Multimodal pain management and fixation techniques in Total Knee Arthroplasty

Bas van Ooij

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Printed by Proefschriftspecialist | proefschriftspecialist.nl
Layout and design: Erwin Timmerman, persoonlijkproefschrift.nl

ISBN 978-94-93483-37-8

The research in this thesis was embedded in Amsterdam Movement Sciences Research Institute, at the department of Orthopedic Surgery and Sports Medicine, Amsterdam UMC, location AMC.

The printing and layout of this thesis were financially supported by:

Multimodal pain management and fixation techniques in Total Knee Arthroplasty

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op dinsdag 16 december 2025, te 13.00 uur

door Bas van Ooij
geboren te Maastricht

Promotiecommissie

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Contents of the thesis

Chapter 1	General introduction and outline of the thesis	9
Chapter 2	Peripheral nerve blocks as part of multimodal pain management in TKA, part 1 Value of Single-Injection or Continuous Sciatic Nerve Block in Addition to a Continuous femoral Nerve Block in Patients Undergoing Total Knee Arthroplasty. A Prospective, Randomized, Controlled Trial. Wegener JT, van Ooij B, van Dijk CN, Hollmann MW, Preckel B, Stevens MF *Reg Anesth Pain Med. 2011 Sep-Oct;36(5):481-8*	37
Chapter 3	Peripheral nerve blocks as part of multimodal pain management in TKA, part 2 Long-term pain and functional disability after total knee arthroplasty with and without single-injection or continuous sciatic nerve block in addition to continuous femoral nerve block: a prospective, 1-year follow-up of a randomized controlled trial. Wegener JT, van Ooij B, van Dijk CN, Karayeva SA, Hollmann MW, Preckel B, Stevens MF *Reg Anesth Pain Med. 2013 Jan-Feb;38(1):58-63*	59
Chapter 4	Cryotherapy after total knee arthroplasty Cryotherapy after Total Knee Arthroplasty provides faster recovery and better ranges of motion in short term follow up. Results of a prospective comparative study. van Ooij B, Wiegerinck JI, Wegener JT, van Dijk CN, Schafroth MU *Acta Orthop Belg. 2020 Sep;86(3):463-469.*	75
Chapter 5	Fixation in total knee arthroplasty, part 1 What is the role of cemented fixation in total knee arthroplasty? The two-year results of a randomized RSA controlled trial. van Ooij B, Sierevelt IN, van der Vis HM, Hoornenborg D, Haverkamp D *Bone Joint J. 2021 Jan;103-B(1):98-104*	91

Chapter 6 Fixation in total knee arthroplasty, part 2 109

Lower revision rates for cemented fixation in a long-term survival analysis of three different LCS designs.

van Ooij B, de Keijzer DR, Hoornenborg D, Sierevelt IN, Haverkamp D

Knee Surg Sports Traumatol Arthrosc. 2022 Aug;30(8):2707-2713

Chapter 7 General discussion 125

Chapter 8 English summary 145

Chapter 9 Dutch summary - Nederlandse samenvatting 155

Appendices PhD Portfolio and Publications 167

Acknowledgments - Dankwoord 172

About the author 175

1

General introduction and outline of the thesis

The knee and osteoarthritis

The knee is considered the largest hinge joint of the human body. A hinge joint is a type of synovial joint that primarily allows flexion and extension in one plane. [40] However, a small degree of motion in several other planes is essential for the natural biomechanics of the knee joint. Movements in these other planes include anterior and posterior translation, internal and external rotation, compression and distraction, medial and lateral translation and varus and valgus rotations. [39] The knee joint is essential for efficient movements such as walking, running and jumping. It consists of the tibiofemoral joint and the patellofemoral joint. In addition, function and stability depend on ligaments, muscles and other connective tissues. Mainly due to the amplification of forces through leveraging of muscle forces and the dynamics of acceleration across the knee, the transmitted forces are believed to be between 2 and 3 times the body weight during normal walking, up to > 4 times during sports, such as jogging and tennis. [30] Therefore, with respect to the different types of pathology of the knee, a good understanding of the kinetics and different types of structures involved is important.

Osteoarthritis (OA) is one of the most common pathological conditions of the knee; it is more prevalent in the elderly population than in the younger population but is also diagnosed in middle-aged patients. [103] Cartilage loss and damage are considered the main characteristics of this disease, but it is a disease of the entire joint, as the surrounding (periarticular) tissues are also involved (Figure 1). [103] Knee injuries, possibly sports-related injuries, such as fractures, ligament tears or meniscus injuries, can also cause OA. Symptoms of knee OA include pain, stiffness, reduced joint movement, muscle weakness and locking symptoms. Second, it can lead to long-term symptoms such as impaired sleep, depression and fatigue and may result in a loss of work. OA of the knee presents on physical examination mainly as swelling, deformity, pain at the site of the joint line, and decreased range of motion (often with crepitus). Conventional radiographs are usually sufficient to confirm OA, which is characterized by joint space narrowing, osteophytes, subchondral sclerosis and possibly cysts. [46] Radiographs alone to diagnose OA are not adequate, as OA is a common incidental asymptomatic finding in older people. Furthermore, radiographs often correlate poorly with symptoms, particularly with early disease. [9] Therefore, it makes sense to perform posteroanterior 45-degree flexion weight-bearing radiographs when early osteoarthritis is suspected (e.g., in younger patients), as greater loss of joint space than extension recordings is observed. [78] Risk factors for the onset of knee OA include a higher Body mass index (BMI), previous knee injury, the presence of Heberden's nodes/hand OA, female sex, older age, intensive physical activity,

certain physical occupational activities (e.g., kneeling, squatting) and increased bone mineral density. [12] The goal of treatment is to reduce pain, improve joint function and quality of life, and modify the abovementioned risk factors to prevent worsening of the disease. The treatment is multimodal and includes nonpharmacologic, pharmacologic and surgical modalities. The most appropriate treatment depends on the person's specific situation and the severity of the condition.

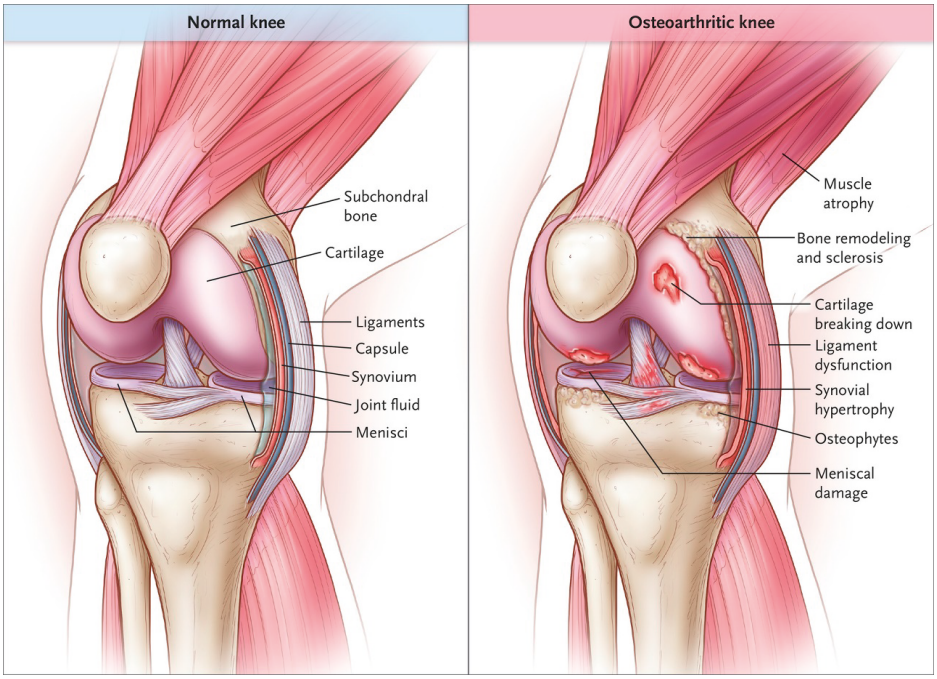

Figure 1. *Osteoarthritis is a disease of cartilage as well as the entire joint, as the surrounding (periarticular) tissues are also involved. Reproduced with permission from Sharma et al. [103] , Copyright Massachusetts Medical Society.*

Conservative treatment of knee osteoarthritis

Evidence-based nonpharmacologic treatment consists of arthritis education, physical exercise programs and weight management. [6] Especially in case of early-stage osteoarthritis, the aim is to follow the best clinical practice, but preferably, avoiding surgery. The stepped-care principle is important. There is moderate to high-quality evidence that ground-based exercises improve knee pain and function for at least two to six months after discontinuation of formal treatment, which can be compared

with the treatment effect of nonsteroidal anti-inflammatory drugs (NSAIDs). [35] Regarding weight management, a systematic review revealed that moderate improvement in physical function and moderate pain relief could be achieved with combined diet and exercise. [41] Assisting devices, such as knee braces or orthotics, could be effective in managing symptoms, but the evidence is conflicting, and the optimal choice of which orthosis to use is still unclear. [32] If the psychosocial impact (such as catastrophizing pain or depression) is severe, pain management training or other psychosocial interventions, such as cognitive behavioral therapy, may be considered. [29]

Pharmacological treatment consists of pain relief and/or anti-inflammatory medication: paracetamol, (topical) NSAIDs or, in more severe cases, opioids. Although paracetamol is often prescribed for knee osteoarthritis, there is strong evidence that it provides only minimal short-term pain relief. [75] NSAIDs have a greater effect on pain levels, with topical NSAIDs having effects similar to those of oral NSAIDs and fewer side effects. [27] Gastrointestinal, renal, and cardiovascular toxicity should be considered. In the case of an increased gastrointestinal risk profile, cyclooxygenase-2 (COX-2) inhibitors should be considered. [6] Opioids are associated with a relatively high risk of side effects such as nausea, drowsiness and increased risk of falls and should therefore be avoided as much as possible. There is evidence that tramadol is associated with increased mortality among patients with OA. [115] Furthermore, several studies have shown that opioids do not reduce pain or improve function more than NSAIDs do. The incidence of adverse events was greater in patients receiving opioids. [23] If the above options do not provide sufficient pain relief, intra-articular injection of glucocorticoids may be considered. This can provide short-term pain relief but often lasts only a few weeks to the previous pain level. There is also evidence that the same short-term pain reduction can be achieved with physiotherapy, with even less pain and disability in patients who undergo physical therapy in the longer term. [28] Multiple injections are not recommended, especially as glucocorticoid injections have been shown to cause more cartilage damage in the longer term than saline injections do, with no significant difference in pain levels, an increased risk of knee arthroplasty and an increased risk of postoperative periprosthetic joint infection after knee arthroplasty. [7, 80, 111] The use of intra-articular hyaluronic acid (HA) is not recommended, as several clinical studies have shown no clinically relevant effect compared with placebo injections. [21] Moreover, HA injections are associated with potential side effects (especially joint infection) and high costs. [57, 94] On this topic, it remains a search for what the “perfect injectable” might be. For example, it is also a longer-term question whether Platelet-Rich Plasma (PRP) may be an option for patients with knee osteoarthritis. The latest meta-analysis showed that PRP offers

better symptom and pain relief and a lower rate of re-intervention compared with alternative non-surgical treatment options, including HA. [88] Moreover, the results of other emerging single-injection viscosupplementation methods, such as cross-linked HA, are promising. [34]

Surgical treatment of Osteoarthritis

If (long-term) conservative and pharmacological treatment does not sufficiently reduce symptoms or increase quality of life, then surgical treatment is the next option. Surgical treatment for moderate to severe knee osteoarthritis is dominated by total knee arthroplasty (TKA), which is highly effective in patients with advanced knee OA when conservative therapies have not provided sufficient reduction of symptoms. [106] The main objectives of TKA are to restore knee function, improve quality of life and relieve pain. For well-selected patients, TKA leads to significant improvements in function and quality of life. [13] TKA consists of resection of the affected joint surfaces of the knee, followed by resurfacing with metal and polyethylene prosthetic components (Figure 2).

The indications for surgical alternatives to TKA must first be assessed. Arthroscopic debridement has been frequently performed in patients with knee OA, eventually in combination with a meniscal tear. However, this is not supported by several randomized trials. [66, 84] Although it seems attractive to arthroscopically "clean" the joint of cartilage debris and osteophytes in unicompartmental (nondiffuse) OA, the results have been proven to be minimal and certainly not long term. [108] This also applies to arthroscopic treatment of degenerative meniscal tears (in combination with OA), as no advantage of such treatment over nonoperative or sham treatments has been demonstrated. [1, 62] Therefore, there is no place for routine arthroscopic treatment in patients with OA, except for those with objective ("true") locking symptoms. [104] For younger, more active patients with predominantly unicompartmental OA, high tibial and distal femoral osteotomies for varus and valgus knees are adequate surgical options. The goal of an osteotomy is to realign the mechanical axis of the leg, resulting in unloading of the affected compartment. [16, 26] Delays in TKA, less functional impairment than arthroplasty and preservation of the natural anatomy are advantages of osteotomy. Furthermore, all osteotomies demonstrated a high rate of return to sport and work. [49, 50, 70] Possible disadvantages and complications include nonunion, failure of fixation, loss of correction and hardware failure, patella baja, changes in the tibial slope and increased complexity of later arthroplasty.

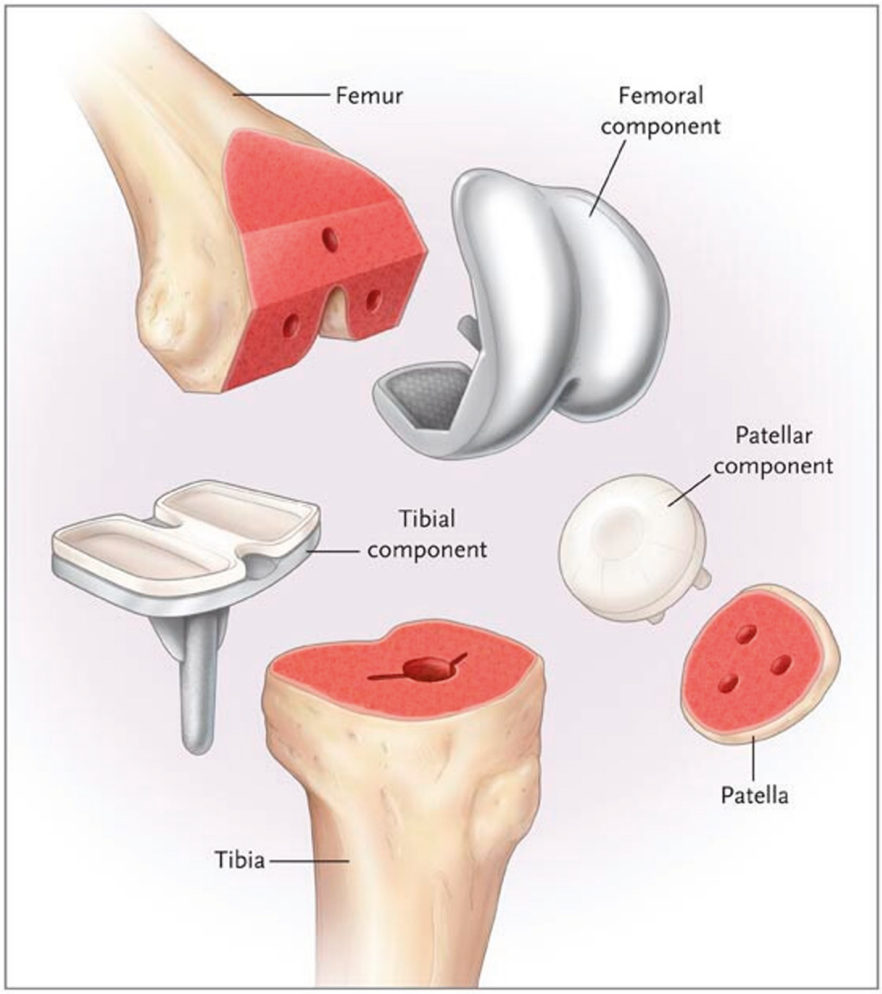

Figure 2. *A total knee prosthesis consists of femoral (on the lower surface of the femur) and tibial metal parts and a polyethylene insert, possibly with a polyethylene part of the patella. Reproduced with permission from Leopold et al. [73], Copyright Massachusetts Medical Society.*

Patients with multiple comorbidities and dependent functional status are more likely to have adverse events, so adequate counseling is important. [24, 109] If end-stage OA is limited to one compartment, unicompartmental arthroplasty is a viable alternative to TKA. As medial compartment osteoarthritis is more common, medial unicompartmental arthroplasty is performed more often, although lateral compartment and patellofemoral replacements can also be performed. Since

unicompartmental arthroplasty is less invasive than TKA is, the recovery rate is faster, the complication rate is lower, and the midterm survival rates are similar. Unicompartmental knee arthroplasty, however, has a greater risk of reoperation than TKA does. Nevertheless, absolute revision rates are relatively low, making unicompartmental arthroplasty a viable alternative to TKA if patients are carefully selected. [105, 112] Even after osteotomy of the knee, unicompartmental arthroplasty can be considered, although the procedure is technically demanding. [72] A relatively new surgical treatment for knee OA is joint distraction, a method whereby an external fixator is used to unload the cartilage and underlying bone for a short period of time. Long-term clinical studies are needed to investigate whether this treatment can act as standard care, but the initial results suggest potential benefits with evidence of an increase in joint space width and symptomatic improvement. [55, 56] Again, it is important to weigh the pros and cons, as this is a procedure with intensive rehabilitation and a significant risk of complications (mainly pin-tract infection). Moreover, there is no standardized technique for this method yet. [54]

General considerations in total knee arthroplasty

As mentioned in the previous sector, for end-stage knee OA, TKA is often chosen as a treatment option. This approach is therefore considered the gold standard for treating end-stage knee OA and is one of the most commonly performed orthopedic procedures. [77] Over the past few decades, the number of TKAs has risen rapidly both nationally and internationally, with at that time 4.0 million adults in the U.S. living with total knee replacement, representing 4.2% of the population 50 years of age or older. [110] In general, TKA is performed for primary and secondary knee OA in more than 95% of patients with indications for surgical treatment. [76] Other indications for TKA include the following:

- Rheumatoid arthritis or other inflammatory diseases that affect the knee joint. The need for TKA in patients with inflammatory arthritis has decreased over time since the introduction of biologic disease-modifying antirheumatic drugs. [22]
- Congenital or developmental deformities of the knee joint cause severe pain and functional impairment.
- Avascular necrosis of the bone, bone or cartilage tumor or sequelae of joint infection.

There are several contraindications for performing TKA. First, an active infection (in the knee or elsewhere) is a strong contraindication. The risk of reactivation of latent

infection or secondary infection after TKA is difficult to assess. Up to one year may elapse between the start of treatment for septic arthritis and the implementation of TKA. Second, a neurological condition is a relative contraindication, as nonfunctional muscles can lead to limited improvement in function and pain and potentially unsuccessful rehabilitation. Finally, untreated peripheral arterial disease (requiring a revascularization procedure first) or skeletal immaturity are also contraindications.

TKA is very effective in reducing symptoms, with generally favorable satisfaction rates and adequate implant longevity. However, the literature reports that approximately 20% of patients experience persistent pain and dissatisfaction. [10, 13] The success of TKA can be evaluated by several factors, including pain relief, functional improvement, patient satisfaction, complications and implant survival. The decision to undergo TKA should be made in consultation with an orthopedic surgeon, who can provide personalized recommendations on the basis of the patient's individual needs, medical history and current status. Importantly, predicting the success of TKA is complex, and outcomes may vary depending on individual patient factors and other variables. It is believed that "patient shared decision making" (PSDM) can be an important part of this process, as surgeons and patients can make thorough considerations together in this process. A systematic review on this topic revealed that PSDM aids in the decision-making process compared with usual care in TKA. [90] With respect to the factors listed below, measuring patient-reported outcomes (PROMs) is also important, as it contributes to the decision to operate. It may also be clear that these PROMs are used in many clinical studies to provide measurable outcomes. [67] There is no single best predictor of success, and the literature shows that several factors can influence the outcome of TKA:

- Preoperative function, expectations and mobility. Patients with better preoperative function and mobility and realistic expectations are more likely to have a successful outcome after TKA. [15] The strongest predictor of patient dissatisfaction after primary TKA was that expectations were not met (10.7 times greater risk). [13] However, an earlier study also showed that pain at night and pain at rest led to worse outcomes after arthroplasty surgery. [44] So waiting too long with operative intervention is also a concern. Therefore, in this case, the stepped-care principle does not seem infinite.
- Age is a significant predictor of TKA success, with older patients generally having better outcomes. Compared with older patients, younger TKA patients were found to have poorer post-TKA pain relief, function and satisfaction. [91]
- BMI. A higher BMI has been associated with worse outcomes after TKA, including an increased risk of complications, decreased function, and decreased implant

survival. [14, 61, 89] For example, Dowsey et al. reported that patients with a BMI greater than 40 had a greater risk of implant revision and worse functional outcomes after TKA. [31]

- Psychological factors. Psychological factors such as anxiety, depression and catastrophizing pain have been associated with worse outcomes after TKA. Patients with preoperative anxiety and depression had worse functional outcomes and less satisfaction after TKA. [33] The pain catastrophizing scale (PCS) and the central sensitization inventory (CSI) can be used for counseling prior to surgery and have been proven useful in hip arthroscopy. [8] Central sensitization was associated with worse PROMs following TKA than in patients without this condition. [64]

In addition to the previously mentioned factors, many other aspects need to be considered, but pain perception remains one of the most important predictors of successful TKA. [15, 101] The severity of pain before surgery is crucial; patients with high levels of preoperative pain are often more likely to have persistent pain and poorer functional outcomes after surgery, which is multifactorial. Therefore, pain management and related rehabilitation are essential for optimal outcomes. Inadequate rehabilitation can lead to delayed recovery, reduced mobility and increased risk of complications. There are many studies on factors that contribute to successful rehabilitation after TKA. Some of the key determinants are as follows:

- Early mobilization. Early mobilization after TKA is associated with better outcomes, including better range of motion, less pain and fewer complications. A systematic review revealed that early mobilization was associated with better functional outcomes and shorter hospital stays. [38]
- Multimodal pain management. Effective pain management is crucial for successful rehabilitation after TKA. A multimodal approach to pain management includes medication, nerve blocks and nonpharmacological interventions such as cryotherapy, also known as cold therapy. It is associated with better pain management and better functional outcomes. Multimodal pain management was associated with less pain and opioid use after TKA. [25, 81]
- Physical therapy. Physical therapy is an essential part of (the early phase of) rehabilitation after TKA. A systematic review revealed that physiotherapy was associated with better functional outcomes and better quality of life after TKA. Patients who participated in more physiotherapy sessions and adhered to their exercise program had better outcomes than those who did not. [82]
- Patient education. Patient education is an important aspect of successful rehabilitation after TKA. Providing patients with information about their

surgery, the rehabilitation process and expected outcomes can reduce anxiety and improve adherence to the rehabilitation program. A specific management program showed that patient education was associated with a reduction in readmissions and reoperations. [93]

- Social support. Social support is a significant factor in successful rehabilitation after TKA. A systematic review revealed that patients with more social support had better functional outcomes and less pain after TKA. [42]

Multimodal pain management in total knee arthroplasty

The key to smooth rehabilitation after TKA is a comprehensive, patient-centered approach that takes into account the unique needs of each individual patient. So-called "enhanced recovery surgical programs" or "fast-track knee arthroplasty" have been introduced to reduce persistent pain and dissatisfaction, but they have not been proven to improve satisfaction and reduce pain levels. [59, 98] However, the clearly defined benefits of such an accelerated program include fewer complications, a shorter length of stay and potentially lower costs, depending on the healthcare financing model. [38] In terms of the length of stay, much has already been achieved. Long-term stays became short-term stays and sometimes even one day of treatment. [60] There is no consensus on which aspects should be standard in this accelerated program. Nevertheless, a multimodal pain treatment program is important here, especially if there are signs of preoperative pain catastrophizing, opioid use and central sensitization of pain. [63] To achieve early mobilization, limiting the "surgical inflammatory response" is also a frequently mentioned goal. Perioperative blood management, the shortest possible operating time, minimal tissue damage and preoperative optimization of comorbidities are important determinants. [59, 60]

There is a trend to optimize multimodal pain management multidisciplinary, with the fastest possible rehabilitation and discharge from the hospital. [5] This includes an approach involving peripheral nerve blocks, periarticular infiltration of local anesthetics, systemic analgesics and possibly cryotherapy. Most TKA patients experience moderate to severe postoperative pain. Significant postoperative pain is known to impair early mobilization and physiotherapy. Therefore, pain management is one of the most crucial factors in accelerating knee rehabilitation. The main goal, in addition to pain reduction, is to facilitate early rehabilitation. In this context, the key focus is avoiding opioids as much as possible, as opioid-related side effects like nausea, sedation and respiratory depression often prevent early mobilization. Moreover, it is important to manage acute pain well, as this can reduce the likelihood

of chronic opioid use. [52] With only patient-controlled intravenous opioids after TKA, moderate to severe pain may persist, especially during mobilization. Compared with opioid therapy, epidural analgesia and peripheral nerve blocks provide improved analgesia and a significantly shortened rehabilitation time. [74] This was confirmed in a Cochrane review in 2014, which also concluded that a femoral nerve block led to fewer complications than epidural analgesia did. In addition, continuous femoral nerve block was in favor of a single shot block to control pain. [18] With continuous femoral nerve block, limited quadriceps function is a concern; patient-controlled administration of medication is an option to (partially) prevent this. [83] Before the clinical trial, presented in Chapters 2 and 3, limited evidence was presented concerning whether an additional sciatic nerve block (continuous or single shot) to a femoral nerve block would lead to even better analgesia (especially in the posterior region of the knee [74]) and a reduction in complications. A meta-analysis revealed that further studies were needed to evaluate the value of an additional sciatic nerve block. [92] Which part of such a "pathway" best achieves this goal is an ongoing point of discussion. [68] Peripheral nerve blocks play a key role in this process. The indications for these nerve blocks are discussed in Chapters 2 and 3 and in the general discussion of this thesis. The possible indication for an additional sciatic nerve block to perform adequate pain control led to the research questions below.

Postoperative cryotherapy (as part of multimodal pain management) is described as another modality to reduce the surgical inflammatory response. In orthopedic surgery and TKA, it is still widely recommended to improve recovery and outcomes. [69] The aim of cryotherapy is to lower the tissue temperature, reduce pain and encourage early mobilization. [2] A reduction in blood flow contributes to a reduced inflammatory response and edema formation. [79] The most recent Cochrane review, published in 2012, concluded that cryotherapy after TKA is safe. It can improve the range of motion of the knee in the first weeks after surgery and can reduce the amount of blood loss. However, the quality of evidence was low, and there were conflicting results in previous trials at that time. Notably, any cryotherapy device aims to lower intra-articular and deep tissue temperatures. Therefore, possible new cryotherapy devices, instead of ice compresses and other manual devices, could be used to apply an optimal cooling dose. [3] This led to the research question below on cryotherapy in one of our clinics, which is discussed further in Chapter 4 and in the general discussion of this thesis.

Prosthetic design and fixation in total knee arthroplasty

In TKA, it is of primary importance to work with a proven implant that provides solid long-term fixation, with the lowest chance of aseptic loosening. Over the years, there have been many different developments in finding the most adequate TKA design and type of fixation. The introduction of the total condylar prosthesis by Insall and colleagues in 1972 was considered the first modern knee prosthesis. This prosthesis was the first to replace all three compartments of the knee. There are many variants of the original design, with the contemporary prosthesis seen as a variant of Insall's original design. [53] Currently, there is no consensus on implant choice, and there are wide variations among countries, states, cities and individual surgeons. The variability of implant design and technique makes it difficult to analyze the reported results and to externalize them to daily practice. National registries allow the calculation of joint replacement survival rates on the basis of revision surgery, which has become a cornerstone of the assessment of knee replacement surgery. [48] TKA survival depends on many factors, and the most important factors are highlighted and expanded upon in the studies presented in this thesis.

Aseptic loosening of TKAs may occur through several mechanisms, including polyethylene wear-induced osteolysis between the implant and bone and component loosening, which may be due to osteolysis and excessive stress on components. In the past, wear of polyethylene was the most common cause of loosening, with loosening being the most frequent complication of TKA. This can be the result of small wear particles and, on the other hand, it can be due to mechanical failure, i.e., breakage of the polyethylene component. [85] With advances in prosthetic models and fixation techniques, the risk of polyethylene failure has decreased over time. [97, 102] Highly cross-linked polyethylene was introduced and has been successful in minimizing polyethylene wear, which over the years has led to less aseptic loosening and revision of TKAs. [107] However, aseptic loosening remains one of the most common complications during long-term follow-up. [43]

Posterior cruciate ligament retaining and posterior stabilized prosthetic designs are the two most commonly used TKA options. Which design is preferable is a long-standing debate, as many factors, such as a better range of motion with a posterior stabilized TKA and better proprioception and stability with a cruciate-retaining TKA, have been discussed. [17, 58] In general, posterior stabilized implants are considered a better option for knees with severe deformities. [58] Regarding long-term survival, the most recent meta-analysis considered TKA with cruciate ligament retaining superior to posterior stabilized implants. [58] Furthermore, the

post- and cam designs of posterior stabilized TKA apply greater constraints than does a design with cruciate ligament retaining, leading to more stress at the bone-implant interface and thus a possibly greater degree of loosening. More constrained designs (e.g., hinged implants) are indicated for situations such as severe deformity, instability and revision surgery. In general, a more constrained implant applies more load on the components, which can lead to higher failure rates. [114] An important observation in this review, based on the study presented in Chapter 5 of this thesis, is that highly or "ultra congruent" polyethylene inserts are increasingly used in knees with posterior cruciate deficiency. This trend may reduce the need for posterior-stabilized TKA, which, as previously discussed, can impose greater stress at the bone-implant interface. This increased stress at the bone-implant interface could be an important factor in deciding whether the prosthesis should be cemented or uncemented. Generally, cemented TKA is considered standard, as it is the most commonly performed method, partly because of past experience. [86] Bone cement, or polymethyl methacrylate (PMMA), is a polymer that allows fast-primary fixation of the implant to the bone. [11] It is actually a filler used to achieve a perfect fit between the prosthesis and bone. By filling or penetrating the trabecular bone, there is mechanical anchorage. [11] Several advantages of cemented TKA are mentioned in the literature, namely, providing antibiotics to prevent infection, acting as a barrier to polyethylene debris (in contrast to the uncemented version), and allowing the filling of (small) bone defects. [20, 36, 65] This could make the procedure less challenging than uncemented TKA, as any less precise bone cuts are filled with bone cement. In addition, there is increasing demand for TKAs in younger patients, with concerns about bone resorption at the bone-cement interface, as the activity level over time is regarded as an important patient factor affecting the loads on the TKA. [19, 71, 87] This complication could be avoided by an uncemented variant, pursuing biological fixation with bone ingrowth and ongrowth. Further advantages mentioned are easier revision and a shorter operating time, as there is no need to wait for the cement to harden in a primary TKA, no need to remove bone cement in a revision TKA, and potentially less need for tourniquet use. [47, 86] In the principles of bone ingrowth and ongrowth in uncemented TKA, the primary stability of the implant is of initial importance. Immediate press fit of the implant is critical to support immediate mobilization of the patient, with a subsequent increase in osseointegration. It is believed that this process is comparable to that described for cup stability in uncemented total hip arthroplasty. This process involves a "transition" from primary stability to secondary stability, and presumably, this transition period (indicated by the red area in Figure 3) is the period at risk for implant failure. [45]

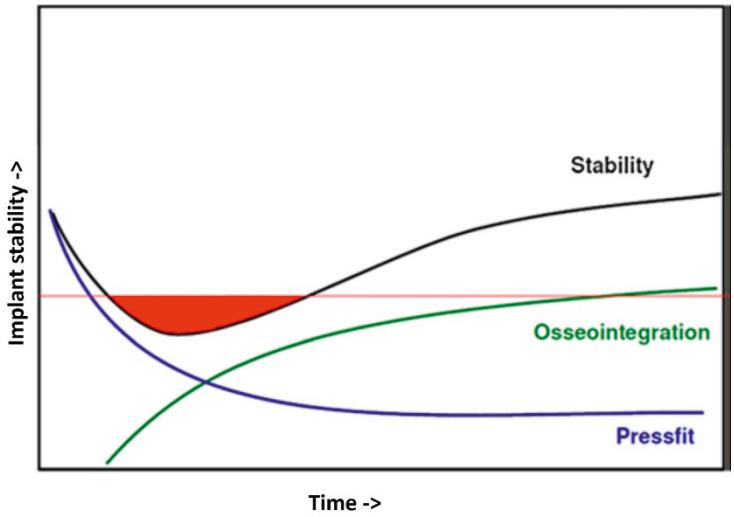

Figure 3. *Distribution of primary and secondary stability over time. The red line indicates the minimum stability needed for safe fixation. The red area is the area where the risk of loosening is present. Adapted from the publication by Haverkamp et al., in which a press-fit cup for total hip arthroplasty was discussed. (Reproduced with permission from Haverkamp et al.) [45]*

Several factors are important in this transition period and subsequent growth of stability, such as implant coating, cut accuracy and bone mineral density (BMD). Some examples of different coatings for implants include highly porous coatings, hydroxyapatite, porous plasma sprays and titanium nitride ceramics. Clearly, over several decades, changes have been made to the implant material, particularly the coating, to improve the overall function and long-term durability of uncemented TKA, in contrast to the high failure rate of the first cementless implants. [100] Meanwhile, radiostereometric analysis (RSA) has proven to be an accurate method for measuring migration patterns, with the ultimate goal of early prediction of aseptic loosening. Among the predictive signs of loosening, migration is the most studied quantitative parameter. [116] The migration pattern can be detected within two years after implantation, making it highly useful to compare different fixation techniques in (cemented or uncemented) TKA. [96]

BMD is another factor discussed in the context of uncemented TKA. Concerns have been raised about low BMD since fixation requires good bone quality, especially for the tibial component. For example, in a study by Andersen et al, low preoperative BMD of the tibia was related to higher migration values, leading to a switch to a cemented technique during surgery. [4] However, in other studies, no statistically

significant negative effect of BMD on component migration was observed after uncemented TKA. [95, 113] It seems that there are no guidelines for including BMD in the decision to perform uncemented TKA. It is often an intraoperative decision to ultimately opt for cement or not. In addition, hybrid TKA (an uncemented femur with a cemented tibia and patella) was introduced to provide a theoretical advantage in preventing loosening of the uncemented tibial component, which resulted in more component migration in most studies. [86]

Following the above stated considerations of cemented or uncemented designs, it is still not clear whether cemented or uncemented fixation of the components has the best long-term survival or which design provides the best functional results. This led to the research questions below concerning cemented and uncemented fixation in one of our clinics, which are further discussed in Chapters 5 and 6 and in the general discussion of this thesis.

Research questions

In summary, a greater understanding of multimodal pain management and the prosthetic design and fixation of TKA can play a key role in improving quality of life and patient satisfaction. Some pieces of this "clinical pathway puzzle" are being combined in this thesis. The aim of this thesis is to address the following research questions:

1. Does the addition of a sciatic nerve block to a patient-controlled femoral nerve block as part of multimodal pain management after TKA shorten the time to discharge and improve knee mobilization and pain relief?
2. Do improved early postoperative pain scores when using an additional sciatic nerve block in addition to a femoral nerve block result in improved long-term functional outcome and pain experience?
3. Does a relatively new cryotherapy device improve knee function and reduce postoperative swelling in the early rehabilitation phase after TKA without increasing the risk of postoperative complications?
4. Does the type of fixation used in Advanced Coated System TKA affect the migration pattern, long-term risk of aseptic loosening and patient-reported outcome measures?
5. Does the type of fixation used in Low-Contact-Stress Mobile-Bearing TKA affect long-term survival, and secondarily, what are the risk factors for revision?

Outline of the thesis

Chapter 1: General introduction and outline of the thesis.

The introduction is an overview of the implications and treatment of osteoarthritis of the knee and the indications for TKA, including TKA outcomes and complications. Special attention is given to what predictors influence the outcome of TKA and what factors are important for successful rehabilitation. It is explained which specific components of multimodal pain management and the outcomes of different fixation techniques led to the presented research questions, which are described in the following chapters.

Chapter 2: Peripheral nerve blocks as part of multimodal pain management in TKA, part 1

In one of our clinics, a continuous femoral nerve block was considered standard care as part of multimodal pain management in TKA. This provides more site-specific analgesia with a lower incidence of complications than epidural analgesia does. [37] However, a femoral nerve block may result in inadequate analgesia in the posterior region of the operated knee. [74] This led to the initial research question of whether the addition of a sciatic nerve block to a patient-controlled femoral nerve block as part of multimodal pain management after TKA can shorten the time to discharge and improve knee mobilization and pain relief. This chapter presents a randomized controlled trial in which patients undergoing TKA were randomized into 3 groups: patient-controlled analgesia via a femoral nerve catheter alone or combined with a single injection or continuous sciatic nerve block until the second postoperative day. The primary outcome was the time to discharge, and the secondary outcomes included pain scores and the use of additional opioids.

Chapter 3: Peripheral nerve blocks as part of multimodal pain management in TKA, part 2

Chapter 3 presents the results of the follow-up outcomes of the study presented in Chapter 2. The research question was whether improved early postoperative pain scores when an additional sciatic nerve block in addition to a femoral nerve block was used would lead to improved long-term functional outcomes and pain perception. After 3 and 12 months, the physical function, stiffness and pain of the initial TKA patients were measured via a combination of patient-reported outcome measures. These outcomes were compared with the preoperative scores and among the 3 groups.

Chapter 4: Cryotherapy after total knee arthroplasty

In one of our clinics, regular cold packs after TKA were used by physiotherapists only on indication. At the time of the clinical trial, a relatively new cryotherapy device was provided for scientific research. The first question was whether this new device would not lead to a greater complication risk; therefore, the complication rate was included as the primary outcome of this study. A prospective cohort of TKA patients is presented with a cryotherapy group and a control group. The secondary outcomes were postoperative functional outcomes and postoperative swelling in the early rehabilitation phase.

Chapter 5: Fixation in total knee arthroplasty, part 1

It is not yet entirely clear which type of prosthesis design and type of fixation provides the best survival and clinical outcomes. Cemented fixation has a greater risk of future aseptic loosening than does cementless fixation, but other studies have reported different results. [86] The main limitation of many studies is their retrospective or noncomparative design. Moreover, the use of radiostereometric analysis (RSA) techniques has been shown to be accurate for the early prediction of late-onset aseptic loosening. [99] In one of our clinics, the Advanced Coated System Mobile Bearing system has been used for TKA, mostly uncemented, for quite some time. This implant has a titanium nitride ceramic coating, which may provide a better surface for bone ingrowth than other designs. [51] This led to the research question of whether the type of fixation used in this design affects migration patterns, the long-term risk of aseptic loosening and patient-reported outcome measures. This chapter presents a randomized controlled trial in which the ACS Mobile Bearing system was used for TKA. In this study, patients who underwent TKA were randomized into 3 groups in a blinded manner. The first group received both components cemented, the second group received both components uncemented, and the third group received a hybrid TKA (tibia cemented and femur uncemented). The primary outcome was the maximum total point motion, a specific value that is part of the RSA. The secondary outcomes were patient-reported outcome measures. These outcomes were measured up to 2 years postoperatively and compared with the preoperative scores and among the 3 groups.

Chapter 6: Fixation in total knee arthroplasty, part 2

The statement in the introduction and Chapter 5 that it is not yet entirely clear which fixation for which prosthetic design provides the best survival and clinical outcomes led to another research question. In many clinics, the Low Contact Stress Mobile Bearing was used for TKA, cemented or uncemented and with different LCS designs. Until the study presented in this chapter, the evidence for long-term survival was

mainly based on small cohorts. Given that this system was used in one of our clinics for a long period of time, the question arose whether the fixation of this design would affect long-term survival. Moreover, the question arose as to what risk factors for revision were present. This chapter presents a retrospective analysis of a large cohort of LCS TKA patients. The primary endpoint was survival time.

Chapter 7: General discussion

This chapter reviews Chapters 1 to 6. For each topic involved, special attention is given to the most recent literature and the current state of the art. Suggestions for future research are also made.

Chapter 8: English summary

This chapter presents the English summary of this thesis.

Chapter 9: Dutch summary - Nederlandse samenvatting

This chapter presents the Dutch summary of this thesis.

Appendices

The first part represents the author's presentations and training courses as part of the PhD training and the author's publications. The acknowledgments are specially dedicated to the people involved in the realization of this thesis. The last part briefly presents the author's biography.

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2

Peripheral nerve blocks as part of multimodal pain management in TKA, part 1

Value of Single-Injection or Continuous Sciatic Nerve Block in Addition to a Continuous Femoral Nerve Block in Patients Undergoing Total Knee Arthroplasty

A Prospective, Randomized, Controlled Trial

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Reg Anesth Pain Med. 2011 Sep-Oct;36(5):481-8.

DOI: 10.1097/AAP.0b013e318228c33a.

PMID: 21857273

Abstract

Background and Objectives: Continuous femoral nerve block in patients undergoing total knee arthroplasty (TKA) improves and shortens postoperative rehabilitation. The primary aim of this study was to investigate whether the addition of sciatic nerve block to continuous femoral nerve block will shorten the time-to-discharge readiness.

Methods: Ninety patients undergoing TKA were prospectively randomized to 1 of 3 groups: patient-controlled analgesia via femoral nerve catheter alone (F group) or combined with a single-injection (Fs group) or continuous sciatic nerve block (FCS group) until the second postoperative day. Discharge readiness was defined as the ability to walk and climb stairs independently, average pain on a numerical rating scale at rest lower than 4, and no complications. In addition, knee function, pain, supplemental morphine requirement, local anesthetic consumption, and postoperative nausea and vomiting (PONV) were evaluated.

Results: Median time-to-discharge readiness was similar: F group, 4 days (range, 2-16 days); Fs group, 4 days (range, 2-7 days); and FCS group, 4 days (range, 2-9 days; $P = 0.631$). No significant differences were found regarding knee function, local anesthetic consumption, or postoperative nausea and vomiting. During the day of surgery, pain was moderate to severe in the F group, whereas Fs and FCS groups experienced minimal pain ($P < 0.01$). Patients in the F group required significantly more supplemental morphine on the day of surgery and the first postoperative day. Until the second postoperative day, pain was significantly less in the FCS group ($P < 0.01$).

Conclusions: A single-injection or continuous sciatic nerve block in addition to a femoral nerve block did not influence time-to-discharge readiness. A single-injection sciatic nerve block can reduce severe pain on the day of the surgery, whereas a continuous sciatic nerve block reduces moderate pain during mobilization on the first 2 postoperative days.

Introduction

Total knee arthroplasty (TKA) reduces pain and improves function resulting in a higher quality of life for patients with knee osteoarthritis. [18] These patients can suffer from considerable postoperative pain, which is known to impair early intensive physical therapy and rehabilitation. Good postoperative pain control is probably the most important factor to accelerate knee rehabilitation. [4, 12, 30] Meanwhile, hospital stay after TKA has been shortened by the introduction of clinical pathways including standardized pain therapy allowing accelerated mobilization: good postoperative pain management should allow intensive physical therapy and early discharge.

With patient-controlled intravenous (IV) opioids alone, moderate to severe pain can persist, especially during mobilization. [10, 21, 30] Continuous epidural analgesia and continuous peripheral nerve blocks provide improved analgesia and a significantly shortened rehabilitation time when compared with pure opioid therapy. [4] In a risk-benefit analysis, peripheral nerve blocks offer more site-specific analgesia with a lower incidence of adverse effects compared with epidural analgesia. [6, 9, 31] For balancing adequate analgesia with limited quadriceps motor impairment, patient-controlled femoral nerve block can be used. [22] Although a recent meta-analysis could not find any advantage of a continuous femoral nerve block in comparison to a single injection, [25] in most institutions, it is considered standard for TKA. [11] However, continuous femoral nerve block might lead to insufficient pain relief in the posterior region of the operated knee. [3, 19] Yet, the discussion continues whether a supplemental sciatic nerve block plus analgesia via a femoral nerve catheter is beneficial in these patients. [3, 5, 17, 28] Pham et al. [27] demonstrated better pain relief at rest and decreased morphine consumption when combining continuous femoral and sciatic nerve blockade. Unfortunately, in this study, data from patients with continuous and single-injection sciatic block were not analyzed separately. Morin et al. [23] reported improved analgesia in patients undergoing TKA with combined continuous femoral and sciatic nerve block for a median of 3 days but also reported more problems while performing active exercises and more insecure walking in patients with an additional sciatic nerve block. Therefore, we shortened the time of nerve blocks to not interfere with early ambulation. Finally, a recent meta-analysis concluded that further studies are needed to evaluate the value of adding sciatic nerve block to femoral nerve block in patients undergoing TKA. [25]

We hypothesize that addition of sciatic nerve block (single- injection or continuously) to a patient-controlled femoral nerve blockade will shorten time-to-discharge readiness and improve postoperative knee mobilization and pain relief after TKA.

Methods

This trial was designed as a single-center, prospective, randomized, controlled study. Approval of the study was obtained by the Medical Ethics Committee of the Academic Medical Centre of Amsterdam (07/321 MEC), and it was registered in the national trial register (NTR2207). Progress of the study and adverse event rates were annually reviewed by the hospital ethics committee.

Study Participants

All eligible patients scheduled for total knee replacement arthroplasty (TKA) in a clinical pathway were enrolled 1 week before knee surgery. After being provided with written and verbal information, the subject's written informed consent was obtained on admission. Inclusion criteria consisted of age older than 18 years and American Society of Anesthesiologists classification I to III. Exclusion criteria were infection near the insertion site of any catheter, coagulation disorders, allergy to local anesthetics, prior surgery near the site of nerve block, inability to use the patient-controlled analgesia device, pregnancy or lactation, known hepatic or renal insufficiency, and preexisting neurologic deficit of the operated leg. Normal motor and sensory function of the operated leg was evaluated before randomization. The study period included the time from admission for TKA until hospital discharge.

Randomization

Eligible patients were randomized into 3 groups using opaque-sealed envelopes containing the treatment assignment. Thus, 90 patients were randomly allocated to 1 of 3 equally sized groups:

F: Patients receiving patient-controlled femoral nerve block only.
Fs: Like the F group combined with a single-injection sciatic nerve block.
FCS: Like the F group combined with a continuous sciatic nerve block.

Preoperative Knee Function and Pain Assessment

Preoperative functional capacity of the knee was assessed by active range of motion, measuring knee flexion with a goniometer. Ratings were documented of preoperative knee pain on a numeric rating scale (NRS; range, 0-10; 0 = no pain, 10 = most imaginable pain) during movement.

Nerve Block Techniques

After establishing venous access and standard hemodynamic monitoring (electrocardiogram, pulse oximetry, noninvasive blood pressure measurement),

peripheral nerve blocks were placed under aseptic conditions in the preoperative holding area by 1 of 3 anesthesiologists with extensive experience in ultrasound-guided nerve block procedures. All patients received a stimulation femoral nerve catheter (Stimucath continuous nerve block set with a 18-gauge Tuohy needle and 20-gauge catheter; Arrow International, Inc, Reading, Pa), inserted via an ultrasound-guided inguinal in-plane approach in supine position. The needle tip was positioned dorsomedial to the femoral nerve under ultrasound guidance (HFL 38 probe connected to MicroMaxx; SonoSite, Inc, Bothell, Wash) and nerve stimulation (Stimuplex HSN 12 [B Braun, Melsungen, Germany]; pulse width, 0.1 millisecond; frequency, 2 Hz). The stimulating catheter was advanced or repositioned aiming for stimulation current less than 0.6 mA. Ultrasound identification of the catheters was difficult in patients with a body mass index greater than 30 kg/m2. The lowest current inducing muscle contractions via the catheter was registered. After negative aspiration, a loading dose of 20 mL of levobupivacaine 0.375% was administered slowly in fractions of 5 mL.

For patients from the Fs and FCS groups, before placement of the femoral nerve catheter, a sciatic nerve block was established via a parasacral approach, as described by Mansour, [20] in the lateral decubitus position with guidance of a nerve stimulator. In the Fs group, a stimulating needle (15-cm 20-gauge needle; Stimuplex A [B Braun]) was used, and in the FCS group, a stimulating needle with a catheter set was used (15-cm 18-gauge needle, 100-cm 20-gauge catheter; Contiplex Tuohy [B Braun]). After eliciting dorsal or plantar flexion of the foot with a current preferably below 0.6 mA, a loading dose of 20 mL of levobupivacaine 0.375% was injected intermittently after negative aspiration. In the FCS group, the catheter was inserted 5 cm beyond the needle tip. Nerve catheters were secured to the skin with a catheter stabilization device (Statlock, for winged catheters; Bard, Inc, Covington, Ga) and covered with a transparent dressing (Tegaderm; 3M, St Paul, Minn).

Time needed for establishing the nerve block from first needle penetration to withdrawal of the needle (for single-injection blocks) and catheter fixation (for continuous techniques) was registered. All electrical stimulation thresholds were noted.

After injection of local anesthetics, sensory and motor block was examined based on a 3-point scale every 5 minutes during the first 45 minutes (Table 1). [24] Femoral sensory function was tested by pinprick 10 cm proximal of the patella and femoral nerve motor function by knee extension. Sciatic motor function was tested by foot

plantar/dorsal extension and sensory function by pinprick sensation at the lateral calf and the dorsum of the foot.

Table 1. *Scale of Sensory and Motor Function*

S1	Normal sensation
S2	Touch sensation, no pain
S3	No sensation
M1	Full power
M2	Decreased power
M3	No power

Examination of sensory and motor block based on a 3-point scale and tested every 5 minutes during the first 45 minutes after femoral and sciatic nerve blocking.

During the Surgery

Patients received lorazepam 1 mg 2 hours and acetaminophen 2 g 1 hour before surgery. At 45 minutes after application of the initial bolus at the femoral nerve site, a continuous infusion of levobupivacaine 0.125% 10 mL/h was started via the femoral nerve catheter in all groups. In the FCS group, a second continuous infusion of levobupivacaine 0.125% 10 mL/h was started via the sciatic catheter 45 minutes after catheter placement.

General anesthesia was induced with propofol target-controlled infusion set to 3 to 5 Kg/mL and remifentanil 0.5 Kg/kg per minute and maintained with 2 to 3 Kg/mL and 0.1 to 0.25 Kg/kg per minute, respectively. Infusion rates were adjusted as required, and patients were ventilated via a laryngeal mask.

A pneumatic tourniquet was placed on the thigh before surgery and inflated to 300 mm Hg during surgery. Total needs of propofol and remifentanil, duration of surgery, and time of tourniquet were recorded.

Postoperatively on Postanesthesia Care Unit

Postoperatively, the continuous femoral nerve infusion was changed to patient-controlled femoral nerve infusion (5-mL bolus, 30-minute lockout; basal rate, 6 mL/h [Perfusor fm; B Braun]) in all groups. In the FCS group, the additional continuous sciatic infusion was maintained during the postoperative period (10 mL/h).

Supplemental morphine IV was administered for pain control if pain score on an NRS was higher than 4. Consumption of morphine and NRS at 1, 2, and 3 hours

postoperatively were noted. The extent of postoperative nausea and vomiting (PONV) was graded as none = 0, mild = 1, and severe = 2. Patients with PONV received ondansetron 4 mg IV and, when the symptoms persisted, droperidol 0.625 mg IV was added.

Postoperatively on Surgical Ward

All patients received standardized postoperative analgesia with acetaminophen 1 g 4 times daily. In the absence of any contraindications, diclofenac 50 mg was added 3 times daily, combined with esomeprazol 20 mg once daily for gastric protection. Alternatively, tramadol was started 50 mg 3 times daily. An extra dose of tramadol (100 mg) was administered before removal of nerve catheters. If NRS remained high despite these treatments, morphine was administered for pain relief as required. Perineural infusions were continued for 36 hours, and catheters were removed on the morning of the second postoperative day (POD 2). Deep vein thrombosis prophylaxis was provided with fondaparinux 2.5 mg/0.5 mL subcutaneously daily, starting the evening on the day of surgery and continued for 4 weeks.

Physical therapy started on POD 1 until discharge. Functional capacity was assessed daily and recorded with the Medical Research Council scale for muscle strength of the quadriceps (MRC-Q) and active range of motion of the knee with a goniometer by the physical therapist.

Readiness to Discharge and Functional Outcome

The primary end point was time-to-discharge readiness. Criteria were as follows:

1. Ability to walk 25 m or more with walking aids and to climb a flight of stairs. This end point was checked daily at 10 AM and 2 PM by a physical therapist.
2. A pain score below 4 on an NRS as taken by nurses educated in pain measurement and therapy.
3. Absence of serious complication as examined by an orthopedic surgeon on a daily basis.

These discharge criteria were checked daily by an investigator. Furthermore, short-term functional capacity was determined by MRC-Q and active flexion of the knee daily by a physical therapist. Duration of actual admission was also noted. Secondary end points were pain scores measured on an NRS at rest and during movement, supplemental consumption of morphine, local anesthetic consumption, and grade of PONV. These variables were noted daily at 8 AM and 6 PM on the ward starting

the day of surgery until the third postoperative day. Patients were assessed daily by the surgeon for complications during admission, as well as 6 weeks postoperatively.

Statistical Analysis

We considered a 25% reduction in discharge readiness to be clinically relevant (normal length of stay 4 days). On the basis of previous data, we assumed a standard deviation of 1 day. Sample size analysis indicated that a group size of 30 patients will allow to show a 25% difference between groups at a 90% power and at a 2-tailed alpha level of 0.05 (after Bonferroni correction for multiple comparisons). Intention-to-treat analysis was conducted.

Comparisons between groups were made by Kruskal-Wallis test and, if significant, by unpaired 2-sided Mann-Whitney U test. Dichotomous variables were compared on contingency table by Fisher exact test. A value of $P < 0.05$ was considered significant. The P values of the primary end points (readiness to discharge) were corrected by Bonferroni-Holmes adjustment for multiple comparisons.

Results

Patients were included between February 2008 and April 2010. A CONSORT flow diagram of eligible and participating patients is demonstrated in Figure 1. Four patients had a staged bilateral TKA. One patient (F group) withdrew consent after randomization and refused to give NRS scores or other data. Therefore, no data from this patient could be analyzed. Patients with primary failed blocks (1 femoral in the FCS group, 2 sciatic blocks in the Fs group) were included in an intention-to-treat analysis.

Demographic data and values for required sedation, block performance, and tourniquet as well as surgery duration are shown in Tables 2 and 3 per group. There were no significant demographic differences between the 3 groups.

Three patients had no signs of nerve block within 40 minutes. The other 86 patients developed signs of motor and sensory block within 15 minutes, whereas complete block took up to 40 minutes. There were no significant differences between groups regarding onset times of blocks.

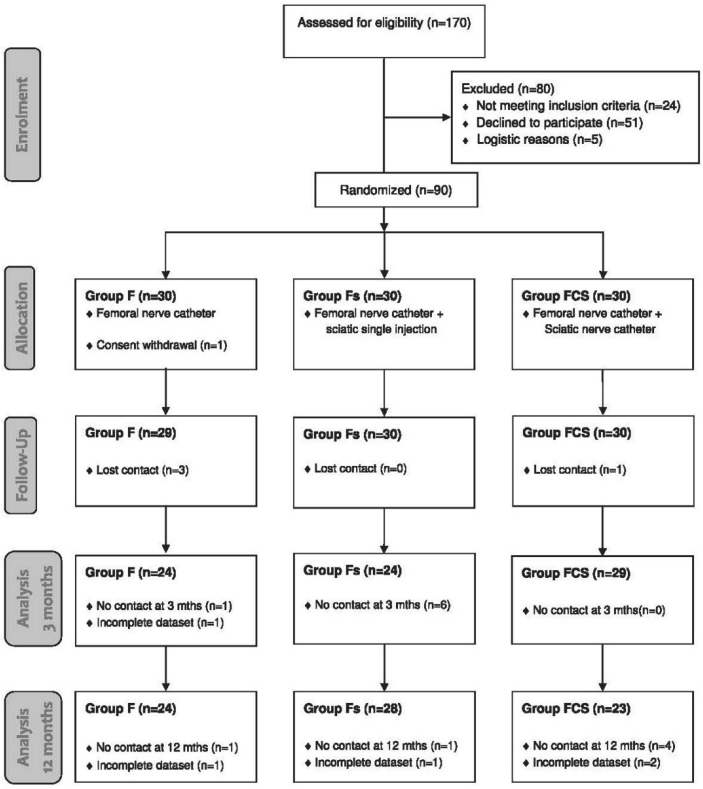

Figure 1. *CONSORT diagram showing flow of patients for TKA through the study.*

Table 2. *Demographic Data*

	F Group (n = 29)	Fs Group (n = 30)	FCS Group (n = 30)
Age, y	62 (50-79)	65 (43-81)	66 (43-83)
Sex (M/F)	11/18	9/21	8/22
Height, cm	174 (158-188)	171 (150-187)	173 (159-188)
Weight, kg	84 (72-116)	82 (62-125)	89 (68-118)
BMI, kg/m^2	30.3 (23.2-39.7)	28.6 (21.0-48.8)	27.8 (22.1-39.6)
ASA I/II/III	13/13/3	13/17/2	9/16/5
NRS preoperatively	5.4 (3.0-7.5)	6.5 (2.0-10)	6.3 (0-10)
AROM, degrees	120 (70-130)	110 (60-135)	110 (80-135)

Patient characteristics presented as median (range) or absolute number as appropriate. There were no significant demographic differences between the 3 groups (P > 0.05).
AROM indicates active range of motion of the knee; ASA, American Society of Anesthesiologists status; BMI, body mass index; NRS, pain score as numeric rating scale.

Table 3. *Characteristics of Block and Surgical Performance per Group*

Variables	F Group (n = 29)	Fs Group (n = 30)	FCS Group (n = 30)
Alfentanil, Kg	500 (250-1000)	1000 (0-1750)	1000 (250-2000)
Propofol, mg	0 (0-40)	0 (0-50)	0 (0-100)
Femoral catheter placing duration, min:s	5:56 (2:30-21:00)	7:41 (2:20-26:00)	6:40 (3:20-24:12)
Femoral catheter threshold, mA	0.44 (0.20-0.80)	0.40 (0.20-0.90)	0.35 (0.1-0.6)
Sciatic injection duration, min:s		3:49 (1:10-22:00)	
Sciatic threshold, mA		0.38 (0.2-0.9)	
Sciatic catheter placing duration, min:s			4:46 (2:00-15:15)
Sciatic catheter threshold, mA			0.30 (0.1-0.60)
Length of surgery, min	93 (51-150)	87 (53-178)	93 (69-134)
Tourniquet time, min	88 (33-152)	75 (14-158)	69 (15-109)

Data are given as median (range). There were no statistical significant differences between groups (P > 0.05).

Readiness to Discharge and Functional Outcome

Median time-to-discharge readiness was similar for all 3 groups: F group, 4.0 days (range, 2.0-16.0 days); Fs group, 4.0 days (range, 2.0-7.0 days); and FCS group, 4.0 days (range, 2.0-9.0 days) (Fig. 2). The actual median length of hospital stay was equal to the time-to-discharge readiness and did not differ between groups: F group, 4 days (range, 3-16 days); Fs group, 4 days (range, 4-10 days); and FCS group, 4 days (range, 4-10 days).

Similarly, no significant differences were found in active knee flexion at the time-to-discharge readiness (F group, 75 degrees [range, 55-90 degrees]; Fs group, 80 degrees [range, 55-95 degrees]; and FCS group, 80 degrees [range, 40-95 degrees]) or in MRC-Q (F group, 3 [range, 3-4]; Fs group, 3 [range, 2-4]; and FCS group, 3 [range, 2-5]). Likewise, there were no significant differences in active flexion (Fig. 3) or MRC-Q between all groups at POD 2, 3, and 4 or at discharge.

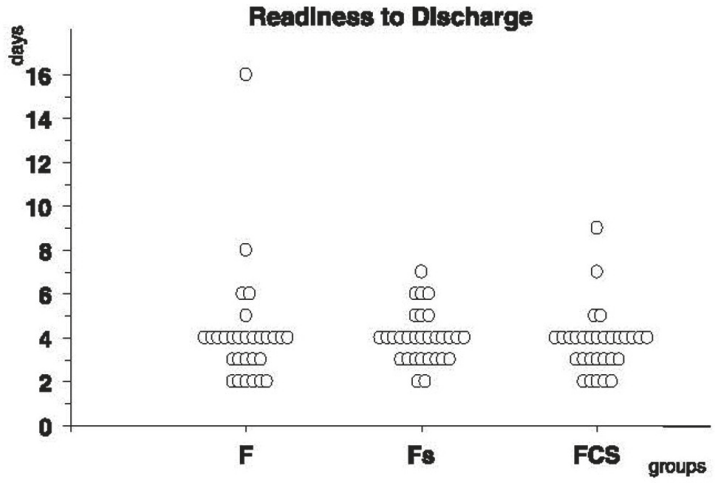

Figure 2. *Time points when each of 89 patients reached discharge criteria for each treatment group. There were no statistical significant differences between groups (P = 0.631).*

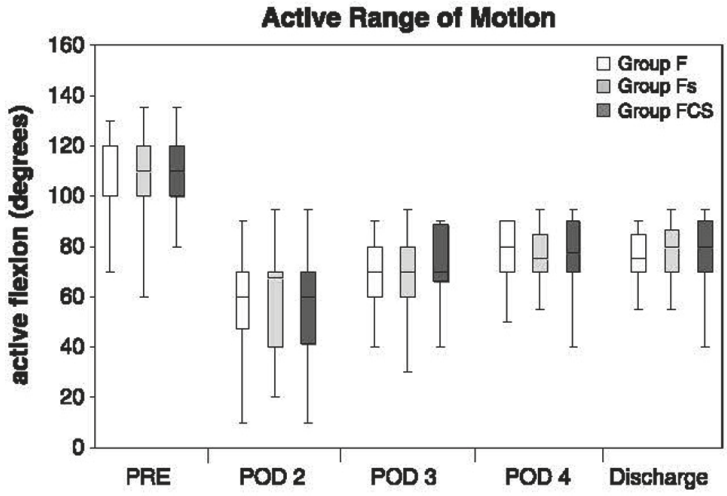

Figure 3. *The range of motion of the different treatment groups over time. Box plots representing the degree of active knee flexion per group and per day. The white boxes represent the F group (only femoral catheter), light gray boxes represent the Fs group (femoral catheter and sciatic single injection), and dark gray boxes represent the FCS group (femoral and sciatic catheter). There were no significant differences between groups at any time.*

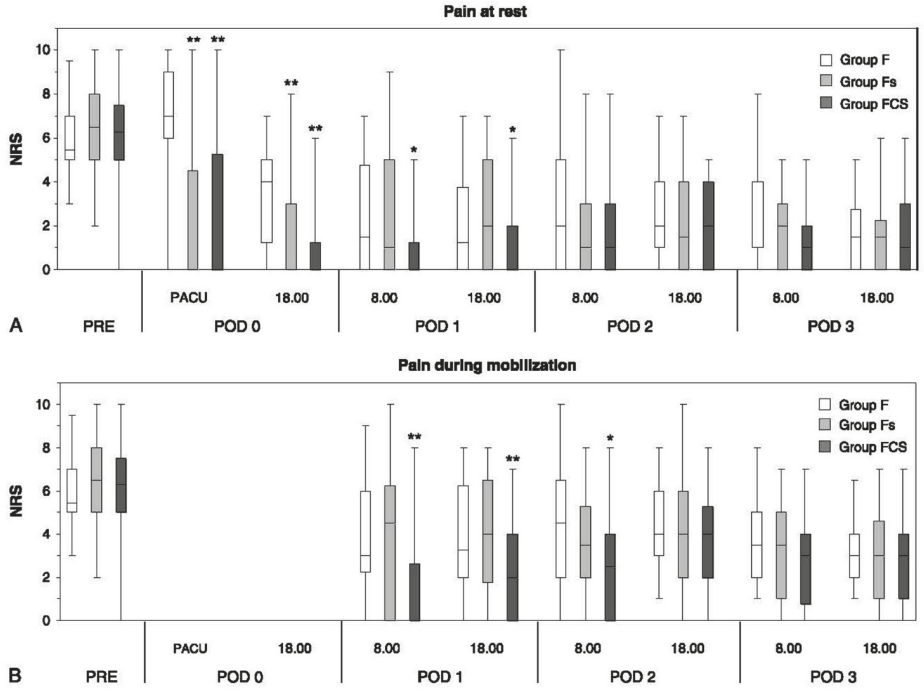

Figure 4. *Pain at rest (A) and during mobilization (B) over time per group. The white boxes represent the F group (only femoral catheter), light gray boxes represent the Fs group (femoral catheter and sciatic single injection), and dark gray boxes represent the FCS group (femoral and sciatic catheter). For each patient, POD 2 pain score measurements (NRS, numeric rating scale) are performed at 8:00 AM (left) and 6:00 PM (right). All patients who received a sciatic block had significant lower pain scores at rest on POD 0 (postanesthesia care unit and 6:00 PM) ($P < 0.01$), whereas only the patients with a sciatic nerve catheter had significantly less pain on POD 1 ($P < 0.05$). Although the differences were clinically relevant on day 0 according to International Association for the Study of Pain (IASP) definition (ΔNRS >2), they were not clinically relevant on day 1. The patients with a continuous sciatic nerve catheter had statistically significant pain reduction during mobilization on POD 1 and 2; however, postoperative pain during mobilization was always below preoperative values in all groups. *$P < 0.05$. **$P < 0.01$.*

Postoperative Pain and Analgesic Consumption

Patients in the F group had significantly more postoperative pain at the day of TKA compared with those in the Fs and FCS groups (Fig. 4). During the first postoperative hours in the postanesthesia care unit, patients of the F group experienced moderate to severe pain with a median pain score of 7 (range, 0-10), whereas patients of the Fs and FCS groups had a median pain score of 0 (range, 0-10; P < 0.01). Patients in the F group needed 16 mg (range, 0-42 mg) of morphine IV in contrast to the Fs (2 mg [range, 0-22 mg]) and FCS groups (0 mg [range, 0-12 mg], P < 0.01; Table 4). When patients still experienced pain scores higher than 4 after morphine 15 to 20 mg IV, supplemental medication like S-ketamine 5 to 10 mg IV and clonidine 75 to 150 Kg were administered (9 patients in the F group, 1 patient in the Fs group, and 1 patient in the FCS group, P < 0.01). Nevertheless, patients in the F group still had more pain at the end of the day (NRS POD 0, at 6 PM in the F group, 4 [range, 0-7]; Fs group, 0 [range, 0-8]; and FCS group, 0 [range, 0-6]; P < 0.01). Until POD 2, pain at rest and during mobilization was significantly less in the FCS group. However, pain during mobilization was moderate in the F and Fs groups (median NRS ≤5; Fig. 4B) and mild at rest in all groups. Rescue medication with morphine was increased in the F group on POD 0 to 2 (Table 4). Incidence of postoperative nausea and vomiting was 6.7% without significant difference between groups.

No significant difference for delivered boluses of levobupivacaine 0.125% applied via the patient-controlled femoral nerve block was found between groups (Table 5).

Table 4. *Postoperative Morphine Consumption*

Morphine (mg/24 h)	F Group (n = 29)	Fs Group (n = 30)	FCS Group (n = 30)	*P*
POD 0	16 (0-42) 27/29	2 (0-22) 16/30	0 (0-16) 11/30	0.000
POD 1	0 (0-48) 5/29	0 (0-5) 1/30	0 (0-0) 0/30	0.006
POD 2	0 (0-48) 7/29	0 (0-8) 3/30	0 (0-0) 0/30	0.011
POD 3	0 (0-40) 3/29	0 (0-13) 1/30	0 (0-0) 0/30	0.149

A significant difference was found between the F group and the other 2 groups on POD 0 and 1 but only between the F group and the FCS group on POD 2. After the day of surgery (POD 1-3), median (range) morphine consumption was 0 mg for all groups. When morphine was administered orally the equipotent dose was calculated (oral/IV; 3:1) and added to the total morphine requirement. The number of patients per group who required morphine is given below.

Table 5. *Bolus Doses of Levobupivacaine 0.125% per Group*

		F Group	Fs Group	FCS Group
		(n = 29)	(n = 30)	(n = 30)
POD 1	8 AM	25 (0-119)	6 (0-163)	6 (0-144)
	6 PM	13 (0-94)	3 (0-106)	0 (0-75)
POD 2	8 AM	6 (0-44)	0 (0-56)	0 (0-25)

Levobupivacaine (mg/12 h) delivered as bolus via patient-controlled femoral nerve block (basic infusion rate of levobupivacaine 0.125%, 6 mL/h). There were no statistically significant differences between groups.

Complications

Twelve patients did not have mobilization according to the schedule because of hematoma, swelling, or wound leakage (4 patients in the F group, 5 patients in the Fs group, and 3 patients in the FCS group). One patient (F group) required surgical drainage on POD 3. The number of patients with delayed mobilization included 3 of the total 4 patients (3 patients in the Fs group and 1 patient in the FCS group), who had fallen because of unaccompanied mobilization on POD 2.

After diagnosis of a full motor block of the foot in 11 patients from the FCS group on POD 1, infusion of continuous sciatic nerve block was interrupted temporarily until motor function was restored and then infusion of levobupivacaine was continued at a lower infusion rate (6 mL/h) and motor block did not reappear in any of these patients.

Discussion

Addition of a single-injection or continuous sciatic nerve block to a continuous femoral nerve block for postoperative pain treatment after TKA did not improve time-to-discharge readiness or knee function in this randomized controlled trial. However, early postoperative pain relief was much better controlled at rest and during mobilization, whereas opioid requirements were reduced in patients with a sciatic nerve block. The group receiving a continuous sciatic catheter had significantly less pain during mobilization.

Patients with continuous femoral nerve block alone experienced severe postoperative pain on the day of TKA, whereas the addition of a sciatic block provided complete pain relief. Thus, sciatic nerve block combined with a continuous femoral nerve block improved the quality of early postoperative analgesia significantly and in a clinically

relevant manner. The difference in median pain score between groups was 7 on an NRS from 0 to 10 and are in line with observational studies [1, 2] and 2 other randomized trials. [7, 26] The high pain scores in the F group are concerning and may be explained by the fact that our patients received only short-acting and ultra short-acting opioids before and during the surgery. However, the use of longer-acting opioids might be insufficient for those patients requiring up to 42 mg of morphine and who still had moderate to severe pain scores during the early postoperative period. Even the addition of S-ketamine and clonidine as nonopioid rescue analgesics was needed frequently in the F group to achieve sufficient pain control.

One may argue that patient-controlled systemic analgesia would have reduced the maximum pain scores and might have been a better indicator for a good postoperative pain therapy. However, it is difficult to include an additional patient-controlled infusion pump and handling 2 patient-controlled systems in elderly patients shortly after a major surgery under general anesthesia.

Because median pain scores at rest were 2.0 or lower in all groups from POD 1 on, we could not demonstrate any advantage of a sciatic nerve block for pain relief at rest from that time on. However, addition of a continuous sciatic nerve block controls pain significantly better during mobilization. Although the pain reduction is according to International Association for the Study of Pain (IASP) definitions clinically relevant, the median pain scores during mobilization were moderate in patients receiving a femoral nerve block with or without single-injection sciatic nerve block.

Readiness to discharge was not affected when combining a sciatic nerve block to a continuous femoral nerve block in our study. While Ilfeld et al. [14, 15] demonstrated in 2 multicenter studies a difference in time to reach discharge criteria when pain was better controlled with an extended continuous femoral nerve block during 4 days compared with a continuous femoral nerve block overnight, addition of a sciatic nerve block did not affect readiness to discharge in our study. However, because discharge criteria, patient population, clinical pathway, and systemic analgesic management were different between the cited study and the present investigation, it is difficult to draw conclusions from comparisons of these 2 studies. [14, 15]

A sciatic nerve block, specially a continuous block, might impair motor function and thereby might have a negative effect on active knee movement, thereby delaying hospital discharge. Of the patients in the FCS group, 36.7% had a motor block on POD 1. Subsequently, the infusion was stopped and later restarted at a lower rate. Thus, none of the patients had a motor block on POD 2; furthermore, all regional

anesthesia was stopped at 6 AM on POD 2. No patient of any group reached discharge criteria on POD 1. Therefore, it is unlikely that the high incidence of motor block in the FCS group had influenced the discharge criteria.

One may also argue that the addition of a sciatic nerve block requires more patient preparation time. Establishing sciatic nerve block took, on average, less than 5 minutes and, therefore, had little impact on the clinical pathway. However, in institutions with less experience in regional techniques, this time might be longer and more relevant.

In patients having considerable more pain (like those in the F group), one should expect an increased demand and delivery of levobupivacaine 0.125%. However, no differences were found between groups in total bolus dose via patient-controlled femoral block.

Worrisome are the 4 falls during mobilization at the beginning of the study period. Falls occurred in 3 patients of the Fs group and 1 patient of the FCS group on POD 2. In all cases our safety instructions for mobilization were violated. We repeated education to nurses and patients about nerve block induced motor weakness and risks of falling and observed no further falls thereafter. Our study is underpowered to draw conclusions on the influence of blocks on fall incidents. Previously, worries about the risk of falling when using a femoral block in patients undergoing TKA have been expressed. [16, 29]

The incidence of falls reported by these authors is lower than the incidence we determined, probably due to underreporting in these retrospective studies. Recently, Ilfeld et al. [13] reanalyzed the risk of falling in their prospective randomized studies in patients undergoing TKA with or without continuous femoral nerve block. The authors observed significantly more fall incidents in the groups with continuous femoral nerve block, although none of the falls led to a change in treatment or delay of hospital discharge. Incidents of falls were moderately higher than the incidents we observed. As shown recently, effective fall prevention is much more than providing an information folder or to just advice the patient that he/she should not ambulate on his own. [8]

A limitation of the study is the absence of blinding of patients.

In conclusion, combining sciatic nerve block to femoral nerve catheter did not influence readiness to discharge or short-term knee function. A single-injection sciatic

nerve block can reduce severe pain on the day of surgery, whereas a continuous sciatic nerve block reduces moderate pain during mobilization on the first 2 postoperative days. Therefore, improved pain therapy cannot simply be translated into reduced hospital stay and improved short-term rehabilitation.

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3

Peripheral nerve blocks as part of multimodal pain management in TKA, part 2

Long-term pain and functional disability after total knee arthroplasty with and without single-injection or continuous sciatic nerve block in addition to continuous femoral nerve block: a prospective, 1-year follow-up of a randomized controlled trial

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Reg Anesth Pain Med. 2013 Jan-Feb;38(1):58-63.

DOI: 10.1097/AAP.0b013e318272523c.

PMID: 23104147

Abstract

Background and Objectives: This is a follow-up to determine long-term outcomes after total knee arthroplasty (TKA) in patients enrolled in a previous randomized trial that found reduced postoperative pain after addition of sciatic nerve block to continuous femoral nerve block for TKA.

Methods: Physical function after TKA was evaluated at 3 and 12 months in patients (n = 89) receiving continuous femoral nerve block alone (group F), combined with a single-injection (group Fs) or continuous sciatic nerve block (group FCS) after TKA, until the second post-operative day. Physical function, stiffness, and pain were measured by using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Oxford Knee Score 12-item knee questionnaires, and visual analog scale at rest and during mobilization before TKA and 3 and 12 months afterward. Post hoc, a median split on poor functioning (WOMAC) was analyzed.

Results: Western Ontario and McMaster Universities Osteoarthritis Index, Oxford Knee Score 12-item knee, and visual analog scale scores improved significantly in all patients, without any differences among groups. Median (range) WOMAC at 3 months were in group F, 83 (20-97); group Fs, 72 (25-99); and group, FCS 76 (28-100) and at 12 months 87 (35-98), 77 (43-100), and 89 (35-100), respectively.

Conclusions: No differences were detected in the secondary outcomes we examined. Thus, improved postoperative outcome did not translate into improved functional outcome or long-term pain.

Introduction

Recently, we demonstrated significant reduction of postoperative pain and analgesic requirements after total knee arthroplasty (TKA), combining a sciatic nerve block (single injection or continuous infusion) with a continuous femoral nerve block in a randomized controlled trial. [23] However, despite improved pain therapy, no differences in short-term function and readiness to discharge could be demonstrated among the 3 study groups.

The same patients were followed up, as a secondary aim of the recently published investigation, [23] to determine whether an additional sciatic nerve block could improve long-term knee function and reduce pain. Thus, we examined functional outcome of the previous study groups at 3 and 12 months' follow-up and present the results in this report.

Preoperative poor knee function and severe pain may be important risk factors for developing chronic postoperative pain and impaired knee function after TKA. [21, 24] Therefore, to generate a new hypothesis to guide future research, we analyzed post hoc whether patients with poor preoperative knee function may benefit, especially from a sciatic nerve block.

Methods

This is a follow-up of a previously performed single-center, prospective, randomized controlled study in patients for TKA, comparing a continuous femoral nerve block with or without a single or continuous sciatic nerve block. The follow-up was prospectively planned as a secondary aim of the randomized controlled trial, which was approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam (07/321 MEC) and registered, including this secondary aim, in the National Trial Register (NTR2207). Before surgery, patients provided written and verbal informed consent. Details of the study methods have been published previously in Regional Anesthesia and Pain Medicine. [23]

Study Intervention

Follow-up took place in 89 patients of the completed randomized controlled study. Patients were previously randomized and divided into 3 groups for TKA: patient-controlled analgesia via femoral nerve catheter alone (group F) or combined with a single-injection (group Fs) or continuous sciatic nerve block (group FCS) until the

second postoperative day. Patients with primary failed blocks (2 sciatic blocks in group Fs, 1 femoral in group FCS) were included in an intention-to-treat analysis. Postoperatively, all patients received standardized oral analgesics containing acetaminophen 1 g at 4 times daily and diclofenac 50 mg at 3 times daily, combined with esomeprazole 20 mg. Alternatively, tramadol was started 50 mg at 3 times daily. Oral analgesics were continued after discharge if necessary. Physical therapy was started within a predefined program twice daily on postoperative day 1 and continued after discharge twice weekly for the first 6 weeks.

Outcome Measurements

Knee function was evaluated through 2 self-reporting validated questionnaires: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire and the Oxford Knee Score (OKS) 12-item knee questionnaire. The WOMAC evaluates quality of life in the dimensions of pain (5 items), stiffness (2 items), and function (17 items). [15] A validated version for the Dutch language was used with a 5-point Likert scale from 0 to 4 for each question. [17] Raw values were summed and standardized (0-100) for each dimension and for WOMAC, where a higher score represents better function and less pain. Western Ontario and McMaster Universities Osteoarthritis Index is recommended in the Osteoarthritis International Research Society's guidelines for clinical trials. [2] Oxford Knee Score questionnaire is a disease- and site-specific questionnaire specifically developed for knee arthroplasty patients. [25] The OKS questionnaire contains 12 items that assess pain and physical disability. Each item is rated from 1 (least difficulty/ severity) to 5 (most difficulty/severity). A Dutch-validated version was used with a 5-point Likert scale for each question, leading to a total score that ranged from a best functional score of 12 to the worst functional outcome of 60, with higher scores representing more severe knee problems. [10] Using both questionnaires for outcome measurements will give a complete view of leg and knee function.

Baseline-written WOMAC, OKS, and visual analog scale (VAS) scores were collected preoperatively. Preoperative VAS was measured at rest only, because there was no standardized mobilization during physiotherapy. At 3 and 12 months after TKA, patients were invited by mail to complete written WOMAC and OKS questionnaires and VAS, at rest and during mobilization. To reduce loss of follow-up, patients were requested by telephone to return completed questionnaires after a waiting period of 2 weeks.

Statistical Analysis

This follow-up is an analysis of the prospectively defined secondary aim of a randomized controlled trial, which was powered for accelerated discharge readiness. Therefore, this analysis of a secondary aim is subject to type II error; that is, an existent difference might not be detected because of small sample size. Intention-to-treat analysis was used. Comparisons among groups were made using Kruskal-Wallis test and unpaired 2-sided Mann-Whitney U test. Dichotomous variables were compared on contingency table using Fisher exact test. $P < 0.05$ was considered significant. The *P* values of the main end points (WOMAC and OKS) were corrected using Bonferroni-Holmes adjustment for multiple comparisons among groups. The different dimensions of the WOMAC and VAS values were also analyzed (WOMAC pain, WOMAC stiffness, WOMAC function, and VAS, at rest and during mobilization).

Because poor preoperative function and severe preoperative pain may be associated with poor postoperative functional outcome and pain, [21, 24] we decided to separately reanalyze patients with poor preoperative function. A post hoc median-split analysis, based on the preoperative functional score (median baseline WOMAC), was applied to test the hypothesis that only patients with severe disabilities and severe pain preoperatively (baseline WOMAC < median baseline WOMAC) might benefit from an improved postoperative pain management. Median baseline WOMAC of all patients could be calculated only after completing inclusion of all patients. Thus, only the preoperatively severely disabled patients were analyzed per group. Naturally, the severely disabled were not evenly distributed among groups. Outcome data of the preoperative severely disabled patients (baseline WOMAC < median baseline WOMAC) were reanalyzed for all 3 groups. The variables tested were improvements in WOMAC score or subscore (WOMAC pain, WOMAC stiff- ness, WOMAC function), OKS, and pain, at rest and during mobilization from preoperatively to 3 or 12 months, respectively. $P < 0.05$ was considered statistically significant. This was done in the light of possible hypothesis generation for future studies and not to delineate any conclusion from a post hoc analysis.

Results

Patients were included between February 2008 and April 2010 during the previously performed randomized controlled trial. After collection of all data, the follow-up was completed in May 2011.

A CONSORT flow diagram of eligible and participating patients in the follow-up is demonstrated in Figure 1. Patients with primary failed blocks (1 femoral in group FCS, 2 sciatic blocks in group Fs) were included in an intention-to-treat analysis. Patients were excluded from analysis if data of both follow-up periods (3 and 12 months) were missing (3 patients in group F [10%] and 1 patient in group FCS [3%]). One patient (group Fs) did not complete baseline questionnaires before randomization, which we considered a protocol violation. Characteristics and preoperative baseline scores of WOMAC, OKS, and VAS of all patients; those lost to follow-up; and those remaining are shown in Table 1. [6]

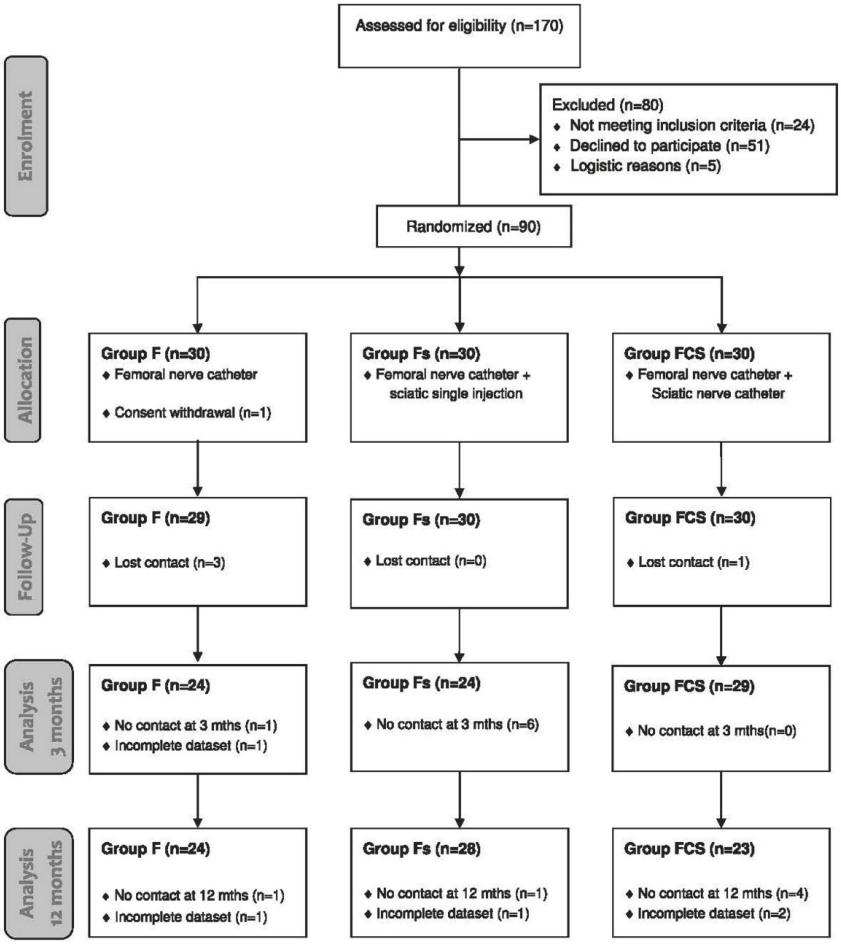

Figure 1. *CONSORT diagram showing flow of patients for TKA through the study.*

Table 1. *Patient Characteristics and Baseline Data*

Patient characteristics	All participants			Lost to follow up			Remaining participants		
	Group F (n = 29)	Group Fs (n = 30)	Group FCS (n = 30)	Group F (n = 3)	Group Fs (n = 0)	Group FCS (n = 1)	Group F (n = 26)	Group Fs (n = 30)	Group FCS (n = 29)
Age	62 (50-79)	65 (43-81)	66 (43-83)	63 (51-77)	-	61	62 (50-79)	65 (43-81)	66 (43-83)
Sex (M/F)	11/18	9/21	8/22	1/2	-	0/1	10/16	9/21	8/21
Height (cm)	174 (158-188)	171 (150-187)	173 (159-188)	165 (160-174)	-	178	175 (160-178)	171 (150-187)	173 (158-188)
Weight (kg)	84 (72-116)	82 (62-125)	89 (68-118)	92 (90-95)	-	72	83 (72-116)	82 (62-125)	90 (68-118)
BMI ($kg.m^{-2}$)	30.3 (23.2-39.7)	28.6 (21.0-48.8)	27.8 (22.1-39.6)	33.8 (31.4-35.2)	-	22.7	29.7 (23.2- 39.7)	28.6 (21.0 -48.8)	28.1 (22.1-39.6)
ASA I/II/III	13/ 13/ 3	13 / 15/ 2	9 /16 / 5	1/2/0	-	1/0/0	12/11/3	13 / 15/ 2	8/16/5
Baseline scores	(n=29)	(n=29)	(n=30)	(n=3)	-	(n=1)	(n=26)	(n=29)	(n=29)
WOMAC index	50(14-69)	34(2-77)	34(7-72)	40(24-50)	-	36.5	51(14-69)	34(2-77)	35(7-72)
OKS	37(27-52)	42(20-50)	41(21-56)	40(38-43)	-	46	35 (27-52)	42(20-50)	40(21-56)
VAS at rest	5.4 (3.0-7.5)	6.5 (2.0-10)	6.3 (0-10)	6.0 (5.0-7.5)	-	6.0	5.2 (5-7.5)	6.5 (2.0-10)	6.6 (0-10)

Patient characteristics are presented as median (range) or absolute number as appropriate of all patients, lost to follow-up, and remaining patients. Median baseline WOMAC group F tended to be higher compared with the other groups, although not statistically significant.

Patients lost to follow-up did not change the baseline patient characteristics systematically. Preoperative level of functioning was not equally distributed among groups, because median baseline WOMAC was better in group F (50) compared with group Fs (34) and group FCS (34), although the difference was not statistically significant (P = 0.09).

Western Ontario and McMaster Universities Osteoarthritis Index improved remarkably in all patients after TKA at the middle- and long-term period (>100%), but no statistically significant differences were found among groups at 3 months (P = 0.75) and 12 months (P = 0.68) (Fig. 2); neither did WOMAC function, WOMAC stiffness, and WOMAC pain show statistically significant differences among groups at 3 and 12 months, nor did the OKS questionnaire (Table 2). Likewise, when pain was measured by VAS at rest and during mobilization, no statistically significant differences among groups were observed at 3 and 12 months (Figs. 3A, B).

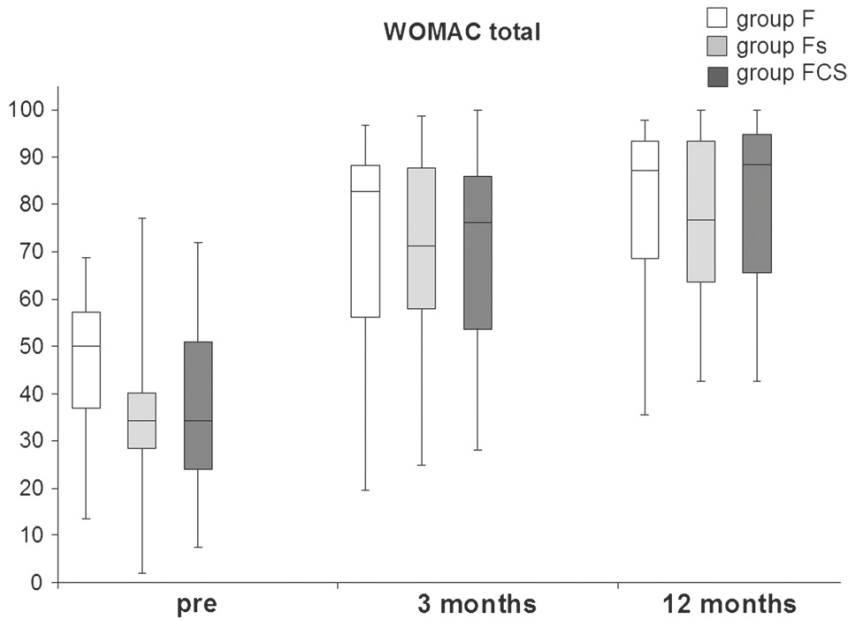

Figure 2. *Postoperative WOMAC (total score) improved greatly (improved function) after the first 3 months in all groups, without any statistically significant differences after 3 months (P = 0.75) or 12 months (P = 0.68).*

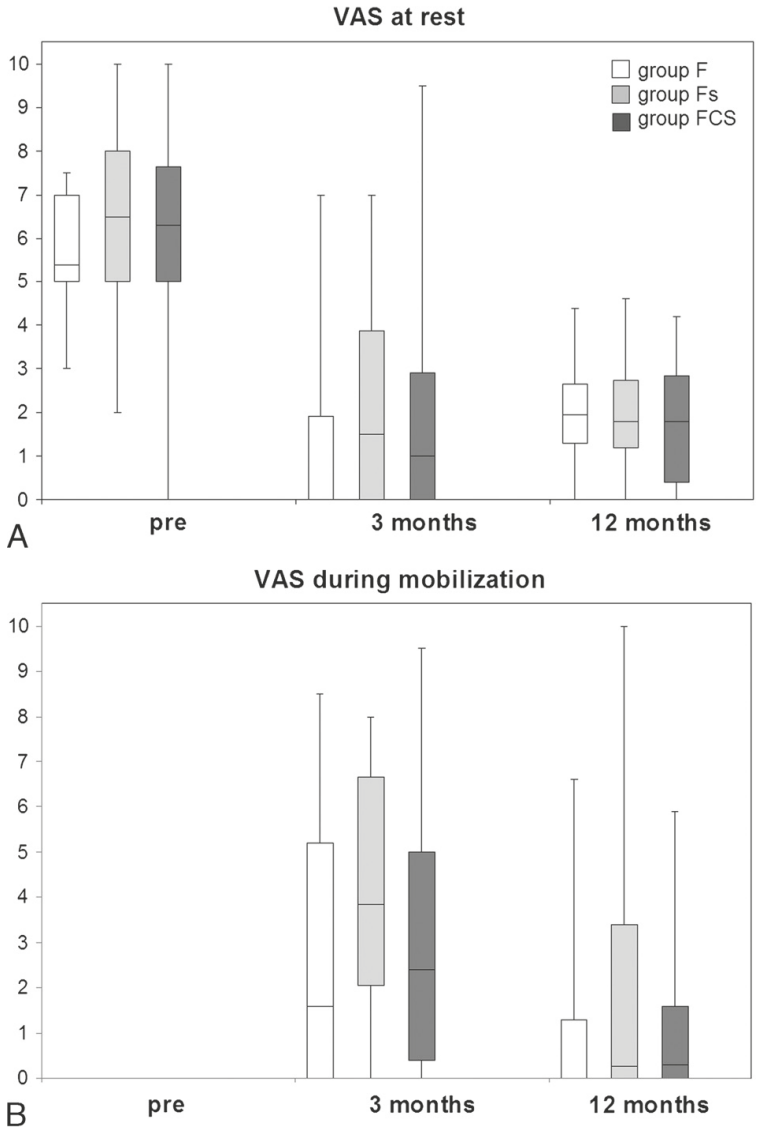

Figure 3. *A, Visual analog scale at rest decreased after TKA in all groups, without any statistically significant differences after 3 months (P = 0.15) or 12 months (P = 0.90). B, Visual analog scale during mobilization was not measured preoperatively, because mobilization was not standardized during physiotherapy. Visual analog scale during mobilization was reduced to a lesser degree than VAS at rest after 3 months, but there were no significant differences in groups or among groups (P = 0.19). Visual analog scale during mobilization was more improved after 12 months, without any statistically significant differences among groups (P = 0.52).*

Table 2. *Outcome of WOMAC Subscores and OKS*

	Group F	Group Fs	Group FCS	P
3 months	n = 24	n = 24	n = 29	
WOMAC pain	85 (30-100)	65 (25-100)	80 (0-100)	0.45
WOMAC stiffness	50 (13-100)	56 (13-100)	75 (25-100)	0.56
WOMAC function	84 (17-99)	75 (27-100)	74 (32-100)	0.58
OKS	23 (12-46)	28 (14-47)	23 (12-45)	0.32
12 months	n = 24	n = 28	n = 23	
WOMAC pain	90 (35-100)	80 (25-100)	90 (55-100)	0.81
WOMAC stiffness	75 (25-100)	75 (25-100)	75 (25-100)	0.48
WOMAC function	87 (34-99)	77 (38-100)	90 (40-100)	0.17
OKS	20 (12-44)	23(12-28)	19 (13-42)	0.69

WOMAC subscores for pain, stiffness, and physical function showed strong improvement after 3 months and in a lesser degree after 12 months of TKA. No statistically significant differences among groups were found.

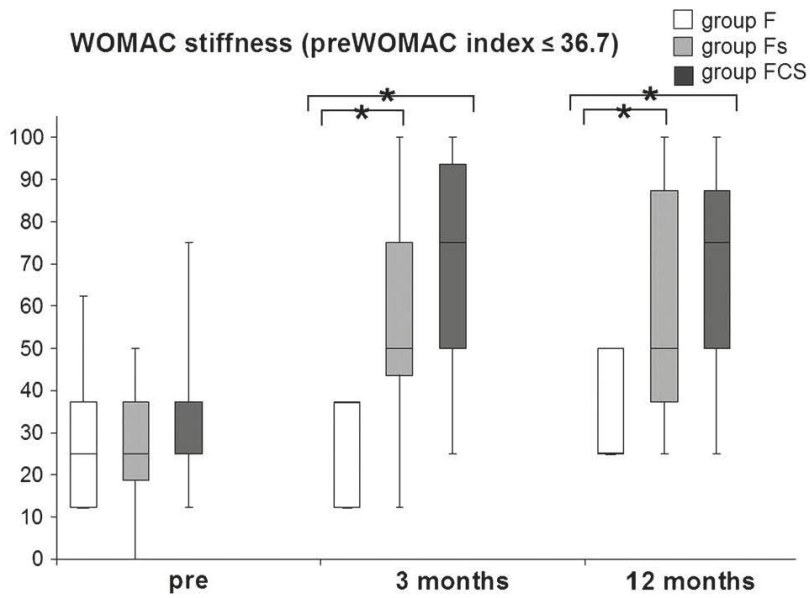

Figure 4. *Patients with moderate to poor preoperative knee function (preoperative WOMAC ≤36.7) demonstrated statistically significant greater improvement in WOMAC stiffness in groups Fs and FCS compared with group F after 3 months (P = 0.010) and after 12 months (P = 0.021).*

We analyzed patients with a moderate to poor preoperative knee function by categorizing patients with a preoperative WOMAC as equal to or less than the median preoperative WOMAC of all patients (WOMAC ≤36.7). Meeting this condition, WOMAC stiffness was found to be statistically significantly worse after 3 (P = 0.01) and 12 months (P = 0.02) in patients of group F compared with groups Fs and FCS (Fig. 4). Also, a statistically significant higher pain score (VAS) during mobilization was found after 3 months in group F (7.5 [3.6-8.5]) compared with the other groups (Fs, 3.5 [0.0-7.1]; FCS, 3.0 [0.0-9.5]), with P = 0.023, whereas no statistically significant differences could be found after 12 months (P = 0.43). No statistically significant differences could be demonstrated in the other scores or subscores.

Discussion

Knee function improved greatly in all patients after TKA. No midterm or long-term effect of the addition of a sciatic nerve block (single injection or continuous) for patients undergoing TKA was found in physical function, knee stiffness, pain at rest, or during mobilization at 3 and 12 months postoperatively. Post hoc subgroup analysis revealed that patients with poor preoperative knee function experienced less knee stiffness and pain during mobilization at the midterm and long term after addition of a sciatic nerve block for TKA. However, because groups and specially subgroups of poor preoperative functioning were small, it is entirely unclear whether this is a chance coincidence or a beneficial effect of the sciatic nerve block.

Ilfeld et al. [11] similarly found no long-term effect on knee function (WOMAC) after extended postoperative femoral perineural infusion for 4 days after TKA. Likewise, 2 other studies failed to show statistically significant differences in recovery of knee function after 3 months in patients with a continuous femoral nerve block compared with a single injection. [18, 20] However, Carli et al. [5] demonstrated a better functional recovery at 6 weeks in patients with a femoral nerve block compared with local infiltration analgesia techniques. Whether an improved functional outcome could have been demonstrated at 3 or 12 months as well has not been studied. Persistent moderate to severe pain during mobilization 1 month after TKA has been reported in 68% patients when a local infiltration analgesia technique was used. On the other hand, regional analgesic techniques (epidural and femoral) facilitated early rehabilitation in patients undergoing major knee surgery when compared with patient-controlled analgesia with morphine. [4, 8, 14]

Thus generally, regional anesthesia techniques have repeatedly been shown to improve acute postoperative pain management and shorten hospital stay and short-term rehabilitation, but no improvement in pain and knee function has been shown after more than 6 weeks postoperatively.

Apparently, there are other important factors that affect the rehabilitation of knee function, pain, and quality of life after TKA. Both surgical and patient-related factors may influence recovery and outcome. [3, 9]

Postoperative knee function after TKA primarily depends on preoperative condition. [7, 9, 12, 13, 16, 19, 22] Because patients undergoing TKA have end-stage knee osteoarthritis, most patients suffer from long-standing pain and impaired physical functioning preoperatively. Patients with high preoperative pain levels, combined with low pain thresholds, have a higher risk for persistent pain after total knee replacement, which is interpreted as central sensitization. [26] Furthermore, joint replacements in patients with severe preoperative pain and poor physical function are associated with worse postoperative outcomes. [1] Thus, pain treatment for TKA should be focused on reducing existing preoperative chronic pain and may be initiated before TKA. Therefore, we analyzed post hoc the category of patients with moderate to poor preoperative functioning (WOMAC ≤36.7).

Study Limitations

The scores reported here (WOMAC, OKS, VAS) were secondary aims for the original study and obviously have no statistical strength of primary outcomes. The study was powered for discharge readiness and long-term functional outcome, with pain only a secondary aim. However, post hoc power analysis revealed that the follow-up had 90% power ($\alpha < 0.05$) to detect a 0.75 ratio in rank sums; that is, it was equally powered for 1 of the long-term outcome parameters, as for the primary aim. Furthermore, squeezed distribution of preoperative functional scores between groups (WOMAC score; Table 1) may have influenced the results. Moreover, one might argue that up to 20% missing data points in some groups might have biased the results. However, even at time points where only 3% of data were missing, no significant differences could be detected.

The statistically significant improvement in self-reported knee stiffness and pain, recorded during mobilization at 3 and 12 months in patients with poor preoperative knee function when a sciatic never block was added for TKA (subgroups Fs and

FCS), should be interpreted with extreme caution. Although it sounds plausible, the reported improvement is subject to considerable error for several reasons. The post hoc median-split analysis divided the groups unevenly, and thus very small numbers were analyzed, leading to high risk of a type I error. Furthermore, only a few subscores displayed significant improvement, but none of the overall scores changed significantly. For example, only pain scores during mobilization at 3 months were improved, not at 12 months. In addition, although a number of parameters were tested at 2 time points, no adjustment for multiple comparisons was performed. The post hoc results can be used to generate hypothesis but cannot be interpreted and definitely should not influence current clinical management.

In conclusion, in patients undergoing TKA, improved short-term postoperative analgesia by means of sciatic nerve block, combined with a continuous femoral nerve block, does not translate into improved long-term knee or leg function, stiffness, or pain level, at rest or during mobilization.

Acknowledgments

The authors thank Leendert Blankevoort and Inge Sierevelt for their advice and assistance with the self-reported questionnaires.

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4

Cryotherapy after total knee arthroplasty

Cryotherapy after Total Knee Arthroplasty provides faster recovery and better ranges of motion in short term follow up. Results of a prospective comparative study

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Acta Orthop Belg. 2020 Sep;86(3):463-469.
PMID: 33581031

Abstract

Cryotherapy is applied in Total Knee Arthroplasty (TKA) to improve functional outcome. The aim of this study is to investigate whether an advanced cryotherapy device does not increase the risk of complications and improves knee function or decreases swelling.

A prospective cohort of TKA patients was formed by a cryotherapy group and a control group. The primary outcome was complication ratio. Our secondary outcomes were functional results and swelling.

No significant differences were found in complication ratio between 31 patients in the cryotherapy group and 31 patients in the control group. The cryotherapy group showed a significant better knee flexion and less swelling in the early rehabilitation phase. No differences were found at the other follow-up moments or in the other outcomes.

This advanced cryotherapy device is safe in respect of postoperative complications, improves knee function and decreases swelling in the early rehabilitation phase. However, it is questionable if an advanced cryotherapy device with its additional costs is necessary to provide the desired effects of cryotherapy.

Introduction

Cryotherapy is generally agreed to be an effective treatment in (sports) injuries and anterior cruciate ligament reconstruction. [5, 14, 17] The cold application enhances vasoconstriction and affects enzyme function by decreasing tissue metabolism. The reduction of blood flow contributes to a decreased inflammatory response and less edema formation. [13] By delaying or elimination of the pain signal transmission, the analgesic effect of local cooling is realized. [1]

Cryotherapy in Total Knee Arthroplasty (TKA) revealed different results but limited studies have been published. [6, 9–12, 15, 18, 23] Kullenberg et al. used cold compression for three days after TKA; the treatment group of 43 patients demonstrated a better range of motion at discharge and three weeks follow-up. Furthermore, the mean time of hospital stay was less in the treatment group than in the control group. [11] Other studies have shown less pain [15, 23] , improved range of motion [12, 15] or less blood loss after cryotherapy. [6, 23] On the other hand, other researchers found no significant difference between cold compression and normal compression. [9, 10, 18] The authors of the most recent Cochrane review, published in 2012, concluded that cryotherapy is generally safe. It may improve the knee range of motion in the first weeks after surgery and it could slightly reduce the amount of blood loss. They discussed that the aim of any cryotherapy device is to reduce intra-articular and deep tissue temperature. Therefore, possible new cryotherapy devices could be adopted to provide an optimum cooling dose. [2]

In previous studies, the Cryocuff device (Aircast, Summit, New Jersey) was the most common used device to apply cold compression. [6, 9, 11, 12, 23] In a postal survey among inpatient orthopedic physiotherapists, the Cryocuff device was the main method of cryotherapeutic application as well (59%), followed by crushed ice (30%). [4] The Cryocuff device covers the entire knee but leaves the popliteal space and patella free of pressure. The cuff is connected to a cooling container and provides 30 mm Hg cold compression. [11] Other reported devices are a cooling flow device (wrapped with a final layer of compressive crepe bandage, also called “continuous-flow cold therapy”) [15] and normal cold packs anterior and posterior to the knee. [10] Another relatively new device is the GameReady device (Coolsystems, Inc.), a “cryopneumatic” device which combines compression and cryotherapy. In a randomized controlled trial, it showed a significant decrease in opioid consumption till two weeks after TKA. [20]

Recently, a relatively new device has been developed : the Cryoceutical Treatment Server 100 (Waegener Research & Development, Beerse, Belgium). This advanced device consists of a "cTreatment Server" (CTS) and a "cTreatment Pad" (CTP). The CTS is a system that exchanges thermo energy with the human body by circulation of a specially developed fluid through the CTP. The CTS runs software which controls the amount of energy to be exchanged and it can execute several protocols for different treatment applications (e.g. TKA, arthroscopy and anterior cruciate ligament reconstruction). [25] The benefits of the system could be a reduction of postoperative swelling, postoperative pain, and perioperative blood loss, a lower risk of postoperative complications and an improved mobility and shorter hospitalization. The possible benefits of Cryoceutical Treatment (CT) has only been investigated in one study as far as we know. Thienpont performed an RCT in which CT was compared with regular cold packs. [21] He found no advantages of CT over regular cold packs. However, no comparison was made with a control group without the use of cryotherapy.

The aim of this study is to investigate whether CT is a safe device regarding postoperative complications and if CT is an effective treatment after TKA regarding knee function, swelling and patients outcomes in the early rehabilitation phase.

Patients and methods

All patients diagnosed with osteoarthritis or rheumatoid arthritis of the knee requiring primary TKA were included in a prospective cohort. The intervention group (the cryotherapy group) was included in a period of four months. The control group was included prior and after inclusion of the intervention group. These patients did not receive any cryotherapy. Patients in the cryotherapy group had to sign informed consent. Patients with cold allergy, intolerance or urticarial signs or requiring revision arthroplasty were excluded. No patients were included in the control group during the intervention period to prevent performance bias.

The pre-treatment evaluation was performed according to our institute's protocol in both groups and consisted of clinical assessment, clinical scores and radiographic evaluation. The surgical procedure was identical. TKA was performed using the Vanguard Complete Knee System (Biomet, Inc, Warsaw, Ind). The tibial component was cemented and the femoral component either cemented or uncemented. Postoperative treatment was conducted using a standard "rapid recovery" protocol with early mobilization from the first postoperative day till readiness for discharge

on the fourth postoperative day. Follow-up was planned postoperatively within one week, at two and six weeks and three months.

Our primary outcome was the number of postoperative complications consisting of superficial surgical site infections, local hematoma, allergic reactions or blisters of the CT, wound leakage more than 4 days, wound dehiscence and bleeding and deep venous thrombosis. Our secondary outcomes were functional results (knee flexion and extension), postoperative swelling, clinical scores and blood loss (difference in hemoglobin levels) and patient satisfaction. Swelling was measured by the circumference of the knee using a tapeline at the middle part of the patella ; the postoperative difference in circumference was calculated for analyses. We used the Knee injury and Osteoarthritis Outcome Score (KOOS) and Oxford Knee Score (OKS) as clinical scores. KOOS is a patient-reported subjective outcome scale, with different subscales : pain, symptoms, function in daily living (ADL), function in sport and recreation (Sport/Rec) and knee-related quality of life (QOL). [7] For this study, we excluded Sport/Rec, because we did not expect any sports activity by TKA patients during study follow up. The OKS is a validated knee-specific outcome measure designed to minimize the influence of comorbidities. [8] Hemoglobin levels were measured preoperative and on the first and third postoperative days.

Patients in the cryotherapy group were asked if they would like to use the system again if they could choose again, on a scale of 0-10 (0 certainly not, 10 certainly), presented as “cryotherapy satisfaction”. Body temperature was measured 1, 2 and 3 hours after surgery (during cryotherapy in the intervention group) and 2 times/ day at the postoperative days. All outcomes were recorded on an assessment form.

CT was available for 32 patients. This number of patients was based on previous research. [6, 9, 16] The treatment server consisted of a standard cryotherapy protocol. The protocol of the CTS included pre- and postoperative periods of cryotherapy with a CTP (size S, M or L) (Figures 1 and 2). The center of the cuff was positioned on the postoperative Robert-Jones bandage of the knee without covering the patella. Two days after surgery, the bandage was removed and cryotherapy was continued directly on the knee. The cryotherapy protocol consisted of a preoperative period of 1 hour at 8-10 °C, at least 1 hour before surgery ; a postoperative period of 3 hours at 8-10 °C, immediately after surgery ; 2 times of 2 hours at 13-15 °C on day 1 and 3 times of 1 hour at 13-15°C on the following days till discharge. The treatment was finished after discharge. For the whole CT treatment, 350 euro is charged per patient in daily practice.

Figure 1. *Cryoceutical Treatment Server 100 consists of a "cTreatment Server" and a "cTreatment Pad".*

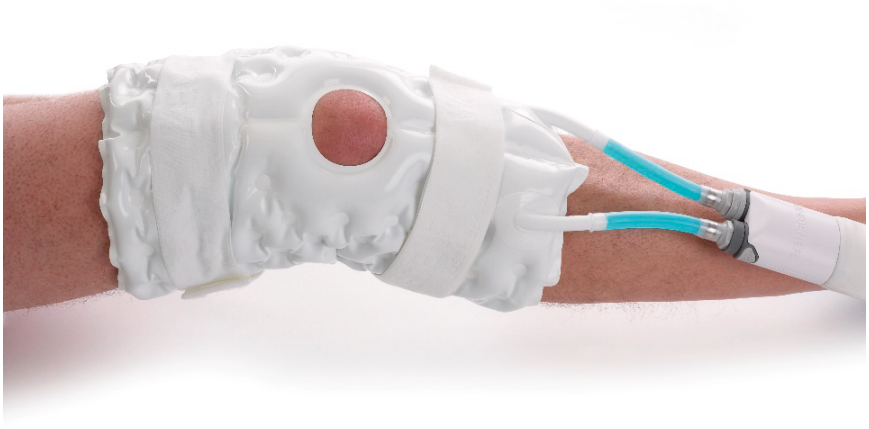

Figure 2. *The "cTreatment Pad" of the knee.*

Cryotherapy was discontinued if patients had an allergic reaction or blisters at the knee, if they experienced chills, or if informed consent was withdrawn.

After the study period, patients from the intervention group were matched to the control group. Matching of the groups was performed by an independent researcher. The matching was based on sex, age (in groups of 5 years difference, e.g. 60-65 years old) and Body Mass Index (BMI, in groups of 5 kg/m2 difference, e.g. 20-25 kg/m2) and was performed randomly; the researcher who analyzed the data was blinded for the results. Data were analyzed according to the intention-to-treat principle. The data of the patients in the intervention group were analyzed in this group, regardless of a possible discontinuation of cryotherapy. We expected that all outcomes were normally distributed. Therefore, repeated measures ANOVA and independent t-tests were used for statistical evaluation. Statistic difference was defined by a p-value of <0.05. We used IBM-SPSS 21.0 for statistical testing.

Results

In our prospective cohort of 70 TKA patients, 32 patients received cryotherapy. The matching strategy resulted in 31 matched couples: 31 patients in the intervention group and 31 patients in the control group. One cryotherapy patient could not be matched as no appropriate match was available. Demographic data are shown in table I. No significant differences were found in these preoperative data.

Table I. *Comparison of preoperative demographic data, presented as mean ± Standard Deviation*

	Cryotherapy group, N=31	Control group, N=31	p-value
Sex: M/V	11/20	11/20	-
Age in years	64.3 ±8.2	64.3 ±7.5	n.s.*2
BMI in kg/m2	30.1 ±5.5	30.0 ±5.8	n.s.
Knee flexion in degrees	113 ±10.5	112 ±14.7	n.s.
Hemoglobin level in mmol/l	8.6 ±0.86	8.4 ±0.94	n.s.
Knee circumference in cm at midpatella	42.1 ±3.5	41.4 ±3.7	n.s.
Oxford Knee Score (12-60)*	43.5± 7.3	39.4± 9.4	n.s.
KOOS (0-100) *1 :			
- Pain	29.7 ±18.1	36.1 ±20.3	n.s.
- Symptoms	41.3 ±17.5	42.1 ±18.8	n.s.
- ADL	33.2 ±20.0	39.5 ±22.3	n.s.
- QOL	13.6 ±11.4	20.5 ±18.7	n.s.

**12 represents the best score and 60 the worst. *1 Knee injury and Osteoarthritis Outcome Score : 100 represents the best score and 0 the worst. *2 n.s. : not significant (p>0.05).*

In the intervention group, 29 patients finished the entire standard cryotherapy protocol. One patient received only preoperative cryotherapy because the orthopedic surgeon excluded her from postoperative cryotherapy. She was known with multiple comorbidities (diabetes, COPD, obesity). One other patient received only two times 1 hour of cryotherapy at the second and third postoperative day, because she felt uncomfortable and experienced chills. Complications are shown in table II. There were 5 hematomas (16.1%) in the cryotherapy group and 3 hematomas (9.7%) in the control group. This difference was not significant. The patient with a superficial infection in the intervention group recovered completely after rest and antibiotics. One allergic reaction was noted, but most likely due to NSAID's, because it did not worsen during cryotherapy and recovered after discontinuation of NSAID's. No re-interventions were needed in the intervention group. In the control group, one patient had bloody wound leakage from the second till fourteenth postoperative day; a re-intervention was needed to evacuate the hematoma and to stop the bleeding. This patient developed a wound dehiscence after the re-intervention, six weeks after the primary operation. Seven patients had a complication in the cryotherapy group, six patients in the control group. No patients in both groups needed a manipulation under anesthetics.

Table II. *Comparison of postoperative complications*

	Cryotherapy group, N=31	**Control group, N=31**
Superficial Infection	1	0
Hematoma	5	3
Allergic reaction	1	0
Wound leakage >4 days	0	1
Wound dehiscence/bleeding	0	1
Deep Venous Thrombosis	0	1

Postoperative results are shown in table III and IV. The cryotherapy group showed a significant better knee flexion at the fourth postoperative day and after two and six weeks. After three months, knee flexion was comparable in both groups. The cryotherapy group had significant less swelling at the fourth postoperative day and after two weeks. After six weeks and three months the difference was no longer present. No differences were found at the other follow-up moments or in the other outcomes.

Table III. *Comparison of postoperative results after the fourth day (/discharge) and 2 weeks, presented as mean ± Standard Deviation.*

	4th day, group 1*	4th day, group 2*	p-value	2 weeks, group 1	2 weeks, group 2	p-value
Knee flexion in degrees	86.1 ± 12.2	77.1 ±14.3	0.01	98.6±11.5	87.1±17.5	0.04
Extension deficit in degrees	2.90 ±4.04	2.93 ±4.54	>0.05	2.42 ±4.45	3.10 ±3.64	n.s. *2
Swelling in cm*1	3.55 ±1.38	4.52 ±2.06	0.04	2.76 ±1.29	3.61 ±1.80	0.04

** Group 1= intervention (cryotherapy) group, group 2 = control group. *1 Swelling was measured using a tapeline at the middle part of the patella ; the postoperative difference in circumference was calculated for analyses. *2 n.s. : not significant (p>0.05).*

Table IV. *Comparison of postoperative results after 6 weeks and 3 months, presented as mean ± Standard Deviation*

	6 weeks, group 1*	6 weeks, group 2*	p-value	3 months, group 1	3 months, group 2	p-value
Knee flexion in degrees	112.6 ±10.2	106.9 ±11.7	0.047	118.2 ±9.4	114.5 ±11.0	n.s.*2
Extension deficit in degrees	2.74 ±4.25	2.68 ±3.59	>0.05	1.61 ±3.26	2.58 ±3.62	n.s.
Swelling in cm*1	1.79 ±1.50	2.58 ±2.00	>0.05	1.63 ± 1.50	2.07 ±1.70	n.s.
Oxford Knee Score (12-60)	29.0 ±8.4	27.7 ±10.9	>0.05	24.7 ±8.5	24.1 ±9.9	n.s.
KOOS (0-100) :						
- Pain	68.8± 21.4	66.6 ±23.9	>0.05	76.0 ±20.6	73.2 ±26.2	n.s.
- Symptoms	63.8±13.2	64.2 ±16.2	>0.05	71.4 ±14.7	66.0 ±18.6	n.s.
- ADL	71.2±18.2	70.7 ±21.3	>0.05	75.4 ±18.5	76.4 ±22.1	n.s.
- QOL	42.5±17.3	50.4 ±23.5	>0.05	53.6 ±21.1	58.1 ±25.9	n.s.

** Group 1= intervention (cryotherapy) group, group 2 = control group. *1 Swelling was measured using a tapeline at the middle part of the patella ; the postoperative difference in circumference was calculated for analyses. *2 n.s.: not significant (p>0.05).*

Hemoglobin levels were 7.2 and 6.7 mmol/l at the first and third postoperative day in the cryotherapy group, compared to 6.7 and 6.5 mmol/l in the control group (p>0.05). Of 30 cryotherapy patients, "cryotherapy satisfaction" was asked. Median score was 7.5, with a range of 0-10. Comparison of body temperature didn't show any statistical differences at either follow up moment.

Discussion

Our study was designed to investigate if this relatively new cryotherapy device is a safe device. Based on the complications, we can conclude that CT is safe to provide cryotherapy after TKA. One superficial infection was found in the intervention group, which is acceptable in comparison with the normal TKA population. These results are in accordance with the Cochrane review, in which 707 TKA patients were included for occurrence of adverse events. [2]

The pooled data in the same review regarding knee range of motion showed the same difference as in our study: a significant better flexion in the cryotherapy group at discharge (4th day) and after two weeks. These results are also in accordance with the other study in which CT was used. [21] Furthermore, our study showed a better flexion at six weeks after surgery and no difference after three months. This indicates that cryotherapy is only favorable in the early rehabilitation phase and could be part of a standard rapid recovery protocol after TKA. On the other hand, in the study of Thienpont a lower active flexion at 6 weeks was noticed in the CT group, indicating that a longer time of immobilizing could also worsen the range of movement. [21] Few studies measured knee swelling after cryotherapy, but no significant differences were found in these studies. Furthermore, swelling was only measured in the first week after surgery. [9, 12, 19, 23] In our study, significant less swelling was measured at discharge and after two weeks, another indication that cryotherapy would be favorable in the early phase. After six weeks and three months, no differences in knee circumference was found, nor in the clinical scores (KOOS and Oxford knee score).

Preceding work showed significant better pain scores in cryotherapy groups, especially on the second day after TKA. [3, 6, 11, 12, 15, 16, 19] Less analgesics were consumed by cryotherapy patients in the first two weeks in one study. [20] It is however not clear in some of these studies, if a standard pain management protocol was used for both study groups. For example, in the randomized trial by Su et al., no standard pain protocol is described. It is known that different pain management

protocols can influence the postoperative pain scores. [24] We did not include VAS pain scores and analgesic consumption for analyses, because the methods of anesthesia differed too much in our cohort. In future studies, a standard pain management protocol should be used to compare pain scores in the most reliable way.

In previous studies, hospitalization time (or length of stay) could be an important outcome. Five studies measured the length of stay [6, 11, 18, 19, 22], but no significant differences were found. In our hospital, we already perform a "rapid recovery" protocol in TKA patients. Most patients are admitted to our hospital for four days. Because of this protocol, we did not expect any differences in hospitalization time and therefore didn't use this outcome in our study. Future studies could use discharge criteria (e.g. VAS pain score <4, 90 degrees knee flexion) as an outcome if a standard rehabilitation protocol exist.

In addition to the complication rate, few negative effects were noted in the cryotherapy group. One patient felt uncomfortable during a few hours of cryotherapy. Patient satisfactory score was high. However, the costs of the treatment are relatively high compared the described effects.

A limitation of this study is that we did not compare this score with satisfaction in the control group. Another negative effect could be a lower body temperature in the cryotherapy group, but we did not found any difference in core temperature.

Our study has several other limitations. First of all, the number of patients (62) is low, but as mentioned, our goal was to investigate if this device does not increase the risk of postoperative complications. We based our number of patients on previous research. Secondly, we did not perform a randomized trial, which would require a larger population. As this cryotherapy system was relatively new, a pilot study was performed initially for safety reasons; we expanded the pilot numbers to create a prospective cohort study, with a matched control group. Furthermore, we couldn't use any blinding strategy; in an ideal situation, the researcher is blinded if patients received cryotherapy or not.

We conclude that CT does not increase the risk of postoperative complications after TKA whereas it induces improved flexion and less swelling in the early rehabilitation phase. However, it is questionable if an advanced cryotherapy device with its additional costs is necessary to provide the desired effects of cryotherapy.

Acknowledgement

We would like to thank drs. I.N. Sierevelt for her help with the matching strategy and statistical support.

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Fixation in total knee arthroplasty, part 1

What is the role of cemented fixation in total knee arthroplasty? The two-year results of a randomized RSA controlled trial

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Bone Joint J. 2021 Jan;103-B(1):98-104.

DOI: 10.1302/0301-620X.103B1.BJJ-2020-0788.R1.

PMID: 33380179

Abstract

Aims: For many designs of total knee arthroplasty (TKA) it remains unclear whether cemented or uncemented fixation provides optimal long-term survival. The main limitation in most studies is a retrospective or non-comparative study design. The same is true for comparative trials looking only at the survival rate as extensive sample sizes are needed to detect true differences in fixation and durability. Studies using radiostereometric analysis (RSA) techniques have shown to be highly predictive in detecting late occurring aseptic loosening at an early stage. To investigate the difference in predicted long-term survival between cemented, uncemented, and hybrid fixation of TKA, we performed a randomized controlled trial using RSA.

Methods: A total of 105 patients were randomized into three groups (cemented, uncemented, and hybrid fixation of the ACS Mobile Bearing (ACS MB) knee system, implantcast). RSA examinations were performed on the first day after surgery and at scheduled follow-up visits at three months, six months, one year, and two years postoperatively. Patient-reported outcome measures (PROMs) were obtained preoperatively and after two years follow-up. Patients and follow-up investigators were blinded for the result of randomization.

Results: RSA secondary stabilization did not show a significant difference between the three types of fixation. A maximum total point motion of less than 0.2 mm in the second postoperative year was shown in each group, which suggests stabilization of the implant. At 24 months after surgery, PROMs significantly improved compared to baseline in all treatment groups. No significant difference was observed between the three groups.

Conclusion: Secondary stabilization measurements in this study demonstrated no significant difference between the groups. In all groups migration stabilized after initial settling of the implant. For this implant the long-term outcome is not expected to be influenced by the type of fixation to the bone.

Introduction

Broadly, both cemented and uncemented fixation designs for total knee arthroplasty (TKA) have demonstrated excellent results overall. The small differences in results between implants make it difficult to show superiority of one design over another. Cemented TKA survival rates have been reported as 99% at 15 years, 94% at 16 years, and 91% at 22 years. [11, 34] Uncemented designs have similar outcomes, with 98% survival reported for the low contact stress (LCS, DePuy, Warsaw, Indiana, USA) implant at 18 years. [5] Some authors have suggested hybrid fixation (uncemented femur and cemented tibia) may be the best option. [23, 29, 39] Despite this, the main limitation in most studies is the retrospective or non-comparative study design. This is important as extensive sample sizes are required to detect any true differences in fixation and durability. Use of radiostereometric analysis (RSA) techniques have been shown to be accurate in early prediction of late occurring aseptic loosening. These changes can be detected by RSA within two years of implantation, making it extremely useful for comparing different fixation techniques in TKA. [30, 31, 36]

It is important to perform RSA in combination with long-term survival studies for new implants. Several years ago, our hospital adopted the Advanced Coated System (ACS MB; Implantcast GmbH, Buxtehude, Germany) knee arthroplasty uncemented implant which is manufactured in cobalt chromium alloy with a titanium nitride ceramic coating, potentially providing a better surface for bony ingrowth. [18] This design has been in use for over ten years, however there are no published studies using RSA to determine its performance on migration. The aim of our randomized controlled trial was to compare migration patterns between cemented, uncemented, and hybrid fixation of ACS MB TKA for a duration of two years follow-up using RSA.

Methods

This study was a prospective, single centre, double-blind randomized controlled trial on primary TKA patients. Patients were recruited between January 2013 and September 2015. After obtaining informed consent, patients were randomized to receive one of the three component fixation types: group A (both components cemented), group B (both components uncemented), or group C (hybrid, tibia cemented, and femur uncemented). All patients were followed up after one and two years. Patients were randomized prior to surgery, using a self-programmed computer program (Sealed Envelope, London, UK) and blinded to the type of fixation.

Patients

A total of 301 patients who were scheduled for primary TKA were screened for eligibility and asked to participate by their treating orthopaedic surgeon. The inclusion criteria were: patients with disabling (inflammatory or noninflammatory) osteoarthritis (OA), age between 21 and 80 years, body mass index (BMI) < 35 kg/m2, in stable health (no major comorbidities), and able to participate in the follow-up programme one and two years later. Patients undergoing revision TKA, or with a Charcot joint, previous patellectomy, or cognitive disorder were excluded. In total 105 patients gave informed consent and were included in the study (Figure 1).

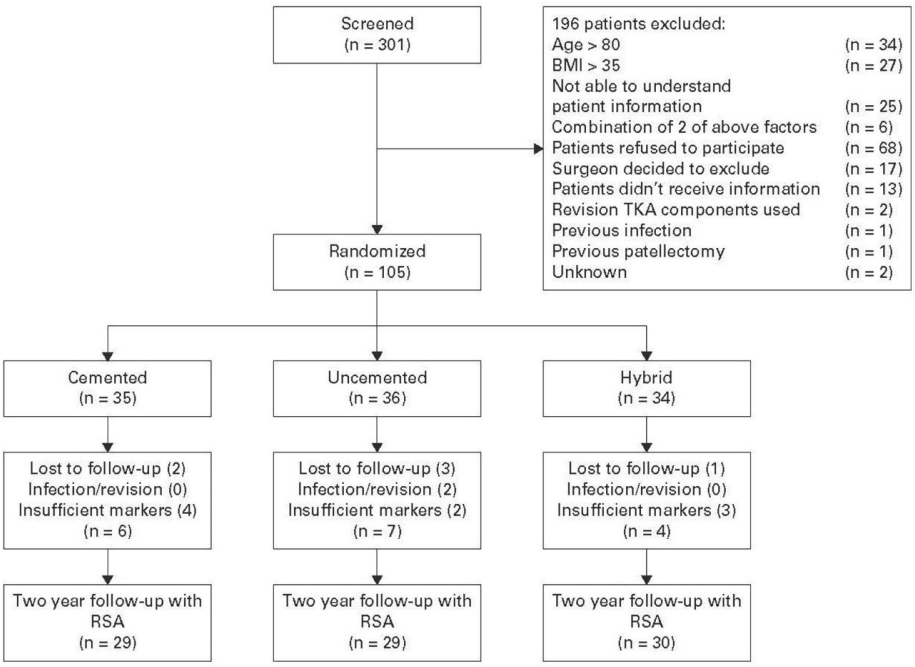

Figure 1. *Flowchart of study.*

Surgical procedure

Surgery was performed under regional or general anaesthesia with or without a local nerve block. The procedures were performed by experienced orthopaedic surgeons (HvdV, DHo and DHa) or under their direct supervision and all surgeons were familiar with the implant and implantation technique. A standard midline incision in combination with a medial arthrotomy was performed in all cases. A posterior cruciate-sacrificing technique was used. With cemented implants, tourniquet use

and pulse lavage was mandatory and antibiotic-loaded cement was used. For RSA measurements, at least five tantalum RSA markers (1.0 mm diameter, Wennbergs Finmek, Sweden and 1.0 mm diameter, X-Medics, Denmark) were inserted in the distal femur as well as in the proximal tibia. [35] The patella was not resurfaced in any of the patients. The surgery was followed by a standard postoperative regime of pain medication, antibiotic prophylaxis, anticoagulation, and physiotherapy.

Radiostereometric analysis

For accurate measurement of migration of both the tibia and femur component, RSA measurements were conducted using the guidelines reported by Ryd et al. [35, 36] All RSA images were acquired with the patient in supine position over a uniplanar calibration box (Medis Carbon Box nr. 011, Medis Specials BV, Netherlands). A ceiling-mounted x-ray source was combined with a portable unit. The x-ray sources were integrated to a single triggering method. At one year follow-up a double examination was performed to assess precision of the measurements. RSA was performed blinded with Model-based RSA software (MBRSA, version 4.1; RSAcore, Leiden, Netherlands). This has the advantage of not having to attach tantalum markers on the implant. [19]

The primary outcome of the study was the maximum total point motion (MTPM), which is defined as the vectorial sum of the 3D translations of the prosthetic marker that moved the most. [36] Based on its proposed prognostic significance, the implants were classified as stable or continuously migrating. Components were considered stable if a change in MTPM between 12 and 24 months of less than 0.2 mm was measured. [31]

Evaluations and outcomes

RSA examinations were performed on the first day after surgery and at scheduled follow-up visits at three months, six months, one year, and two years. We included patient-reported outcome measures (PROMs) as secondary outcomes preoperatively and after two years follow-up. The PROMs consisted of The Knee injury and Osteoarthritis Outcome Score (KOOS), [13] the Short Form (SF) 36 questionnaire (Physical Component Score), [10] and the Kujala score (also known as the anterior knee pain score). [20] Additionally, a visual analogue scale (VAS, 0 = no pain and 100 = unbearable pain) was used for pain in the last week before follow-up moments.

Statistical analysis

Sample size was estimate (performed by author DHa) based on a clinically relevant difference of 0.6 mm of MTPM. Based on a SD of 0.6 mm, a power of 90%, and significance level of 0.01 (adjusted for multiple testing), 30 patients were required

in each treatment group. [31] With an expected dropout rate (due to secondary exclusion by insufficient marker placing, revision surgery, withdrawal, or otherwise) of 15%, a total of 105 patients were included for randomization. Data analysts and the investigators who processed the data were blinded to the fixation type by numerical coding of the performed intervention. Data were analyzed according to the intention-to-treat principle. Revisions were considered an endpoint of the study. Reinterventions not consisting of replacement of the implant was not an endpoint, but were documented and included in the analysis.

Demographics and clinical characteristics are described as means with SDs in case of continuous variables, and frequencies with accompanying proportions in case of categorical variables.

Differences between the three groups were assessed by use of analysis of variance (ANOVA) and chi-squared testing.

To investigate the progression of the MTPM between the three groups during two years follow-up, mixed model analyses were performed for both femur and tibia components. Early setting (until six months) and secondary stabilization (between 12 and 24 months) were modelled separately. The effect of fixation was entered as a model factor (with hybrid as reference) and interaction with follow-up time was evaluated to assess differences in progression of migration between the fixation types during follow-up. In the event of significant time-treatment interaction, migration was analyzed for each group separately and compared by use of ANOVA (with hybrid as reference). Migration in the secondary stabilization phase was calculated as the mean difference between 24 and 12 months follow-up (with 95% confidence intervals (CIs)). Additionally, ANOVA was used at each follow-up to assess differences in migration between the groups at each timepoint separately. Precision was calculated by use of the SD of the differences of the repeated measurements, multiplied by 1.96. [33]

PROMs were analyzed as change from baseline values, and comparisons between the groups were performed by use of ANOVA. Statistical analysis was performed in SPSS version 26.0 (IBM, Armonk, New York, USA). A p-value < 0.05 was considered statistically significant.

Ethics, registration, funding, and potential conflicts of interest

This trial was approved by the medical ethical committee (entry no. NL42872.048.12) and performed in compliance with the Declaration of Helsinki [40] and Good Clinical

Practice guidelines. [7] The study protocol was registered in the Dutch Trial Register prior to enrolment (NTR3893), and reported in accordance with the CONSORT statement. [24] The study was partially funded by Implantcast (GmbH, Buxtehude, Germany). The sponsor was not involved in the design, analysis, or interpretation of the results.

Results

After screening 301 patients, 105 patients were randomly assigned into group A (cemented, n = 35), group B (uncemented, n = 36), or group C (hybrid, n = 34) (Figure 1). Two patients in group B had to be revised in an early phase. Both patients were suspected to have septic loosening, with confirmation by positive cultures in one patient however the other patient remained negative. Both patients were treated using a two-stage revision protocol with good results. Due to low intraoperative quality of the bone, the surgeon decided that two patients in group B and two patients in group C needed fully cemented implants. One cemented TKA was placed uncemented, due to an error. However, only one of these crossovers could be included for the RSA analysis (one of the uncemented to cemented TKA) as no or insufficient markers were placed in the other patients. Analysis was possible in the remaining 29 patients in group A, 29 patients in group B, and 30 patients in group C. Baseline results were comparable (Table I).

Table I. *Baseline demographics and clinical characteristics*

Characteristic	Cemented	Uncemented	Hybrid
n	29	29	30
Sex (M/F)	10/19	15/14	12/18
Mean age, yrs (SD)	70.9 (6.6)	64.6 (7.7)	69.0 (5.8)
Mean BMI, kg/m² (SD)	29.6 (3.6)	29.2 (3.4)	27.4 (4.2)
KOOS symptoms (SD)	48.5 (12.3)	46.1 (11.5)	48.1 (13.2)
KOOS, pain (SD)	47.7 (20.5)	42.0 (18.3)	48.8 (15.0)
KOOS, ADL (SD)	50.2 (20.1)	49.0 (16.0)	54.3 (18.5)
KOOS, QoL (SD)	25.0 (13.0)	21.8 (15.5)	30.5 (17.7)
SF-36 PCS (SD)	36.2 (6.8)	32.7 (7.4)	35.5 (7.3)
VAS, pain (SD)	42.8 (31.7)	52.3 (31.1)	39.6 (30.3)

ADL, activities of daily living; BMI, body mass index; KOOS, Knee injury and Osteoarthritis Outcome Score; QoL, quality of life; SF-36 PCS, Short Form 36 questionnaire Physical Component Score; VAS, visual analogue scale.

Migration

RSA data at all follow-up moments (MTPM compared to baseline values) are presented in Table II. Double examination for the MTPM revealed a precision of 0.87 mm for the tibial component and 0.62 mm for the femoral component.

Table II. *Radiostereometric analysis of mean maximum total point motion in 95% confidence intervals.*

MTPM, mm	Cemented mean (95% CI)	Uncemented mean (95% CI)	Hybrid mean (95% CI)	p-value*
Femur				
3 mths	0.68 (0.53 to 0.83)	0.95 (0.73 to 1.18)	0.92 (0.66 to 1.17)	0.154
6 mths	0.75 (0.56 to 0.94)	1.03 (0.81 to 1.25)	1.10 (0.74 to 1.45)	0.145
12 mths	0.94 (0.79 to 1.09)	1.11 (0.85 to 1.38)	1.25 (0.82 to 1.67)	0.347
24 mths	0.96 (0.78 to 1.14)	1.16 (0.90 to 1.43)	1.30 (0.88 to 1.73)	0.298
Tibia				
3 mths	0.89 (0.68 to 1.11)	1.18 (0.93 to 1.44)	0.86 (0.69 to 1.03)	0.063
6 mths	0.95 (0.71 to 1.19)	1.31 (1.06 to 1.56)	0.97 (0.76 to 1.18)	0.045
12 mths	1.10 (0.77 to 1.44)	1.24 (1.02 to 1.46)	0.91 (0.72 to 1.11)	0.181
24 mths	1.14 (0.78 to 1.50)	1.41 (1.13 to 1.68)	0.87 (0.70 to 1.04)	0.020

**Analysis of variance. CI, confidence interval; MTPM, maximum total point motion.*

Initial setting

Regarding the femur, during the first six months all prostheses significantly migrated ($p < 0.001$ using mixed model analysis), but there was no significant difference in MTPM between the fixation groups ($p = 0.166$, mixed model analysis) (Table III).

Regarding the tibia, during the first six months all prostheses significantly migrated ($p < 0.001$, mixed model analysis). There was a significant difference in MTPM between the cemented and the uncemented ($p = 0.033$, mixed model analysis) as well as between the uncemented and the hybrid group ($p = 0.024$, mixed model analysis). There was no significant difference in MTPM between the cemented and hybrid group ($p = 0.930$, mixed model analysis).

Table III. *Mean difference in maximum total point motion between the groups during initial setting and secondary stabilization phase (Hybrid reference).*

Group	Initial setting (0 to 6 months)		Secondary stabilization (12 to 24 months)	
	β (95% CI)	p-value	**β** (95% CI)	p-value
Femur		0.166		0.301
Cemented	-0.18 (-0.40 to 0.03)	0.092	-0.32 (-0.74 to 0.09)	0.123
Uncemented	-0.01 (-0.22 to 0.19)	0.894	-0.14 (-0.54 to 0.25)	0.463
Hybrid	REF		REF	
Tibia		0.037		0.073*
Cemented	0.01 (-0.18 to 0.20)	0.930	0.10 (-0.13 to 0.33)	0.894
Uncemented†	0.22 (0.03 to 0.40)	0.024	0.22 (-0.01 to 0.45)	0.068
Hybrid	REF		REF	

**Due to significant time-treatment interaction (p = 0.023), between-group differences were assessed by use of analysis of variance (ANOVA) with posthoc pairwise comparisons, with hybrid as reference (with Bonferroni correction). All other between-group differences (with hybrid as reference) were calculated using of mixed model analysis.*
†Uncemented vs cemented: b (95% CI) = 0.21 (95% CI 0.02 to 0.40), p = 0.033, mixed model analysis. CI, confidence interval.

Secondary stabilization

For femoral components, between 12 and 24 months after operation no significant difference in MTPM was observed between the groups (p = 0.301, mixed model analysis) (Table III). MTPM of the component did not change significantly during this period (p = 0.080, mixed model analysis) with values of 0.01 mm (95% CI -0.14 to 0.17) in the cemented group, 0.07 mm (95% CI 0.00 to 0.15) in the uncemented group, and 0.07 mm (95% CI -0.01 to 0.16) in the hybrid group.

For tibial components, although a significant time-treatment interaction was observed between cemented and hybrid treatment groups (p = 0.023, mixed model analysis), no significant migration of the component was observed during the second year in any of the groups. MTPM during this period was 0.03 mm (95% CI -0.09 to 0.15), 0.15 mm (95% CI -0.04 to 0.34), and -0.07 mm (95% CI -0.15 to 0.01) for the cemented, uncemented, and hybrid group, respectively. No significant differences were observed between the groups (p = 0.073, ANOVA).

A mean MTPM of less than 0.2 mm in the second postoperative year was shown in each fixation group for the tibia as well as the femur, which suggests stabilization of the implants (Figures 2 and 3). [31]

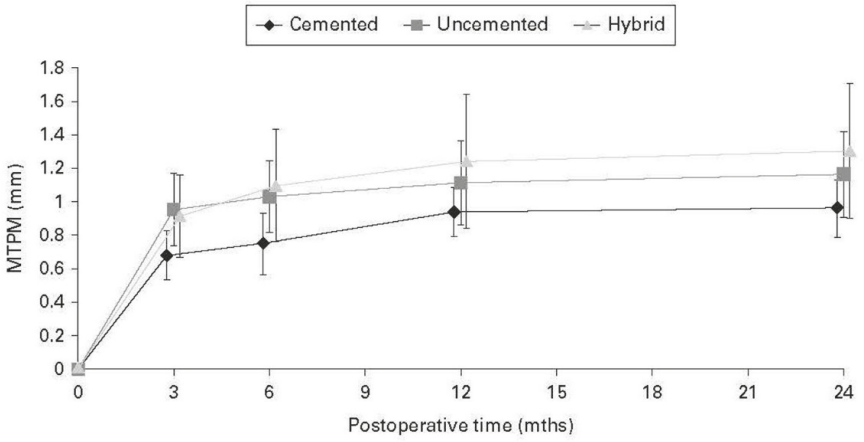

Figure 2. *Maximum total point motion (MTPM) pattern of the femur between fixation groups.*

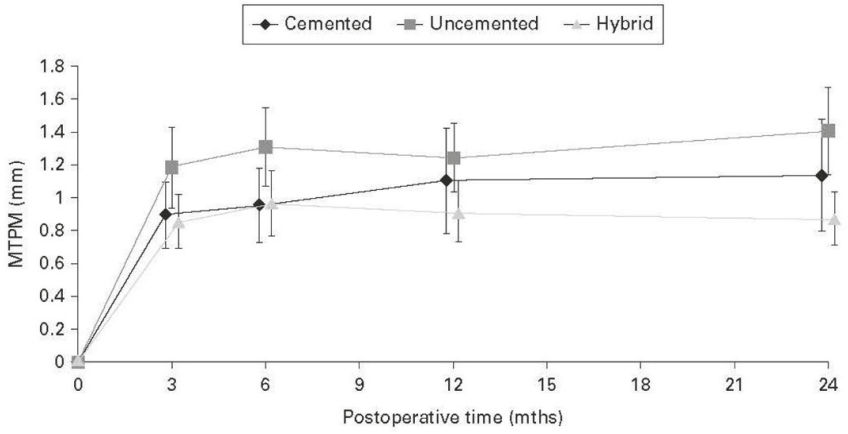

Figure 3. *Maximum total point motion (MTPM) pattern of the tibia between fixation groups.*

Functional outcome

At 24 months after surgery, the KOOS domain scores (pain, activities of daily living (ADL), and quality of life (QoL)), SF-36, Kujala scores, and VAS pain significantly improved compared to baseline in all treatment groups ($p < 0.001$ for all comparisons, using ANOVA tests). No significant difference was observed between the three groups ($p = 0.073$ for all comparisons, Table IV and Figure 4).

Table IV. *Improvement of patient-reported outcome measures after two years did not differ significantly between the three groups (p > 0.073 for all comparisons, using ANOVA tests). All scores reported as means (95% confidence intervals).*

PROM	Cemented (n = 29)	Uncemented (n = 29)	Hybrid (n = 30)	p-value
KOOS symptoms	13.2 (7.3 to 19.0)	14.8 (9.8 to 19.9)	14.0 (8.2 to 19.8)	0.912
KOOS pain	35.7 (27.9 to 43.6)	42.6 (33.8 to 51.4)	39.0 (31.4 to 46.5)	0.480
KOOS ADL	33.1 (25.1 to 41.2)	35.8 (29.4 to 42.2)	31.8 (23.8 to 39.8)	0.744
KOOS QoL	52.6 (43.3 to 61.9)	49.3 (40.9 to 57.8)	38.1 (27.3 to 48.8)	0.073
SF-36 PCS	11.5 (7.8 to 15.3)	14.3 (9.9 to 18.8)	10.2 (7.2 to 13.3)	0.278
VAS pain	-27.4 (-39.0 to -15.7)	-42.5 (-54.9 to -30.1)	-29.6 (-39.7 to -19.5)	0.122

ADL, activities of daily living; KOOS, Knee injury and Osteoarthritis Outcome Score; PROM, patient-reported outcome measure; QoL, quality of life; SF-36 PCS, Short Form 36 questionnaire Physical Component Score; VAS, visual analogue scale.

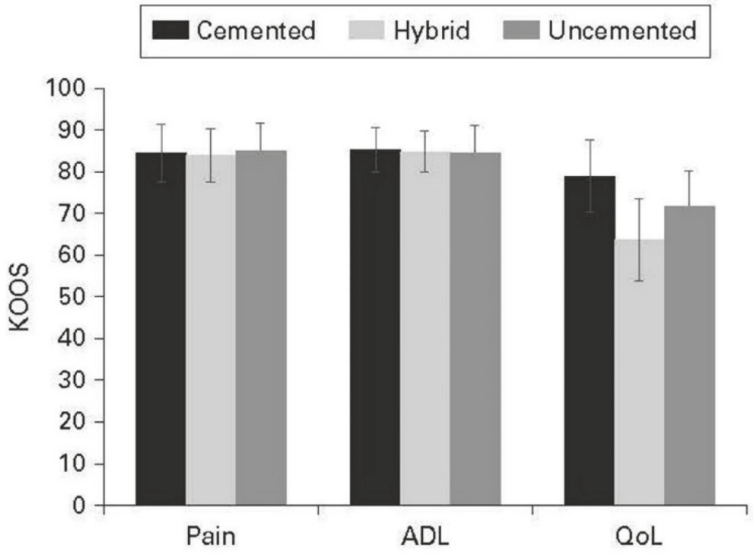

Figure 4. *Knee injury and Osteoarthritis Outcome Score (KOOS) of the three fixation groups at two year follow-up. ADL, activities of daily living; QoL, quality of life.*

Discussion

The results from this study showed no significant difference in secondary stabilization between cemented, uncemented, and hybrid fixation of the ACS MB TKA after two year follow-up. PROMs did not differ significantly between the three groups. These results are in line with previously published studies on uncemented fixation in TKA. Henricson et al. [15] performed a comparative RSA-based study comparing uncemented NexGen (Zimmer Biomet, Warsaw, Indiana, USA) trabecular metal components and cemented NexGen components in patients less than 60 years old. They found uncemented fixation showed beneficial migration patterns, over long-term follow-up [16] and concluded that excellent results can be achieved with an annual migration of 0.1 mm in uncemented titanium fibre mesh coated femoral implants. [17] Dunbar et al. [9] showed a stable migration pattern in peri-apatite coated uncemented tibial components, but these were not compared with cemented components. The largest cohort of TKA patients (n = 360), [21] in which uncemented fixation was compared with cemented fixation using RSA, showed significantly less motion in the cemented group after one year follow-up, but this difference did not persist after two years. Another RSA-based study by Nilsson et al. [28] hydroxyapatite-coated uncemented TKA (with or without screws) showed no difference compared to cemented TKA after two year follow-up. Van Hamersveld et al. [14] reported significantly higher MTPM of cemented TKA after two and five years compared to peri-apatite coated uncemented TKA, without any clinical differences. In contrast, there remains debate around the use of uncemented TKA components as, according to level I and II studies, cemented fixation would be preferable. [32] Uncemented components, especially newer generation TKA, are reported with equal survival compared to cemented fixation. [12, 27] The latest Cochrane review strengthens the use of uncemented components by showing that the long-term risk of aseptic loosening was higher in cemented TKA, despite a smaller migration pattern after two and five years compared to uncemented fixation. [26] RSA-based level I studies, in combination with long-term survival studies, will play an important role in detecting changes in migration patterns of new implants compared to the “conventional” implants. Good to excellent long-term survival rates have been published for uncemented TKA. Bouras et al. [4] reported a 95.7% and 93.6% survival with aseptic loosening as an endpoint at ten and 15 years respectively, for uncemented titanium plasma coated TKA. For porous tantalum coated uncemented TKA, a 96.9% survivorship for revision for any reason (with 100% survivorship for aseptic loosening) was reported after a minimum of ten years follow-up, [22] which was replicated by DeFransesco et al. [6] In a cohort of morbidly obese patients (BMI > 40), a higher survival was reported for uncemented fixation (99.1% vs 88.2%) at eight year follow-up, [37]

similar to the findings by Bagsby et al. [3] who found significantly more revisions after cemented fixation also in obese patients. Despite these studies, there remains concerns about low bone mineral density (BMD) when using uncemented fixation, especially for the tibial component, as fixation depend on bone quality. Andersen et al. [1] found that low preoperative BMD of the tibia is related to a higher MTPM of the component potentially justifying a switch to a cemented technique, as occurred with four patients in our study. One study reported a beneficial increase in BMD after porous titanium coated uncemented TKA, and that a hydroxyapatite-coated TKA did not have a negative effect on the BMD. [38] Elsewhere, older patients, aged 75 and over, receiving hydroxyapatite-coated uncemented TKA showed the same functional results in comparison to younger patients. [8]

Our study has several limitations. Firstly, only 29 cases out of 35 (cemented group) and 36 (uncemented group) were available for analysis due to dropouts and insufficient markers, which is one less than our calculated sample size. However, this sample size is similar if not larger than in previous RSA studies. [9, 14, 15, 25, 28] Secondly, our power analysis was based on one year follow-up data published by Pijls et al. [31] while our two year follow-up measurements were conducted using the guidelines reported by Ryd et al. [36] Thirdly, two patients in the uncemented group were revised for suspected septic loosening, one of whom had infection confirmed by positive cultures. Although antibiotic-loaded cement could theoretically reduce the risk of an infection, it has not been proven that uncemented fixation is a risk factor for infection. [2] Finally, five crossovers were noted. We used an intention-to-treat analysis to show this in our results. As only one of these five crossovers was included in the RSA analysis, we think that the impact on interpretation of the results was minimal.

In conclusion, the secondary stabilization measurements from this study showed no significant difference at two years between cemented, uncemented and hybrid fixation of the ACS MB TKA. In all groups migration stabilized after initial settling of the implant. For this implant the longer outcome would not expect to be influenced by the type of fixation to the bone.

Take home message

- We report no significant difference in secondary stabilization between cemented, uncemented, and hybrid fixation of the Advanced Coated System Mobile Bearing total knee arthroplasty after two-year follow-up.
- Patient-reported outcome measures did not differ significantly between the three groups.
- For this implant the long-term outcome is not influenced by the type of fixation to the bone.

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6

Fixation in total knee arthroplasty, part 2

Lower revision rates for cemented fixation in a long-term survival analysis of three different LCS designs

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Knee Surg Sports Traumatol Arthrosc. 2022 Aug;30(8):2707-2713.
DOI: 10.1007/s00167-021-06587-8. Epub 2021 May 2.
PMID: 33934194

Abstract

Background: In primary Total Knee Arthroplasty (TKA), it is still not clear if cemented or uncemented fixation has the best long-term survival. The Low Contact Stress (LCS) mobile-bearing (MB) knee system was introduced in 1977. The aim of this study is to investigate the long-term survival of this design with a minimum of 15-year follow-up.

Methods: A retrospective analysis was performed, with the primary endpoint for survival defined as revision. Cox regression analysis was performed to assess the association between type of fixation and the risk of revision, while correcting for potential confounders (diagnosis, design, age and sex).

Results: 1271 cases were included with inflammatory joint disease (IJD) (657 cases) and non-IJD (614 cases). TKAs were performed cemented in 522 cases and uncemented in 749 cases. A bicruciate retaining design was used in 180 cases, a rotating platform design in 174 cases and an anterior posterior glide posterior cruciate-retaining (PCR) design in 916 cases. Cumulative incidence of component revision at 15 years was 2.7% (95% CI 1.6; 4.5) for cemented and 10% (95% CI 8.1; 12.4) for uncemented TKA, respectively. The 20-year cumulative incidence was 2.9% (95% CI 1.7; 4.7) for cemented and 10.9% (95% CI 8.8; 13.4) for uncemented TKA, respectively. Age, non-IJD and PCR design were associated with a significantly higher risk of revision, regardless of the type of fixation.

Conclusion: Long-term survival for patients undergoing cemented or uncemented TKA using the LCS MB system revealed lower revision rates for cemented fixation. Revision risk was higher in younger, non-IJD patients who had the PCR design, regardless of the type of fixation. For the LCS MB TKA design, it is recommended to use cemented fixation.

Introduction

For many designs of Total Knee Arthroplasty (TKA), it is still not clear if cemented or uncemented fixation of the components has the best long-term survival or which design provides the best functional and clinical results. For cemented TKAs, survival rates of 99% at 15 years, 91% at 22 years and 94% at 16 years have been published. [12, 23] In other studies, good to excellent survival rates were reported (93.6% at 15 years and 96.9% at a minimum of 10 years) for uncemented TKA. [3, 17] However, concerns have been expressed in the latest Cochrane review about the long-term risk of aseptic loosening with cemented fixation. [19] Possible advantages of uncemented TKA could be biological fixation, absence of retained cement and reduced operative time. [19]

The Low Contact Stress (LCS) mobile-bearing (MB) knee system (DePuy, Warsaw, Indiana) was introduced in 1977. The fundamental concept of the LCS MB knee system, analogous to the natural menisci [13] , comprises a mobile polyethylene (PE) bearing that has a high congruency with the articular surface area to promote load sharing. In theory, this design could reduce PE wear, contact stress peaks and contact strain peaks at the bone–implant interface and thereby reduce the risk of loosening. [6, 14] Three designs of tibial components and PE inlays of the LCS MB knee have been used since its introduction: the meniscal bearing bicruciate retaining (BCR) component, the rotating platform (RP) bicruciate sacrificing component and the anterior posterior glide posterior cruciate-retaining (PCR) component. The developers reported 98% survival rate of the uncemented LCS implant at 18-year follow-up and 97.7% of the cemented LCS implant after 20 years. [4, 5] Other studies reported slightly lower survival rates of 94% at 16 years (uncemented), 80.2% at 25 years (uncemented) and 96.5% at 20 years (cemented). [1, 7, 25] As it stands, the evidence for long-term survival of the fixation of this implant design is based on small cohorts, making it challenging to interpret the overall performance of this implant. A large-scale study comparing survival rates of cemented and uncemented fixation is needed to provide stronger evidence upon which to base future development of fixation methods in TKA.

The purpose of this study is to investigate the long-term survival in a large cohort of cemented and uncemented LCS MB TKA implants by comparing fixation types at a minimum follow-up of 15 years. The hypothesis was that both cemented and uncemented provide acceptable and comparable results at long-term follow-up. In addition, other factors associated with survival of the LCS MB were identified including age, implant design and diagnosis.

Materials and methods

Patients

The procedures of this study were approved by the local ethical board of the former Slotervaart Medical Centre (local registration number P1833, in compliance with the Helsinki Declaration). 1315 primary TKAs, including all LCS MB TKAs, were retrospectively screened. After exclusion of patients with post-traumatic osteoarthritis or patients undergoing revision arthroplasty, 1271 cases were included. All procedures were performed between 1984 and 2003 in the former Slotervaart Medical Centre and were performed in patients with symptomatic knee osteoarthritis based on non-inflammatory joint disease (non-IJD) or inflammatory joint disease (IJD). This period was chosen to guarantee the minimum of 15-year follow-up. Each patient received one of the three LCS designs using either cemented or uncemented fixation.

Surgical procedure

All procedures were performed under general or epidural anaesthesia by seven experienced orthopaedic surgeons who were all familiar with the implant and implantation technique. Every surgeon used a high thigh tourniquet, which was released following skin closure. A standard midline incision and medial parapatellar approach was used. Based on the condition of the cruciate ligaments they were both resected or retained. After sufficient soft tissue balancing (adequate quality of cruciate ligaments and collateral ligaments), a decision was made to use either BCR, RP or PCR components. This decision varied based on the experience and philosophy of the surgeon. The indication was not exactly known, but at least the posterior cruciate ligament (in case of a PCR component) or both cruciate ligaments (in case of a BCR component) had to be intact. The general philosophy of the clinic during the inclusion period was to use uncemented fixation, if possible. For cemented implants, (manual) pulse lavage was mandatory. Uncemented LCS implants were coated with porous titanium coating (POROCOAT®, DePuy, Warsaw, Indiana). The patella was resurfaced upon indication based on the experience and philosophy of the surgeon. The general philosophy was to perform patella resurfacing. Implantation of a drain before wound closing was performed in all cases. A standard postoperative regime of pain medication, antibiotic prophylaxis, anticoagulation and physiotherapy was followed, in which patients were allowed to partial weight-bear for 6 weeks.

Evaluations and outcomes

Medical records of patients were reviewed for prosthesis survival, and surgical and demographic information (diagnosis, implant design, age and sex and Charnley

classification). Patients without a revision report in their medical record were contacted by telephone unless they were deceased. When revision had been performed, surgical revision information and the revision date were registered. When a revision had not been performed, the last follow-up date was registered. The primary outcome was survival. Survival time was determined separately for the cemented and uncemented group, which was computed by subtracting the operation date from the revision date, date of death without revision or last follow-up date without revision. The endpoint for survival was revision, which was defined as removal or revision of one of the primary components or conversion of the TKA to a knee arthrodesis. Secondary resurfacing of the patella without tibial or femoral component revision was not considered a revision for this analysis. Censoring dates were determined based on the last follow-up date or date of death. The last follow-up date was defined as the date the patient was last seen at the outpatient clinic or based on the telephone contact. The last follow-up date was only noted if it was certain that the inserted prosthesis had not been revised.

Statistical analysis

Student's t tests and Chi-square tests were used to assess differences in patient demographics and clinical characteristics between the cemented and uncemented group. Due to the long follow-up and large proportion of deceased patients during follow-up, primary competing risk analysis was performed (with death as competing risk) to assess the cumulative incidence of both the cemented and uncemented TKAs. [24, 27] Subsequently, a multivariate Cox regression analysis was applied to assess the association between cementing and the risk of revision. Correction was performed for potential confounders (diagnosis, implant design, age and sex). Multivariate Cox regression analysis was also used to identify factors associated with risk of revision. Hazard Ratios were calculated with accompanying 95% Confidence Intervals (95% CI). Due to a considerable amount of missing Charnley scores, sensitivity analysis was performed with a limited sample to assess the confounding effect of the Charnley scores (n = 839). In addition, a log-rank test was used to perform sub-analyses for type of design and diagnosis (IJD and non-IJD). Kaplan–Meier cumulative revision rates were calculated and compared for fixation type, IJD and type of prosthesis. SPSS version 26 (Armonk, NY: IBM Corp) was used for all statistical analyses. Significance was defined as a p value < 0.05.

Results

1271 TKAs were included of which 522 (41.1%) were performed cemented and 749 (58.9%) uncemented. Patient demographics are shown in Table 1. The mean age of patients at time of surgery was 74.8 years (SD 7.6) for the cemented group and 59.0 years (SD 13.0) for the uncemented group, which was statistically different ($p < 0.001$). Revision rates were ascertained at a median follow-up of 20.6 years (IQR 6.1; 23.7) in the cemented group and 20.5 years (IQR 19.6; 24.7) in the uncemented group. The high number of IJD cases (657) can be explained by the fact that the hospital was specialised in IJD. There were significantly more uncemented cases in the IJD group ($p < 0.001$).

Table 1. *Patient demographics and clinical characteristics*

	Cemented (522)	Uncemented (749)	p value
Age, years	74.8 (7.6)	59.0 (13.0)	< 0.001
Mean (SD)			
Follow-up time,	20.6 (6.1; 23.7)	20.5(19.6; 24.7)	0.004
Years			
Median (IQR)			
Sex, n (%)			
Female	445 (85%)	590 (79%)	0.003
Male	77 (15%)	159 (21%)	
Side, n (%)			
Left	259 (50%)	348(47%)	0.28
Right	263 (50%)	401 (53%)	
Diagnosis[a], n (%)			
IJD	206 (40%)	451 (60%)	< 0.001
Non-IJD	316 (60%)	298 (40%)	
Design[b], n (%)			
BCR	10 (2%)	170 (23%)	< 0.001
RP	66 (13%)	108(14%)	
PCR	446 (85%)	470 (63%)	
Missing	1		

[a]IJD inflammatory joint disease; non-IJD non-inflammatory joint disease. [b]BCR meniscal bearing bicruciate retaining; RP rotating platform; PCR anterior posterior glide posterior cruciate retaining

In the cemented LCS TKA group, 22 revisions were performed with component exchange. Two of these revisions were septic. In the uncemented TKA group, 106 revisions were performed with component exchange, 10 of these revisions were septic. Cemented TKA were significantly less likely to fail (defined by need for revision) compared to uncemented prostheses (HR 0.51, 95% CI 0.28; 0.93, p = 0.03). The cumulative incidence of component revision at 15 years was 2.7% (95% CI 1.6; 4.5) and 10% (95% CI 8.1; 12.4) for cemented and uncemented TKA, respectively. The 20 years cumulative incidence was 2.9% (95% CI 1.7; 4.7) and 10.9% (95% CI 8.8; 13.4), respectively (Fig. 1).

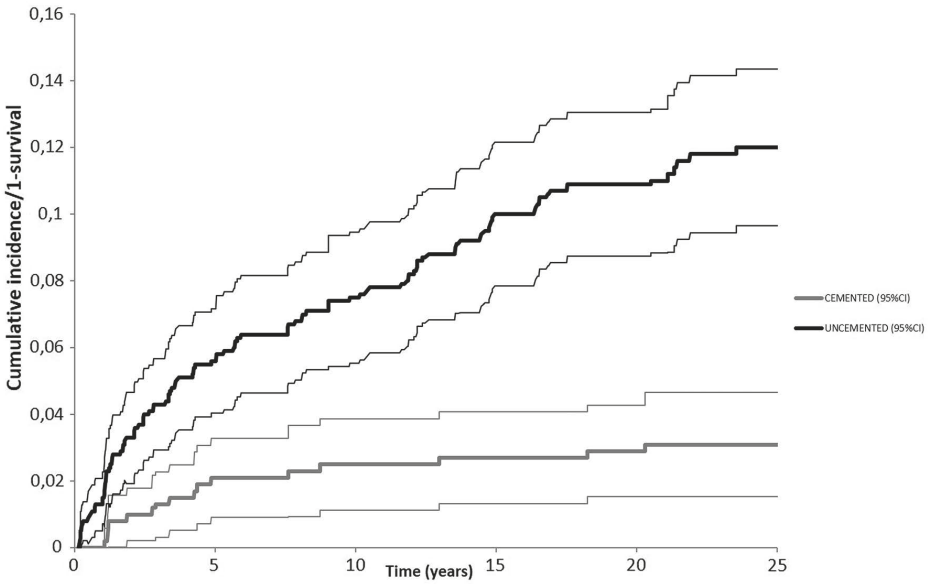

Figure 1. *Competing risk analysis for the cumulative incidence of revision showed a significantly higher revision rate for uncemented fixation. The 95% CI are included in the figure.*

Similar results were found using the Kaplan–Meier analysis. Kaplan–Meier cumulative revision rates were 3.2% and 11.2% for the cemented and uncemented group at 15 years and 3.5% and 12.4% at 20-year follow-up (Table 2). In the non-IJD cases and in the PCR design, significantly higher revision rates were found in the uncemented group (Table 2). Uncemented TKAs were significantly more likely to be revised than cemented prostheses with an unadjusted HR of 3.61 (95% CI 2.12; 6.15) and an adjusted HR of 2.32 (95% CI 1.24; 4.27) (Table 3). A lower age, non-IJD and PCR design were significantly associated with a higher risk of revision, regardless of the type of fixation (Table 3). Sensitivity analysis revealed that adjustment for the Charnley score

was not required as there was no confounding effect of this variable. A post hoc power analysis for univariate cox regression (Crude model) revealed a power of 99%.

Table 2. *15 and 20 years Kaplan-Meier revision rates, stratified for diagnosis and type of design (Log Rank test)*

Overall	**Cemented**	**Uncemented**	***p* value**
15 years	3.2% (1.6; 4.8)	11.2 (8.8; 13.6)	< 0.001
20 years	3.5% (1.7; 5.3)	12.4 (9.8; 15.0)	< 0.001
IJD			
Yes			
15 years	2.6% (0.1; 5.2)	8.4% (5.7; 11.1)	0.02
20 years	2.6% (0.1; 5.2)	9.0% (6.1; 11.9)	0.02
No			
15 years	3.5% (1.3; 5.7)	15.4% (11.1; 19.7)	< 0.001
20 years	4.0% (1.6; 6.4)	17.2% (12.7; 21.7)	< 0.001
Type of prosthesis			
BCR			
15 years	0%[a]	20.4% (13.7; 27.1)	0.18
20 years	0%[b]	22.1% (15.2; 29.0)	0.16
RP			
15 years	3.4% (0.0; 8.1)	4.1% (0.2; 8.0)	0.85
20 years	3.4% (0.0; 8.1)	4.1% (0.2; 8.0)	0.85
PCR			
15 years	3.2% (1.5; 5.0)	9.6% (6.9: 12.3)	< 0.001
20 years	3.6% (1.6; 5.6)	10.8% (7.9; 13.7)	< 0.001

[a] Only 10 BCR designs were placed cemented. [b] One revision after 20.3 years

Table 3. *Multivariate cox proportional hazard analysis to identify factors associated with risk of revision*

		Crude model		Adjusted model [a]	
	N	**HRcrude (95% CI)**	**p value**	**HRadj (95% CI)**	**p value**
Fixation					
Cemented (ref)	522	1.0		1.0	
Uncemented	749	3.61 (2.12–6.15)	< 0.001	2.32 (1.26–4.27)	< 0.001
Age	1271	0.96 (0.96–0.98)	< 0.001	0.97 (0.96–0.99)	0.001
Gender					
Male (ref)	236	1.0		1.0	
Female	1035	0.73 (0.46–1.16)	0.184	0.89 (0.56–1.41)	0.613
IJD					
No (ref)	614	1.0		1.0	
Yes	657	0.74 (0.50–1.09)	0.133	0.42 (0.28–0.65)	< 0.001
Type of prosthesis					
BCR (ref)	180	1.0		1.0	
RP	174	0.17 (0.07–0.40)	< 0.001	0.22 (0.09–0.53)	0.001
PCR	916	0.33 (0.22–0.50)	< 0.001	0.52 (0.34–0.80)	0.003

[a] *Adjusted for fixation, age, gender, IJD and type of prosthesis. Sensitivity analysis revealed that adjustment for the Charnley score was not required as there was no confounding effect of this variable*

Discussion

The most important finding of the present study was that TKA with the LCS MB system showed acceptable long-term revision rates for both cemented and uncemented fixation at a follow-up of up to 33 years. Cemented fixation was significantly less likely to fail, especially in non-IJD and with the PCR design. These results are generally in accordance with the reported survival rates of previous studies which included the LCS TKA implant. The latest report by McMahon et al. showed a cumulative survival rate of 97.4% in 500 LCS TKA implants using an uncemented tibial component, after 17 years of follow-up. [18] Buechel et al. reported survival rates of 83% for uncemented fixation at 16-year follow-up [4] and 97.7% for cemented fixation at 20-year follow-up. [5] Callaghan et al. published a survival rate of 96.5% for cemented fixation after 20 years. [7] However, these studies consisted of small cohorts and the indication was mostly non-IJD. The strength of the current study is the large cohort of 1271 LCS TKAs for both IJD and non-IJD with a long-term follow-up of at least 15 years with a mean of 25 years. To the authors' knowledge, this is the largest cohort and the longest follow-up to date. Compared to the above-mentioned studies, the

higher revision rate of uncemented fixation could be related to more physical activity of the relatively (and significantly) young aged group.

In IJD, uncemented fixation was previously shown to have a survival rate of 94% after 16 years [25] , 88.9% after 20 years and 80.2% after 25 years. [1] Again, cohorts were small and these studies were non-comparative in design. The finding that the IJD patient group in this study had a lower risk of revision than the non-IJD patients may suggest that uncemented fixation is sufficient in IJD patients. The Kaplan–Meier revision rate analysis also showed a slightly higher revision rate for uncemented fixation in the IJD, but this was not statistically significant. Furthermore, the fact that significantly more uncemented than cemented cases were performed in the IJD group, could also explain the finding that more uncemented cases required revision. A lower bone mineral density (BMD) in IJD could be another risk factor. However, studies in which the BMD was investigated showed that uncemented fixation did not have a negative effect on the BMD. [21, 28]

In previous research comparing cemented and uncemented fixation, better survival rates were reported for cemented fixation than for uncemented fixation. Cloke et al. reported a survival of 93% for cemented and 77% for uncemented fixation of Kinemax TKA after 10-year follow-up. [9] Duffy et al. reported improved survival rates for cemented over uncemented fixation of Press Fit Condylar TKA of 94.2% and 72.7% at 10-year follow-up. [11] Furthermore, Chockalingam et al. reported a failure rate of femoral components with a so-called shot-blast CoCr alloy of 0.6% in cemented fixation and 9.8% in uncemented fixation. [8] However, in these last two studies, it was unclear if patient demographics were matched between groups, which makes it challenging to interpret the results. This applies to the current study as well as the cemented patient group was significantly older than the uncemented group. On the contrary, more recent studies revealed no survival differences between cemented and uncemented designs [3, 10, 17] or have even found a better survival for uncemented designs but this applied to obese patients. [2, 26] Moreover, concerns have been reported in the latest Cochrane review about a higher risk of septic loosening in cemented TKA. [19] It appears that the debate on fixation methods will continue as the general level of evidence in publications is low. [22] But, more and more, radiostereometric analysis (RSA)-based studies confirm that cemented and uncemented components result in the same outcomes or even better outcomes for uncemented fixation. [15, 16, 20] Outcomes could differ from the results of the current study as relatively newer implants are used in more recent RSA-based studies. RSA-based studies, in both IJD and non-IJD will play an important role in the introduction of new fixation methods and designs, in combination with long-term survival studies.

This study has some limitations. First, patients could have been lost to follow-up due to the retrospective study design employed here. More specifically, patients undergoing revision surgery in another hospital may have been lost to follow-up, however, efforts were made to mitigate this by contacting patients by telephone. The loss to follow-up, missing data and inclusion of different implant designs (with significantly smaller BCR and RP groups) are an important risk of (selection) bias. Second, possible confounding factors not included in the analysis are (mis) alignment, preoperative range of motion, level of activity and perioperative bone quality. Third, demographic details of the cemented and uncemented patient groups differed significantly in terms of age and diagnosis. While demographic matching was not possible due to the retrospective study design, the influence of demographic differences on revision rates was accounted for in the Cox regression analysis. Ideally, demographic factors should be matched in a prospective cohort. Finally, the exact indication for using a certain component, which type of fixation and whether patella resurfacing was performed was unknown. These elements could represent a source of bias but require future investigation. As the general philosophy was to use uncemented fixation, it is possible that in complex cases, cemented fixation was used. However, this was not verified. These insights could contribute to future scientific studies on fixation methods of TKA.

Conclusions

Long-term revision rates for patients undergoing cemented or uncemented TKA using the LCS MB system showed significantly higher survival for cemented fixation. In subgroup analysis, a lower age, non-IJD and the PCR design were associated with a higher revision risk, regardless of the type of fixation. For the LCS MB TKA design, it is recommended to use cemented fixation.

Acknowledgements

The authors would like to thank Dr. L. Václavů for her language proofing.

Funding

There is no funding source.

Declarations

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: The procedures of this study were approved by the local ethical board of the former Slotervaart Medical Centre (local registration number P1833, in compliance with the Helsinki Declaration).

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7

General discussion

This discussion relates the results of the studies presented in this thesis in relation to current literature, thus arriving at the conclusions and suggestions for the future.

Multimodal pain management after total knee arthroplasty: peripheral nerve blocks and local infiltration

In Chapters 2 and 3, a randomized controlled trial is presented addressing the question of whether the addition of a sciatic nerve block (SNB, especially to relieve postoperative posterior pain) to a patient-controlled femoral nerve block (FNB) as part of multimodal pain management after total knee arthroplasty (TKA) could shorten the time to discharge and improve knee mobilization and pain relief. Moreover, the additional question was whether improved early postoperative pain scores when supplementary SNB in addition to FNB was used would lead to improved long-term functional outcomes and pain perception. First, the results showed that, compared to FNB only, a single injection or a continuous SNB led to better early postoperative pain relief and a statistically significant reduction in the need for opioids, which was believed to be clinically relevant. In addition, continuous SNB led to less pain during mobilization. However, the pain reduction did not lead to improvements in time to discharge and knee function. Notably, the time to discharge can also be partly determined by logistical routing in the hospital, e.g., arrangements for postoperative X-rays and arrangements with home care, rather than actual pain. Additionally, 36.7% of the continuous SNB group had a transient motor block (footdrop), which is of concern and could have impaired early active knee function, thereby delaying hospital discharge. Additionally, falls during mobilization were reported in the SNB groups. The concern about these falls is consistent with the literature at that time. [50] Second, the short-term improvement in postoperative analgesia did not translate into improved long-term knee function or other benefits evaluated via patient-reported outcome measures (PROMs). Logically, these outcomes led to the question of whether SNB is the appropriate method to facilitate early rehabilitation, as the aim is that pre-, intra- and postoperative pain management potentially promotes the speed of rehabilitation and reduces pain after rehabilitation. [3] The one-year results did not support this finding. Notably, in addition to the presented functional outcomes after 1 year, studies on longer-term outcomes are very rare. On the basis of a later meta-analysis and a systematic review by Grape et al. [20] (in which the study presented was included in the analysis) it was concluded that VAS pain scores and morphine use in the first 12 hours after surgery decrease with SNB, which is consistent with the findings of the presented study. However, advancements have also revealed other methods of pain reduction around

TKA, possibly with alternatives to FNB, which is historically the most widely used peripheral nerve block. The main reason for the introduction of other methods is the muscle weakness that nerve blocks can cause, resulting in a possible increased risk of falls and possibly a slower rehabilitation. Importantly, these falls can also be caused by other factors (advanced age, comorbidities, effects of surgery and sedatives). Pain itself can also be a cause. [1, 39] It is generally accepted that appropriate fall prevention should be used in all hospitalized patients. [27] Many institutions have developed their own pathways or protocols for perioperative care, which include pain management, prevention of postoperative nausea and vomiting and other aspects of perioperative care; the optimal components of such pathways for TKA are debated. [31] A dedicated care pathway and long-standing expertise in TKA perioperative care may lead to bias in clinical trials, as outcomes achieved in such specialized settings may not be generalizable to other institutions. Individualization on the basis of patient factors (i.e., prior opioid use, comorbidities) and the type of surgery (e.g., revision or complicated surgery) seems paramount here.

One alternative to FNB (with or without SNB) is periarticular (or local) infiltration of anesthetics (LIA). LIA consists of a series of injections that the surgeon performs intraoperatively in areas of the knee where pain fibers are known to be present, such as in the capsular structure around the knee. LIA has become increasingly popular in fast-track TKA to facilitate early mobilization and physiotherapy, especially in patients with limited comorbidities and without preoperative opioid use. One of the first randomized controlled trials, published in 2015, compared LIA with continuous FNB and single-shot SNB. [52] Comparable pain scores were reported between the groups, with a shorter duration of hospitalization in the LIA group. However, there was greater analgesic use in the LIA group. Nonetheless, this study group switched to LIA as “standard care” instead of peripheral nerve blocks while maintaining a place for peripheral nerve blocks in revision or otherwise complex arthroplasty. [52] Several studies have since compared LIA with other pain management methods. One of the most recent systematic reviews reported that pain relief from LIA was similar to that from FNB and that LIA was even associated with less analgesic use. No differences in range of motion or length of stay between FNB and LIA were found. The preferred standard of care was LIA, although it was suggested that this should be further investigated in multicenter studies. [34] Moreover, studies on LIA are difficult to compare because there is no clear consensus on solutions, for instance, about additional corticosteroids [24] and type of medication [64] or infiltration techniques for LIA. Future independent studies with a standardized protocol are needed to provide clear unbiased evidence.

An adductor canal block (ACB) was introduced as an alternative to FNB in total knee surgery. This has become an important option because it is a selective block of the sensory nerves, while FNB also results in a motor block. One of the first papers addressing an ACB suggested that it would provide better early mobilization and fewer accidental falls during hospitalization than would FNB. [38] A 2019 Cochrane review could not fully confirm these findings due to limited data. It reported uncertainty about whether pain at rest or during movement was reduced with ACB, and whether opioid-related side effects or accidental falls were less common compared to sham treatment and FNB. Notably, 11 studies were still ongoing or awaiting classification. [49] Most trials have focused on quadriceps muscle strength or opioid use rather than the number of patients with complications such as accidental falls during hospital care. In this context, studies comparing complication rates require a relatively considerable number of patients (approximately 10.000 patients when the expected difference is small in case of a rare event [11]), which is challenging in daily practice. For example, the study by Elkassabany et al. reported greater retention of quadriceps muscle strength after ACB than after FNB, but this did not lead to a reduction in fall risk. [15] In a systematic review and meta-analysis supporting the combined clinical practice guidelines of several professional societies, 56 publications concerning regional nerve blocks were analyzed. It was concluded that ACB and LIA provided comparable postoperative analgesia and opioid use, whereas FNB was associated with quadriceps weakness (while providing the same type of analgesia). Therefore, the preferred method was ACB or LIA, possibly with a combination of these 2 methods for best pain control and a continuous method instead of a single shot for poor pain control. [17] However, in one of the most recent systematic reviews, the shift from continuous FNB to ACB as the preferred method was considered "premature", as pain control was not improved and hospital stay was not shortened with ACB compared with continuous FNB. [6] This finding is not consistent with the recent results of the meta-analysis by Gong et al. in PLOS one. [19] Continuous ACB was found to be better than continuous FNB in maintaining quadriceps muscle strength and shortening discharge readiness time while having a similar effect on pain relief.

The next method to address is the "interspace between the popliteal artery and posterior capsule of the knee" (IPACK) block. This method blocks the distal branches of the genicular nerves and the popliteal plexus, which innervate the posterior capsule of the knee joint, while preserving the trunk of the tibial and common peroneal nerves. [30] It provides pain relief for the posterior part of the knee only, so it can be seen as an alternative to SNB and as part of multimodal pain management in TKA. The results of clinical trials are conflicting. Positive results were published for

an IPACK block compared with a sham block along with an ACB [45] and for an IPACK block and ACB in addition to "modified" LIA compared with LIA alone. [30] On the other hand, other randomized trials have reported no benefit of adding IPACK to LIA plus continuous ACB. [29, 57] One of the latest systematic reviews and meta-analyses revealed that the addition of IPACK block to ACB significantly reduces opioid use in the early postoperative period. [60] Another recent meta-analysis assessing the addition of IPACK to "other analgesic methods" (mostly single-shot or continuous ACB) in 1347 TKAs also concluded that adding an IPACK results in better pain scores, functional outcomes and lower opioid use; however, the differences were small, and the clinical relevance was questioned. [54]

The last methods we aim to briefly discuss as alternatives for SNB are selective tibial nerve block (TNB) and genicular nerve block (GNB). With respect to the TNB, Singha et al. concluded that this selective block in TKA avoids a full motor peroneal nerve block and results in similar postoperative analgesia. [51] A recent randomized study compared this selective TNB with partial LIA for posterior pain, with both groups also receiving ACB. It was concluded that pain relief was similar and that the technique chosen ultimately depended on surgical preference, the anesthetist's familiarity with the technique, the patient's circumstances and the postoperative hospital environment and settings. [46] Compared with IPACK, GNB was the most effective option for relieving motion pain 24 hours after surgery. [63] However, in literature, TNB and GNB are less studied methods than IPACK and LIA are.

These findings support the argument that standardized protocols are needed if any of the mentioned methods are used with which medical specialists are familiar. An overview of the main methods discussed can be found in Table 1.

Table 1. *Overview of the possible methods of regional anesthetics in TKA with the most recent outcomes.*

Type of block	Outcomes	Level of evidence
FNB Femoral nerve block	- Proven long-used method to be effective in reducing opioid use and shortening hospital stays. - Associated with quadriceps weakness and functional impairment. - Associated with an increased risk of fall.	Systematic reviews and meta-analysis of randomized controlled trials [28, 59]
ACB Adductor canal block	- Comparable level of pain relief and opioid use in comparison to FNB. - Better quadriceps power, longer ambulation distance and shorter hospital stay in comparison to FNB. - Decreased risk of falls in comparison to FNB.	Systematic reviews and meta-analysis of randomized controlled trials [28, 59]
SNB Sciatic nerve block	- Combined with FNB, more pain relief compared to FNB alone, especially within the first postoperative 24 hours. - Combined with FNB, more pain relief and less opioid use compared with LIA alone. - High incidence of transient motor block (footdrop) with possible impaired early active knee function.	Systematic reviews of randomized controlled trials and meta-analysis ([37, 66] and results presented in Chapters 2 and 3).
LIA Periarticular (or local) infiltration of local anesthetics	- As effective as ACB and FNB in postoperative pain and opioid use. - Less analgesic use compared to FNB. - Possible as an additional method with ACB; a combination showed the best reduction in opioid use and pain relief. - No clear consensus on solutions, type of medication or infiltration techniques.	Systematic reviews of randomized controlled trials and meta-analysis. [17, 34, 66]
IPACK Interspace between the popliteal artery and posterior capsule of the knee	- Combined with ACB, the most efficacious method for improving ambulation ability and shortening the length of hospital stay. - Combined with ACB, the best (both resting en movement) pain relief and reduction of opioid use at 48 hours postoperatively. - Combined with FCB, the best resting pain relief and reduction of opioid use at 24 hours postoperatively.	Bayesian network meta-analysis and systematic review [63]

Concluding Chapters 2 and 3 and this part of the multimodal approach to pain control in TKA, the results concerning an additional SNB to FNB have contributed to the search for the best methods within multimodal pain management. The methods described above have been developed to be equally effective at managing postoperative posterior knee pain after TKA, with fewer complications, especially no footdrop, which is common after SNB. In the meantime, it has also been proven that ACB provides as good pain relief as an FNB for anterior knee pain relief, with better quadriceps strength. In addition, there is evidence that an additional method is important for controlling postoperative posterior pain. To date, varying results have been presented when LIA, IPACK and other less studied blocks were compared. In the context of fast-track TKA, ACB with LIA or IPACK as an additional method for posterior pain seems the most appropriate, with FNB as a proven long-used alternative but with more quadriceps weakness in the early postoperative phase. These findings are supported by the latest network meta-analysis and systematic review. [63] Because of the high incidence of foot drops, there no longer seems to be a clear place for an additional SNB in primary TKA, if early mobilization is aimed at. For complex knee surgery, where early mobilization may be less important than in fast-track TKA, (continuous) FNB and additional (continuous or single shot) SNB remain good methods to achieve complete analgesia, especially as it is known that the first postoperative 48 hours in these procedures can be associated with severe pain, which can be well controlled with these methods for longer periods. In conclusion, there are numerous techniques currently used for postoperative pain management in TKA, the evidence is still evolving, and the search for the most effective and balanced approach continues. As it stands now, the choice of which methods to use also depends on clinical preference and experience of the medical specialist.

Multimodal pain management after total knee arthroplasty: cryotherapy

In Chapter 4 of this thesis, a clinical trial is presented addressing the research question of whether a relatively new, computer-assisted cryotherapy device would improve knee function and reduce swelling in the early rehabilitation phase after TKA without increasing the risk of postoperative complications. In the present prospective cohort, the new device did not increase the risk of postoperative complications compared with the control group, which did not receive cryotherapy. The number of patients was low, making it difficult to compare the complication rate with that of a control group and to draw conclusions on this outcome. For safety reasons, a pilot study was performed first. Other trials investigating computer-assisted cryotherapy did not find

more adverse effects of cryotherapy than did the control groups. [9, 56] Moreover, the results showed that patients who received computer-assisted cryotherapy had a better range of motion and less swelling in the early rehabilitation phase, which may support a rapid recovery program in TKA. The question, however, is whether such a computer-controlled device is needed to achieve the same clinical results compared to traditional cold packs. It also involves higher costs than conventional methods do. For example, Thienpont et al. reported in a randomized study that the same device did not add value compared with "normal" cold packs. [55] Unfortunately, pain scores were not included as outcomes, as the methods of pain management differed greatly. This highlights the need for a standard protocol for multimodal pain management in fast-track TKA if cryotherapy is scientifically investigated herein. While the evidence at the time of the cited Cochrane review was conflicting [2], a recent systematic review focused primarily on postoperative opioid use in the first postoperative week and concluded that cryotherapy provided a positive result in terms of opioid reduction. The level of pain also decreased, but swelling and range of motion did not. [61] However, there was considerable heterogeneity in the postoperative care and surgical technique protocols of the included studies, which made comparisons difficult. This was also concluded in another review. [32] In that latter review (and meta-analysis) by Krampe et al., cryotherapy also improved the range of motion of the knee. It was not possible to compare different cryotherapy methods in these reviews. Liu et al., in another systematic review, concluded that continuous cryotherapy may lead to additional costs and that current evidence does not support this method compared with traditional methods. [33] Again, significant heterogeneity between studies was observed, which can be explained by the significant difference in cryotherapy protocols and 5 different devices. By reviewing the literature and the results, it can be concluded that cryotherapy is a safe and convenient method to support an opioid-sparing rehabilitation program in TKA, but the heterogeneity of the studies requires further randomized trials with larger sample sizes. There is no evidence that modern continuous cryotherapy methods yield better results than traditional methods do and involve higher costs, so this method can be discouraged unless future well-designed studies with larger samples provide evidence to the contrary.

Prosthetic design and fixation in total knee arthroplasty

In Chapter 5 of this thesis, a blinded, randomized controlled trial is presented reporting the outcome of cemented, uncemented and hybrid fixation of the Advanced Coated System (ACS) Mobile Bearing TKA, which has a coating of titanium nitride

ceramic and uses a highly congruent polyethylene inlay, with sacrifice of the posterior cruciate ligament, without a posterior stabilized component. Mobile bearing TKA, in addition, is a design in which polyethylene is not attached to the tibial metal component but slides over it. This could theoretically lead to more self-alignment of the knee arthroplasty and less stress on the bone-implant surface. However, the latest systematic review revealed no difference in survival. [58] Other separate studies suggested reduced anterior knee pain and increased joint awareness with a mobile bearing design [4, 8], but there was no longer any difference in anterior knee pain compared with the fixed bearing design after almost 8 years. [7] In the present study, radiostereometric analysis (RSA) was used up to 2 years postoperatively. Results were compared with preoperative scores and among the three different fixation groups (cemented, uncemented and hybrid). The results revealed that secondary stabilization measurements, the migration outcome used to predict long-term aseptic loosening, did not differ between the groups. In all the groups, migration stabilized after initial implant placement. This is consistent with other publications on uncemented fixation for TKA with relatively new implants or new coatings at that time. [18, 21, 42] Moreover, the 2-year RSA results are supported by a follow-up study in which the results revealed no differences in survival or functional outcomes among the 3 groups after 5 years of follow-up. [16] Another study reported the outcomes of ACS implants in a clinical trial using RSA. Nivbrant et al. also conducted a blinded, randomized clinical trial and reported late subsidence and significantly greater movement of the uncemented ACS tibial component than of the cemented variant. Therefore, they recommended caution in the use of this uncemented tibial component even though the PROMs did not differ. There was no association between the clinical scores and migration profiles. [44] Although inconsistent with our findings, there was an important difference between the studies, namely, that Nivbrant et al. used a posterior stabilized ACS design and that the present study used a highly congruent polyethylene insert, which does not contain a cam-and-post. This could mean that a posteriorly stabilized design causes too much stress and micromotion between the bone and the implant and thus does not provide sufficient stability in the risk period until sufficient osseointegration occurs. This finding is supported by a biomechanical analysis in posterior-stabilized TKA, in which tibial loading increased the tibial bone-prosthesis interface. [13] This would also mean that the (tibial component) of the ACS prosthesis should only be placed uncemented if a cruciate retaining or highly congruent polyethylene design is used. In the near future, it will be important to monitor these groups of patients closely, with an additional role for the national registries to measure survival rates on the basis of revision surgery.

In Chapter 6 of this thesis, a retrospective analysis comparing cemented and uncemented Low Contact Stress mobile bearing TKA (LCS MB TKA) is presented. This implant design has been widely used over an extended period. [67] In this study, LCS implants were coated with porous titanium. Cox regression analysis was used to investigate the association between fixation type and implant survival. The results showed a statistically significant advantage for cemented fixation. After 20 years, the survival rate was almost 9% higher in the cemented group, a difference considered clinically relevant. The risk of revision was also influenced by patient and implant characteristics. Patients with osteoarthritis ("non-inflammatory joint disease") had a higher risk of revision than patients with inflammatory joint disease. The risk of revision was also higher in younger patients and in patients who received the "anterior posterior glide posterior cruciate-retaining LCS" (PCR) design, which retains the posterior cruciate ligament.

One likely reason for the higher failure rate in the PCR LCS design is anteroposterior instability, which has been reported in multiple studies. [25, 40] This may partly explain the higher revision rate observed in the uncemented group. Additionally, the use of older LCS designs may have contributed. Over time, LCS prostheses have evolved, ultimately leading to newer designs such as the ACS implant discussed in Chapter 5. Experimental data from preclinical studies support the importance of these design improvements. For example, a cadaveric study comparing a modern uncemented TKA design (Attune) with the LCS showed that Attune exhibited less micromotion under loading conditions simulating walking and deep knee bending. [5] These findings suggest that advanced technology improves stability and osseointegration in uncemented TKA. In any case, cemented fixation was recommended for all of the described LCS MB TKA designs. The debate between cemented and uncemented fixation continues. A systematic review and meta-analysis of 26 studies including 5023 TKA patients revealed no difference in revision rates between the two methods. However, uncemented fixation showed better long-term functional outcomes, based on PROMs. [35] This 2021 review did not include the results of Nivbrant et al. (2020) [44] or the results presented in Chapter 5. Moreover, the most recent Cochrane review on this topic dates from 2012 and concluded that cemented fixation is associated with a higher risk of aseptic loosening. This review requires an update. [41] A more recent meta-analysis of randomized trials revealed that uncemented, posterior cruciate ligament retaining TKA resulted in better knee scores, less pain and similar revision rates and complication rates compared to cemented TKA. [12] The authors recommended uncemented TKA for younger patients due to better bone quality and easier revision in the future, while cemented fixation was suggested for older patients with lower revision risk. Interestingly, these studies often do not distinguish

between fixed and mobile bearings, which introduces heterogeneity into the results. In contrast, a recent systematic review focusing on posterior-stabilized TKA found no difference in revision rates between cemented and uncemented fixation. [10] This highlights the importance of distinguishing between posterior-stabilized and cruciate-retaining designs and between different bearings in future studies.

Other examples of advancing technology in knee replacement surgery include the development of sex-specific and "high-flex" TKA components. While these types of design could theoretically improve functional outcomes and survival, there is not sufficient evidence that this is the case. [43, 48] The same applies to developments such as patient-specific instrumentation, computer navigation and robotic-assisted TKA. [22, 23, 36] However, patient-specific instrumentation and robot-assisted TKA can improve the alignment of the prosthesis without proven patient reported outcome benefits. [53, 65] For many such new techniques, the longer-term outcomes remain to be determined.

Another factor related to surgical technique is alignment in TKA. The standard approach for TKA has long been to align the implant mechanically, with the hip, center of the reconstructed knee and ankle aligned. [26] Kinematic alignment was introduced as an alternative implantation strategy with the goal of mimicking the orientation of joint surfaces before disease. It is thought that this procedure is intended to optimize ligament balance and knee kinematics without the need to release ligaments and/or capsules. [47] To date, there do not seem to be significant functional differences between kinematic and mechanical alignment. This new method does not seem to be inferior to the traditional method, which is therefore considered an at least equally good alternative [14], especially since a systematic review revealed shorter operating times and possibly better functional results. [62] Again, long-term follow-up and larger, well-designed trials are important for the future.

On the basis of the results in Chapters 5 and 6 and the literature, many developments are still ongoing in the field of fixation modalities and prosthesis designs in TKA. The presented studies have contributed to the development of these methods. For new prosthetic models in which the coating of uncemented TKA is adapted to modern technology, the results appear comparable to those of cemented fixation. This is not the case for posterior stabilized designs where possibly more stress occurs at the bone-implant interface and possibly not for older prosthetic models. New prosthetic developments will have to be introduced in a stepwise approach with

initial preclinical studies and then clinical studies using RSA to assess migration patterns before being used in large groups of patients.

Conclusions and suggestions for the future

Based on the findings presented in Chapters 2-6, the following conclusions can be drawn in response to the research questions of this thesis:

1. The addition of a sciatic nerve block to a patient-controlled femoral nerve block as part of multimodal pain management after total knee arthroplasty results in improved early postoperative pain relief and reduced opioid use. However, it does not result in shorter hospital stays or improved mobilization and the continuous sciatic nerve block is associated with a high incidence of transient motor block (e.g., foot drop), making it less suitable for fast-track rehabilitation protocols.
2. Improved early postoperative pain scores with the addition of a sciatic nerve block do not translate into superior long-term functional outcomes or patient-reported outcomes. As such, the long-term clinical benefit of a sciatic nerve block remains questionable in the context of routine total knee arthroplasty pain management.
3. Computer-assisted cryotherapy was found to be a safe modality in total knee arthroplasty that reduced postoperative swelling and improved knee function in the early rehabilitation phase, without increasing the risk of complications. However, given the additional costs and lack of proven superiority over conventional cryotherapy methods, there is currently no indication that this needs to be used in standard practice.
4. In the case of the Advanced Coated System mobile bearing total knee arthroplasty, no significant differences in implant migration or functional outcomes were observed between cemented, uncemented, and hybrid fixation methods up to two years postoperatively. For this implant the longer outcome would not expect to be influenced by the type of fixation to the bone. These findings suggest that modern uncemented fixation may be a viable alternative to cemented fixation.
5. For Low-Contact-Stress mobile bearing total knee arthroplasty, cemented fixation demonstrated superior long-term implant survival compared to uncemented fixation. Risk factors for revision included younger patient age, primary osteoarthritis, and the use of the “anterior posterior glide posterior cruciate-retaining” design. These findings highlight the importance of matching fixation strategies to patient characteristics and implant design.

After reviewing the results in Chapters 2-6, the discussion and the conclusions, a number of suggestions can be made:

- Since many institutions have developed their own pathways or protocols for perioperative care that include pain management in total knee arthroplasty, future multicenter studies with a standardized protocol are needed to provide clear, unbiased evidence that can serve as input for the development of clinical guidelines.
- In future studies, an adductor canal block as the standard peripheral nerve block can be recommended, combined with an additional block for posterior pain. In particular, periarticular (or local) infiltration of anesthetics and "interspace between the popliteal artery and posterior capsule of the knee" as additional methods are adequate options for comparison in well-designed randomized studies.
- Because of the considerable heterogeneity of studies involving cryotherapy in total knee arthroplasty, future well-designed studies with a standard multimodal pain management protocol and larger samples are needed to confirm the positive effect on reducing the surgical inflammatory response.
- Since there is inconsistency in the literature on functional outcomes (including patient-reported outcome measures) and survival between uncemented and cemented total knee arthroplasty, it will be important to monitor these groups of patients closely, with a special role for radiostereometric analysis and national registries. Comparative studies and systematic reviews should clearly distinguish which prosthetic designs are used, as this may also be a crucial factor for survival.
- The introduction of various modern technologies in total knee arthroplasty should be safely guaranteed; therefore, a stepwise, scientific build-up of evidence is needed.

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8

English Summary

Chapter 1

General introduction and outline of the thesis

Osteoarthritis (OA) of the knee is a common degenerative joint disease, particularly prevalent in the aging population. It is characterized by progressive cartilage degradation and pathological changes in the periarticular tissues. Risk factors for developing knee OA include older age, female sex, high Body Mass Index, previous knee injuries and intensive physical activity. Symptoms such as pain, stiffness and functional limitations affect quality of life and sometimes lead to depression or loss of work.

Initial treatment of knee OA favors conservative, symptom-relieving approaches, including patient education, exercise therapy and weight reduction, as no curative therapies are currently available. These interventions are supported by moderate-to high-quality evidence for pain relief and functional improvement. When nonpharmacologic therapy proves insufficient, pharmacologic treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) or intra-articular corticosteroids are considered, although the latter should be used with caution because of possible long-term cartilage damage. New injectables such as platelet-rich plasma and new viscosupplementation techniques are promising but require further investigation, also in terms of cost-effectiveness.

Surgical intervention is the next step when conservative and pharmacologic therapies do not achieve symptom reduction. Total knee arthroplasty (TKA) remains the gold standard for end-stage OA. TKA reliably improves function and reduces pain, although approximately 20% of patients remain dissatisfied, often due to unmet expectations or poor rehabilitation outcomes. Alternative procedures such as high tibial osteotomy or unicompartmental arthroplasty are valid options if the indication is adequate, mainly in younger and more active patients.

Successful rehabilitation after TKA relies on multimodal pain management, early mobilization, and physical therapy. Enhanced recovery protocols have reduced hospital stays and complications, although their impact on long-term satisfaction and pain levels remains unclear. The use of peripheral nerve blocks, especially femoral and possibly sciatic blocks, has shown efficacy in pain control and reducing opioid use. Cryotherapy is another adjunct modality that may assist in reducing postoperative swelling and improving early mobility.

Implant design and fixation techniques are crucial to TKA success. TKA cementation with polymethylmetacrylate (PMMA) remains the standard as it is the most performed method and provides immediate fixation. However, uncemented and hybrid designs aim to improve biological fixation, ease future revisions and reduce operative time. Radiostereometric analysis has proven to be an accurate method for measuring TKA-component migration over time, a key indicator of long-term stability. Implant coatings contribute to fixation success in uncemented TKA.

This thesis explores several aspects of perioperative care in TKA. First, it investigates the effectiveness of adding sciatic nerve blocks to a femoral nerve block as part of a multimodal pain management strategy. Second, it evaluates the role of cryotherapy in the early recovery phase after TKA. Third, it examines how different fixation methods affect implant stability and patient outcomes. Together, these studies aim to refine perioperative protocols and enhance long-term results for patients undergoing TKA.

Chapter 2

Peripheral nerve blocks as part of multimodal pain management in TKA, part 1

This randomized trial investigated whether adding a sciatic nerve block (SNB) to a continuous femoral nerve block (FNB) shortens time-to-discharge readiness following TKA. Ninety patients were randomized into three groups: FNB alone (F group), FNB with single-injection SNB (Fs group), or FNB with continuous SNB (FCS group). Discharge readiness was defined by functional independence, pain score <4 at rest, and absence of complications.

Median time-to-discharge readiness was comparable: F group, 4 days (range, 2-16 days); Fs group, 4 days (range, 2-7 days); and FCS group, 4 days (range, 2-9 days; $P = 0.631$). No significant differences were found regarding knee function, local anesthetic consumption, or postoperative nausea and vomiting. During the day of surgery, pain was moderate to severe in the F group, whereas patients in the Fs and FCS groups experienced minimal pain ($P < 0.01$). Patients in the F group required significantly more supplemental morphine on the day of surgery and the first postoperative day. Until the second postoperative day, pain was significantly less in the FCS group ($P < 0.01$).

A single-injection or continuous SNB in addition to FNB did not influence time-to-discharge readiness. A single-injection SNB can reduce severe pain on the day of

the surgery, whereas a continuous SNB reduces moderate pain during mobilization on the first 2 postoperative days.

Chapter 3

Peripheral nerve blocks as part of multimodal pain management in TKA, part 2

This is a follow-up study to determine long-term outcomes after TKA in patients enrolled in the randomized trial described in Chapter 3.

Physical function after TKA was evaluated at 3 and 12 months in patients (n = 89) receiving continuous femoral nerve block alone (group F), combined with a single-injection (group Fs) or continuous sciatic nerve block (group FCS) after TKA, until the second postoperative day. Physical function, stiffness, and pain were measured by using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Oxford Knee Score 12-item knee questionnaires, and visual analog scale at rest and during mobilization before TKA and 3 and 12 months afterward.

All groups demonstrated significant improvements postoperatively; however, no significant differences were found between the groups. Median (range) WOMAC at 3 months were in group F, 83 (20-97); group Fs, 72 (25-99); and group, FCS 76 (28-100) and at 12 months 87 (35-98), 77 (43-100), and 89 (35-100), respectively.

Improved short-term analgesia via a sciatic nerve block did not translate into enhanced functional or long-term pain outcomes.

Chapter 4

Cryotherapy after total knee arthroplasty

This prospective cohort study explored the effects of a computer-assisted cryotherapy device in patients undergoing TKA. The primary outcome was the complication rate; secondary outcomes included swelling, knee function and other functional results, measured by the Knee injury and Osteoarthritis Outcome Score and Oxford Knee Score.

A total of 62 patients were included, with 31 patients receiving cryotherapy and 31 controls. No significant differences were observed in postoperative complication rates. The cryotherapy group exhibited significantly better early knee flexion and

reduced swelling. These benefits did not persist at later follow-up intervals or in the other outcomes.

The cryotherapy device appears safe and effective for early-phase rehabilitation but may not offer advantages over conventional cold therapy considering the increased cost.

Chapter 5

Fixation in total knee arthroplasty, part 1

For many designs of TKA it remains unclear whether cemented or uncemented fixation provides optimal long-term survival. Studies using radiostereometric analysis (RSA) techniques have shown to be highly predictive in detecting late occurring aseptic loosening at an early stage. This randomized controlled trial evaluated cemented, uncemented, and hybrid fixation in 105 patients receiving Advanced Coated System Mobile Bearing (ACS MB) TKA. RSA was performed at day 1, 3 months, 6 months, 1 year, and 2 years postoperatively. Patient-reported outcome measures were collected preoperatively and at 2 years. Patients and investigators were blinded to allocation.

All fixation methods demonstrated comparable migration patterns, with maximum total point motion <0.2 mm at 2 years, indicating stable implants. Patient-reported outcome measures improved significantly in all groups without statistically significant between-group differences.

In all groups migration stabilized after initial settling of the implant. For this implant the long-term outcome is not expected to be influenced by the type of fixation to the bone.

Chapter 6

Fixation in total knee arthroplasty, part 2

This retrospective study assessed long-term survival of cemented versus uncemented fixation in 1,271 Low Contact Stress (LCS) mobile-bearing (MB) TKAs with a minimum 15-year follow-up. Cox regression analysis was performed to assess the association between type of fixation and the risk of revision, while correcting for potential confounders (diagnosis, design, age and sex).

Cemented TKA showed superior survival: 15-year revision incidence was 2.7% (cemented) vs. 10% (uncemented); 20-year revision rates were 2.9% and 10.9%, respectively. Higher revision risk was associated with younger age, non-inflammatory joint disease, and "anterior posterior glide posterior cruciate retaining" (PCR) design, regardless of the type of fixation.

Cemented fixation is recommended for this specific design and patient subgroups.

Chapter 7

General discussion

This general discussion integrates the findings of the studies from the presented chapters and places them in the context of current literature on multimodal pain management and prosthetic fixation in TKA.

The first section focuses on multimodal pain management, specifically the use of peripheral nerve blocks. The addition of a sciatic nerve block (SNB) to a femoral nerve block (FNB) improved early postoperative pain relief and reduced opioid use. However, it did not lead to better functional outcomes or shorter hospital stays. In addition, SNB was associated with a high incidence of footdrop and increased risk of falls, raising concerns about its routine use in fast-track TKA. Alternative nerve blocks such as the adductor canal block (ACB) offer comparable analgesia without the motor impairment caused by FNB and may therefore be preferable. Periarticular local infiltration analgesia and "interspace between the popliteal artery and posterior capsule of the knee block" are also promising, especially when combined with ACB. However, more standardized and multicenter studies are needed for these methods to definitively prove their benefits.

The second part addresses cryotherapy as part of multimodal pain management after TKA. A pilot study using a computer-controlled cryotherapy device showed improved early knee mobility and reduced swelling without increasing complication rates. However, cost-effectiveness and superiority over traditional cold therapy remain unproven, and the evidence is heterogeneous. Future studies with standard protocols and larger samples are required to further prove any benefits.

The third part discusses fixation techniques in TKA. A randomized controlled trial compared cemented, uncemented, and hybrid fixation in a modern design (ACS Mobile Bearing TKA). Radiostereometric analysis showed no significant differences

in early implant migration. Long-term outcomes were comparable. However, a retrospective analysis of an older design (LCS mobile-bearing TKA) showed higher survival rates with cemented fixation. Evidence suggests that modern uncemented designs can perform at least as well as cemented ones, but posterior-stabilized implants may pose a higher risk of loosening when used uncemented. These findings highlight the importance of distinguishing between different prosthetic designs when evaluating the results of fixation methods.

Finally, technological innovations like robotic surgery, patient-specific instrumentation and new alignment strategies show potential, but so far without improved functional outcomes. These innovations therefore require further scientific validation.

The following conclusions were drawn:

- Adding a sciatic nerve block to a femoral nerve block in total knee arthroplasty improves early pain relief and reduces opioid use, but it does not improve long-term outcomes, and may limit fast-track rehabilitation due to motor block.
- Computer-assisted cryotherapy is safe, reduces swelling, and aids early recovery after total knee arthroplasty, but offers no clear advantage over conventional methods and does not appear to be cost-effective for routine use.
- Fixation strategy and outcomes in total knee arthroplasty vary depending on implant design. For the Advanced Coated System, cemented, uncemented, and hybrid fixation showed comparable implant migration and functional outcomes up to two years postoperatively, suggesting that uncemented fixation may be a viable alternative. In contrast, for the Low-Contact-Stress design, cemented fixation was associated with superior long-term implant survival, particularly in younger patients and those with non-inflammatory joint disease or “anterior posterior glide posterior cruciate-retaining” component. These findings highlight the importance of matching fixation strategies to patient characteristics and implant design.

This discussion and these conclusions emphasize the need for well-designed, multicenter trials with standardized protocols of multimodal pain management, long-term follow-up, and a stepwise introduction of various modern technologies in TKA.

9

Nederlandse samenvatting

Hoofdstuk 1

Introductie

Knieartrose is een veelvoorkomende gewrichtsaandoening, wat met name bij de oudere populatie voorkomt. De aandoening wordt gekenmerkt door toenemend kraakbeenverlies en pathologische veranderingen rond het gewricht. Risicofactoren voor het ontwikkelen van knieartrose zijn onder meer een hogere leeftijd, vrouwelijk geslacht, een hoge Body Mass Index, eerder knieletsel en intensieve fysieke belasting, zoals topsport. Symptomen zoals pijn, stijfheid en functionele beperkingen beïnvloeden de kwaliteit van leven en leiden soms tot depressie of verlies van werkvermogen.

De initiële behandeling van knieartrose bestaat uit conservatieve therapie om klachten te verlichten, waaronder patiënten-educatie, oefentherapie en gewichtsreductie, aangezien er momenteel geen genezende behandelingen beschikbaar zijn. Voor deze interventies is matig tot hoogwaardig bewijs beschikbaar als het gaat om pijnverlichting en functionele verbetering. Wanneer niet-medicamenteuze therapie onvoldoende effect heeft, wordt overgegaan op medicamenteuze behandeling zoals niet-steroïde anti-inflammatoire geneesmiddelen (NSAID's) of een injectie met corticosteroïden in het gewricht, hoewel voorzichtigheid geboden is bij het gebruik van corticosteroïden vanwege mogelijk schadelijke effecten op het kraakbeen op de lange termijn. Nieuwe injectietechnieken, zoals plaatjesrijk plasma, zijn veelbelovend, maar vereisen nog verdere wetenschappelijke onderbouwing, ook wat kosteneffectiviteit betreft.

Chirurgische interventie is de volgende stap wanneer conservatieve en medicamenteuze therapieën onvoldoende symptoomverlichting bieden. Een totale knieprothese (TKP) blijft de gouden standaard bij vergevorderde artrose. Een TKP leidt doorgaans tot verbetering van de functie en pijnreductie, hoewel circa 20% van de patiënten ontevreden blijft, vaak als gevolg van onbevredigde verwachtingen of teleurstellende revalidatie-uitkomsten. Alternatieve procedures zoals een hoge tibiakop-osteotomie of een unicondylaire (halve) knieprothese zijn goede alternatieven, mits de indicatie goed gesteld is, vooral bij jongere en actievere patiënten.

Succesvolle revalidatie na een TKP vereist multimodale (gecombineerde) pijnbestrijding, vroege mobilisatie en fysiotherapie. Versnelde herstelprotocollen hebben geleid tot verkorte opnameduur en minder complicaties, hoewel het effect op lange termijn tevredenheid en pijnscores nog niet volledig duidelijk is. Het

gebruik van perifere zenuwblokkades, met name femoralis blokkade en mogelijk ook ischiadicus blokkade, blijkt effectief voor pijnbestrijding en het verminderen van opioïdgebruik. Cryotherapie (koudetherapie) is een aanvullende methode die kan helpen bij het verminderen van postoperatieve zwelling en het verbeteren van vroege mobiliteit.

Het ontwerp van de prothese en de fixatietechniek zijn cruciaal voor het succes van een TKP. Een gecementeerde TKP (met gebruik van botcement) blijft de standaard omdat dit de meest uitgevoerde methode is en directe fixatie biedt. Ongecementeerde en hybride ontwerpen streven naar biologische fixatie, kunnen toekomstige revisieoperaties gemakkelijker maken en de operatietijd verkorten. Radiostereometrische analyse is een nauwkeurige methode gebleken om migratiepatronen te meten, wat een belangrijke indicator is voor de lange termijn stabiliteit van een TKP. De coating (oppervlaktelaag) van het implantaat draagt bij aan het succes van fixatie bij een ongecementeerde TKP.

Dit proefschrift onderzoekt diverse aspecten van perioperatieve zorg bij een TKP. Ten eerste wordt de effectiviteit onderzocht van het toevoegen van een ischiadicus zenuwblokkade aan een femoralis zenuwblokkade als onderdeel van gecombineerde pijnbestrijding. Ten tweede wordt de rol van cryotherapie in de vroege herstelperiode na een TKP geëvalueerd. Ten derde wordt onderzocht hoe verschillende fixatiemethoden de stabiliteit van het implantaat en de uitkomsten voor de patiënt beïnvloeden. Samen beogen deze studies de perioperatieve protocollen te verfijnen en de langetermijnresultaten voor patiënten die een TKP-operatie ondergaan te verbeteren.

Hoofdstuk 2

Perifere zenuwblokkades als onderdeel van multimodale pijnbestrijding bij een totale knieprothese - deel 1

In dit gerandomiseerde onderzoek werd onderzocht of het toevoegen van een ischiadicus zenuwblokkade (IZB) aan een continue femoralis zenuwblokkade (FZB) de tijd tot gereedheid voor ontslag na een TKP verkort. In totaal werden 90 patiënten gerandomiseerd in drie groepen: alleen een FZB (F-groep), een FZB met eenmalige IZB-injectie (Fs-groep), of een FZB met continue IZB (FCS-groep). Gereedheid voor ontslag werd gedefinieerd als functionele onafhankelijkheid, een pijnscore <4 in rust, en de afwezigheid van complicaties.

De mediane tijd tot gereedheid voor ontslag was vergelijkbaar tussen de groepen: F-groep, 4 dagen (range 2–16 dagen); Fs-groep, 4 dagen (range 2–7 dagen); en FCS-groep, 4 dagen (range 2–9 dagen; P = 0.631). Er werden geen significante verschillen gevonden in kniefunctie, verbruik van lokale anesthetica, of postoperatieve misselijkheid en braken. Op de operatiedag werd matige tot ernstige pijn ervaren in de F-groep, terwijl patiënten in de Fs- en FCS-groepen minimale pijn ervoeren (P < 0.01). Patiënten in de F-groep hadden significant meer aanvullende morfine nodig op de operatiedag en de eerste postoperatieve dag. Tot en met de tweede postoperatieve dag was de pijn significant lager in de FCS-groep (P < 0.01).

Het toevoegen van een eenmalige of continue IZB aan een FZB had geen invloed op de tijd tot gereedheid voor ontslag. Een eenmalige IZB kan ernstige pijn op de operatiedag verminderen, terwijl een continue IZB matige pijn tijdens mobilisatie op de eerste twee postoperatieve dagen vermindert.

Hoofdstuk 3

Perifere zenuwblokkades als onderdeel van multimodale pijnbestrijding bij een totale knieprothese - deel 2

Dit vervolgonderzoek was gericht op het beoordelen van de lange termijn resultaten van patiënten die deelnamen aan het gerandomiseerde onderzoek dat in hoofdstuk 2 is beschreven.

De fysieke functie na een TKP werd geëvalueerd bij 89 patiënten na 3 en 12 maanden postoperatief. Zij hadden een continue femoralis zenuwblokkade gekregen (groep F), gecombineerd met een eenmalige (groep Fs) of continue ischiadicus zenuwblokkade (groep FCS), tot en met de tweede postoperatieve dag. De kniefunctie, stijfheid en pijn werden gemeten met de Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), de Oxford Knee Score (12-item), en een visuele analoge schaal voor pijn in rust en tijdens mobilisatie, zowel vóór als 3 en 12 maanden na een TKP.

Alle groepen lieten postoperatief significante verbeteringen zien; er werden echter geen significante verschillen tussen de groepen gevonden. De mediane (range) WOMAC-scores na 3 maanden waren voor groep F: 83 (20–97), groep Fs: 72 (25–99), en groep FCS: 76 (28–100); en na 12 maanden respectievelijk 87 (35–98), 77 (43–100), en 89 (35–100).

Verbeterde korte termijn pijnstilling via een ischiadicus zenuwblokkade leidde niet tot betere functionele of lange termijn pijnuitkomsten.

Hoofdstuk 4

Cryotherapie na een totale knieprothese

Deze prospectieve cohortstudie onderzocht de effecten van een computergestuurd cryotherapietoestel bij patiënten die een TKP ondergingen. De primaire uitkomstmaat was het complicatiepercentage; secundaire uitkomsten waren zwelling, kniefunctie en overige functionele resultaten, gemeten met de Knee injury and Osteoarthritis Outcome Score en de Oxford Knee Score.

In totaal werden 62 patiënten geïncludeerd, waarvan 31 cryotherapie ontvingen en 31 fungeerden als controlegroep. Er werden geen significante verschillen waargenomen in het postoperatieve complicatiepercentage. De cryotherapiegroep vertoonde een significant betere vroege flexie van de knie en minder zwelling. Deze voordelen hielden niet aan bij latere follow-up intervallen of bij de andere uitkomsten.

Dit cryotherapietoestel lijkt veilig en effectief in de vroege revalidatiefase, maar biedt mogelijk geen voordeel ten opzichte van conventionele koudetherapie, zeker gezien de hogere kosten.

Hoofdstuk 5

Fixatie bij een totale knieprothese - deel 1

Bij veel ontwerpen van een TKP is het onduidelijk of gecementeerde dan wel ongecementeerde fixatie op lange termijn beter is. Studies met radiostereometrische analyse (RSA) zijn zeer voorspellend gebleken voor het vroegtijdig detecteren van loslating zonder infectie. Deze gerandomiseerde studie evalueerde gecementeerde, ongecementeerde en hybride fixatie bij 105 patiënten met een Advanced Coated System Mobile Bearing (ACS MB) TKP. RSA werd uitgevoerd op dag 1, na 3 maanden, 6 maanden, 1 jaar en 2 jaar postoperatief. Patiënt gerapporteerde uitkomsten werden verzameld vóór de operatie en na 2 jaar. Zowel patiënten als onderzoekers waren geblindeerd voor de uitkomst van randomisatie.

Alle fixatiemethoden vertoonden vergelijkbare migratiepatronen, met een maximale totale puntverplaatsing <0.2 mm na 2 jaar, wat wijst op stabiele protheses. Patiënt

gerapporteerde uitkomsten verbeterden significant in alle groepen, zonder statistisch significante verschillen tussen de groepen.

In alle groepen stabiliseerde de migratie na de initiële fixatie van het implantaat. Voor dit type implantaat wordt niet verwacht dat de lange termijn uitkomst beïnvloed wordt door het type fixatie aan het bot.

Hoofdstuk 6

Fixatie bij een totale knieprothese - deel 2

Deze retrospectieve studie onderzocht de lange termijn overleving van gecementeerde versus ongecementeerde fixatie bij 1.271 Low Contact Stress (LCS) mobile-bearing TKP's met een minimale follow-up van 15 jaar. Cox regressieanalyse werd uitgevoerd om de samenhang tussen het type fixatie en het risico op revisieoperatie te beoordelen, waarbij gecorrigeerd werd voor potentieel verstorende variabelen (diagnose, ontwerp, leeftijd en geslacht).

Gecementeerde TKP liet een superieure overleving zien: de revisie-incidentie na 15 jaar was 2.7% (gecementeerd) versus 10% (ongecementeerd); na 20 jaar respectievelijk 2.9% en 10.9%. Een verhoogd revisierisico hing samen met jongere leeftijd, niet-inflammatoire gewrichtsziekte en een "anterior posterior glide posterior cruciate-retaining" (PCR)-ontwerp, ongeacht het type fixatie.

Gecementeerde fixatie wordt aanbevolen voor dit specifieke ontwerp en voor de bovengenoemde patiëntsubgroepen.

Hoofdstuk 7

Algemene discussie

Deze algemene discussie omvat de bevindingen van de voorafgaande hoofdstukken en plaatst deze in de context van de actuele literatuur over gecombineerde pijnbestrijding en prothese-fixatie bij een TKP.

Het eerste deel richt zich op gecombineerde pijnbestrijding, met name het gebruik van perifere zenuwblokkades. De toevoeging van een ischiadicus zenuwblokkade (IZB) aan een femoralis zenuwblokkade (FZB) leidde tot verbeterde vroege postoperatieve pijnverlichting en een verminderd opioïdgebruik. Echter, dit vertaalde zich niet in

betere functionele uitkomsten of kortere ziekenhuisopname. Bovendien ging IZB gepaard met een hoge incidentie van uitval van de voetheffers en verhoogd valrisico, wat twijfels oproept over routinematig gebruik bij een “versneld revalidatie” protocol. Alternatieve zenuwblokkades zoals de adductorkanaal blokkade (AKB) bieden vergelijkbare pijnbestrijding zonder de motorische belemmering die FNB veroorzaakt, en kunnen daarom de voorkeur hebben. Lokale verdoving in de omliggende weefsels en de “tussenruimte tussen de popliteale slagader en het achterste kapsel van de knie blokkade” zijn eveneens veelbelovend, met name in combinatie met AKB. Er zijn echter meer gestandaardiseerde en multicenteronderzoeken nodig om de voordelen van deze methoden definitief te bewijzen.

Het tweede deel behandelt cryotherapie als onderdeel van pijnbestrijding na een TKP. Een pilotstudie met een computergestuurd cryotherapietoestel liet verbeterde vroege kniemobiliteit en minder zwelling zien, zonder toename in complicaties. De kosteneffectiviteit en superioriteit ten opzichte van traditionele koudetherapie methodes zijn echter niet aangetoond en het bewijs is heterogeen. Verdere studies met gestandaardiseerde protocollen en grotere populaties zijn van belang.

Het derde deel bespreekt fixatietechnieken van een TKP. Een gerandomiseerde trial vergeleek gecementeerde, ongecementeerde en hybride fixatie bij een modern ontwerp (Advanced Coated System Mobile Bearing TKP). Radiostereometrische analyse toonde geen significante verschillen in prothese migratie. De uitkomsten op lange termijn waren vergelijkbaar. Daarentegen liet een retrospectieve analyse van een ouder ontwerp (Low-Contact-Stress Mobile Bearing TKP) betere overleving zien met gecementeerde fixatie. De huidige evidence suggereert dat moderne ongecementeerde ontwerpen minstens even goed presteren als gecementeerde varianten. Posterior-stabilized implantaten lijken echter een hoger loslatingsrisico te hebben als ze ongecementeerd worden geplaatst. Dit onderstreept het belang van onderscheid tussen protheseontwerpen bij de beoordeling van fixatiemethoden.

Tot slot lijken technologische innovaties zoals robotchirurgie, patiënt-specifieke instrumentatie en nieuwe uitlijnstrategieën veelbelovend, maar er is vooralsnog geen verbetering van functionele uitkomsten aangetoond. Verdere wetenschappelijke onderbouwing is noodzakelijk.

De volgende conclusies werden getrokken:

- Het toevoegen van een ischiadicus zenuwblokkade aan een femoralis zenuwblokkade bij een totale knieprothese verbetert de vroege postoperatieve

pijnverlichting en vermindert het opioïdgebruik. Het leidt echter niet tot betere langetermijnresultaten en kan snelle revalidatie belemmeren door (tijdelijke) motorische uitval.

- Computergestuurde cryotherapie is veilig, vermindert zwelling en ondersteunt het vroege herstel na een totale knieprothese, maar biedt geen duidelijk voordeel ten opzichte van traditionele koudetherapie methoden en lijkt voor routinematig gebruik niet kosteneffectief.
- De keuze voor fixatiestrategie en de bijbehorende resultaten bij een totale knieprothese zijn afhankelijk van het implantaatontwerp. Bij het Advanced Coated System lieten gecementeerde, ongecementeerde en hybride fixatie tot twee jaar postoperatief vergelijkbare waarden voor implantaatmigratie en functionele uitkomsten zien, wat erop wijst dat ongecementeerde fixatie een goed alternatief is. Daarentegen werd bij het oudere Low-Contact-Stress-ontwerp een betere langetermijnoverleving van het implantaat gevonden met gecementeerde fixatie, vooral bij jongere patiënten, patiënten met niet-inflammatoire gewrichtsziekte en bij gebruik van een "anterior posterior glide posterior cruciate-retaining" component. Deze bevindingen onderstrepen het belang van het afstemmen van de fixatiestrategie op patiëntkenmerken en implantaatontwerp.

Deze discussie en deze conclusies benadrukken de noodzaak van goed ontworpen, multicentrische studies met gestandaardiseerde gecombineerde pijnprotocollen, lange termijn follow-up en stapsgewijze introductie van moderne technologieën bij een TKP.

PhD Portfolio and Publications

Acknowledgments – Dankwoord

About the author

PhD Portfolio

Name PhD student:

Bas van Ooij

PhD period

April 2009 – August 2025

Names of PhD supervisor(s) & co-supervisor(s):

Dr. ir. Leendert Blankevoort (promotor)
Dr. Matthias Ulrich Schafroth (co-promotor)
Dr. Daniël Haverkamp (co-promotor)

General courses	Year	ECTS
- Pubmed and Reference Manager	2009	1
- Oral Presentation in English	2009	1
- Good Clinical Practice	2009	1
- Basic Course Legislation and Organization for Clinical Researchers	2009	1.5
- Scientific writing in English	2010	1.5
- Clinical Epidemiology	2010	1.5
- Practical Biostatistics	2010	1.5
- Good Clinical Practice, UK (NHS)	2018	1
Specific courses	**Year**	**ECTS**
- All required courses as part of the residency in Orthopedic Surgery. Including ATLS (+ refresher), AO Fracture management (+ advanced), hip and knee arthroplasty courses, knee and shoulder arthroscopy courses, several dissection courses and three national exams.	2011 - 2017	10
- All required courses as part of the residency in Occupational Health. Including a Critical Appraised Topic, training in legislation, conversation skills, lifestyle medicine, workplace conflicts, broad medical training and regular exams.	2019 - 2022	10
- Yearly education in maritime medicine.	2023 - 2025	2
Presentations	**Year**	**ECTS**
- "Knowledge acquisition of orthopaedic residents in total knee replacement: a preliminary study using the Audience Response System". Nordic Orthopaedic Federation Congress, Aarhus, Denmark	2010	0.5
- "The effect of per-and postoperative pain treatment on functional outcome after total knee arthroplasty. A prospective, randomised trial". Dutch Orthopaedic Society, Spring Meeting, Utrecht	2011	0.5

- "What Is The Role Of Cementing On Survival Of A Total Knee Arthroplasty? A Blinded Randomized RSA Trial." 18th EFORT Congress, Vienna, Austria	2017	0.5
- "What Is The Role Of Cementing On Survival Of A Total Knee Arthroplasty? The 2 years results of a randomized controlled trial." 18th ESSKA Congress, Glasgow, UK	2018	0.5
- "Does Cementing Have An Influence On The Long-Term Survival Of Low Contact Stress Mobile Bearing Total Knee Arthroplasty? A 15-33-Year Survival Analysis Of 3 Different LCS Designs." 20th EFORT Congress, Lisbon, Portugal	2019	0.5
(Inter)national conferences	**Year**	**ECTS**
- Dutch Orthopedic Society (NOV) congresses, yearly	2008 - 2017	5
- Nordic Orthopaedic Federation Congress, Aarhus, Denmark	2010	1
- International Trauma symposium of the Royal Edinburgh Hospital, with Ride for Research	2016	1
- 18th EFORT Congress, Vienna, Austria	2017	1
- Bristol Hip Meeting, UK	2017 - 2018	2
- 18th ESSKA Congress, Glasgow, UK	2018	1
- 13th Congress of the European Hip Society The Hague, Netherlands	2018	1
- 20th EFORT Congress, Lisbon, Portugal	2019	1
- Dutch Association for Occupational Medicine (NVAB), yearly	2020 - 2025	4
Other	**Year**	**ECTS**
- Weekly journal clubs (Amsterdam UMC/ORCA)	2009 - 2011	2
- Organizer of the national knee arthroplasty residents course	2009 - 2010	2
- Amsterdam Foot and Ankle Course support, Prof. Dr. C.N. van Dijk	2009 - 2011	2
- Skate for Science, Kuopio, Finland	2015	1
- Organizer ESSKA Cycle for Science Amsterdam-Barcelona, in collaboration with Prof. C.N. van Dijk	2016	1
- Member of the guideline "Ganglion of the wrist" for the Dutch Society for Surgery, on behalf of the Dutch Association for Occupational Medicine (NVAB)	2022 - 2023	2
- Expert group member of the Hand and Wrist cluster for "Kennisinstituut", on behalf of the Dutch Association for Occupational Medicine (NVAB)	2023 - present	1

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Acknowledgments - Dankwoord

Ik ben dit wetenschappelijke avontuur natuurlijk niet alleen aangegaan. Ik ben alle mensen om me heen die me hebben geholpen de hobbels te overwinnen die ik onderweg tegenkwam enorm dankbaar. Wetenschappelijk onderzoek is tenslotte altijd een teamprestatie. De volgende mensen wil ik hierbij graag in het bijzonder in het zonnetje zetten.

Dr. ir. L. Blankevoort, beste Leendert. Jij nam het stokje over van prof. van Dijk toen we zochten naar een oplossing om dit proefschrift tot een goed einde te brengen. Ik ben je ontzettend dankbaar voor de kans die je me hebt gegeven. Dankzij jouw begeleiding en inzet heb ik de kwaliteit van mijn proefschrift kunnen verbeteren. Geniet van je welverdiende pensioen!

Dr. D. Haverkamp, beste Daniël. Jij zag de kans om de basis die ik als onderzoeker in het AMC had gelegd verder uit te breiden met twee mooie onderzoeken in het Slotervaart Ziekenhuis. Vooral het samenwerken in de Locker-trial was een feestje. Heel erg bedankt dat je dat mogelijk hebt gemaakt. Daarnaast was jij een belangrijke motivator om later alles toch in één "boekje" te bundelen; dat zal ik nooit vergeten. Ik heb altijd veel respect gehad voor hoe je je werk als hardwerkende clinicus weet te combineren met wetenschappelijk onderzoek.

Dr. M.U. Schafroth, beste Matthias. Onder jouw hoede mocht ik mijn eerste wetenschappelijke stappen zetten. Het was mooi om jouw klinische blik steeds terug te zien in de plannen voor nieuwe projecten. De plannen die we in eerste instantie hadden liepen anders dan gedacht. Zo gaat dat nu eenmaal in de academie en samen vonden we passende oplossingen. Wat was het vervolgens leuk om dat bijzondere koelingsapparaat los te laten op de orthopedieafdeling. Dank voor het helpen bij het leggen van deze wetenschappelijke basis én voor de mooie samenwerking tijdens mijn opleiding.

Prof. dr. C.N. van Dijk, beste Niek. Ik kreeg van jou de kans om een onderzoeksplek te bemachtigen binnen de zeer gewaardeerde ORCA. Dit heeft mij, niet alleen op wetenschappelijk vlak, enorm veel gebracht. Ik ben je erg dankbaar voor deze kans. Dank ook voor de fijne samenwerking tijdens zowel mijn onderzoek als mijn opleiding. Het was mooi geweest als ik alles met jou als promotor had kunnen afronden maar gelukkig betekent uitstel in dit geval geen afstel.

Drs. I.N. Sierevelt, beste Inger. Zonder jouw expertise op het gebied van statistiek was het allemaal niet zover gekomen. Mixed model-analyses, ANOVA's, Bonferroni-correcties - mijn hoofd duizelt er nog steeds van. Je vond altijd dat ik wel talent had voor SPSS, maar ik ben jou vooral erg dankbaar voor al je ondersteuning bij de gepubliceerde onderzoeken. Ik had het niet zonder jou kunnen doen.

Dr. J.T. Wegener, beste Jessica. Hartelijk dank dat ik direct met jou mocht samenwerken toen ik begon als onderzoeker. Klinisch onderzoek blijft het leukst, zeker als je dat samen kunt doen. Mijn "opmerkelijke" enthousiasme en interesse in de anesthesiologie waren oprecht!

Leden van de promotiecommissie, prof. dr. N. van der Velde, prof. dr. J.A.M. Bramer, prof. dr. P.A. Nolte, prof. dr. M.A.H. Steegers, dr. P.P.F.M. Kuijer en prof. dr. M. Maas. Hartelijk dank voor het kritisch beoordelen en goedkeuren van mijn manuscript. Ik kijk ernaar uit om op 16 december met jullie van gedachten te wisselen.

Oud opleiders orthopedie/vooropleiding chirurgie: prof. dr. G.M.M.J. Kerkhoffs, prof. dr. C.N. van Dijk, dr. H.M. van der Vis, prof. dr. D. Eygendaal en prof. dr. L. van der Laan. Beste Gino, Niek, Harm, Denise en Lijckle. Hartelijk dank voor jullie prettige begeleiding en samenwerking tijdens mijn opleiding tot orthopedisch chirurg. We hebben met veel humor vooral ook veel plezier gehad! Zoals een van jullie enkele jaren geleden zei: "wij hebben je ook wel meer meegegeven dan alleen operatie-skills". Dat klopt helemaal en daar ben ik jullie (en alle collega's van de vakgroepen in het Amphia Ziekenhuis, het Slotervaart Ziekenhuis en het AMC) dankbaar voor.

Alle oud-collega's van de ORCA/afdeling G4: Christiaan, Peter, Sjoerd, Maayke, Gabriëlle, Mikel, Laurens (jazeker dr. Kaas, ik draai nog steeds "liftmuziek" tijdens het werken), Geert, Aimee en Jan Joost. Dank jullie wel voor het samenwerken en inspireren in alles wat met de wetenschap te maken heeft. Arthur Kievit, ik wil jou specifiek bedanken voor je inspiratie. Je was mijn opvolger en promoveerde niet zo lang geleden; blijven doorzetten werpt zo zijn vruchten af! Ook dank aan alle oud-collega's in het Slotervaart Ziekenhuis die hebben meegeholpen met de patiënteninclusie van de Locker-trial. Tim en Sjaak; ik weet dat jullie het niet alleen voor de fles wijn deden!

Praktijkopleiders Anouk Kraft en Mark Droogers en instituutsopleider Inge van der Ende, allen bedrijfsartsen. Dankzij jullie begeleiding heb ik de kans gekregen om me te ontwikkelen in het nieuwe vakgebied van de bedrijfsgeneeskunde. Dank voor

jullie fijne begeleiding en samenwerking tijdens mijn “zij-instroom” opleiding tot bedrijfsarts.

Collega’s van VisieCare Arbo & HR. Dank jullie wel voor de samenwerking bij onze mooie arbodienst in de volle breedte van de bedrijfsgeneeskunde. Als nieuwe medeeigenaar ben ik extra trots op jullie en op het waardevolle werk dat wij samen verrichten. Karin, Thijs en inmiddels oud-collega Theo, ik wil jullie in het bijzonder bedanken voor de kans die ik heb gekregen om met jullie samen te werken en in VisieCare te stappen. Op naar veel mooie ontwikkelingen!

Paranimfen Ivo en Maurice. Wie had dat nog gedacht? Ik mocht jullie jaren geleden nog bijstaan als paranimf (bij Maurice zelfs nog in mijn studenten-rokkostuum). Ik beloofde dat ik jullie ook ooit zou vragen en ik ben blij dat de rollen nu zijn omgedraaid. Veel dank daarvoor!

Pa en moeders. Dank jullie wel voor jullie jarenlange oprechte interesse in dit promotietraject en voor jullie steun, op welk vlak dan ook. Het heeft even geduurd, maar “als je je best maar doet”, toch? De vrijdagen die jullie samen met Fien en Saar hebben doorgebracht waren enorm waardevol. Ik heb de tijd optimaal voor dit proefschrift kunnen benutten en zij hebben fantastische dagen bij jullie gehad. Ook veel dank aan de broers, Juud en Lena. Nu zijn we inclusief pa in totaal met vijf PhD’s, dat lijkt me wel genoeg, toch? Ik ben blij dat we het allemaal zo goed hebben. Pim en Lena, jullie in het bijzonder nog dank voor het brainstormen en de hulp bij het “native speaking”-Engels.

Last but not least, lieve Nik. Wat heb jij mij geduldig (ja, echt!) bijgestaan tijdens dit “project” in de afgelopen jaren. Voor jou was niets te veel: brainstormen, aanhoren, tabellen omtoveren, dpi’s verhogen, meedenken, noem het maar op. Wat ben ik blij met jou aan mijn zijde, op alle fronten in mijn leven. Wat gaan we met onze meiden nog veel avonturen beleven. Heel veel dank voor alles en nu: op naar veel plezier in Indonesië en Australië!

About the author

Bas was born and raised in Maastricht, in the southern part of the Netherlands. He enjoyed a warm and happy childhood alongside his two brothers. In 2000, he moved to Rotterdam to study Medicine at Erasmus University Medical Center, where he graduated in 2007.

He began his clinical career in orthopedic surgery, working at the Medical Center Alkmaar and for a short period at the VU Medical Center in Amsterdam. In 2009, he was given the opportunity to further develop his scientific career at the Academic Medical Center Amsterdam (AMC, now AUMC) in collaboration with the Orthopedic Research Center Amsterdam (ORCA). This two-year research period, under the supervision of prof. dr. C.N. van Dijk and dr. M.U. Schafroth laid the foundation for the PhD trajectory that would follow in the years to come.

From 2011 to 2013, he completed his general surgical residency at Amphia Hospital in Breda. His orthopedic specialization took place from 2013 to 2017 at the AMC Amsterdam, the Amphia Hospital in Breda, and the now-closed Slotervaart Medical Center in Amsterdam. It was at this last institution that his academic work received a further boost, in collaboration with dr. D. Haverkamp. Later, after prof. dr. C.N. van Dijk retired, dr. ir. L. Blankevoort (previously his research director at ORCA) took over the supervision and guided this thesis to completion.

After completing his formal residency in orthopedic surgery, he participated in two fellowships, focusing primarily on hip and knee surgery, first at Southmead Hospital in Bristol (UK) and then at St. Antonius Hospital in Utrecht. In mid-2019, he made the deliberate decision to transition to occupational medicine. After a satisfying period at occupational health service Cohesie and successfully completing his residency in occupational medicine, he started working independently in September 2023 and began a collaboration with VisieCare Arbo & HR. In this role, he can practice occupational medicine as he intended: with great satisfaction, variety, and professional challenges.

Outside of work, he leads an active social and sportive life. He currently lives in Haarlem with his partner Nicky and their two lively young daughters Fien and Saar.

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