31%.[70,72,101,121-123] This wide variation in prevalence is at least partly explained by different definitions of PPP and the time points used for its measurement. Nevertheless, those who experience lower reduction in pain over time are more likely dissatisfied after TKA than those who have better reduction in pain.[119,120]

Identifying risk factors for PPP after TKA has been the aim of multiple studies. The effects of age and sex in particular have been examined extensively. In a meta-analysis published in 2015, younger age and female sex were associated with higher pain after TKA; however, those effects were small and regarded as of minimal clinical importance.[124] More recent studies have found either no association between age and PPP or an association that disappeared during follow-up; these studies also reported no association between sex and PPP after TKA.[72,122,125]

The intensity of preoperative pain is a significant predictor of PPP after TKA.[72,91,122,124] Similarly, pain in other locations of the body than the target knee is a known predictor.[72,91,122,124] Additionally, the intensity of acute postoperative pain

has been associated with PPP.[72,91,125,126] Multiple other risk factors for PPP after TKA, such as catastrophizing,[124] mental health,[124] trait anxiety[72] and expected pain,[72] have also been reported.

Even though data on risk factors are substantial, predicting the risk of PPP for individual patients remains challenging. Althaus and colleagues addressed this issue by developing a predictive risk index for PPP.[8] During the development process, they used risk factor data derived from previous studies and conducted multivariate analyses concerning 150 mixed surgery patients.[8] Their final model included 5 risk factors (Table 3), each of which is assessed as absent or present. The researchers suggested that patients with 0–1 risk factors would have a low risk of PPP, whereas 2 risk factors would correspond to moderate risk and 3–5 risk factors to high risk of PPP.[8]

Table 3. *Risk factors of the predictive risk index for persistent postsurgical pain*[8]

Risk factor	**Note**
Preoperative	
Pain in the area of surgery	
Pain elsewhere than in area of surgery	
Capacity overstrain in previous 6 months	
Co-morbid stress symptom	One or more of the following: sleeping disorder or intake of sleeping pills, exhaustion, dizziness, tachycardia, trembling hands, frightening thoughts, feeling misunderstood
Postoperative	
High-intensity acute pain	Average pain intensity of ≥ 5 on the numerical rating scale from the first to fifth postoperative day.

From a clinical perspective, this risk index[8] appears promising. It is easy to use and includes only modifiable risk factors, thus enabling targeted interventions to reduce the risk of PPP. Additionally, the external validity of the risk index was recently supported by a study investigating mixed surgery patients.[127] However, whether the risk index is applicable to patients undergoing TKA has not been examined.

3 AIMS OF THE STUDY

The primary aim of this doctoral study was to compare the effects of spinal and general anaesthesia and the use and non-use of a surgical tourniquet on in-hospital outcomes and PPP after TKA. In addition, we aimed to investigate the predictive performance of BFP on in-hospital and long-term outcomes following TKA. Finally, we investigated whether a previously presented predictive risk index for PPP is applicable to patients who undergo TKA.[8]

The specific aims in Studies I to IV were as follows:

1. To investigate whether TKA performed under spinal or general anaesthesia and with or without a surgical tourniquet is associated with differences in acute postoperative pain, pain management, PONV, adverse events, haemoglobin levels or LOS. (Study I)
2. To compare the effects of spinal and general anaesthesia and tourniquet use and non-use on PPP at 3 and 12 months after TKA. (Study II)
3. To assess the predictive performance of BFP on TKA-related outcomes during hospital stay (postsurgical pain, pain management, PONV, adverse events, operation time and LOS) and 12-month follow-up (readmissions, thromboembolic events and surgical site infections within 90 postoperative days; ROM and patient-reported pain, function, quality of life and satisfaction to TKA at 3 and 12 months after operation; and manipulation under anaesthesia, revision surgery and mortality within 12 months after TKA). In addition, we sought to assess the predictive performance of BMI on the same outcomes. (Study III)
4. To assess the applicability of a previously presented predictive risk index for PPP to patients undergoing TKA. (Study IV)

4 MATERIALS AND METHODS

This doctoral study was a combination of a single-centre, open-label, parallel, longitudinal RCT (Study I) and prespecified secondary analyses of the trial (Studies II to IV). The study was carried out at Peijas Hospital of HUS Helsinki University Hospital.

The trial was approved by the Finnish Medicines Agency Fimea (reference number KL27/2016; 20 May 2016) and the ethics committee of HUS Helsinki University Hospital, Surgery (reference number HUS/1703/2016; 8 June 2016) and registered with EudraCT (2016-002035-15; 12 May 2016). Every participant provided written informed consent.

The participants underwent TKA between October 2016 and December 2018 and attended follow-up visits 3 and 12 months after surgery. All follow-ups were completed by December 2019.

4.1 Patients

Patients referred for TKA at Peijas Hospital were eligible for this study. The decision to operate was done independent of the study and before patients arrived at the preoperative outpatient clinic where study recruitment took place.

We included patients aged 18 to 75 years who had Kellgren–Lawrence grade 3 to 4 knee arthritis[14] that was unresponsive to conservative treatment. We excluded patients with BMI of > 40 kg/m^2, American Society of Anesthesiologists (ASA) physical status classification of ≥ 4,[128] ongoing usage of strong opioids, need for bridging anticoagulation, contraindication to medications or anaesthesia methods used in the study, bilateral operation or cognitive impairment. Additionally, we excluded patients with prior major surgery, varus or valgus malalignment of > 15°, extension deficit of > 20° or flexion deficit of < 90° of the target knee. From the BFP analyses (Study III), we further excluded patients who had a cardiac pacemaker or prior metallic endoprosthesis because we did not measure their BFPs in accordance with the manufacturer's and institutional instructions concerning the reliability and safety of measurements with BIA.

4.2 Randomization and blinding

Study participants were simultaneously randomized into spinal and general anaesthesia groups and into no-tourniquet and tourniquet groups. Thus, the following four randomization groups were formed in a 1:1:1:1 allocation ratio: spinal anaesthesia and no tourniquet, spinal anaesthesia and tourniquet, general

anaesthesia and no tourniquet and general anaesthesia and tourniquet. Randomization was conducted using sealed opaque envelopes that were created by a nonparticipating anaesthesiologist in blocks of 20. The randomization envelopes were stored in a locked room and opened no more than 2 hours before the beginning of the operation by nurses who were not affiliated with the study. Blinding was not considered feasible because of the study design.

4.3 Interventions

4.3.1 Anaesthesia

Participants were premedicated with oral diazepam 5 mg, paracetamol 1 g and ibuprofen 400 to 800 mg according to ideal body weight (IBW), defined as the weight that would produce a BMI of 22 kg/m^2 based on patient height: thus, IBW = 22 kg/m^2 x height (m) x height (m).[129] Patients with IBW of < 60 kg received ibuprofen 400 mg; most of those with IBW of > 60 kg received 600 mg, except those aged < 65 years with IBW of > 80 kg, who received ibuprofen 800 mg preoperatively.

Spinal anaesthesia was induced with intrathecally administered plain bupivacaine 15 mg (5 mg/ml). After sufficient spinal anaesthesia was verified, patients were lightly sedated by infusing propofol with a maximum flow rate of 4 mg/kg/h. Sedation level was aimed at 0 to −2 on the Richmond Agitation Sedation Scale.[130] Additionally, during the induction of spinal anaesthesia, intravenous diazepam 2.5 to 5 mg and fentanyl 25 to 50 µg were permitted, if necessary.

General anaesthesia was induced and sustained with target-controlled infusions of propofol and remifentanil. Prior to commencing target-controlled infusions, patients received intravenous lidocaine 20 mg to reduce possible pain caused by propofol and glycopyrronium 0.2 mg, when necessary. Propofol was infused using the Schnider formula, and the effect site was adjusted between 3 to 8 µg/ml to achieve and maintain a GE Entropy level of 30 to 50 (GE Healthcare Finland Oy, Helsinki, Finland). Remifentanil was infused using the Minto formula, and the effect site was adjusted between 1 to 8 ng/ml according to patient blood pressure and heart rate. Intravenous rocuronium 0.5 mg/kg was used to facilitate intubation; additional doses of 0.1 to 0.2 mg/kg were given only if required in surgery. Once wound closure began, general anaesthesia patients received intravenous oxycodone 0.1 mg/kg (IBW).

4.3.2 Tourniquet use

Surgical tourniquet was prepared for every patient in case it was needed to deal with severe intraoperative bleeding. However, tourniquet was inflated only for those patients who were randomized into the tourniquet group. The maximum usage time was 2 hours, and pressure was set to 250 mmHg.

4.3.3 Surgery and local infiltration analgesia

TKAs were performed through a midline incision and with medial parapatellar approach using a single type of cruciate-retaining cemented implant, Triathlon® (Stryker, Kalamazoo, Michigan, USA). Instrumentation and implantation were conducted according to manufacturer guidelines. Patellas were resurfaced, and no drains were used. During surgery, every participant received LIA, which was injected using an organized multipuncture technique and consisted of a mixture of epinephrine 0.5 mg (0.1 mg/ml), ropivacaine 300 mg (2 mg/ml) and ketorolac 30 mg (30 mg/ml). Additionally, wound edges were infiltrated with ropivacaine 100 mg (2 mg/ml).

4.3.4 Other perioperative care

Antibiotic prophylaxis consisted of a single intravenous dose of cefuroxime 3 g administered 30 to 60 minutes before the surgery. In case of cephalosporin allergy, intravenous clindamycin 600 mg was administered four times over 24 hours.

Intravenous tranexamic acid 1 g was administered 5 to 10 minutes before surgery (no-tourniquet group) or 5 to 10 minutes before releasing tourniquet pressure (tourniquet group), and intravenous ondansetron 4 mg was given to all patients at the end of surgery to reduce the risk of PONV.

4.3.5 Postoperative care

4.3.5.1 Management of pain

Upon arrival to recovery room, patients were given a PCA device to be used for the following 24 hours. Patients could self-administer intravenous oxycodone with single doses of 0.04 mg/kg (IBW) up to four times per hour. The lock-up time between single doses was set at 10 minutes. Baseline infusion was not used.

Ibuprofen and paracetamol were given to patients three times a day with premedication doses. However, ibuprofen was discontinued after first postoperative day if patients were at high risk for adverse events from NSAIDs.

After PCA was discontinued, patients received one tablet of extended-release oxycodone 5 to 15 mg and, on request, repeated oral doses of immediate-release oxycodone 5 to 15 mg based on IBW (5 mg for those with IBW < 50 kg, 10 mg for those with IBW 50 to 75 kg and 15 mg for those with IBW > 75 kg). Intramuscular oxycodone with repeated doses of 4, 8 or 12 mg according to the respective IBWs was allowed if a patient was unable to take oral oxycodone. From the morning of the second postoperative day, patients were given either one or two tablets of a combination of paracetamol 500 mg and codeine 30 mg or tramadol 50 mg up to three times a day. Pregabalin 75 to 300 mg twice a day was used as rescue analgesic

in case the immediate-release oxycodone was insufficient. If the systemic analgesic drugs did not provide sufficient analgesia, peripheral nerve blocks were allowed.

Pain management after hospital discharge was not controlled. However, as was routine practice at Peijas Hospital, patients with no contraindications received prescriptions for NSAID, paracetamol and a weak opioid (codeine combined with paracetamol or tramadol). Gabapentinoids or strong opioids were prescribed only if an anaesthesiologist or surgeon considered routine analgesics insufficient.

4.3.5.2 Management of postoperative nausea and vomiting

Possible PONV was treated with intravenous antiemetics. These included dehydrobenzperidol 0.5 to 0.75 mg, ondansetron 4 mg, dexamethasone 0.1 mg/kg (IBW) and promethazine 6.25 mg.

4.3.5.3 Other treatments

Patients received oral macrogol 12 g once daily to reduce the risk of opioid-induced constipation. Subcutaneous enoxaparin with a dose of 40 mg once daily was used for thromboprophylaxis for 2 postoperative weeks. Other anticoagulants or doses of enoxaparin were allowed if required by patient comorbidities.

Patients were mobilized on the day of surgery or the day after at the latest. Physiotherapists gave personal guidance to all patients in the surgical ward.

Hospital discharge criteria included the following requirements: postoperative pain was under control with analgesics, ambulation was safe, patient could urinate, secretion from the wound was minor, further care and home conditions were arranged, and patient understood home care instructions, use of medications and prescriptions.

4.4 Data collection

4.4.1 Preoperatively collected data and questionnaires

Patients were examined and interviewed approximately 1 to 2 weeks before TKA at the preoperative outpatient clinic. We collected detailed data concerning patient characteristics such as comorbidities, haemoglobin levels, medications and knee ROM. In addition, we measured preoperative BFP from eligible patients with a tetrapolar BIA device (Omron BF-500; Omron Healthcare, Kyoto, Japan), which yields results that are comparable to dual-energy X-ray absorptiometry.[110,111] We also inquired about the presence of the four preoperative risk factors for PPP that are included in the predictive risk index of Althaus and colleagues (Table 3).[8]

Patients reported preoperative pain and function with the Brief Pain Inventory–Short Form (BPI-SF)[131] and Oxford Knee Score (OKS)[132-134] questionnaires and health-related quality of life with a 15-dimension (15D) questionnaire.[135]

4.4.1.1 Brief Pain Inventory–Short Form

The BPI-SF is a validated and self-administrated pain questionnaire that is widely used in clinical studies. On this questionnaire, patients rate four pain severity variables (worst and least pain in the last 24 hours, average pain and current pain) and seven pain interference variables (walking, general activity, working, sleeping, mood, relations with others and enjoyment of life during the previous 24 hours) on an NRS (0 = no pain interference/pain, and 10 = worst imaginable pain interference/pain).[131]

4.4.1.2 Oxford Knee Score

The OKS is a validated and self-administered questionnaire designed for TKA patients. It measures knee function and pain and consists of 12 questions in which patients are asked to reflect on their situation during the previous 4 weeks.[132-134] Each answer is rated from 0 to 4 (0 = worst outcome, 4 = best outcome) on a verbal scale. Seven of 12 questions concern pain and constitute the pain subscale, while five are related to function and constitute the function subscale.[133] Thus, pain subscale scores range from 0 to 28 and function subscale scores from 0 to 20. However, it is recommended that scores of both subscales be adjusted to range from 0 to 100 (0 = worst outcome, 100 = best outcome).[133]

4.4.1.3 15-dimension health-related quality of life questionnaire

The 15D is a generic, standardized, self-administered questionnaire.[135] Patients use a 5-point verbal scale to rate the following 15 dimensions: mobility, usual activities, breathing, vision, hearing, eating, speech, excretion, sleeping, discomfort and symptoms, distress, depression, mental function, vitality and sexual activity.[135,136] Based on responses, a single 15D score between 0 to 1 is generated (0 = death, 1 = full health). The minimal important change in 15D scores within a group or a person is defined as ±0.015.[136] It has been suggested that the same ±0.015 could be used for MCIDs between groups.[136]

4.4.2 Data collected during hospital stay

Data concerning operation and recovery room events were collected, as were data concerning intravenous oxycodone consumption during the first 24 postoperative hours, the use of other analgesics and pain-relieving methods and the use of

antiemetics. Furthermore, we collected data on postoperative haemoglobin levels, vomiting, other adverse events and LOS.

During the in-hospital period, patients were asked to assess acute postoperative pain and nausea in the recovery room prior to transfer to the surgical ward and at 24 hours after surgery, using the NRS (0 = no pain/nausea, 10 = worst imaginable pain/nausea). Inability to walk because of pain or reported pain of NRS ≥ 5 after walking 5 meters 24 hours after surgery were recorded. These variables were used to indicate the presence or absence of the postoperative risk factor for PPP – that is, high-intensity acute postoperative pain – that is included in the risk index of Althaus and colleagues.[8]

4.4.3 Data collected after hospital discharge

We investigated data concerning readmissions, thromboembolic events and surgical infections up to 90 postoperative days. Additionally, we studied prescriptions for strong opioids and gabapentinoids and data concerning revision surgery, manipulation under anaesthesia and mortality for up to 1 year after TKA.

The patients completed the BPI-SF, OKS and 15D questionnaires 3 and 12 months after surgery. In addition, patients completed a self-administered questionnaire specifically designed for this study at 3 and 12 months after TKA. In this questionnaire, satisfaction with TKA was rated using an NRS (0 = totally dissatisfied, 10 = totally satisfied). We considered patients to be satisfied with TKA when they reported NRS scores of 9 or 10. Finally, knee ROM measurements were conducted at 3 and 12 months after TKA.

4.5 Outcomes

Study I

The primary outcome of Study I was the total amount of intravenous oxycodone that patients took with PCA during the first 24 postoperative hours. Secondary outcomes included the use of oral oxycodone, other analgesics, peripheral nerve blocks and antiemetics during hospital stay, along with patient-reported pain (on the NRS) and incidence of nausea (NRS > 0) in the recovery room and 24 hours after surgery, vomiting during the first 24 postoperative hours, change in haemoglobin levels between preoperative value and first postoperative day, postoperative adverse events during hospital stay and LOS.

Study II

The main outcome of Study II was the change in the BPI-SF “average pain” (i.e., the difference between postoperative and preoperative NRS values) at 12 months after TKA. The change in the BPI-SF average pain at 3 months and changes in the other

three BPI-SF pain severity variables, in the arithmetic mean of all four pain severity variables and in the arithmetic mean of all seven pain interference variables at 3 and 12 months after TKA were secondary outcomes. In addition, some secondary outcomes were added post hoc, including the number of patients who received prescriptions for opioids (except codeine and tramadol) or gabapentinoids due to study TKA during 1-year follow-up and the prevalence rates of moderate to severe PPP, using four different definitions, at 3 and 12 months after TKA. Three definitions were derived from the BPI-SF average pain (NRS with cut-offs of ≥ 3, ≥ 4 and ≥ 5) and the fourth from the OKS question concerning usual knee pain in the previous 4 weeks (moderate or severe).[134]

Study III

In Study III, we assessed the associations between BFP (and BMI) and the following continuous outcomes: duration of surgery, LOS, the use of intravenous oxycodone with PCA during the first 24 postoperative hours, total postoperative oxycodone consumption during hospital stay, pain (as measured by NRS) in the recovery room and 24 hours after surgery (supine at rest and after walking 5 meters) and pain (BPI-SF average pain, mean pain severity and mean pain interference and OKS pain subscale), function (OKS function subscale and ROM) and quality of life (15D) at 3 and 12 months after surgery. We also examined the following dichotomous outcomes: aberration in anaesthesia, bleeding requiring red blood cell transfusion, hypotension and hypertension requiring medication in the operation room, postoperative adverse events during hospital stay and post-discharge adverse events (thrombotic events, surgical site infections and readmissions within 90 days after surgery and mortality, manipulation under anaesthesia and revision surgery within 1 year after study TKA).

Study IV

In Study IV, the OKS pain subscale and BPI-SF (average pain, worst and least pain in 24 hours, current pain, mean pain severity and mean pain interference) scores at 12 months after TKA were the main outcomes. The same pain scores at 3 months were secondary outcomes, as were changes in these pain scores at 3 and 12 months after TKA, which were examined in a post hoc sensitivity analysis. We also explored the occurrence of significant PPP at 3 and 12 months after TKA according to a number of risk factors. Based on earlier studies[8,101,121,122,126,137,138], we used five different definitions for significant PPP to illustrate the effect of the definition on the results and to enable comparability between studies. Two definitions were derived from the OKS (answers between moderate and severe to the question concerning usual knee pain in the previous 4 weeks and OKS pain subscale scores of ≤ 14/28) and three from the BPI-SF average pain (NRS with cut-offs of ≥ 3, ≥ 4 and ≥ 5).

4.6 Statistical analyses

4.6.1 Sample size calculations

Sample sizes were calculated with parametric methods. We used two-tailed tests with an alpha level of 0.05 and a power of 0.8. After calculations, we increased the results by 16% to adjust for possible non-parametric analyses.

Study I

We used the results of a previously published RCT[7] to approximate intravenous opioid consumption during the first 24 postoperative hours after TKA. In that RCT, the median consumption of morphine with PCA during those 24 hours was 19 mg (interquartile range [IQR] 11–28) in the general anaesthesia group and 54 mg (IQR 37–78) in the spinal anaesthesia group. In Study I, a 20% difference in opioid consumption between groups was defined as clinically significant. Thus, the minimum sample size in two-group comparisons was calculated as 104 participants/group. To detect overall differences in four-group comparisons, the minimum sample size was calculated as 71 participants/group.

Studies II and IV

For Studies II and IV, sample size calculation addressed BPI-SF average pain. In a previous study, the mean BPI-SF average pain as measured by NRS before TKA was 5.4 (standard deviation [SD] 2.2).[139] We set an NRS of 1.0 as the MCID between groups.[68,69] Thus, the minimum sample size for non-parametric comparisons was 90 participants/group.

Study III

We used correlations for sample size calculations in Study III. To detect the threshold for weak correlation (Pearson correlation coefficient = 0.3) and possible correlation (Pearson correlation coefficient ≥0.5) between BFP and continuous outcomes, the minimum sample sizes were 85 and 29 participants, respectively.

4.6.2 Data presentation and analyses

Categorical data were presented as frequencies with percentages, normally distributed data as means with SDs, and non-normally distributed data as medians with IQRs.

We used IBM SPSS (IBM Corp., Armonk, NY, USA) versions 25 (Study I), 26 (Study II) and 27 (Studies III and IV) for all analyses except for the stratified Mann–Whitney *U*-test, which was conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Studies I and II

Categorical data were analysed using binary logistic regression in two-group comparisons and the χ^2 test or Fisher's exact test in four-group comparisons, with further Bonferroni adjustments used in pairwise comparisons.

In Study I, normally distributed data were analysed using the independent samples *t*-test in two-group comparisons and one-way analysis of variance (ANOVA) in four-group comparisons, with Tukey's method applied in pairwise comparisons. Non-normally distributed data were analysed using the Mann–Whitney *U*-test in two-group comparisons and Kruskal–Wallis test in four-group comparisons, with Bonferroni-adjusted Mann–Whitney *U*-test used in pairwise comparisons.

In Study I, in addition to unadjusted analyses, we conducted an analysis in which the comparisons between the anaesthesia groups were adjusted for tourniquet use and comparisons between tourniquet and no-tourniquet groups were adjusted for anaesthesia method. Adjusted analyses were conducted using logistic regression for categorical data, linear model for normally distributed data, and stratified Mann–Whitney *U*-test for non-normally distributed data. The results were reported as odds ratios (ORs, 95% confidence interval [CI]), mean differences (95% CI), and Hodges–Lehmann estimates for median differences (95% CI).

In Study II, continuous data concerning changes in pain scores at 3 and 12 months postoperative versus preoperative scores were analysed using two-way ANOVA, with main effects for tourniquet (tourniquet versus no tourniquet) and anaesthesia (general versus spinal) and an interaction effect between tourniquet and anaesthesia. The results in Study II were reported as ORs (95% CI) and as estimated marginal mean differences (95% CI).

Study III

We analysed continuous outcomes using the Spearman and Pearson correlations for non-normally and normally distributed data, respectively. We also analysed continuous data using the general linear model adjusted for sex, age, anaesthesia method (spinal or general), tourniquet use (yes/no), ASA classification (class I to II or III) and primary diagnosis (primary OA or other); the preoperative score of the corresponding postoperative score was set as the covariate for applicable variables.

Significantly positively skewed data were transformed to follow normal distribution with natural logarithm. In addition, we conducted a sensitivity analysis for slightly negatively skewed data by using square transformations, for slightly positively skewed data by using square root transformations or by removing outliers.

We analysed dichotomous outcomes with adjusted and unadjusted binary logistic regression. If the number of events was fewer than 10 per adjusting variable (i.e., less than 60 events overall), we included the outcome in a sensitivity analysis with a reduced number of adjusting variables to estimate the possible effect of

overparameterization. The results were presented as correlation coefficients and as regression coefficients (95% CI) and ORs (95% CI) for 1-unit increases in BMI or BFP.

Study IV

Owing to uneven patient distribution in different risk groups (i.e., 33 patients in the low-risk group, 100 in the moderate-risk group and 259 in the high-risk group), the main analyses in Study IV were conducted by comparing the combined low- to moderate-risk group with the high-risk group. Otherwise, the power in the analyses would not have been sufficient. However, an additional sensitivity analysis was performed to explore possible differences between all the separate risk groups.

Categorical data were analysed using the χ^2 test and Fisher's exact test, with further Bonferroni adjustments in pairwise comparisons in cases where more than two groups were analysed. In two-group comparisons, we analysed normally distributed continuous data using the independent samples *t*-test and non-normally distributed continuous data using the Mann–Whitney *U*-test. In three-group comparisons, we analysed normally distributed continuous data using one-way ANOVA, with Tukey adjustments in pairwise comparisons, and non-normally distributed continuous data using the Kruskal–Wallis test, with Bonferroni-adjusted Mann–Whitney *U*-test in pairwise comparisons. The results were presented as Hodges–Lehman estimates of median differences (95% CI) and mean differences (95% CI).

4.6.3 Handling of randomization deviations and missing data

Intention-to-treat analysis is recommended over per-protocol analysis in RCTs.[140] However, after discussions with the biostatistician of our study, it was concluded that the use of per-protocol analyses would be appropriate due to the very low number of randomization deviations.

In Studies II to IV, the means of the BPI-SF pain interference and severity scores were included in the analyses if at least four of seven interference variables and three of four severity variables were rated. In Studies III and IV, we imputed missing values of the OKS subscales with the mean value of rated variables in that subscale when only a single value was missing. In Study III, we imputed missing values in the 15D by using a multiple imputation procedure if a maximum of three of 15 values were missing.

5 RESULTS

5.1 Timeline

We began to recruit patients in October 2016, and the last TKA was performed in December 2018. Thus, 3-month follow-ups were completed in March 2019 and 12-month follow-ups in December 2019.

5.2 Patient recruitment, randomization and exclusions

During the recruitment phase, we evaluated a total of 2783 patients, 413 of whom agreed to participate in the study. Reasons for excluding patients are presented in Table 4. Ultimately, 404 patients were randomized (Figure 1).

Table 4. *Reasons for exclusion*

	n	**%**
Evaluated patients	2783	100
Recruited patients	413	15
Excluded patients	2370	85
Age above 75 years	579	21
Patient did not want to participate	335	12
Contraindication(s) to study medication	257	9
Orthopaedic surgeon did not participate in the study	232	8
Endoprosthesis type differed from study protocol	200	7
Day of surgery was not feasible for study personnel	136	5
Prior major surgery on the target knee	128	5
Contraindication(s) to spinal or general anaesthesia	128	5
Patient was unable to understand study information (cognition or language)	79	3
Knee anatomy (severe malalignment, flexion or extension deficit, type of osteoarthritis)	65	2
Body mass index greater than 40 kg/m^2	62	2
Surgery cancelled or postponed	38	1
Patient had already participated in this study	37	1
Bilateral knee arthroplasty	23	1
Patient required bridging anticoagulation or had a bleeding disorder	23	1
Other	48	2

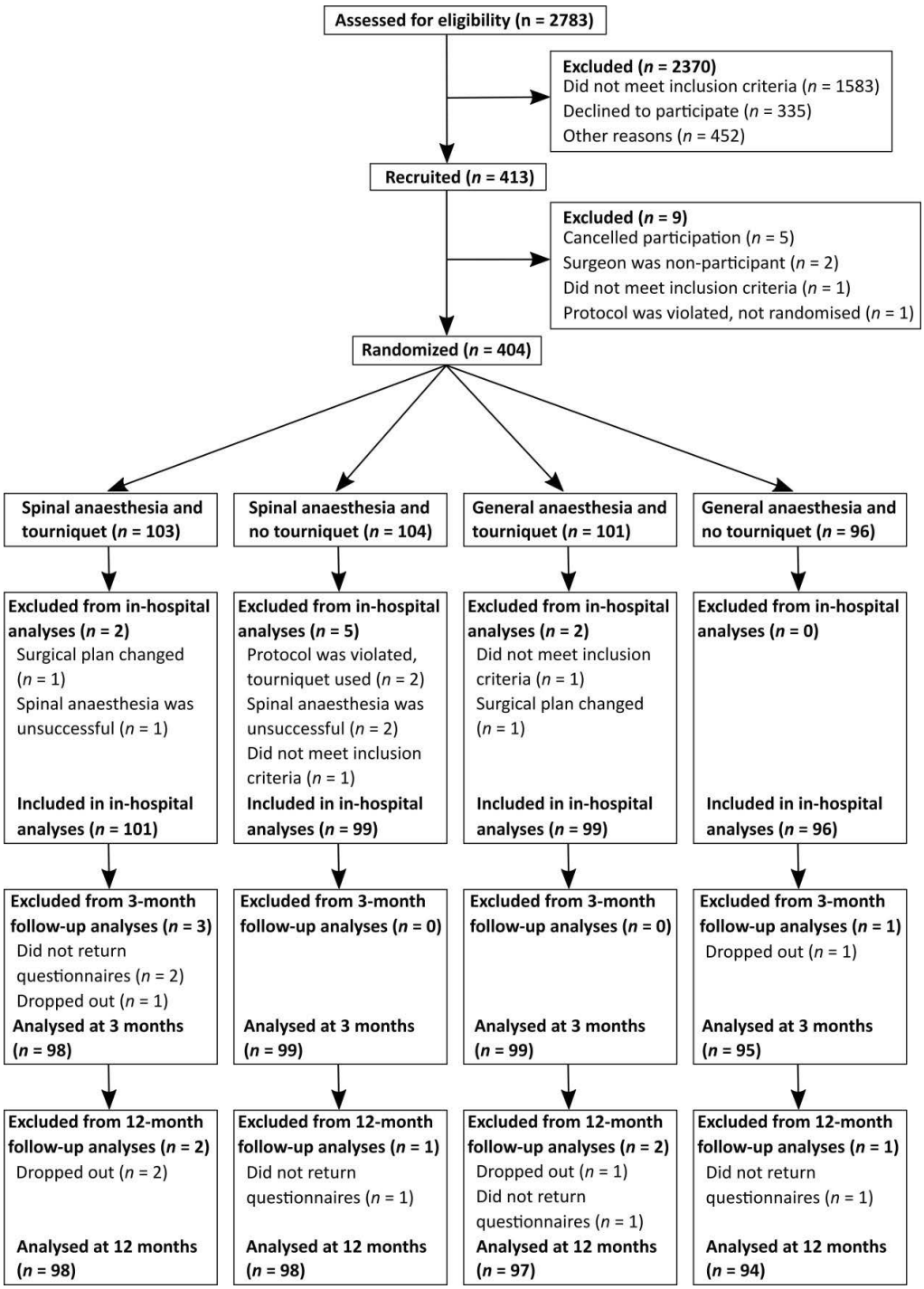

Figure 1. Consolidated Standards of Reporting Trials flow diagram, Studies I and II.

In Studies I to IV, two randomized patients were excluded from the analyses because their surgical plan changed, and they received non-protocol prostheses. Two other patients were excluded because they did not meet the study's Kellgren–Lawrence grade inclusion criterion. Furthermore, data on one patient with unsuccessful spinal anaesthesia were not collected by mistake. Thus, baseline data included information on 399 patients.

In Studies II to IV, two patients withdrew from the study prior to the 3-month follow-up. In addition, three patients informed us that they would not attend the 12-month follow-up visit or return the 12-month questionnaires.

5.3 Studies I and II: Effects of anaesthesia and tourniquet methods

5.3.1 Patients

In Studies I and II, five patients with randomization deviations (including the patient with unsuccessful spinal anaesthesia whose data were not collected, two other patients with unsuccessful spinal anaesthesia and two patients whose protocol concerning tourniquet use was violated) were excluded from the analyses (Figure 1). Thus, in-hospital data were analysed from 395 patients (Table 5).

Table 5. *Patient characteristics in randomization groups, Studies I and II*

Characteristic	Spinal anaesthesia and tourniquet (*n* = 101)	Spinal anaesthesia and no tourniquet (*n* = 99)	General anaesthesia and tourniquet (*n* = 99)	General anaesthesia and no tourniquet (*n* = 96)
Age, mean years (SD)	64 (7)	63 (8)	63 (7)	65 (7)
Females, *n* (%)	73 (72)	58 (59)	61 (62)	59 (61)
Body mass index, mean kg/m^2 (SD)	31 (5)	31 (4)	31 (4)	30 (4)
American Society of Anesthesiologists classification, *n* (%)				
I	10 (10)	8 (8)	10 (10)	8 (8)
II	57 (56)	63 (64)	62 (63)	62 (65)
III	34 (34)	28 (28)	27 (27)	26 (27)
Reason for operation, *n* (%)				
Primary osteoarthritis	93 (92)	91 (92)	93 (94)	92 (96)
Rheumatoid or psoriatic arthritis	5 (5)	4 (4)	1 (1)	2 (2)
Posttraumatic arthritis	1 (1)	3 (3)	3 (3)	1 (1)
Other	2 (2)	1 (1)	2 (2)	1 (1)

In Study II, the 3- and 12-month follow-up data were analysed from 391 and 387 patients, respectively (Figure 1), while the 12-month data concerning prescriptions for strong opioids and gabapentinoids were derived from 390 patients.

5.3.2 Results concerning in-hospital outcomes

The primary outcome in Study I – cumulative oxycodone consumption with PCA during the first 24 postoperative hours – did not differ significantly between the anaesthesia or tourniquet groups. In the comparison between the spinal and general anaesthesia groups, the median doses were 37.7 mg (IQR 25.3–57.4) and 42.4 mg (IQR 26.7–62.5), respectively, and the estimate for median difference was −3.1 mg (95% CI −7.4 to 1.2, $P = 0.15$). In a comparison between the no-tourniquet and tourniquet groups, the median doses of oxycodone by PCA were 40 mg (IQR 26.0–57.5) and 40 mg (IQR 27.3–62.0), respectively, and the estimate for median difference was −0.8 mg (95% CI −5.1 to 3.5, $P = 0.72$). In addition, comparison between the combined spinal anaesthesia and tourniquet (38.0 mg [IQR 26.0–61.6]), spinal anaesthesia and no-tourniquet (36.6 mg [IQR 24.0–55.2]), general anaesthesia and tourniquet (42.5 mg [IQR 28.6–62.5]) and general anaesthesia and no-tourniquet (42.3 mg [IQR 27.2–63.5]) groups revealed a non-significant difference in cumulative doses of oxycodone with PCA ($P = 0.42$). Furthermore, no significant differences in the two- or four-group comparisons in the use of oral oxycodone, pregabalin or peripheral nerve blocks during the hospital stay were detected.

In the recovery room, the spinal anaesthesia group reported less pain than the general anaesthesia group (median NRS 0.0 [IQR 0.0–0.0] vs 2.0 [IQR 0.0–3.0], difference −2.0 [95% CI −2.5 to −2.0], $P < 0.001$). At 24 hours after surgery, the spinal anaesthesia group reported more pain than the general anaesthesia group in supine position at rest (mean NRS 3.6 [SD 2.1] vs 3.1 [SD 2.3], difference 0.5 [95% CI 0.1 to 0.9], $P = 0.025$), after flexing hip 45° (mean NRS 5.7 [SD 2.5] vs 5.1 [SD 2.4], difference 0.6 [95% CI 0.1 to 1.1], $P = 0.021$) and after walking 5 meters (mean NRS 5.7 [SD 2.1] vs 5.2 [SD 2.3], difference 0.5 [95% CI 0.02 to 0.9], $P = 0.039$). However, as the mean differences between the groups remained below NRS 1.0, they were not considered clinically important. Whether surgery was performed with or without a tourniquet had no significant effect on reported pain in the recovery room or at 24 hours after TKA. In the four-group comparisons, spinal anaesthesia groups had less pain in the recovery room than the general anaesthesia groups, regardless of whether tourniquet was used. However, differences in pain between the four groups were not significant at 24 hours.

The incidence of postoperative nausea at 24 hours and vomiting during the first 24 hours was higher in the spinal than in the general anaesthesia group (45 % vs 28%, OR 2.1 [95% CI 1.4 to 3.1], $P < 0.001$ and 21% vs 13%, OR 1.8 [95% CI 1.05 to 3.1], $P = 0.034$, respectively). The tourniquet groups did not differ significantly regarding

incidence of PONV. In four-group comparisons, the general anaesthesia and tourniquet group reported less nausea at 24 hours than the spinal anaesthesia and tourniquet and the spinal anaesthesia and no-tourniquet group (23% vs 49%, *P* = 0.001 and 23% vs 41%, *P* = 0.043, respectively). However, the use of antiemetics did not differ in any comparison.

The anaesthesia groups did not differ in terms of changes in haemoglobin level at first postoperative day versus preoperative level. However, changes in haemoglobin level were more substantial in the no-tourniquet than in the tourniquet group (−3.0 g/dl vs −2.5 g/dl, mean difference −0.48 [95% CI −0.65 to −0.32], *P* < 0.001). Similarly, in four-group comparisons, haemoglobin levels decreased more in the no-tourniquet than in the tourniquet groups. However, none of the differences in the incidence of red blood cell transfusion was significant. The incidence of adverse events did not differ significantly in two- or four-group comparisons. The median LOS was not significantly different between the spinal and general anaesthesia groups (53 hours [IQR 49–72] vs 53 hours [IQR 48–72], respectively; difference 0.0 [95% CI −1.0 to 2.0], *P* = 0.58) or between the no-tourniquet and tourniquet groups (54 hours [IQR 49–72] vs 52 hours [IQR 49–72], respectively; difference 1.0 [95% CI −1.0 to 2.0], *P* = 0.36). Similarly, median LOS did not differ significantly between the combined spinal anaesthesia and tourniquet (52 hours [IQR 50–72]), spinal anaesthesia and no-tourniquet (54 hours [IQR 48–72], general anaesthesia and tourniquet (52 hours [IQR 48–72]) and general anaesthesia and no-tourniquet (53 hours [IQR 49–73]) groups (*P* = 0.43).

All the results from the adjusted analyses in two-group comparisons (anaesthesia methods adjusted for tourniquet use and vice versa) were similar to the results of the unadjusted analyses.

5.3.3 Results concerning persistent pain

In Study II, the change in average pain (postoperative minus preoperative) 12 months after surgery did not differ significantly between the spinal and general anaesthesia groups (NRS −2.6 [SD 2.5] vs −2.3 [SD 2.5], respectively; difference −0.4 [95% CI −0.9 to 0.1], *P* = 0.150).

In other comparisons between anaesthesia groups, the mean of seven pain interference scores decreased more in the spinal than in the general anaesthesia group at both 3 months (NRS −2.3 [SD 2.5] vs −1.6 [SD 2.7]; difference −0.7 [95% CI −1.2 to −0.1], *P* = 0.014) and 12 months (NRS −3.1 [SD 2.5] vs −2.4 [SD 2.5]; difference −0.8 [95% CI −1.3 to −0.3], *P* = 0.003) after TKA. In addition, at 12 months, the spinal anaesthesia group reported larger decreases than the general anaesthesia group in the BPI-SF scores concerning the least pain in the previous 24 hours (NRS −1.4 [SD 1.9] vs −0.9 [SD 1.8]; difference −0.6 [95% CI −0.9 to −0.2], *P* = 0.003) and in the mean scores of four pain severity variables (NRS −2.3 [SD 2.2] vs

−1.8 [SD 2.1]; difference −0.5 [95% CI −0.9 to −0.05], *P* = 0.029). However, none of the differences reached the predefined MCID threshold of NRS = 1.0.

In comparisons between tourniquet groups, the no-tourniquet group reported lower reductions in average pain at 12 months than the tourniquet group (NRS −2.1 [SD 2.7] vs −2.8 [SD 2.3]; difference 0.6 [95% CI 0.1 to 1.1], *P* = 0.012). However, this difference did not reach the predefined MCID threshold of NRS = 1.0.

At 3 months after TKA, no differences in changes in pain scores between tourniquet groups were detected. However, at 12 months, the no-tourniquet group reported smaller reductions than the tourniquet group in BPI-SF pain scores concerning worst and least pain in the previous 24 hours (NRS −2.4 [SD 3.2] vs −3.2 [SD 2.8]; difference 0.8 [95% CI 0.2 to 1.4], *P* = 0.014, and NRS −1.0 [SD 1.9] vs −1.3 [SD 1.8]; difference 0.4 [95% CI 0.03 to 0.8], *P* = 0.036, respectively), current pain (NRS −1.4 [SD 2.7] vs −2.1 [SD 2.4]; difference 0.6 [95% CI 0.1 to 1.1], *P* = 0.016) and mean of four pain severity variables (NRS −1.7 [SD 2.3] vs −2.3 [SD 2.0]; difference 0.6 [95% CI 0.2 to 1.0], *P* = 0.005). Again, these differences were not regarded as clinically important.

The interaction effect between anaesthesia and tourniquet remained non-significant in all pain variables at 3 and 12 months after TKA, indicating that the effect of anaesthesia on pain did not differ between the tourniquet and no-tourniquet groups and that the effect of tourniquet on pain did not differ between the spinal and general anaesthesia groups.

In post hoc analyses based on the OKS-derived definition of moderate to severe knee pain, the prevalence of PPP was lower in the spinal than in the general anaesthesia group at 12 months after surgery (4% vs 10%, OR 0.4 [95% CI 0.2 to 0.9], *P* = 0.028). However, using three definitions based on the BPI-SF, the prevalence of moderate to severe PPP did not differ significantly between anaesthesia groups at 3 or 12 months after TKA. Regardless of how PPP was defined, its prevalence was not significantly different between tourniquet groups at either 3 or 12 months after TKA.

Only eight of 390 patients (2%) were prescribed oxycodone, while 40 patients (10%) received prescriptions for gabapentinoids because of study operation within 1 year after surgery. Neither anaesthesia nor tourniquet groups differed in terms of the number of patients who received prescriptions for these analgesics.

5.4 Study III: Predictive performance of adiposity status

5.4.1 Patients

In Study III, all 399 patients were included in the BMI cohort. However, the BFP cohort consisted of 294 patients, as we did not measure BFP in 104 patients, and one patient's BFP was recorded incorrectly. Patient characteristics of the BMI and BFP cohorts are presented in Table 6.

Table 6. *Patient characteristics, Study III*

Characteristic	Body mass index cohort (*n* = 399)	Body fat percentage cohort (*n* = 294)
Age, mean year (SD)	64 (7)	64 (7)
Females, *n* (%)	251 (63)	180 (61)
Body fat percentage, mean % (SD)	-	37 (10)
Body mass index, mean kg/m^2 (SD)	30 (4)	31 (4)
American Society of Anesthesiologists classification, *n* (%)		
I	37 (9.3)	29 (9.9)
II	246 (61.7)	188 (63.9)
III	116 (29.1)	77 (26.2)
Reason for operation, *n* (%)		
Primary osteoarthritis	373 (93.5)	274 (93.2)
Rheumatoid or psoriatic arthritis	12 (3.0)	6 (2.0)
Posttraumatic arthritis	8 (2.0)	8 (2.7)
Other	6 (1.5)	6 (2.0)

Note: The body fat percentage cohort is a subgroup of the body mass index cohort.

5.4.2 Results

All correlations between BFP and continuous outcomes remained under the threshold of weak correlation. In multivariable analyses, preoperative BFP was predictive of only a single studied outcome. Baseline adjusted knee ROM decreased 0.37° (95% CI −0.60 to −0.12, *P* = 0.003) for a 1-unit increase in BFP at 12 months after TKA. BFP was not significantly associated with duration of surgery, LOS, oxycodone consumption, pain in the recovery room or 24 hours after surgery nor patient-reported pain, function or health-related quality of life at 3 or 12 months after surgery.

In the adjusted analyses, BPF was not significantly associated with any of the studied dichotomous outcomes, such as patient satisfaction with TKA 3 and 12 months after surgery. Sensitivity analyses concerning slightly skewed continuous data and dichotomous data with reduced number of adjusting variables revealed results that were in line with the main analyses.

In post hoc analyses, none of the correlations between BMI and continuous outcomes reached the threshold for weak correlation. In multivariable analyses, increase in BMI was significantly associated with increased duration of surgery (a 1-unit increase in BMI added time by 0.57 minutes [95% CI 0.10 to 1.04], $P = 0.018$) but not with LOS, oxycodone consumption or pain in the recovery room and 24 hours after surgery. Increase in BMI decreased mean pain severity and mean pain interference scores at 3 months after TKA (NRS −0.04 [95% CI −0.08 to −0.00], $P = 0.048$, and NRS −0.06 [95% CI −0.11 to −0.004], $P = 0.035$ for 1-unit increases in BMI, respectively). Consistently, a 1-unit increase in BMI was associated with increase in OKS pain subscale scores at 3 months (0.52 [95% CI 0.10 to 0.95], $P = 0.016$). However, at 12 months, BMI was no longer significantly associated with reported pain. ROM decreased by 0.47° (95% CI −0.74 to −0.20, $P < 0.001$) for a 1-unit increase in BMI at 12 months. However, BMI was not significantly associated with patient-reported function or health-related quality of life at either 3 or 12 months after TKA.

In the adjusted analyses concerning dichotomous outcomes, the odds of the use of antiemetics during the hospital stay decreased when BMI increased (OR 0.92 [95% CI 0.87 to 0.97] for a 1-unit increase in BMI, $P = 0.002$). However, other outcomes, such as vomiting during the first 24 postoperative hours or nausea at 24 hours, were not significantly associated with BMI. Sensitivity analyses concerning dichotomous data with a reduced number of adjusting variables and slightly skewed continuous data revealed results in line with the main analyses.

5.5 Study IV: Applicability of the predictive risk index for persistent pain

5.5.1 Patients

In Study IV, data concerning acute postoperative pain after walking 5 meters or inability to walk due to pain were missing from 14 of 399 patients. However, we were able to include seven of these patients in the high-risk group for PPP based on their preoperative risk factors. Thus, 392 patients were included in the baseline analyses (Table 7).

Table 7. *Patient characteristics in risk groups for persistent postsurgical pain, Study IV*

Characteristic	Low to moderate risk (*n* = 133)	High risk (*n* = 259)	*P*-value
Age, mean years (SD)	65 (7)	63 (7)	0.004[a]
Females, *n* (%)	72 (54)	177 (68)	0.006
Body mass index, mean kg/m^2 (SD)	30 (4)	31 (4)	0.009[b]
Depression, *n* (%)	3 (2)	24 (9)	0.009
Rheumatological disease, *n* (%)	3 (2)	27 (10)	0.004
American Society of Anesthesiologists classification, *n* (%)			0.029
I	16 (12)	19 (7)	
II	89 (67)	155 (60)	
III	28 (21)	85 (33)	0.045[c]
Reason for operation, *n* (%)			0.059
Primary osteoarthritis	130 (98)	236 (91)	
Rheumatoid or psoriatic arthritis	1 (1)	11 (4)	
Posttraumatic arthritis	2 (2)	6 (2)	
Other	0 (0)	6 (2)	

Notes: [a]Mean difference 2.2 (95% CI 0.72 to 3.8); [b]Mean difference −1.2 (95% CI −2.1 to −0.3); [c]Bonferroni-adjusted *P*-value.

5.5.2 Results

Patients in the high-risk group were younger and had higher BMI than patients in the low- to moderate-risk group (Table 7). In addition, patients in the high-risk group were more often females and had rheumatological disease, depression or ASA class III than patients in the low- to moderate-risk group (Table 7).

The OKS pain subscale scores were higher (i.e., better) in the low- to moderate-risk group than in the high-risk group preoperatively (52 [SD 13] vs 47 [SD 13]; mean difference 5 [95% CI 2 to 8], $P < 0.001$), at 3 months after TKA (76 [SD 16] vs 70 [SD 18]; mean difference 6 [95% CI 3 to 10], $P < 0.001$), and at 12 months after TKA (93 [IQR 86–100] vs 89 [IQR 79–96]; estimated median difference 4 [95% CI 0 to 4], $P = 0.027$). However, although these differences were statistically significant, they did not reach the MCID threshold between groups (OKS subscale scores of ≥ 10/100).

All BPI-SF derived NRS pain scores were significantly higher in the high-risk than in the low- to moderate-risk group at all time points, with one exception: least pain in the last 24 hours did not differ significantly between the groups at 12 months after TKA. Preoperatively, all differences between the groups reached the predefined MCID thresholds; that is, NRS differences were either −1.0 or −1.5. In addition, at 3 months after surgery, all but the least pain in the last 24 hours score reached the predefined MCID thresholds; that is, NRS differences ranged from 0 to −1.5. However, at 12 months, only the difference concerning the worst pain in the last 24 hours reached the MCID threshold between the low- to moderate-risk and high-risk groups (NRS 2.0 [IQR 0.0 to 4.0] vs 3.0 [IQR 0.0 to 5.0], respectively; estimated median difference −1.0 [95% CI −1.0 to 0.0], $P = 0.003$).

In sensitivity analysis regarding changes in pain scores at 12 months, the low- to moderate-risk group reported less improvement than the high-risk group in scores concerning the arithmetic mean of seven pain interference variables (NRS −2.4 [SD 2.3] vs −3.0 [SD 2.6]; mean difference 0.7 [95% CI 0.1 to 1.2], $P = 0.013$), least pain in the last 24 hours (NRS −0.9 [SD 1.7] vs −1.3 [SD 2.0]; mean difference 0.5 [95% CI 0.1 to 0.9], $P = 0.025$), and current pain (NRS −1.4 [SD 2.5] vs −2.0 [SD 2.6]; mean difference 0.6 [95% CI 0.1 to 1.2], $P = 0.025$). However, none of these differences reached the MCID threshold.

In the additional sensitivity analyses concerning three separate risk groups, no differences in postoperative pain scores between the low- and moderate-risk groups appeared. The patients in the high-risk group reported more pain 3 and 12 months postoperatively than patients in the low-risk and moderate-risk groups, but the changes in pain scores were not significantly different between the three groups at 3 months. Moreover, at 12 months, only a single significant difference in change scores arose: pain interference had declined less in the low-risk than in the high-risk group (NRS −1.9 [SD 1.8] vs −3.0 [SD 2.6]; mean difference 1.2 [95% CI 0.1 to 2.3], $P = 0.033$).

The prevalence rates for significant PPP (using five different definitions) at 3 and 12 months after TKA according to the number of the risk factors are presented in Figure 2. With the different definitions used, the prevalence rates for PPP at 12 months after TKA ranged from 2% to 29% in the low- to moderate-risk group and from 4% to 41% in the high-risk group.

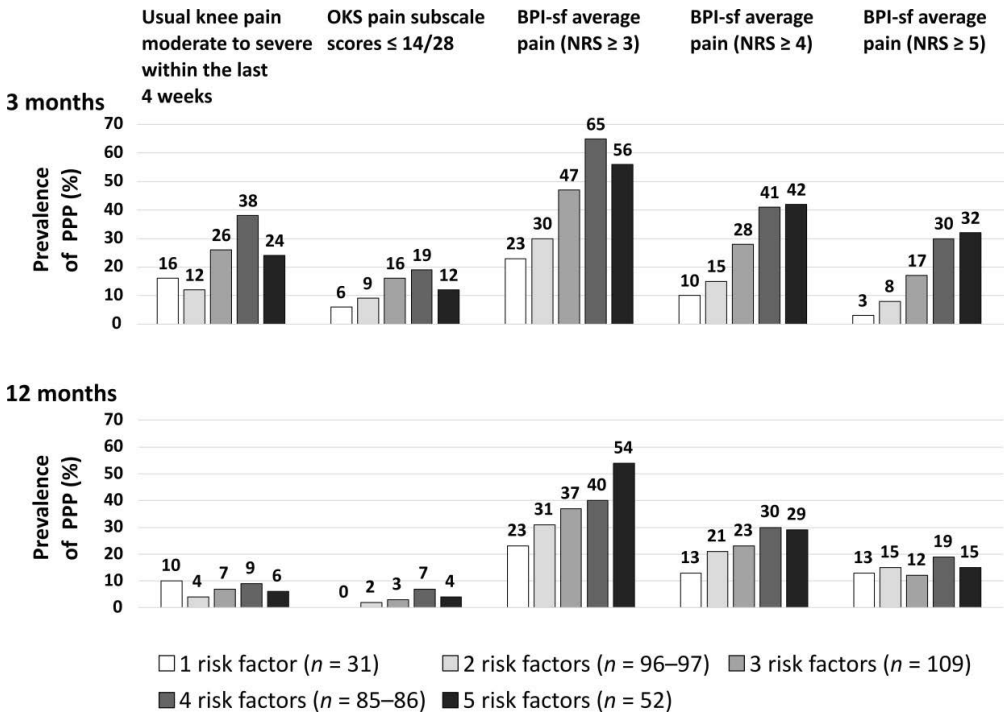

Figure 2. Association between the number of predictive risk factors for PPP and the prevalence of PPP after TKA, according to five different definitions. Data concerning two patients who reported no risk factors are not shown.

6 DISCUSSION

Owing to limited previous data, we conducted a randomized trial and a prespecified secondary analysis to investigate the effects of anaesthesia methods (spinal versus general) and tourniquet use (yes versus no) on early recovery, including pain management, pain, PONV, adverse events and LOS, as well as on PPP at 3 and 12 months after TKA. We hypothesized that the effects of the compared anaesthesia methods and tourniquet regimens would not differ significantly. In addition, we investigated the predictive performance of BFP and BMI on multiple TKA-related outcomes and the applicability of a previously presented predictive risk index for PPP to TKA patients. Our hypotheses were that increase in BFP would be predictive of poor outcomes and that the risk index would be applicable to predicting PPP on TKA patients.

6.1 Anaesthesia methods, in-hospital results and persistent pain after TKA

The cumulative doses of intravenous oxycodone taken by the patients by PCA during the first 24 postoperative hours did not differ significantly between the spinal and general anaesthesia groups. Thus, our results were not in line with a previous RCT of 120 patients that reported higher morphine consumption by PCA during the first 24 hours in the spinal anaesthesia group.[7] This difference between the results might have originated from slight differences in study designs and especially sample size differences. Additionally, no significant differences in the use of oral oxycodone or rescue pain-relieving methods during the hospital stay emerged between the anaesthesia groups. This is consistent with previous studies.[83,84,88]

The spinal anaesthesia group reported less pain in the recovery room prior to transfer to surgical ward than the general anaesthesia group. This was an expected finding because sensory recovery after spinal anaesthesia was not required before the transfer. At 24 postoperative hours, the spinal anaesthesia group reported more pain than the general anaesthesia group. However, unlike in the previous RCT with a similar finding,[7] the differences in pain on the first postoperative day did not reach the MCID threshold we established in our study. Thus, our results are consistent with a recent retrospective study that reported no differences in early acute pain between the spinal and general anaesthesia groups.[88]

The incidence of nausea at 24 postoperative hours and vomiting during the first 24 hours after TKA was higher in the spinal than in the general anaesthesia group; a comparable result was previously reported.[7] These findings are interesting because the use of general instead of regional anaesthesia is considered a risk factor for

PONV.[141] This raises the question of whether the recommendation[141] to use regional anaesthesia in order to decrease the risk of PONV should be applied to TKA patients.

The number of adverse events, decreases in haemoglobin levels, number of red blood cell transfusions and LOS did not differ significantly between the spinal and general anaesthesia groups. Thus, our results were not consistent with a recent meta-analysis that supported the use of neuraxial over general anaesthesia because of lower risk of postoperative complications and blood transfusions and LOS that was approximately 2 hours shorter.[75] However, in our study, the sample size was not large enough to investigate the incidence of rarely occurring complications. Additionally, we analysed only adverse events concerning the in-hospital period, and spinal anaesthesia was the only neuraxial method studied. Thus, our divergent results may arise at least partly from these differences in the studies.

At 3 and 12 months after TKA, some pain scores had decreased more in the spinal than in the general anaesthesia group; however, none of the differences between the groups was regarded as clinically important. In post hoc analysis, the prevalence of OKS-based moderate to severe knee pain at 12 months was higher in the general than in the spinal anaesthesia group; however, results based on the BPI-SF revealed no differences between the groups in PPP prevalence at 12 months. These results support earlier reports which indicated that the type of anaesthesia is not predictive of PPP after TKA.[72,83]

The number of patients who received prescriptions for gabapentinoids or strong opioids for postoperative knee pain within 1 year after TKA did not differ between the anaesthesia groups. Overall, only 2% were prescribed strong opioids. This is consistent with another study which reported that only a low proportion of patients received prescriptions for strong opioids after TKA.[142] These data suggest that prescriptions for strong opioids are only rarely necessary after TKA, at least in the Finnish population.

6.2 Tourniquet use, in-hospital results and persistent pain after TKA

The tourniquet and no-tourniquet groups did not differ in terms of pain management during the hospital stay in our study. This result is in line with the results of two small RCTs.[57,61]

In our results, pain in the recovery room and at 24 hours after surgery did not differ between the groups. These findings were not consistent with previous studies, which reported that the use of tourniquet increases acute pain.[53,54,56,58,59] However, some of the previously reported differences[56,59] might be regarded as only statistically significant and not clinically important (i.e., differences between groups

were < 1.0 on the NRS or on a visual analogue scale from 0 to 10). Some studies have also reported that acute pain did not differ between the tourniquet and no-tourniquet groups.[51,60]

In the current study, the use of tourniquet reduced declines in haemoglobin levels. This was inconsistent with studies that reported no differences in total blood loss between tourniquet and no-tourniquet groups.[55-58] Timepoints of haemoglobin measurements might explain at least some of the differences between the results. Nevertheless, in our results, the mean difference in change of haemoglobin levels between the groups was approximately 0.5 g/dl, which might be regarded clinically unimportant. Additionally, no difference in the need for blood transfusions emerged, a finding that is in line with earlier reports.[52-56,59]

A recent meta-analysis with 995 patients from 12 studies reported that tourniquet use in TKA increased LOS.[58] However, some of the studies included in that meta-analysis were published more than 20 years ago. In our results, LOS did not differ significantly between the tourniquet groups. Similarly, those groups did not differ in terms of PONV or adverse events such as peroneal nerve damage or falling. Thus, our results did not support previous data suggesting that tourniquet use is associated with a higher rate of complications than operating without a tourniquet.[49,55] However, the sample size in our study was not large enough to investigate possible differences in the incidence of rare adverse events.

Our result concerning the effect of tourniquet use on PPP after TKA revealed that the tourniquet group had better improvements in pain severity outcomes than the no-tourniquet group at 12 months after surgery. However, the differences between the groups were not considered clinically important. Additionally, regardless of the definition of PPP, its prevalence did not differ between the groups at 3 or 12 months after TKA. Furthermore, no differences concerning prescriptions for gabapentinoids or strong opioids appeared. These results support previous data which indicated no difference in PPP after TKA between patients who underwent surgery with or without a tourniquet.[52,53,57,59,60,64]

6.3 Combined anaesthesia and tourniquet regimens and outcomes after TKA

In Study I, in addition to comparing the effects of spinal versus general anaesthesia and tourniquet versus no tourniquet on TKA-related outcomes, we compared the effects of combined anaesthesia and tourniquet regimens. The idea was to explore whether a given combination would lead to significantly better outcomes than the others. We did not find any corresponding comparisons from previous literature.

Briefly put, none of the four combined anaesthesia (spinal or general) and tourniquet (yes or no) regimens revealed clear advantages over the others during

the hospital stay. Patients in the spinal anaesthesia groups had less pain in the recovery room than patients in the general anaesthesia groups, regardless of tourniquet use. However, at 24 hours after TKA, pain scores did not differ across the four groups. The combined general anaesthesia and tourniquet group had less nausea than the spinal anaesthesia and tourniquet or the spinal anaesthesia and no-tourniquet group 24 hours after surgery. However, differences in the incidence of vomiting and use of antiemetics were not significant. Regardless of anaesthesia method, tourniquet groups had lower decreases in haemoglobin levels, but no differences in blood transfusion rates were detected across the four groups. Similarly, differences in the incidence of adverse events and LOS were not significant.

In Study II, instead of comparing the four combined groups separately, we investigated the interaction effect between anaesthesia and tourniquet. This effect was not significant in any pain variable at 3 or 12 months after surgery.

6.4 Predictive performance of adiposity status on TKA-related outcomes

Of all the investigated outcomes in Study III, increase in BFP was only significantly associated with a decrease in ROM at 12 months after surgery, and the clinical importance of this finding is debatable. Duration of surgery, LOS, pain management during the hospital stay and pain in the recovery room, at 24 hours, 3 months and 12 months after surgery were not associated with increasing BFP. Similarly, BFP was not predictive of adverse events or patient-reported function, health-related quality of life or satisfaction with TKA during the 12-month follow-up. Thus, our results were not consistent with the results of two previous studies which indicated that BFP might have predictive ability regarding pain, function and adverse events after total hip and knee arthroplasty.[116,117] However, follow-up times, sample sizes, patient cohorts and outcome questionnaires differed, which might help explain differences in the results.

In the post hoc analyses of Study III, increase in BMI increased the duration of surgery, in line with previous reports.[94-96] Increase in BMI also decreased baseline-adjusted ROM 12 months after TKA, as previously reported.[104] However, we did not consider this result clinically relevant. Previous data also suggest that increasing BMI is associated with increased risk of infections,[97,98] revision surgery[97,98] and pulmonary embolism.[96] In our study, only three patients in the BMI cohort had superficial surgical site infection, none had deep infection, three underwent revision surgery, and four were diagnosed with pulmonary embolism. Thus, the number of these adverse events was too low for adequately powered analyses.

Previous data on the effect of increasing BMI on PPP after TKA are conflicting.[99,101,106] In our results, increase in BMI was associated with slight

improvements in pain outcomes at 3 months after TKA. However, at 12 months, no association between increasing BMI and pain scores appeared. Similarly, BMI was not predictive of patient-reported function in our results. This was not consistent with earlier data suggesting that obesity is associated with increased short- and long-term disability.[99] Nevertheless, although obese patients might have poorer function scores after TKA than normal-weight patients, improvements in these scores might not be associated with BMI.[102,103,106] This is further supported by our study, which found no association between increasing BMI and health-related quality of life or satisfaction with TKA 1 year after surgery.

6.5 Applicability of the predictive risk index for persistent pain to TKA patients

In Study IV, we investigated the applicability of a previously presented predictive risk index for PPP[8] to TKA patients. We divided patients into a low- to moderate-risk group and a high-risk group based on the number of risk factors for PPP (0–2 and 3–5, respectively). In the results, the high-risk group reported worse pain scores than the low- to moderate-risk group at both 3 months and 1 year after TKA. At 3 months, differences between the groups in five of seven pain variables reached the MCID threshold. However, only a single of seven differences between the groups reached that threshold at 1 year after surgery. Sensitivity analysis revealed that some of the pain scores improved less in the low- to moderate-risk group than in the high-risk group at 1-year follow-up, but the differences in these improvements did not reach the predefined MCID threshold. The results of additional sensitivity analysis with three separate risk groups were in line with the main analysis.

In the risk index study,[8] the presence of PPP was assessed 6 months after surgery, and the definition of PPP differed from our definitions. The prevalence rates for PPP in that study were higher than in our study, although we used multiple definitions for PPP. These differences might explain, at least partially, why the risk index failed to predict clinically important differences in PPP between the risk groups at 1 year after TKA in our results. However, the 1-year follow-up in our study was well grounded, because 6 months appears to be an insufficient amount of time to assess patient-reported long-term outcomes after TKA,[71,72,143] while 1 year appears to be adequate.[28-30,144]

6.6 Strengths and limitations

A major strength of this thesis is the prospective design of the studies. Study I was an RCT, and Studies II to IV were prespecified secondary analyses of the RCT. Additionally, in each study, the number of patients was substantial, and drop-out rates were consistently low. The inclusion criteria were broad, and the fact that

patients were treated by numerous anaesthesiologists and orthopaedic surgeons might improve the generalizability of the results. The patients were treated according to standardized and modern fast-track protocols, thus reducing the effects of confounding factors and increasing the validity of the results compared to some earlier studies. In addition, the thesis focused strictly on TKA, whereas multiple previous studies investigated combined total hip and knee arthroplasty cohorts. Finally, follow-up time was sufficient, as patient-reported outcomes after TKA appear to remain at the levels found 1 year after surgery.[30,144]

This thesis does have certain notable limitations. The studies were conducted at a single centre, and the exclusion rate was high, limiting the generalizability of the results. In Studies I and II, patients and personnel were not blinded because it was impossible to blind the patients in terms of anaesthesia method and reliably in terms of tourniquet use in the spinal anaesthesia group. Additionally, personnel in the operating room had first-hand knowledge of the methods used, and other participating personnel had free access to these data. Although we instructed personnel not to discuss the methods used with the patients, many patients were able to speak with one another in the surgical ward during their hospital stay. This might have influenced patient-reported outcomes. In Studies I and II, five patients were excluded because of randomization deviation instead of conducting intention-to-treat analysis. This may have biased the results in these studies. Furthermore, the power in Studies I and III was not sufficient to address rarely occurring adverse events.

In Study III, we conducted BFP measurements without regard to patients' prior dietary intake and physical activity, although it is recommended to conduct BIA under standardized conditions.[145] This may have impacted the results, even though the effect of dietary intake on BFP results might not be clinically relevant,[146] approximately 93% of our patients had fasted for at least 2 hours prior to BIA, most came to the preoperative clinic in the morning and no physical stress (apart from examinations and short transitions) was induced. Another limitation in Study III is that we did not control for intertester accuracy concerning ROM measurements.

It should also be noted that morbidly obese patients were excluded from all four studies and that the BPI-SF does not focus strictly on pain in the surgical site. Thus, it is possible that some patients referred to pain that was not in the target knee area when they answered this questionnaire (Studies II to IV).

6.7 Implications for future studies

Perioperative treatments and protocols in TKA are constantly evolving. To keep up to date and facilitate comparisons between different studies, some suggestions for future studies are appropriate. First, large-scale, multicentre RCTs are warranted to investigate whether spinal and general anaesthesia are associated with different

risks for major complications after TKA. In addition, patients undergoing TKA should be investigated as their own group and not combined with total hip arthroplasty patients. After all, total hip and knee arthroplasties are different operations with different outcomes.

Furthermore, terminology regarding PPP should be more accurate. Based on a recent definition, “chronic postsurgical pain” after arthroplasty should refer to pain that develops after surgery and persists for at least 3 months.[147] Thus, if residual pain from before an operation cannot be distinguished from possible chronic postsurgical pain, we suggest using the term PPP.

We also suggest favouring knee-specific outcome measures like the OKS pain subscale in pain assessments regarding TKA. This might reduce the risk of biased results compared with universal pain questionnaires. In addition, the optimal threshold for MCID between groups in pain scores of TKA patients is unclear and should be established. Finally, the timepoints for measuring PPP after TKA have varied in previous research. As pain appears to decrease for up to 1 year after TKA[70-72] but not significantly after that,[121,148,149] we propose that PPP be measured at 1 year after TKA.

7 CONCLUSIONS

In conclusion, the results from Studies I to IV suggest the following:

1. There are no clinically important differences in the effects of spinal and general anaesthesia on acute pain, pain management, in-hospital adverse events, blood loss or LOS after TKA. Thus, both anaesthesia methods appear suitable for this operation, although spinal anaesthesia does appear to be associated with a higher risk of PONV than general anaesthesia. The use of tourniquet in TKA does not affect acute postoperative pain, pain management, LOS or the incidence of PONV and in-hospital adverse events. It might reduce blood loss, although at a level that is not clinically relevant. Thus, performing TKA with or without a tourniquet both remain suitable options.
2. Spinal and general anaesthesia do not result in clinically relevant differences in PPP at 3 and 12 months after TKA. Similarly, whether TKA is performed with or without a tourniquet has no important effect on PPP.
3. For patients who are not morbidly obese, BFP and BMI are poor predictors of TKA-related in-hospital and patient-reported 1-year outcomes. Patients with higher BMI benefit from TKA at least as much as those with lower BMI.
4. The investigated risk index for PPP might predict some MCIDs in pain between the risk groups at 3 months after TKA. However, it does not seem to be applicable to predicting PPP at 12 months after TKA.

ACKNOWLEDGEMENTS

This study was conducted at HUS Helsinki University Hospital and the University of Helsinki. It was carried out between 2016 and 2022 as a joint effort of the Departments of Anaesthesiology, Intensive Care and Pain Medicine and Orthopaedics and Traumatology. Peijas Hospital at Vantaa was the base of the study.

I wish to express my sincere gratitude to my supervisors, Docent Anne Vakkuri and Professor Klaus Olkkola. Anne took me to work at Peijas Hospital and encouraged me to join the study group. Thank you, Anne, for all the trust you gave me in clinical work and in this study. Your support during my years at Peijas was crucial both for the progress of this thesis and for my wellbeing. Thank you also for reminding me for the importance of life outside of work.

Similarly, Professor Klaus Olkkola offered constant support and guidance, from study design to the thesis manuscript. I am sure that without your expertise, I would still be far away from reaching this point. Your skills in communicating with editors and reviewers are especially amazing. Thank you for making sure that our study group stood on solid financial ground.

I want to thank Noora Skants, MD, PhD, for managing the ups and downs of patient recruitment with me and for sharing the everyday work and challenges related to this study. Thank you for your help in solving unexpected problems and for guidance and support during all these years.

I warmly thank Docents Mikko Pitkänen and Merja Vakkala for reviewing this thesis. I also thank Antti Aho, MD, PhD, and Docent Pekka Tarkkila for overseeing me during this thesis project.

In addition, I am very grateful to the members of our study group. I thank Mikko Rantasalo, MD, PhD, for taking the path towards a doctoral thesis with me. Your peer support and help in orthopaedic issues were essential. I warmly thank Tero Vahlberg, MSc, for introducing me to the amazing world of biostatistics and for confirming that our statistical analyses and results were solid. I also thank Docent Rami Madanat, Elina Reponen, MD, PhD, and Rita Linko, MD, PhD, for all the time and expertise they devoted to this project. Additionally, my warmest thanks to Katarina Lahtinen, MD, and research nurse Arja Mäkelä for their massive work in data collection.

I am grateful to Pekka Kairaluoma, MD, PhD, and Docent Eero Pesonen for their contribution to the study and to all the other anaesthesiologists, orthopaedic surgeons, anaesthesia nurses, operating room nurses and personnel in the preoperative outpatient clinic and on the surgical wards at Peijas Hospital. Of course, I also thank all the participating patients who made this study possible.

In addition, I want to thank all the anaesthesiologists at Central Finland Hospital Nova for allowing me be part of a five-star community. In particular, I thank Juha Nevantaus, MD, for enabling my study project beyond my hospital work.

I received personal grants for this thesis project from many sources. For this, I thank the Finnish Medical Society Duodecim, Paulo Foundation, Finnish Medical Foundation, Orion Research Foundation, Research Foundation for Orthopaedics and Traumatology, Finnish Arthroplasty Society and Finnish Society of Anaesthesiologists.

I am privileged to have great friends around me. I especially thank Topias for his friendship since early childhood and for the constant support in all aspects of life. Similarly, I am grateful to Antti for all the shared experiences, especially those arctic walks, and to Elisa, Kaisa, Riikka, Tiina and Venla, who have spiced up my world for more than 20 years.

I warmly thank my brother Jere, his wife Tiia and their children Sami and Suvi for being part of my life. Spending time with you, whether at the “Karppa” or anywhere else, has given me much needed energy and brought joy to both me and to my family.

I am very grateful to my mother Marketta and father Olavi, who have been a constant source of support during this thesis project. Thank you also for your love, guidance and help throughout my life.

Finally, my deepest gratitude and love goes to my wife Reetta and to my sons Niilo and Olli. Thank you for enduring this project for all these years. I know it has demanded a lot from you. Reetta, thank you for your support, advice and love. They carried me to the end of this path. Niilo and Olli, watching you grow, being part of your lives and feeling your happiness and love is the best there is.

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