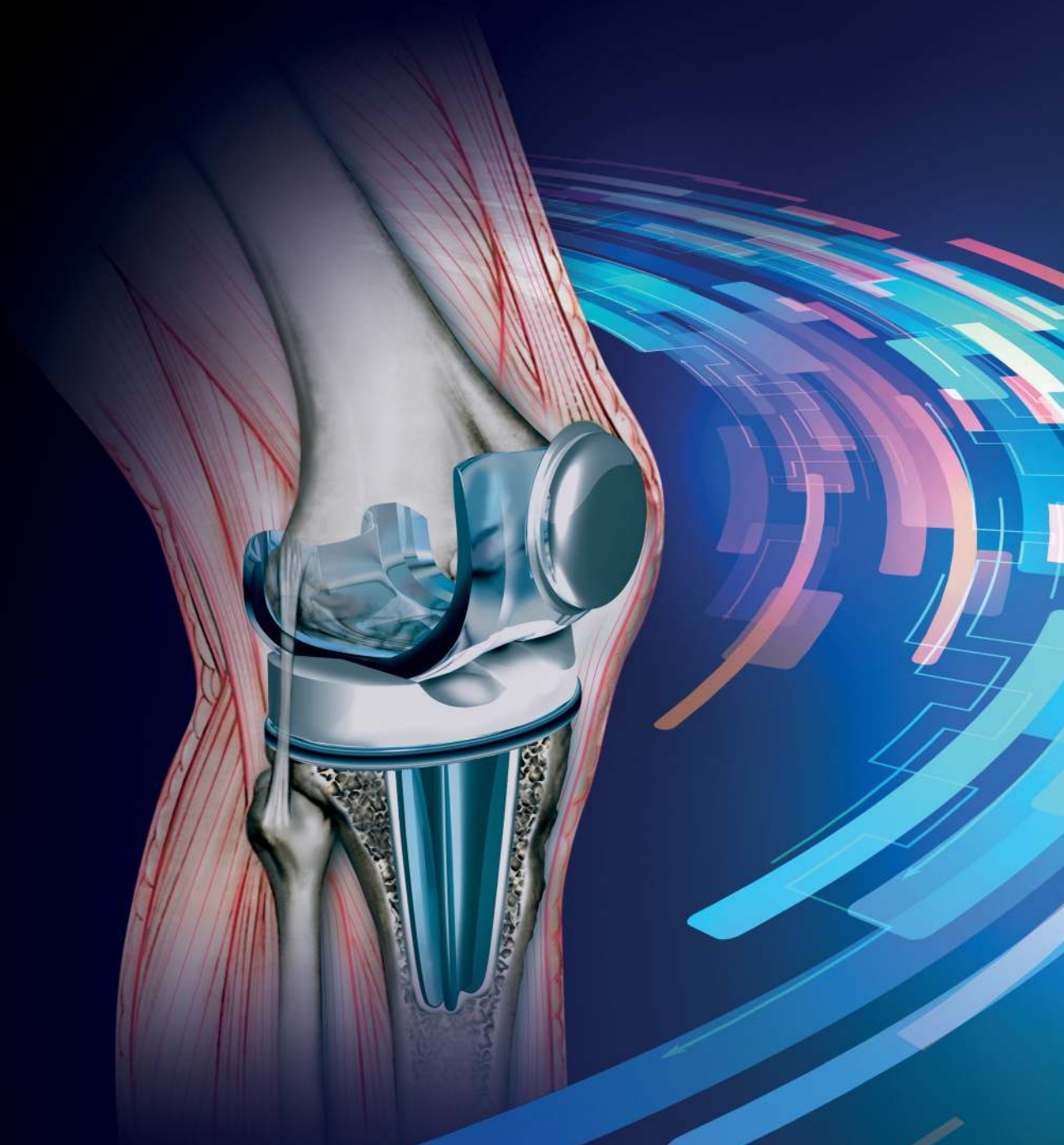
OPTIMIZING FAST-TRACK PROTOCOLS FOR PRIMARY TOTAL KNEE ARTHROPLASTY

Jeroen Cornelis van Egmond



Optimizing Fast-Track Protocols for Primary Total Knee Arthroplasty

Jeroen Cornelis van Egmond

Colofon

Optimizing fast-track protocols for primary total knee arthroplasty

The work described in this thesis was performed at the Department of Orthopaedics, Reinier de Graaf, Delft, the Netherlands and the Department of Orthopaedics, Reinier Haga Orthopedisch Centrum, Zoetermeer, the Netherlands.

Cover design: Jeroen van Egmond en Olof Borgwit (Optima Grafische Communicatie, Rotterdam)

Lay-out and printing: Optima Grafische Communicatie, www.ogc.nl, Rotterdam, the Netherlands

ISBN: 978-94-6361-726-0

Printing of this thesis was financially supported by (in no particular order): ChipSoft, Centrum Orthopedie Rotterdam, Stichting Research Orthopedie Delft, Wetenschapsraad Reinier de Graaf Stichting, Anna Fonds|NOREF, afdeling Orthopedie & Sportgeneeskunde Erasmus Medisch Centrum, Bauerfeind, Nederlandse Orthopaedische Vereniging (NOV) en Link Lima Nederland.

Optimizing Fast-Track Protocols for Primary Total Knee Arthroplasty

Optimalisatie van fast-track protocollen voor
primaire totale knieprothesiologie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. A.L. Bredenoord
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
dinsdag 18 oktober 2022 om 15:30 uur

door

Jeroen Cornelis van Egmond
geboren te Bergschenhoek

Erasmus University Rotterdam

Erasmus

PROMOTIECOMMISSIE

Promotor:	Prof.dr. J.A.N. Verhaar
Overige leden:	Prof.dr. S.M.A. Bierma-Zeinstra Prof.dr. R.J. Stolker Prof.dr. T.P.M. Vliet Vlieland
Copromotor:	Dr. N.M.C. Mathijssen

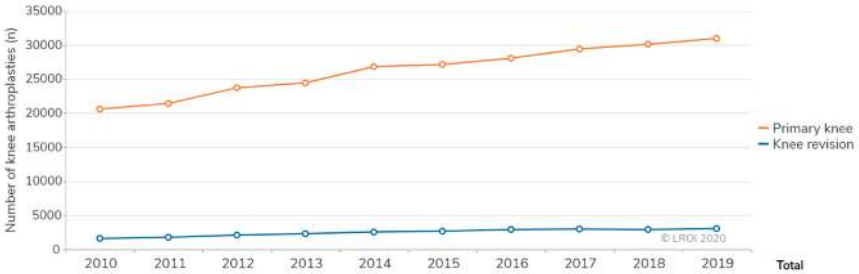
TABLE OF CONTENTS

Chapter 1

General introduction

Primary Total Knee Arthroplasty (TKA) is a surgical procedure that is frequently performed worldwide.[1] If conservative treatment of knee osteoarthritis fails, TKA is a good option to alleviate pain and limitations.[2-4]

During the last decade, the number of TKAs performed in the Netherlands increased from 20.610 in 2010 to 30.968 in 2019.[5] (Figure 1) Given the aging population of the Netherlands and the age-related incidence of osteoarthritis of the knee, a further increase of TKA is to be expected during the following decades.[3,6-8] This increased surgical load necessitates good performance of the prosthesis as well as a good perioperative care system.



Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total
Type of procedure (n)											
Primary knee	20,610	21,430	23,731	24,454	26,841	27,143	28,077	29,427	30,123	30,968	**262,804**
Knee revision	1,624	1,794	2,116	2,310	2,557	2,685	2,926	2,997	2,931	3,069	**25,009**
Total:	**22,234**	**23,224**	**25,847**	**26,764**	**29,398**	**29,828**	**31,003**	**32,424**	**33,054**	**34,037**	**287,813**

Figure 1. *Numbers of primary knee arthroplasties and knee revision arthroplasties registered in the Netherlands the period 2010-2019 (LROI annual report 2020)*

Since the introduction of TKA, both the implant and the surgical technique have continuously been improved. Overall, the percentage of patients in whose implant is removed and received a new TKA implant is limited. Ten years after the implantation of TKA, the revision rate is approximately 4 to 6%.[9,10] The revision rate further increases after these 10 years.[11] The main risk factors for revision are a first implantation at a young age, male gender, and postoperative infection.[12-16] Moreover, pain relief of TKA is not as effective as pain relief of Total Hip Arthroplasty (THA).[17]

The relatively low percentage of revisions is not a reliable indicator for the outcome of the procedure, because the decision to perform a re-operation is often made by the surgeon and the patient. Despite the low revision rates, 7 to 20% of the results of TKA are moderate or poor.[18-22] The dissatisfaction rate is up to 20%, and in younger patients 1 in 3 patients is not happy with their knee implant.[23,24] To further improve the performance of and satisfaction with TKA, many new implantation techniques have been developed. However, techniques such as computer-assisted surgery, patient-specific guides, and alternative alignment techniques have not led to significant improvement compared to the standard implantation technique.[25]

On the other hand, recovery after TKA has been greatly enhanced during the last decades.[26] This is mainly due to the fact that the perioperative treatment has been changed by the introduction of fast-track protocols.[27,28] Fast-track protocols can be defined as a perioperative approach aiming to reduce surgical stress, providing effective (opioid sparing) pain treatment, and early mobilisation in order to accelerate postoperative recovery, which results in a short length of stay in the hospital.[29-31] Further improvement of the outcome after TKA can be achieved by improving perioperative care, for instance with enhanced recovery programs.[12]

The beginning of fast-track

As early as 1997, Kehlet already recognized and described rehabilitation problems after major surgery, such as pain, thromboembolic complications, nausea, fatigue, and prolonged convalescence.[32] He introduced multimodal interventions to optimize postoperative rehabilitation. (Figure 2) A further change in care was made when Kehlet identified characteristics of fast-track surgery programs in 2002.[33]

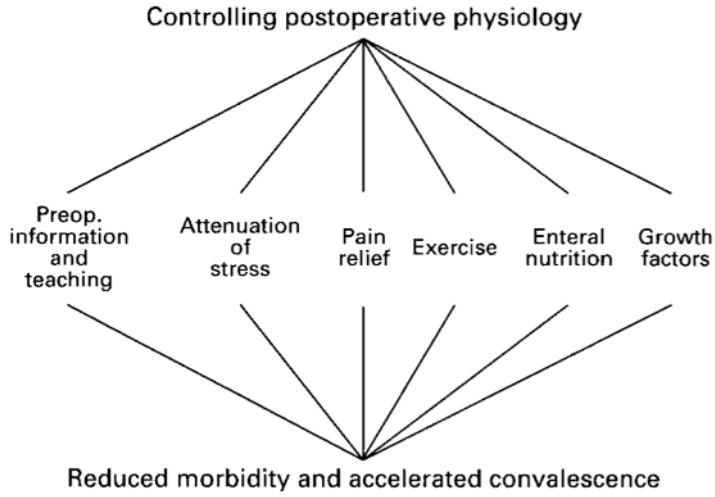


Figure 2. *Multimodal interventions (Kehlet 1997)*

The fast-track recovery concept is based on questions, “Can the operation be done as an outpatient procedure?” and if not, “Why is the patient in the hospital?”, subsequently focusing on the individual factors that delay early recovery.[34] Moreover, the fast-track concept is based on “first better, then faster”.[34] During the last decade, fast-track protocols have been introduced globally for various kinds of surgical procedures in orthopaedics and other specialties.[35]

Fast-track - a change in care of TKA

Historically, patients were hospitalized for several weeks after arthroplasty, which mainly consisted of bed rest.[36] This radically changed after the introduction of fast-track protocols. The experiences of Kehlet in Denmark lead to a clear recommendation to introduce fast-track protocols in orthopaedics.

The introduction of fast-track protocols in hospitals requires changes in care of various involved care specialists and therefore the implementation of fast-track protocols is a gradual process.[37] To enable early mobilization, which is preferably started on the day of surgery, several changes need to be made in the usual care.[38] 'Old traditions' such as using urine catheters and wound drains need to be eliminated because they limit ambulation.[39] General anaesthesia needs to be replaced by spinal anaesthesia.[40] To further reduce pain and enabling ambulation, local infiltration anaesthesia and opioid-sparing pain medication should be used. To reduce the length of hospital stay, the fulfilment of discharge criteria needs to be checked twice a day. Preoperative patient education needs to be provided, in particular during the start of the implementation of fast-track, patients and medical staff need to be well informed. In order to feel confident that an early hospital discharge is safe, a mental change is necessary for both the patients as well as the involved care specialists.

Advantages of fast-track

Fast-track protocols reduce the length of hospital stay after TKA to only a few days. In selected cases, it is even possible to perform primary THA, shoulder arthroplasty, and TKA in outpatient setting.[41,42] Recent studies even measured the length of hospital stay in hours instead of in weeks, emphasizing the significantly reduced hospital stay.[43]

Besides the reduced length of stay, fast-track protocols also leads to lower complication rates, including fewer thromboembolic complications[44] and reduced mobilization under anaesthesia for stiffness of the knee.[45] Additionally, fast-track patients reported significantly lower pain scores and better functional outcome during the first week and better quality of life during the first three postoperative months than non-fast-track patients.[46,47]

Importantly, however, the implementation of fast-track protocols did not result in more readmissions.[48,49] Some studies even described a reduction of mortality rates.[50,51] Moreover, a lower risk of postoperative delirium was found in elderly patients with fast-track TKA and THA.[52,53] This indicates that fast-track protocols are safe, even for the elderly patients, who constitute a notable proportion of the orthopaedic patient population.[54,55]

Since patients mobilize on the day of surgery, the need for deep venous thrombosis prophylaxis is debated.[56] Low incidence of deep vein thrombosis and pulmonary embolism have been described after fast-track THA and TKA.[57] Several studies have demon-

strated that early mobilisation led to a reduction of the duration of low molecular weight heparin (LMWH) prophylaxis.[44,58] Consequently, guidelines have been changed from six weeks prophylaxis to two or four weeks.[59]

A short hospital stay is beneficial for patients since hospital stay has been related to medication errors and sleep disturbances, both of which can prolong rehabilitation.[60] Moreover, sleep deprivation can induce hyperalgesia.[61]

Finally, shorter hospital stay reduce hospital costs.[62-64] In a recently published Spanish article, a cost reduction of 1266 euro was found in total knee replacement.[65] Although health care and reimbursement are organized differently in the Netherlands, a recent Dutch trial found a reduction of costs as well.[66]

Interdisciplinary implications of fast-track

Since fast-track protocols are multimodal treatment protocols, their implementation requires adjustments in the treatment of various specialties related to orthopaedic care. Some of these specialties are described below.

Anaesthesia

Early mobilization requires changes in anaesthesia protocols.[67] In fast-track care, spinal anaesthesia is preferred over general anaesthesia because spinal anaesthesia is associated with less early postoperative pain, nausea, vomiting, and morphine consumption.[68] To further optimize anaesthesia in fast-track protocols, the dosage of spinal anaesthesia needs to be optimized since high doses of spinal anaesthesia render patients unable to mobilize for several hours after TKA. Additionally, opioid-sparing pain treatment is introduced since mobilization is hampered by the adverse effects of opioid medication, such as nausea, vomiting, sedation, and confusion.[69,70]

The policy of prolonged preoperative fasting is a remnant of the era of general anaesthesia, as it was initially introduced to prevent pulmonary aspiration of gastric contents during general anaesthesia. Until today, a minimum of six hours preoperative fasting period is still prescribed, despite the negative effects of fasting. Bilku et al. described that recovery may be delayed by a catabolic state and that these symptoms could be reduced by the administration of preoperative carbohydrate drinks.[71] It is assumed that reducing the fasting period will reduce orthostatic hypotension and intolerance and thereby improve postoperative mobilization and recovery.

Physical therapy

To enhance early mobilization, the patients should be visited by a physical therapist shortly after surgery.[72] Furthermore, reduced length of hospital stay requires changes in physical therapy provided by physical therapists outside the hospital, since they are now responsible for almost the entire rehabilitation of patients who only remain in hos-

pital for one or two days. Therefore, an evidence-based treatment protocol is needed to inform and guide physical therapists working outside the hospital.[73,74] Further studies are warranted to improve physical therapy rehabilitation.[75,76] The main questions are when to start and stop, who needs physical therapy, what the duration of the sessions should be, and what the sessions should consist of. Recently, the Dutch PaTIO study started to investigate the outcomes of a standardized physical therapy protocol with the current care.[77]

Nursing

Fast-track protocols also require motivated and skilled nurses.[78] Mobilization, patient education, and optimal pain treatment depend on the nurses, who at the same time have to deal with a high turnover of patients.

Optimizing fast-track TKA protocols

To further optimize fast-track protocols, it is important to understand which factors are associated with prolonged hospital stay. In a recent retrospective study, a prolonged hospital stay after TKA was associated with female gender, older age, high American Society of Anaesthesiologists (ASA) score, living alone, general anaesthesia, and the presence of neurological comorbidity.[79] Husted et al. identified three types of reasons for prolonged hospital stay: early organ dysfunction, the appearance of complications, and organizational factors.[69] The main complaints of early organ dysfunction are nausea, vomiting, fatigue, weakness, and dizziness. Further studies are needed to reduce these symptoms.

Porsius et al. investigated which patient factors are related to less satisfaction and to negative postoperative results after THA.[80] They found that rehabilitation after arthroplasty is not “one size fits all” and identified distinct recovery trajectories after THA. Subsequently, the recovery trajectories were associated with various satisfaction rates. Finally, these trajectories were associated with specific patient characteristics including age and gender. The authors concluded that care pathways (recovery) for THA should be further tailored to the needs of specific subgroups. Their study was repeated on a larger scale with national register data of THA, which resulted in a comparable outcome.[81] Recently a single institutional trial confirmed distinct recovery trajectories in TKA patients.[82] However trajectories in TKA needs to be further investigated to further optimize and personalize fast-track protocols for TKA.

Outline of this thesis

The main aim of this thesis was to investigate how perioperative care for TKA patients can be further optimized. Therefore, the first aim was to obtain more detailed insight into patient experiences regarding rehabilitation in the first postoperative period. The

second aim was to identify recovery patterns after TKA, and the third aim was to identify possible improvements in current fast-track protocols.

This thesis is subdivided in three parts:

1. the early postoperative phase after primary TKA in a fast-track setting
2. recovery after fast-track TKA
3. possible adjustments in peri-operative care of fast-track TKA protocols

Part I – Opening the black box

Chapter 2 presents the outcomes of an observational cohort study, in which we held two focus group interviews with twenty patients who recently underwent THA or TKA. The goal was to qualitatively assess how patients experienced the short hospital stay and which problems they encountered during the early rehabilitation before the first outpatient visit.

Chapter 3 is a sequel to chapter 2 and describes the outcomes of a detailed quantitative analysis of patient experiences during the first six weeks after hospital discharge following fast-track primary TKA. Their experiences were examined by means of various questionnaires combined in a diary, which were completed by 30 patients during the first six weeks after hospital discharge following fast-track primary TKA.

Part II – Recovery after total knee arthroplasty

In **Chapter 4** we present a retrospective analysis of early functional outcome after fast-track TKA. We assumed that distinct functional recovery patterns already exist in the first months after primary TKA. Therefore, care pathways for TKA might need to be tailored to comply with the needs of specific subgroups. Patterns of functional improvement during the first three months after TKA were explored using patient-reported outcome measures (PROMs). Secondly, a non-responder analysis was performed and we determined patient characteristics of non-responders during early functional recovery.

Chapter 5 presents a retrospective analysis of TKA procedures performed nationwide using data from the Dutch national arthroplasty register (Landelijke Registratie Orthopedische Implantaten: LROI). Since not all patients are satisfied after TKA, we assumed that recovery trajectories might also differ in the long term. To determine the distinct rehabilitation patterns of different patient groups, we classified groups of patients according to their trajectories of functional recovery using Latent Class Growth Modelling (LCGM). Moreover, the predictors of class membership were identified using multivariable multinomial logistic regression analysis.

Part III – Optimizing fast-track protocols for total knee arthroplasty

In **Chapter 6** we present a prospective study that aimed to determine the optimal dose of intrathecal bupivacaine to enhance early mobilization. Since the current dosage of

bupivacaine results in sensory and motor impairments that persist for several hours postoperatively, this dosage postpones mobilization and hence impedes rehabilitation. This problem might be solved by lowering the dose of bupivacaine. The optimal dosage of intrathecal bupivacaine was determined by means of the Dixon and Massey allocation model.

Since the main reasons for prolonged hospital stay after TKA are postoperative nausea, vomiting, fatigue, orthostatic intolerance, and pain, rehabilitation might be improved by perioperatively administering corticosteroids, which have a positive effect on nausea, vomiting, and pain. In **Chapter 7** we present the outcomes of a systematic review regarding the perioperative use of corticosteroids in primary unilateral TKA. In this systematic review, we outline the effects of different corticosteroid dosages on postoperative nausea, vomiting, pain, and length of hospital stay.

The study in **Chapter 8** was based on the hypothesis that preoperative administration of a carbohydrate drink would decrease postoperative orthostatic hypotension and intolerance and thus improve early postoperative mobilization. In this randomized controlled trial, patients were randomized into two groups, a control group of patients who observed currently prescribed fasting periods (6 hours for food and 2 hours for clear liquids) and an intervention group of patients who received a carbohydrate drink 2-3 hours before surgery. Blood pressure and orthostatic intolerance were measured during first-time postoperative mobilization. Moreover, we compared data on nausea, vomiting, and length of hospital stay between both groups.

REFERENCES

1. Kurtz SM, Ong KL, Lau E, Widmer M, Maravic M, Gomez-Barrena E, et al. International survey of primary and revision total knee replacement. International orthopaedics. 2011;35(12):1783-9.
2. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, et al. A Randomized, Controlled Trial of Total Knee Replacement. The New England journal of medicine. 2015;373(17):1597-606.
3. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, et al. Knee replacement. Lancet. 2012;379(9823):1331-40.
4. Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. JAMA. 2021;325(6):568-78.
5. Dutch Arthroplasty Register (in Dutch: LROI). Online LROI annual report 2020 Available from: https://www.lroi-report.nl/app/uploads/2021/03/PDF-LROI-annual-report-2020.pdf.
6. Kurtz SM, Lau E, Ong K, Zhao K, Kelly M, Bozic KJ. Future young patient demand for primary and revision joint replacement: national projections from 2010 to 2030. Clinical orthopaedics and related research. 2009;467(10):2606-12.
7. Otten R, van Roermund PM, Picavet SJ. Trends in aantallen knie- en heupartroplastieken. Ned Tijdschrift Geneeskd. 2010;154(A1534):1-7.
8. Singh JA. Epidemiology of knee and hip arthroplasty: a systematic review. Open Orthop J. 2011;5:80-5.
9. National Joint Registry. 14th annual report 2017. National Joint Registry for England, Wales, Northern Ireland and the Isle of Man: surgical data to 31 December 2016. 2017.
10. Robertsson O, Sundberg M, Lidgren L, W-Dahl A. Annual report 2016—The Swedish Knee Arthroplasty Register. 2016.
11. Evans JT, Walker RW, Evans JP, Blom AW, Sayers A, Whitehouse MR. How long does a knee replacement last? A systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up. Lancet. 2019;393(10172):655-63.
12. Price AJ, Alvand A, Troelsen A, Katz JN, Hooper G, Gray A, et al. Knee replacement. Lancet. 2018;392(10158):1672-82.
13. Jasper LL, Jones CA, Mollins J, Pohar SL, Beaupre LA. Risk factors for revision of total knee arthroplasty: a scoping review. BMC Musculoskelet Disord. 2016;17:182.
14. Bottle A, Parikh S, Aylin P, Loeffler M. Risk factors for early revision after total hip and knee arthroplasty: National observational study from a surgeon and population perspective. PLoS One. 2019;14(4):e0214855.
15. Dy CJ, Marx RG, Bozic KJ, Pan TJ, Padgett DE, Lyman S. Risk factors for revision within 10 years of total knee arthroplasty. Clinical orthopaedics and related research. 2014;472(4):1198-207.
16. Judge A, Arden NK, Cooper C, Kassim Javaid M, Carr AJ, Field RE, et al. Predictors of outcomes of total knee replacement surgery. Rheumatology (Oxford). 2012;51(10):1804-13.
17. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ open. 2012;2(1):e000435.
18. Baker PN, van der Meulen JH, Lewsey J, Gregg PJ, National Joint Registry for England and Wales. The role of pain and function in determining patient satisfaction after total knee replacement. Data from the National Joint Registry for England and Wales. J Bone Joint Surg Br. 2007;89(7):893-900.

19. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KD. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clinical orthopaedics and related research. 2010;468(1):57-63.
20. Dunbar MJ, Richardson G, Robertsson O. I can't get no satisfaction after my total knee replacement: rhymes and reasons. Bone Joint J. 2013;95-B(11 Suppl A):148-52.
21. Lange JK, Lee YY, Spiro SK, Haas SB. Satisfaction Rates and Quality of Life Changes Following Total Knee Arthroplasty in Age-Differentiated Cohorts. J Arthroplasty. 2018;33(5):1373-8.
22. Heath EL, Ackerman IN, Cashman K, Lorimer M, Graves SE, Harris IA. Patient-reported outcomes after hip and knee arthroplasty: results from a large national registry. Bone Jt Open. 2021;2(6):422-32.
23. Scott CE, Oliver WM, MacDonald D, Wade FA, Moran M, Breusch SJ. Predicting dissatisfaction following total knee arthroplasty in patients under 55 years of age. Bone Joint J. 2016;98-B(12):1625-34.
24. Parvizi J, Nunley RM, Berend KR, Lombardi AV, Jr., Ruh EL, Clohisy JC, et al. High level of residual symptoms in young patients after total knee arthroplasty. Clinical orthopaedics and related research. 2014;472(1):133-7.
25. Verhaar J. Patient satisfaction after total knee replacement-still a challenge. Acta orthopaedica. 2020;91(3):241-2.
26. Berg U, A WD, Rolfson O, Naucler E, Sundberg M, Nilsdotter A. Influence of fast-track programs on patient-reported outcomes in total hip and knee replacement (THR/TKR) at Swedish hospitals 2011-2015: an observational study including 51,169 THR and 8,393 TKR operations. Acta orthopaedica. 2020;91(3):306-12.
27. Hansen TB. Fast track in hip arthroplasty. EFORT open reviews. 2017;2(5):179-88.
28. Galbraith AS, McGloughlin E, Cashman J. Enhanced recovery protocols in total joint arthroplasty: a review of the literature and their implementation. Ir J Med Sci. 2018;187(1):97-109.
29. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, et al. What determines length of stay after total hip and knee arthroplasty? A nationwide study in Denmark. Archives of orthopaedic and trauma surgery. 2010;130(2):263-8.
30. Husted H, Jensen CM, Solgaard S, Kehlet H. Reduced length of stay following hip and knee arthroplasty in Denmark 2000-2009: from research to implementation. Archives of orthopaedic and trauma surgery. 2012;132(1):101-4.
31. Husted H, Solgaard S, Hansen TB, Soballe K, Kehlet H. Care principles at four fast-track arthroplasty departments in Denmark. Danish medical bulletin. 2010;57(7):A4166.
32. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. British journal of anaesthesia. 1997;78(5):606-17.
33. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002;183(6):630-41.
34. Kehlet H. History and future challenges in fast-track hip and knee arthroplasty. Orthopade. 2020;49(4):290-2.
35. Ansari D, Gianotti L, Schroder J, Andersson R. Fast-track surgery: procedure-specific aspects and future direction. Langenbeck's archives of surgery. 2013;398(1):29-37.
36. Moiniche S, Hansen BL, Christensen SE, Dahl JB, Kehlet H. Patients' activity and length of stay after hip arthroplasty with balanced analgesia and early mobilization. Ugeskr Laeger. 1992;154(21):1495-9.
37. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. JAMA Surg. 2017;152(3):292-8.

38. Kehlet H, Thienpont E. Fast-track knee arthroplasty -- status and future challenges. The Knee. 2013;20 Suppl 1:S29-33.
39. Husted H, Gromov K, Malchau H, Freiberg A, Gebuhr P, Troelsen A. Traditions and myths in hip and knee arthroplasty. Acta orthopaedica. 2014;85(6):548-55.
40. Memtsoudis SG, Cozowicz C, Bekeris J, Bekere D, Liu J, Soffin EM, et al. Anaesthetic care of patients undergoing primary hip and knee arthroplasty: consensus recommendations from the International Consensus on Anaesthesia-Related Outcomes after Surgery group (ICAROS) based on a systematic review and meta-analysis. British journal of anaesthesia. 2019;123(3):269-87.
41. Hartog YM, Mathijssen NM, Vehmeijer SB. Total hip arthroplasty in an outpatient setting in 27 selected patients. Acta orthopaedica. 2015;86(6):667-70.
42. van Kampen DA, de Vries LMA, Hillen RJ, La Guardia P, van Beek R. Prospective cohort study of outpatient shoulder arthroplasty. Nederlands Tijdschrift voor Orthopedie. 2020;27(3):50-4.
43. McCulloch R, Cottingham P, Chrismas B, Pearce O. Is It Time We Changed How We Measure Length of Stay for Hip and Knee Arthroplasty? J Am Acad Orthop Surg Glob Res Rev. 2017;1(6):e032.
44. Husted H, Otte KS, Kristensen BB, Orsnes T, Wong C, Kehlet H. Low risk of thromboembolic complications after fast-track hip and knee arthroplasty. Acta orthopaedica. 2010;81(5):599-605.
45. Husted H, Jorgensen CC, Gromov K, Troelsen A. Low manipulation prevalence following fast-track total knee arthroplasty. Acta orthopaedica. 2015;86(1):86-91.
46. Larsen K, Sorensen OG, Hansen TB, Thomsen PB, Soballe K. Accelerated perioperative care and rehabilitation intervention for hip and knee replacement is effective: a randomized clinical trial involving 87 patients with 3 months of follow-up. Acta orthopaedica. 2008;79(2):149-59.
47. Fransen BL, Hoozemans MJM, Argelo KDS, Keijser LCM, Burger BJ. Fast-track total knee arthroplasty improved clinical and functional outcome in the first 7 days after surgery: a randomized controlled pilot study with 5-year follow-up. Archives of orthopaedic and trauma surgery. 2018;138(9):1305-16.
48. Dowsey MM, Kilgour ML, Santamaria NM, Choong PF. Clinical pathways in hip and knee arthroplasty: a prospective randomised controlled study. The Medical journal of Australia. 1999;170(2):59-62.
49. Zhu S, Qian W, Jiang C, Ye C, Chen X. Enhanced recovery after surgery for hip and knee arthroplasty: a systematic review and meta-analysis. Postgrad Med J. 2017;93(1106):736-42.
50. Malviya A, Martin K, Harper I, Muller SD, Emmerson KP, Partington PF, et al. Enhanced recovery program for hip and knee replacement reduces death rate. Acta Orthop. 2011;82(5):577-81.
51. Berg U, A WD, Nilsdotter A, Naucler E, Sundberg M, Rolfson O. Fast-Track Programs in Total Hip and Knee Replacement at Swedish Hospitals-Influence on 2-Year Risk of Revision and Mortality. J Clin Med. 2021;10(8).
52. Petersen PB, Jorgensen CC, Kehlet H, Lundbeck Foundation Centre for Fast-track H, Knee Replacement Collaborative G. Delirium after fast-track hip and knee arthroplasty - a cohort study of 6331 elderly patients. Acta Anaesthesiol Scand. 2017;61(7):767-72.
53. Krenk L, Rasmussen LS, Hansen TB, Bogo S, Soballe K, Kehlet H. Delirium after fast-track hip and knee arthroplasty. British journal of anaesthesia. 2012;108(4):607-11.
54. Jorgensen CC, Kehlet H. Role of patient characteristics for fast-track hip and knee arthroplasty. British journal of anaesthesia. 2013;110(6):972-80.
55. Petersen PB, Jorgensen CC, Kehlet H. Fast-track hip and knee arthroplasty in older adults-a prospective cohort of 1,427 procedures in patients ≥85 years. Age Ageing. 2020 Apr 27;49(3):425-431.
56. Jorgensen CC, Petersen PB, Reed M, Kehlet H. Recommendations on thromboprophylaxis in major joint arthroplasty - many guidelines, little consensus? J Thromb Haemost. 2019;17(2):250-3.

57. Jorgensen CC, Kehlet H. Early thromboembolic events ≤ 1week after fast-track total hip and knee arthroplasty. Thrombosis research. 2016;138:37-42.
58. Jorgensen CC, Jacobsen MK, Soeballe K, Hansen TB, Husted H, Kjaersgaard-Andersen P, et al. Thromboprophylaxis only during hospitalisation in fast-track hip and knee arthroplasty, a prospective cohort study. BMJ open. 2013;3(12):e003965.
59. Wainwright TW, Gill M, McDonald DA, Middleton RG, Reed M, Sahota O, et al. Consensus statement for perioperative care in total hip replacement and total knee replacement surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Acta orthopaedica. 2020;91(1):3-19.
60. Krenk L, Jennum P, Kehlet H. Sleep disturbances after fast-track hip and knee arthroplasty. British journal of anaesthesia. 2012;109(5):769-75.
61. Cremeans-Smith JK, Millington K, Sledjeski E, Greene K, Delahanty DL. Sleep disruptions mediate the relationship between early postoperative pain and later functioning following total knee replacement surgery. Journal of behavioral medicine. 2006;29(2):215-22.
62. Meyers SJ, Reuben JD, Cox DD, Watson M. Inpatient cost of primary total joint arthroplasty. J Arthroplasty. 1996;11(3):281-5.
63. Andreasen SE, Holm HB, Jorgensen M, Gromov K, Kjaersgaard-Andersen P, Husted H. Time-driven Activity-based Cost of Fast-Track Total Hip and Knee Arthroplasty. J Arthroplasty. 2017;32(6):1747-55.
64. Buttner M, Mayer AM, Buchler B, Betz U, Drees P, Susanne S. Economic analyses of fast-track total hip and knee arthroplasty: a systematic review. Eur J Orthop Surg Traumatol. 2020 Jan;30(1):67-74
65. Wilches C, Sulbaran JD, Fernandez JE, Gisbert JM, Bausili JM, Pelfort X. Fast-track recovery technique applied to primary total hip and knee replacement surgery. Analysis of costs and complications. Revista espanola de cirugia ortopedica y traumatologia. 2017;61(2):111-6.
66. Jansen JA, Kruidenier J, Spek B, Snoeker BAM. A cost-effectiveness analysis after implementation of a fast-track protocol for total knee arthroplasty. The Knee. 2020;27(2):451-8.
67. Turnbull ZA, Sastow D, Giambrone GP, Tedore T. Anesthesia for the patient undergoing total knee replacement: current status and future prospects. Local and regional anesthesia. 2017;10:1-7.
68. Harsten A, Kehlet H, Toksvig-Larsen S. Recovery after total intravenous general anaesthesia or spinal anaesthesia for total knee arthroplasty: a randomized trial. British journal of anaesthesia. 2013;111(3):391-9.
69. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta orthopaedica. 2011;82(6):679-84.
70. Beverly A, Kaye AD, Ljungqvist O, Urman RD. Essential Elements of Multimodal Analgesia in Enhanced Recovery After Surgery (ERAS) Guidelines. Anesthesiol Clin. 2017;35(2):e115-e43.
71. Bilku DK, Dennison AR, Hall TC, Metcalfe MS, Garcea G. Role of preoperative carbohydrate loading: a systematic review. Ann R Coll Surg Engl. 2014;96(1):15-22.
72. Sarpong NO, Lakra A, Jennings E, Cooper HJ, Shah RP, Geller JA. Same-Day Physical Therapy Following Total Knee Arthroplasty Leads to Improved Inpatient Physical Therapy Performance and Decreased Inpatient Opioid Consumption. J Arthroplasty. 2019 Dec;34(12):2931-2936
73. Pozzi F, Snyder-Mackler L, Zeni J. Physical exercise after knee arthroplasty: a systematic review of controlled trials. European journal of physical and rehabilitation medicine. 2013;49(6):877-92.
74. Peter WF, Nelissen RG, Vlieland TP. Guideline recommendations for post-acute postoperative physiotherapy in total hip and knee arthroplasty: are they used in daily clinical practice? Musculoskeletal care. 2014;12(3):125-31.

75. Falvey JR, Burke RE, Malone D, Ridgeway KJ, McManus BM, Stevens-Lapsley JE. Role of Physical Therapists in Reducing Hospital Readmissions: Optimizing Outcomes for Older Adults During Care Transitions From Hospital to Community. Physical therapy. 2016;96(8):1125-34.
76. Roos EM. Effectiveness and practice variation of rehabilitation after joint replacement. Curr Opin Rheumatol. 2003;15(2):160-2.
77. Groot L, Gademan MGJ, Peter WF, van den Hout WB, Verburg H, Vliet Vlieland TPM, et al. Rationale and design of the PaTIO study: PhysiotherApeutic Treat-to-target Intervention after Orthopaedic surgery. BMC Musculoskelet Disord. 2020;21(1):544.
78. Specht K, Kjaersgaard-Andersen P, Kehlet H, Pedersen BD. Nursing in fast-tack total hip and knee arthroplasty: A retrospective study. Int J Orthop Trauma Nurs. 2015;19(3):121-30.
79. Mathijssen NM, Verburg H, van Leeuwen CC, Molenaar TL, Hannink G. Factors influencing length of hospital stay after primary total knee arthroplasty in a fast-track setting. Knee surgery, sports traumatology, arthroscopy: official journal of the ESSKA. 2016;24(8):2692-6.
80. Porsius JT, Mathijssen NMC, Klapwijk-Van Heijningen LCM, Van Egmond JC, Melles M, Vehmeijer SBW. Early recovery trajectories after fast-track primary total hip arthroplasty: the role of patient characteristics. Acta Orthop. 2018:1-7.
81. Hesseling B, Mathijssen NMC, van Steenbergen LN, Melles M, Vehmeijer SBW, Porsius JT. Fast Starters, Slow Starters, and Late Dippers: Trajectories of Patient-Reported Outcomes After Total Hip Arthroplasty: Results from a Dutch Nationwide Database. J Bone Joint Surg Am. 2019;101(24):2175-86.
82. Harmelink KEM, Dandis R, der Van der Wees Pj PJ, Zeegers A, der Sanden MWN, Staal JB. Recovery trajectories over six weeks in patients selected for a high-intensity physiotherapy program after Total knee Arthroplasty: a latent class analysis. BMC Musculoskelet Disord. 2021;22(1):179.

Part I

Opening the black box

Chapter 2

Early follow-up after primary total knee and total hip arthroplasty with rapid recovery: Focus groups

J.C. van Egmond, MD[1]
H. Verburg, MD[1]
S.B.W. Vehmeijer, MD, PhD[1]
N.M.C. Mathijssen, PhD[1]

Acta Orthop Belg. 2015 Sep;81(3):447-53.

[1] Department of Orthopedic Surgery, Reinier de Graaf Groep, Delft, the Netherlands

ABSTRACT

Rapid recovery protocols reduce the length of hospital stay after Total Knee Arthroplasty (TKA) and Total Hip Arthroplasty (THA). However, little is known about the early post-operative phase. The purpose of this study was to examine which problems patients encountered during the first six weeks after primary TKA or THA surgery with rapid recovery.

We invited twenty patients for a focus group meeting which discussed various subjects regarding the first six weeks after hospital discharge. The focus group meetings were analyzed qualitatively.

Patients were mostly satisfied by the short length of hospital stay. Patients who lived alone needed more care and would like to stay longer in the hospital. After THA surgery all patients complained of inability to sleep. More patients experienced pain after TKA surgery compared to THA surgery. All patients had various experiences regarding physical therapy therefore an evidence-based rehabilitation protocol might be needed.

INTRODUCTION

Historically, the length of hospital stay after primary Total Hip Arthroplasty (THA) and primary Total Knee Arthroplasty (TKA) exceeded several weeks, which mainly consisted of a period of bed rest.[1] However, in the past decades, the length of hospital stay decreased and is currently reduced to only a few days.[2] This decrease can be explained by the introduction of rapid recovery protocols for elective primary THA and TKA.[2-10] Also, a decrease in complications was described[4,11] as well as an increase in quality of life after three months.[12] The number of readmissions did not increase after fast track TKA or THA.[5,13] Rapid recovery is safe for all patients including elderly patients.[14]

Rapid recovery protocols are based on analysis of clinical care principles and pain management in combination with revision of organizational factors, allowing an optimized perioperative period which is safe for the patient.[3,7,9]

Introduction of the rapid recovery protocol for primary THA and TKA at our institution was completed in February 2011. The introduction resulted in a reduced length of hospital stay after primary THA.[15] No increase of complications, readmissions, and reoperations was found.[15]

Although many papers discuss the results during the hospital stay, little is known about the early postoperative phase after hospital discharge. Patients might experience specific problems following hospital discharge after rapid recovery, in particular during the first weeks. Therefore, the early postoperative phase of six weeks after hospital discharge after primary TKA or THA surgery with rapid recovery was studied in focus group meetings. The results of this study might be used to optimize the early postoperative phase after rapid recovery.

PATIENTS AND METHODS

Study design

Twenty patients, who underwent THA or TKA surgery at our institution between July 2012 and February 2013, were invited to join a focus group meeting in April 2013. Two focus group meetings were organized, one with ten patients after THA surgery and one with ten patients after TKA surgery. Both groups were interviewed separately, since both groups of patients possibly encountered different problems.

We composed two representative patient groups from our clinical practice. To achieve that, we carefully selected patients based on home situation (single vs. living together), age, gender, and discharge destination (nursing home vs. home). These criteria were divers in order to collect all possible problems which patients could encounter during the first weeks after hospital discharge.

Before the start of the focus group meetings, permission was asked to audio record the discussion. All included patients gave their written informed consent.

The duration of both focus group meetings was 90 minutes. Two independent moderators ensured the focus group meeting progressed smoothly and all topics were covered. Both moderators were experienced with focus group meetings.

Questions

The focus group meetings started with a brief introduction of the moderators and the purpose of the session. Both focus groups had one topic: 'how do patients experience the first six weeks after hospital discharge after TKA or THA surgery with rapid recovery'. Several subtopics like pain, rehabilitation, physical therapy, functional devices, wound care, quality of life, and complications were addressed. Questions were asked in an interactive group setting in which participants were free to talk with other group members. The first question was an engagement question to introduce participants to the topic of the discussion and make them comfortable with this. Thereafter questions were posted to explore the experiences of patients. Finally, an exit question was posted in order to determine if something was missed during the discussion. Table 1 presents the focus group questions.

Engagement question:
• How did you experience the first six weeks after hospital discharge after THA or TKA surgery with rapid recovery?
Exploration questions:
• How did you cope with the pain during the first six weeks after hospital discharge? • Did you receive physical therapy? How often? What sort of treatment did you get? • How was your functional rehabilitation? (stair climbing, get out of bed) • Did you use functional devices the first six weeks? • Did you use medication? Which medication? How many? Did you received clear instructions when to use the medication? Did you notice improvement? • Did you have to deal with adverse events? • How was your general health during the first weeks after hospital discharge? • Did you use home care services? • How did you experience the attainability of the hospital? Did you receive enough information regarding the first weeks after hospital discharge?
Exit question:
• Do you have additional subjects you missed during this meeting regarding the first period after hospital discharge?

Table 1. *Questions during the focus group meeting*

Data analysis

Both focus group meetings were audio recorded and notes were made during the meeting. We analyzed the focus group meetings qualitative by describing and summarizing the reactions of patients on the various topics of the focus group. Since the group num-

bers were small a quantitative analysis was not valid. Answers during the focus group were not linked to a patient; therefore, no correlation was obtained between patient characteristics and answers. We used IBM SPSS Statistics for Windows (version 20.0 Armonk NY: IBM Corp), to describe patient characteristics.

RESULTS

One patient did not show up at the TKA focus group meeting, therefore, nine patients who underwent TKA surgery and ten patients who underwent THA surgery attended the focus group meetings. Patient characteristics are summarized in table 2.

	Total (n = 19)	TKA group (n = 9)	THA group (n = 10)
Age, years	69.9 (6.5)	68.2 (5.3)	71.4 (7.4)
Sex, female	12 (63.2%)	6 (66.7%)	6 (60.0%)
Hospital stay, days	3.4 (1.3)	3.3 (0.7)	3.5 (1.7)
Direction of discharge:			
– Home	17 (89.5%)	8 (88.9%)	9 (90.0%)
– TNH	2 (10.5%)	1 (11.1%)	1 (10.0%)
Home situation:			
– Single / widow	7 (36.8%)	4 (44.4%)	3 (30.0%)
– Together with partner	12 (63.2%)	5 (55.6%)	7 (70.0%)

Table 2. *Patient characteristics of the total study population and separately for TKA and THA focus group*
Abbreviations: TKA, Total Knee Arthroplasty; THA, Total Hip Arthroplasty; TNH, Temporary Nursing Home.
All values are presented as mean (standard deviation, SD), or as n (%).

Pain

The amount of experienced pain was highly variable between patients, despite all patients were provided with appropriate pain medication. It seemed more patients experienced pain after TKA surgery than after THA surgery. The need for rescue medication was limited to one TKA patient. Patients experienced most pain during the first weeks after hospital discharge and the pain diminished in time.

Physical therapy

Patients had different experiences regarding physical therapy. All patients received standardized physical therapy at our institution during their hospital stay. Patients learned to walk with crutches, to climb the stairs, and to make transfers before discharge. Moreover, patients started with muscle strength exercises during their hospital stay. At home patients continued their treatment with a local physical therapist. However, all physical therapists had different treatment strategies and some patients were doubtful regarding

the quality of their physical therapist. Several patients proposed to establish a list of local physical therapists specialized in rehabilitation after joint surgery.

Sleep

All patients who underwent THA surgery complained about their inability to sleep during the first weeks. The reason for their inability to sleep was mostly due to our instructions to sleep only supine or on the operated side during the first six weeks. Both positions were painful and interfered with sleep. In order to gain some sleep, several patients used sleep medication. Patients who underwent TKA surgery did not have any sleeping disturbances.

Wound

Most patients experienced no problems in the treatment of their own wound. Several patients received home care services. In these cases, the wound was treated by a trained nurse. Situations when patients needed to contact the orthopedic consultant for wound infection control were described in our hospital folder and patients were satisfied with that. One patient had doubts concerning his wound and therefore contacted the orthopedic consultant.

Home care services/nursing home

Several patients of both groups used home care services. Mostly, these patients were living alone. Patients, who lived with their partner or had their children living nearby, did not use home care services. Two single living patients choose to go to a temporary nursing home for the first period after hospital discharge.

Functional devices

Patients, in particular single living patients, complained about the use of crutches. Most patients preferred to use a rollator. This device made it possible to transport drinks, food or other objects and still have walking support. Patients numerated several other functional devices which were used during the rehabilitation period at home as special laces, reachers, and devices to put on socks.

Attainability of the hospital

All patients were satisfied regarding the attainability of the hospital. As stated before, patients had the opportunity to call an orthopedic consultant for questions regarding pain, wound care, etc. This was highly appreciated by all patients. Two focus group patients contacted the orthopedic consultant. One for severe pain and one for wound irritation.

Anticoagulation

Anticoagulation medication is prescribed for six weeks after TKA and THA surgery. Every day patients had to inject Fraxiparine into their subcutaneous abdominal fat. During their hospitalization patients learned to inject themselves. In case the patient received home care services, the injections were administered by trained nurses. Patients mentioned that although they got used to the injections, it still remained strange to do. A few patients would prefer oral medication instead of injections.

Complications

In two patients' persistent wound leakage after TKA surgery prolonged their hospital stay for two days. The two patients mentioned earlier, who contacted the orthopedic consultant, visited the outpatient clinic of the hospital during the first weeks.

Overall, patients were satisfied with the moment of discharge. Some patients would have liked to stay longer because of doubts managing themselves in their home situation. However, despite of their doubts these patients were discharged and experienced no problems during the first weeks.

Patients mentioned that after several weeks, one gets inventive which makes the situation better to handle. In particular the first days after discharge, patients described they did not know how to handle the situation.

Patients who had arthroplasty surgery before, mentioned to be better prepared for the second postoperative situation than during the first joint surgery. These patients knew better what to expect the first days after discharge, although, all patients mentioned the first surgery was not comparable to the second surgery.

Almost all patients who lived single stated that the first weeks after discharge were hard to deal with. The reason was the combination of pain, loneliness, and doubts of prosthesis outcome. Especially this patient group would like to have home care service or would like to go to a nursery home for a few weeks.

DISCUSSION

The aim of this present study was to examine which problems patients encountered during the early postoperative phase of six weeks after hospital discharge after primary TKA or THA with rapid recovery. To the best of our knowledge, this is the first study which examines the first weeks after hospital discharge with rapid recovery.

In general, all nineteen patients were satisfied with the hospital stay, attainability of the hospital and with the reduced length of hospital stay. This is in accordance with two studies by Husted et al, in which a high patient satisfaction after rapid recovery has been described.[6,7]

However, despite the high satisfaction rate, several points of improvement came forward during the focus group meetings. Patients who underwent THA surgery complained about their inability to sleep during the first weeks. All patients were instructed to sleep supine or on the operated side after THA surgery, which are in general not the most favorite positions to sleep in. Krenk et al. (2012) described sleep deprivation might delay the rehabilitation process and could lead to several problems including hyperalgesia.[16] Cremeans-Smith et al. (2006) described that sleep is an essential part of the healing process after TKA surgery.[17] Moreover, they suggest that interventions targeting sleep disruptions may improve the speed and quality of TKA recovery.[17] Therefore, we might adjust our instructions of sleep positions, in order to obtain more comfort for the patient and thereby optimize the rehabilitation. Fewer limitations of sleep positions should lead to better sleep.

Patients had various experiences regarding physical therapy. Physical therapists used different treatment strategies for rehabilitation after TKA and THA surgery. An evidence-based protocol for THA and TKA rehabilitation might be needed. This is in accordance with the results of the systematic review of Pozzi et al. (2013).[18] They described the lack of established standards for exercise treatment after TKA surgery. They concluded that strengthening and functional exercises are good treatment options after TKA surgery and should be performed under supervision of a trained physical therapist.[18] Di Monaco et al. (2013) concluded that there is insufficient evidence to build a detailed evidence-based exercise protocol after hip arthroplasty.[19] An evidence-based protocol is needed, although evidence to make such a protocol is apparently lacking.

Since not all physical therapists are experienced with rehabilitation after prosthesis surgery a referral system might also result in optimized rehabilitation. Schneider et al. (2009) concluded that good physiotherapy needs to be available for rapid recovery rehabilitation.[20] In their study only 12% of the THA and 50% of the TKA patients received physiotherapy at home. This is in contrast to the results of our study; all participating patients had a local physical therapist who visited the patient during the first weeks of their rehabilitation.

We suppose single living patients should be considered as a separate patient group. Apparently living alone makes the first period after hospital discharge more difficult. This group of patients more often needs home care services. Moreover, they would prefer to go to a nursing home for the first days after hospital discharge. Regarding the pain and doubts in patients living alone, extra care at a nursing home before discharge to home might be a good option for these patients. Forrest et al. (1999) described that patients who were older, live alone or have a high American Society of Anaesthesiologists (ASA) score were more likely to need admission to a rehabilitation unit after total joint replacement with rapid recovery.[21]

Patients experienced more often pain after TKA surgery compared to THA surgery, despite appropriate pain medication at the moment of hospital discharge. We were not able to obtain the exact course and intensity of pain during the early follow-up period. However, in these groups, most pain was clearly experienced during the first weeks after hospital discharge and diminished in time. This is also described by Chan et al. (2013) who performed a pain assessment two weeks after discharge after TKA surgery, concluding that effective pain relief after hospital discharge after TKA is a challenge.[22]

Overall, patients were satisfied with the moment of discharge. Some patients would have preferred to stay longer at the hospital because of doubts managing themselves in their home situation. However, no problems occurred during the first weeks, despite of their doubts. It appeared to be a manner of uncertainty which has been confirmed by the patients during the focus group meetings.

There are some limitations of this study, which need to be addressed.

First, we invited participants who were selected based on age, gender, and home situation to join the focus group meetings. We attempted to compose a representative group of patients from our clinical practice in order to find all encountered problems. We are aware of the fact this small number of patients could influence our conclusions and therefore we interpret our results with caution. However, this is a qualitative study and this small number of patients is consistent with qualitative research methods.[23]

Secondly, patients spoke anonymously during the focus group meeting. We were therefore not able to link answers to patient characteristics. Moreover, during simultaneous speaking it was not possible to count the number of reactions on the audio record. However, this was not the purpose of our study. Further studies need to be performed to link specific patient characteristics to the encountered problems.

Thirdly, no objective measurements were obtained during the focus group meeting. This was not possible due to patients who talked simultaneously. Moreover, the patient group was too small for statistical analysis. Still, as mentioned before, this is a qualitative study which has specific qualities and restrictions.

Finally, one surgeon was present at the focus group meeting. He did not interfere the discussion. We assumed patients were not influenced by the presence of their surgeon during the focus group meeting and were able to speak freely.

Patients were mostly satisfied by the rapid recovery protocol and the short length of hospital stay. Patients described difficulties during sleep after THA surgery. Several patients had doubts regarding physical therapy and an evidence-based protocol for THA and TKA rehabilitation might be needed. The use of a rollator is superior above crutches. Especially patients who lived alone needs more care and would like to stay longer in the hospital or would like to go to a nursery home for rehabilitation. Further studies regarding the first weeks after hospital discharge need to be performed.

ACKNOWLEDGEMENTS

The authors would like to thank all patients for their effort to join the focus group meeting.

REFERENCES

1. Berger RA, Sanders SA, Thill ES, Sporer SM, Della Valle C. Newer anesthesia and rehabilitation protocols enable outpatient hip replacement in selected patients. Clin Orthop Relat Res. 2009;467(6):1424-30.
2. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta Orthop. 2011;82(6):679-84.
3. Kehlet H, Thienpont E. Fast-track knee arthroplasty -- status and future challenges. Knee. 2013;20 Suppl 1:S29-33.
4. Barbieri A, Vanhaecht K, Van Herck P, Sermeus W, Faggiano F, Marchisio S, et al. Effects of clinical pathways in the joint replacement: a meta-analysis. BMC Med. 2009;7:32.
5. Dowsey MM, Kilgour ML, Santamaria NM, Choong PF. Clinical pathways in hip and knee arthroplasty: a prospective randomised controlled study. Med J Aust. 1999;170(2):59-62.
6. Husted H, Holm G, Jacobsen S. Predictors of length of stay and patient satisfaction after hip and knee replacement surgery: fast-track experience in 712 patients. Acta Orthop. 2008;79(2):168-73.
7. Husted H, Jensen CM, Solgaard S, Kehlet H. Reduced length of stay following hip and knee arthroplasty in Denmark 2000-2009: from research to implementation. Arch Orthop Trauma Surg. 2012;132(1):101-4.
8. Weingarten S, Riedinger MS, Sandhu M, Bowers C, Ellrodt AG, Nunn C, et al. Can practice guidelines safely reduce hospital length of stay? Results from a multicenter interventional study. Am J Med. 1998;105(1):33-40.
9. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002;183(6):630-41.
10. Kim S, Losina E, Solomon DH, Wright J, Katz JN. Effectiveness of clinical pathways for total knee and total hip arthroplasty: literature review. J Arthroplasty. 2003;18(1):69-74.
11. Malviya A, Martin K, Harper I, Muller SD, Emmerson KP, Partington PF, et al. Enhanced recovery program for hip and knee replacement reduces death rate. Acta Orthop. 2011;82(5):577-81.
12. Larsen K, Sorensen OG, Hansen TB, Thomsen PB, Soballe K. Accelerated perioperative care and rehabilitation intervention for hip and knee replacement is effective: a randomized clinical trial involving 87 patients with 3 months of follow-up. Acta Orthop. 2008;79(2):149-59.
13. Husted H, Otte KS, Kristensen BB, Orsnes T, Kehlet H. Readmissions after fast-track hip and knee arthroplasty. Arch Orthop Trauma Surg. 2010;130(9):1185-91.
14. Jorgensen CC, Kehlet H. Role of patient characteristics for fast-track hip and knee arthroplasty. Br J Anaesth. 2013;110(6):972-80.
15. Hartog YM, Mathijssen NM, Vehmeijer SB. Reduced length of hospital stay after the introduction of a rapid recovery protocol for primary THA procedures. Acta Orthop. 2013.
16. Krenk L, Jennum P, Kehlet H. Sleep disturbances after fast-track hip and knee arthroplasty. Br J Anaesth. 2012;109(5):769-75.
17. Cremeans-Smith JK, Millington K, Sledjeski E, Greene K, Delahanty DL. Sleep disruptions mediate the relationship between early postoperative pain and later functioning following total knee replacement surgery. J Behav Med. 2006;29(2):215-22.
18. Pozzi F, Snyder-Mackler L, Zeni J. Physical exercise after knee arthroplasty: a systematic review of controlled trials. Eur J Phys Rehabil Med. 2013 Dec;49(6):877-92.
19. Di Monaco M, Castiglioni C. Which type of exercise therapy is effective after hip arthroplasty? A systematic review of randomized controlled trials. Eur J Phys Rehabil Med. 2013 Dec;49(6):893-907.

20. Schneider M, Kawahara I, Ballantyne G, McAuley C, Macgregor K, Garvie R, et al. Predictive factors influencing fast track rehabilitation following primary total hip and knee arthroplasty. Arch Orthop Trauma Surg. 2009;129(12):1585-91.
21. Forrest GP, Roque JM, Dawodu ST. Decreasing length of stay after total joint arthroplasty: effect on referrals to rehabilitation units. Arch Phys Med Rehabil. 1999;80(2):192-4.
22. Chan EY, Blyth FM, Nairn L, Fransen M. Acute postoperative pain following hospital discharge after total knee arthroplasty. Osteoarthritis Cartilage. 2013;21(9):1257-63.
23. Kitzinger J. Qualitative research. Introducing focus groups. BMJ. 1995;311(7000):299-302.

Chapter 3

The first 6 weeks of recovery after total knee arthroplasty with fast track – A diary study of 30 patients

J.C. van Egmond, MD[1]
H. Verburg, MD[1]
N.M.C. Mathijssen, PhD[1]

Acta Orthop. 2015;86(6):708-13.

[1] Department of Orthopedic Surgery, Reinier de Graaf Groep, Delft, the Netherlands

ABSTRACT

Background and purpose

During the last decade, many hospitals have implemented fast-track protocols for total knee arthroplasty (TKA). These protocols reduce the length of hospital stay, but there is no literature on the first period after hospital discharge. We determined how patients experienced the first 6 weeks after hospital discharge after fast-track TKA surgery.

Patients and methods

34 consecutive patients who had TKA surgery with fast track received a diary for 6 weeks, which contained various international validated questionnaires. In addition, general questions regarding pain, the wound, physiotherapy, and thrombosis prophylaxis injections were posed.

Results

4 of the 34 patients were excluded during the study. Of the remaining 30 patients, 28 were positive regarding the short length of hospital stay. Pain gradually decreased and quality of life and function gradually improved during the 6 weeks. Mean hours of weekly physiotherapy were 0.6 for the first week and 0.9 during the sixth week, with high variance of treatment modalities due to the lack of standardized treatment protocols. Additional clinical consultations were needed in 9 patients during the 6-week period.

Interpretation

28 of 30 patients were satisfied with the short length of hospital stay. The intensity of physiotherapy was surprisingly low. The quality of life 6 weeks after discharge was similar to that before the surgery.

INTRODUCTION

Historically, patients were usually hospitalized for several weeks after total knee arthroplasty (TKA), which mainly consisted of a period of bed rest.[1] However, the length of hospital stay after TKA has decreased in the last decade through implementation of fast-track protocols.[2-6] Moreover, the quality of life after TKA with fast-track improves substantially during the first three months after hospital discharge, compared to the quality of life of patients treated with a non-fast-track protocol.[7] Also, a decrease in the number of complications and readmissions can be achieved with fast-track.[8,9] The prevalence of manipulation under anesthesia for stiffness of the knee has been found to be lower or comparable with the use of fast-track protocols, compared to conventional pathways[10] and the risk of thromboembolic complications is reduced.[11] Fast-track protocols have proven to be safe for patients, including the elderly.[12]

Most studies of fast-track surgery have focused on optimizing the hospital stay or have evaluated functioning of the patient six weeks after surgery. To our knowledge, no studies have been performed in which the first weeks after hospital discharge following TKA surgery with fast-track protocol were analyzed. We therefore determined how patients experienced the first six weeks after hospital discharge after TKA surgery with fast-track.

PATIENTS AND METHODS

Patients

Consecutive primary TKA patients, operated at the Reinier de Graaf Hospital, Delft, between January 2014 and November 2014 were asked to participate. Exclusion criteria were: patients with revision TKA surgery, patients with an insufficient command of Dutch, mentally disabled patients, and patients in which a prosthesis in another joint of the ipsilateral or contralateral lower limb had been placed within six months before TKA surgery. All patients received the NexGen prosthesis (Zimmer, Warsaw, IN) through an anteromedial approach.

The fast-track protocol in our institution is summarized in Table 1. The discharge criteria were functional: patients had to be able to walk 30 meters with crutches, climb stairs, dress independently, and go to the toilet independently. In addition, sufficient pain relief had to have been achieved by oral medication before discharge, with a numeric rating scale (NRS) pain score below three at rest and below five during mobilization.

- Preoperative education
- Spinal anesthesia with additional local infiltration anesthesia
- Standardized protocol for pain medication
- Opioid medication only on request (rescue medication)
- No drains
- No standard urine catheters
- Start rehabilitation and mobilization on day of surgery
- Checking the fulfillment of discharge criteria twice a day
- Optimization of the aftercare

Table 1. *Summary of the fast-track protocol*

Measurements

Preoperatively, all the patients completed an NRS pain score, the Knee injury and Osteoarthritis Outcome Score–Physical Function Short Form (KOOS-PS), Oxford knee score (OKS), and the Euro Quality of Life (EQ-5D). At discharge, all the patients received a diary which contained specific questionnaires for each day. The questionnaires included were: KOOS-PS, OKS, EQ-5D, SF-12, and the Intermittent and Constant Osteoarthritis Pain score (ICOAP). The SF-12 provides a physical component subscale (PCS) and a mental component subscale (MCS).[13] The EQ-5D score varies between −0.333 and 1.000, in which 1.000 represents full health.[14] The OKS score ranges from 0 to 48, where 48 is the best function and pain score. The KOOS-PS score ranges from 0 to 100%, where 0 represents no difficulty in physical functioning. NRS for pain was scored every day, which represented the mean pain score for that day.

The preoperative questions were answered digitally a few weeks before the surgery. Patients started to complete the diary on the day of discharge. Occasions when patients had to complete the questionnaires are shown in Table 2. In addition, general questions regarding pain, the wound, physiotherapy, and thrombosis injections were added each day. Table 3 (see Supplementary data) provides an English translation of the general questions. These questions were composed based on the outcome of two focus group meetings, which we organized before we performed the present study.[15]

The length of hospital stay was defined by the number of nights the patients were kept in hospital. At discharge, all patients received a prescription for one week of celecoxib (200 mg once a day), which could be used in addition to paracetamol (1 g 4 times a day). If necessary, additional pain medication such as tramadol (50 mg) or oxycodone (5 mg) was prescribed. During the study, we called all patients every week to check if there were problems in completing the questions in the diary. After six weeks, the patients returned their completed diary when they visited the outpatient clinic.

Questionnaire	Frequency
KOOS-PS	Preoperatively, twice a week
OKS	Preoperatively, once a week
EQ-5D	Preoperatively, twice a week
SF-12	Once at week 2, once at week 6
ICOAP	Once a week
General satisfaction	Once a week

KOOS-PS: Knee injury and Osteoarthritis Outcome Score - Physical Function Short Form score;
OKS: Oxford knee score;
SF-12: 12-item Short Form Health Survey score;
EQ-5D: Euro Quality of Life 5-dimensions score;
ICOAP: Intermittent and Constant Osteoarthritis Pain score.

Table 2. *Frequency of the questionnaires*

Statistics

No sample size calculation was done, since this was an observational pilot study. Missing data were handled according to the rules of the specific questionnaire. The distribution of the outcomes was determined by the Shapiro-Wilk test, given the number of patients included in this study. Descriptive statistics were obtained to evaluate the results. Generalized estimating equations (GEE) analyses with an exchangeable correlation structure were applied to study the changes in pain, quality of life, and function scores over time. We used IBM SPSS statistics for Windows version 21 for statistical analysis. Any p-value of 0.05 or less was considered to be statistically significant.

Ethics

The study protocol (NL45040.098.13) was approved by the local ethics committee and all participants gave their written informed consent.

RESULTS

Between January 2014 and November 2014, 78 patients were eligible for the study of which 13 patients were excluded due to insufficient command of Dutch or to comorbidity, and 31 patients declined participation. During the study, four patients were excluded: for three of them, the diary was not completed correctly and more than half of the answers were missing. In one patient, the TKA was complicated by a lateral collateral ligament rupture; the patient was treated with a brace and was therefore excluded.

The mean age of the remaining 30 patients was 68 (range 52–85) years old, and 18 patients were female. Mean BMI was 29 (range 19–40). Patients were admitted on the day of surgery. Since length of stay was not normally distributed, the median was 2.5

(IQR 1) nights. All patients went home after discharge. No complications were found during the hospital stay.

Pain

The mean preoperative NRS pain score was 3.6 (SD 2.3) during rest. The mean pain scores on day 1 and day 42 were 3.6 (SD 1.5) and 1.9 (SD 1.4), respectively ($p < 0.01$). In all patients, the NRS pain score gradually decreased over the six-week period (Figure 1). GEE showed a statistically significant decrease from day 14 compared to day 1, and this persisted to day 42. (All pain scores given are a mean pain score for the day).

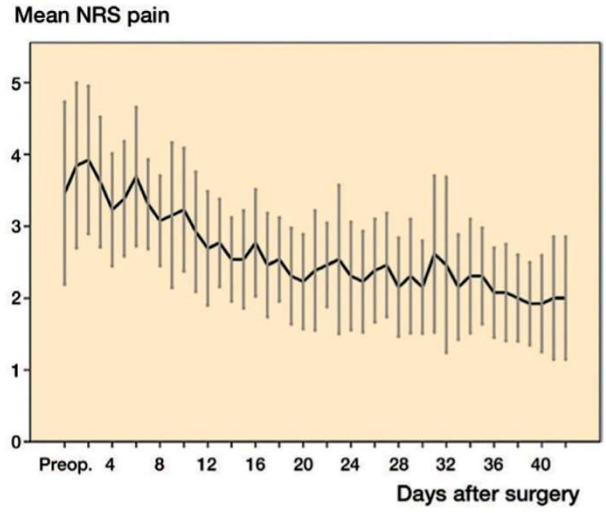


Figure 1. *Mean NRS pain score. Error bars are 95% CI.*

Moreover, the mean ICOAP total score gradually decreased. The mean total ICOAP score for week 1 was 21 (SD 6.7) on a scale from 0 to 44, where 44 is maximum pain, and for week 6 it was 12 (SD 7.1). The ICOAP total score decreased after week two ($p < 0.01$) which was maintained during the following weeks (Figure 2).

Pain medication

During the first week, all patients used paracetamol, 27 patients used celecoxib, 12 patients used tramadol, and five patients used oxycodon. The use of pain medication slightly declined over the following weeks.

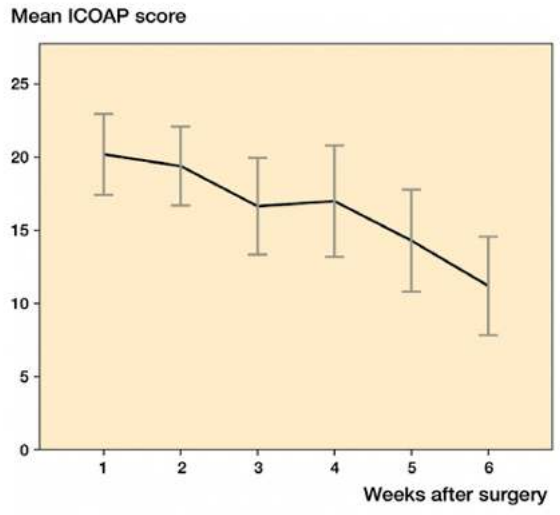


Figure 2. *Mean ICOAP score. Error bars are 95% CI.*

Wound care

In 13 patients, the wound leaked blood or wound serum on the first day after discharge, which had decreased but persisted in four patients at the end of week two. After discharge, four patients experienced problems with dressing the wound. These problems were mostly based on fear and uncertainty in treating the wound correctly.

Anticoagulation

All patients were prescribed low-molecular-weight heparin injections once a day for six weeks, which they had to inject into their subcutaneous abdominal fat. The complaints regarding the injections increased during the six weeks. Six patients had complaints regarding the injections on week one. This had increased to 12 patients by week six.

Complications

During the first six weeks after hospital discharge, before the patients had had their first outpatient control visit, nine patients had visited a doctor because of health problems related to the TKA, such as (groundless) fear of wound infection and problems sleeping. Most of the visits (five patients) were during the first week after hospital discharge. Six patients visited the outpatient clinic for wound leakage, fear of infection, pain, and extension deficit. In one of the cases, medication was prescribed; the other cases were treated by watchful waiting. Three patients visited their general practitioner for insomnia and for fear of wound infection; all of them were given medication. None of the patients had to be readmitted to hospital.

Physiotherapy

The mean amount of physiotherapy per week was 0.6 hours during week one and 0.9 hours during week six. The treatment modality of the physiotherapist varied between patients.

Functioning

Preoperatively, the OKS was 23 (SD 8.1). In the first week after discharge, the mean the OKS was 25 (SD 4.3). After week two, the OKS gradually increased to 35 (SD 6.4) at week six ($p < 0.01$) (Figure 3).

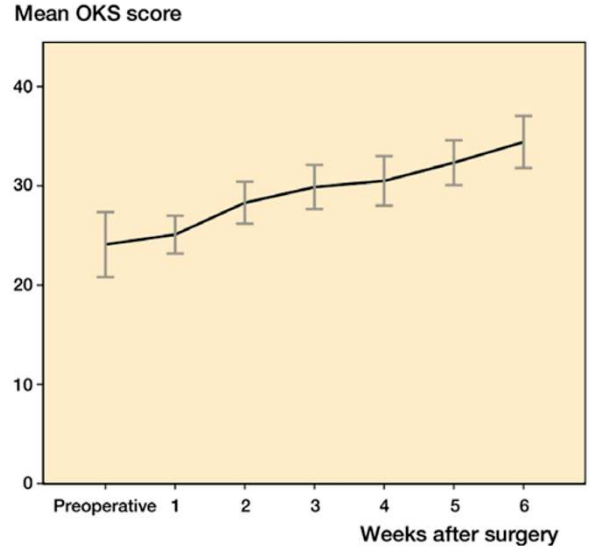


Figure 3. *Mean OKS score. Error bars are 95% CI.*

The preoperative KOOS-PS score was 50 (SD 12). From week three to week six, a gradual decrease occurred ($p < 0.01$) (Figure 4).

Sleep

During the first two weeks, 70–80% of the patients rated their sleep to be good or reasonable. At week six, all the patients had good or reasonable sleep.

Quality of life

The median daily mean SF-12 scores on the second week after discharge were 31 (IQR 6.5) on the PCS and 54 (IQR 18.8) on the MCS. At week six, the median daily mean PCS score had increased to 35 (IQR 8.5) ($p < 0.01$). On the other hand, the median daily mean MCS did not increase significantly, and was 55 (IQR 15.8) at week six ($p = 0.3$).

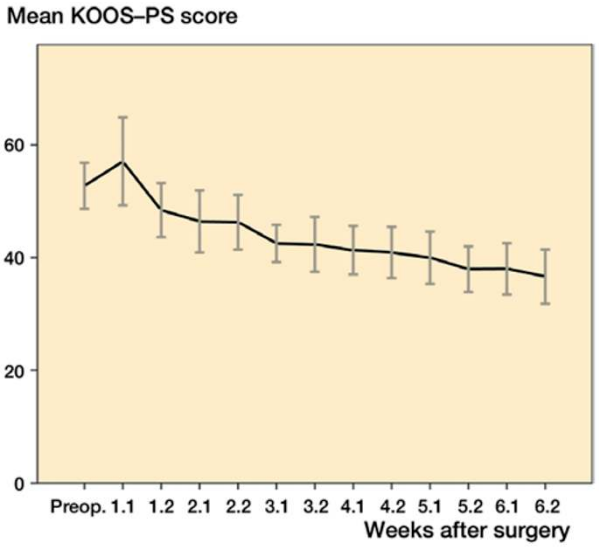


Figure 4. *Mean KOOS-PS score, scored twice every week. Error bars are 95% CI.*

The mean EQ-5D was 0.63 before surgery and decreased to 0.28 one week after discharge ($p < 0.01$). During the weeks that followed, the EQ-5D gradually increased until week five ($p < 0.05$). At week six, patients scored 0.51 for the EQ-5D. However, the mean daily score at week six was still less than preoperatively ($p = 0.2$) (Figure 5).

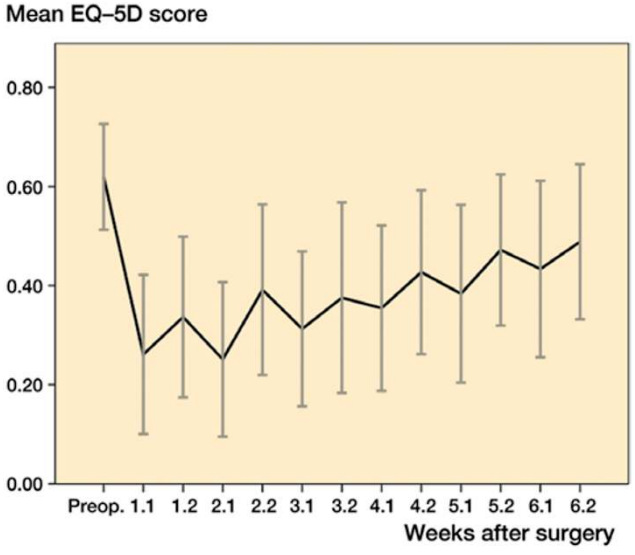


Figure 5. *Mean EQ-5D score, scored twice every week. Error bars are 95% CI.*

General patient satisfaction

28 patients were pleased with the short hospital stay. The reason that two patients would have liked to have stayed longer in hospital was because both of them did not feel ready to be at home, despite the fact that they met the discharge criteria. After six weeks, patients rated their satisfaction regarding the effect of the prosthesis as 7.7 on a scale from 0 to 10. 20 patients indicated that there was an improvement in functioning during daily activities compared to their preoperative function.

DISCUSSION

In general, most patients were satisfied with their short hospital stay, and preferred to complete the rehabilitation at home instead of in hospital.

9 of 30 patients visited a doctor before the routine outpatient control visit at six weeks. Husted et al. found a readmission rate of 16% at 90 days after fast-track TKA.[16] The high rate of medical consultation in our study might be explained by the easy access to the hospital for patients who undergo arthroplasty. A specialized nurse can be contacted during the weeks after surgery, and when patients are in doubt, an appointment can be made with the doctor. This procedure is part of the fast-track protocol. Most patients visited a doctor because they were concerned about possible health problems. In most cases, no treatment was needed; in the other cases, oral antibiotics were prescribed.

The patients experienced most pain during the first two weeks after discharge, and five patients needed oxycodone in the second week to achieve enough pain relief. Otherwise, good pain relief had been achieved with the standard prescribed medication. We presume that the high intake of paracetamol was probably the result of its accessibility, since it is available without a doctor's prescription. The high pain scores during the first two weeks are in accordance with the findings of Chan et al.[17] Andersen et al. found moderate pain scores and concomitant use of opioid medication in half of the patients one month after TKA.[18]

As described by Lee et al., the minimal clinically important difference (MCID) in a functional outcome score is of more importance than a significant change in that score.[19] Beard et al. have found that an MCID of nine points in the OKS is needed to detect a change over time in a group of patients.[20] In the present study, an increase of 10 points was measured in six weeks, and therefore knee functioning improved beyond the MCID. Singh et al. found that the MCID for the ICOAP was 18.5 points and that it was 2.2 points for the KOOS-PS.[21] We found a decrease of nine points in six weeks for the ICOAP and a decrease of 20 points in 6 weeks for the KOOS-PS.

In contrast to the study by Schneider et al. in which 12% of the patients were given physiotherapy, all our patients received physiotherapy.[22] However, the total number of

hours of physiotherapy was lower than we had expected. Moreover, the type of treatment varied between patients. As concluded by Bandholm et al., physiotherapy exercises, including strength training, should be initiated early after surgery and should be intensive to reduce the loss of muscle strength and function.[23] On the other hand, a study by Jakobsen et al. concluded that additional progressive strength training does not give any improvement in functional performance.[24] No standardized treatment protocol for physiotherapy is available; only recommendations have been made by the KNGF (Dutch physical therapy organization). In these recommendations, massage, balance exercise, and gait exercise are not recommended. There is a need for a standardized rehabilitation protocol as described in the systematic review by Pozzi et al. and also by Peter et al.[25,26]

In our previous study, patients described difficulties in injecting themselves with anticoagulation medication.[15] In the present study, 12 of 30 patients experienced problems in injecting themselves. Thus, the type of anticoagulation treatment should be reconsidered. Furthermore, there is a lower risk of thromboembolic incidents in fast-track, so a shorter duration of anticoagulation therapy should be considered.[11,27,28]

In this study, most patients slept well during the first six weeks. Pain was the most frequent reason given for insomnia, and only three patients needed a prescription for sleep medication.

The study had some limitations. Firstly, since this was a pilot study, the patient numbers were small. Secondly, it was a single-arm study with no controls. Thirdly, no objective physical examination function scores were used only questionnaires. Fourthly, we attempted to have a representative patient group from our clinical practice, so the inclusion and exclusion criteria were straightforward. Although we excluded several patients because of other prosthesis surgery or poor command of the language (Dutch), we presume that our patient group was representative of our clinical practice. Since an appreciable amount of effort is needed to complete all the questionnaires in the diary, several patients refused to join the study. This may have led to selection bias, so that only the motivated patients completed the questionnaires. Based on the variety of reactions of the patients, we presume that this had no influence on the outcome.

Lastly, healthcare in the Netherlands is in several ways differently organized from that in other countries, so the outcome of this study cannot always be compared to the outcomes of other studies. Moreover, the infrastructure is different: all patients have quite easy access to a physiotherapist, a general practitioner, and a hospital. In addition, general practitioners and hospitals have an almost round-the-clock care system.

In conclusion, with concomitant use of analgesics patients experienced most pain during the first two weeks after discharge. The pain and the use of analgesics gradually decreased over six weeks. Moreover, functioning increased, and even during the first week after surgery patients had a better function score than preoperatively. Although 28 of 30 patients were positive regarding their early discharge after TKA with fast track, nine

patients had consulted their general practitioner or our institution before the outpatient visit six weeks after discharge. Most consultations were for anxiety about wound infection, pain, or insomnia, and most patients were treated with watchful waiting.

ACKNOWLEDGEMENT

We thank the Foundation for Scientific Research of Reinier de Graaf Groep, Delft, for funding this study. We are grateful to all the patients for their efforts in completing their diaries, and we especially thank N. de Esch for her help during the study.

AUTHOR CONTRIBUTION

JE composed the diary, and performed the data collection and data analysis. He wrote and revised the manuscript. NM designed the study, supported data analysis, and critically reviewed the manuscript. HV operated several of the patients, designed the study, and critically reviewed the manuscript.

REFERENCES

1. Berger RA, Sanders SA, Thill ES, Sporer SM, Della Valle C. Newer anesthesia and rehabilitation protocols enable outpatient hip replacement in selected patients. Clin Orthop Relat Res. 2009;467(6):1424-30.
2. Weingarten S, Riedinger MS, Sandhu M, Bowers C, Ellrodt AG, Nunn C, et al. Can practice guidelines safely reduce hospital length of stay? Results from a multicenter interventional study. Am J Med. 1998;105(1):33-40.
3. Husted H, Jensen CM, Solgaard S, Kehlet H. Reduced length of stay following hip and knee arthroplasty in Denmark 2000-2009: from research to implementation. Arch Orthop Trauma Surg. 2012;132(1):101-4.
4. Husted H, Holm G, Jacobsen S. Predictors of length of stay and patient satisfaction after hip and knee replacement surgery: fast-track experience in 712 patients. Acta Orthop. 2008;79(2):168-73.
5. Barbieri A, Vanhaecht K, Van Herck P, Sermeus W, Faggiano F, Marchisio S, et al. Effects of clinical pathways in the joint replacement: a meta-analysis. BMC Med. 2009;7:32.
6. Kim S, Losina E, Solomon DH, Wright J, Katz JN. Effectiveness of clinical pathways for total knee and total hip arthroplasty: literature review. J Arthroplasty. 2003;18(1):69-74.
7. Larsen K, Sorensen OG, Hansen TB, Thomsen PB, Soballe K. Accelerated perioperative care and rehabilitation intervention for hip and knee replacement is effective: a randomized clinical trial involving 87 patients with 3 months of follow-up. Acta Orthop. 2008;79(2):149-59.
8. Dowsey MM, Kilgour ML, Santamaria NM, Choong PF. Clinical pathways in hip and knee arthroplasty: a prospective randomised controlled study. Med J Aust. 1999;170(2):59-62.
9. den Hertog A, Gliesche K, Timm J, Muhlbauer B, Zebrowski S. Pathway-controlled fast-track rehabilitation after total knee arthroplasty: a randomized prospective clinical study evaluating the recovery pattern, drug consumption, and length of stay. Arch Orthop Trauma Surg. 2012;132(8):1153-63.
10. Husted H, Jorgensen CC, Gromov K, Troelsen A, Collaborative Group of the Lundbeck Foundation Center for Fast-Track H, Knee R. Low manipulation prevalence following fast-track total knee arthroplasty. Acta Orthop. 2015;86(1):86-91.
11. Husted H, Otte KS, Kristensen BB, Orsnes T, Wong C, Kehlet H. Low risk of thromboembolic complications after fast-track hip and knee arthroplasty. Acta Orthop. 2010;81(5):599-605.
12. Jorgensen CC, Kehlet H, Lundbeck Foundation Centre for Fast-track H, Knee Replacement Collaborative G. Role of patient characteristics for fast-track hip and knee arthroplasty. Br J Anaesth. 2013;110(6):972-80.
13. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34(3):220-33.
14. Lamers LM, Stalmeier PFM, McDonnell J, Krabbe PFM, van Busschbach JJ. Kwaliteit van leven meten in economische evaluaties: het Nederlands EQ-5D-tarief. Ned Tijdschr Geneeskd. 2005(149):1574-8.
15. van Egmond JC, Verburg H, Vehmeijer SBW, Mathijssen NMC. Early follow-up after primary total knee and total hip arthroplasty with rapid recovery: Focus groups. Acta Orthopaedica Belgica. 2015 Sep;81(3):447-53
16. Husted H, Otte KS, Kristensen BB, Orsnes T, Kehlet H. Readmissions after fast-track hip and knee arthroplasty. Arch Orthop Trauma Surg. 2010;130(9):1185-91.
17. Chan EY, Blyth FM, Nairn L, Fransen M. Acute postoperative pain following hospital discharge after total knee arthroplasty. Osteoarthritis Cartilage. 2013;21(9):1257-63.

18. Andersen LO, Gaarn-Larsen L, Kristensen BB, Husted H, Otte KS, Kehlet H. Subacute pain and function after fast-track hip and knee arthroplasty. Anaesthesia. 2009;64(5):508-13.
19. Lee JS, Hobden E, Stiell IG, Wells GA. Clinically important change in the visual analog scale after adequate pain control. Acad Emerg Med. 2003;10(10):1128-30.
20. Beard DJ, Harris K, Dawson J, Doll H, Murray DW, Carr AJ, et al. Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. J Clin Epidemiol. 2015;68(1):73-9.
21. Singh JA, Luo R, Landon GC, Suarez-Almazor M. Reliability and clinically important improvement thresholds for osteoarthritis pain and function scales: a multicenter study. J Rheumatol. 2014;41(3):509-15.
22. Schneider M, Kawahara I, Ballantyne G, McAuley C, Macgregor K, Garvie R, et al. Predictive factors influencing fast track rehabilitation following primary total hip and knee arthroplasty. Arch Orthop Trauma Surg. 2009;129(12):1585-91.
23. Bandholm T, Kehlet H. Physiotherapy exercise after fast-track total hip and knee arthroplasty: time for reconsideration? Arch Phys Med Rehabil. 2012;93(7):1292-4.
24. Jakobsen TL, Kehlet H, Husted H, Petersen J, Bandholm T. Early progressive strength training to enhance recovery after fast-track total knee arthroplasty: a randomized controlled trial. Arthritis Care Res (Hoboken). 2014;66(12):1856-66.
25. Pozzi F, Snyder-Mackler L, Zeni J. Physical exercise after knee arthroplasty: a systematic review of controlled trials. Eur J Phys Rehabil Med. 2013;49(6):877-92.
26. Peter WF, Nelissen RG, Vlieland TP. Guideline recommendations for post-acute postoperative physiotherapy in total hip and knee arthroplasty: are they used in daily clinical practice? Musculoskeletal Care. 2014;12(3):125-31.
27. Jorgensen CC, Jacobsen MK, Soeballe K, Hansen TB, Husted H, Kjaersgaard-Andersen P, et al. Thromboprophylaxis only during hospitalisation in fast-track hip and knee arthroplasty, a prospective cohort study. BMJ Open. 2013;3(12):e003965.
28. Kjaersgaard-Andersen P, Kehlet H. Should deep venous thrombosis prophylaxis be used in fast-track hip and knee replacement? Acta Orthop. 2012;83(2):105-6.

SUPPLEMENTARY DATA

Pain
• Give a pain score between 0 and 10, in which 0 is no pain and 10 is the worst possible pain. Complete one for average pain and one for the worst occasion today.
Medication
• What medication and which doses did you use today?
Sleep
• How did you sleep last night?
Physiotherapy
• Did you have physiotherapy this week?
• What kind of intervention did you receive?
Wound
• Did the wound leak?
• Did you change the bandage?
• Did you experience problems/anxiety regarding changing of the bandage?
Homecare service
• Did you use the homecare service this week?
Thrombosis injections
• Did you experience problems with the thrombosis prophylaxis injection?
Complications
• Did you contact a doctor this week for your operated knee?

Table 3. *General questions*

Part II

Recovery after total knee arthroplasty

Chapter 4

Short-term functional outcome after fast-track primary total knee arthroplasty: analysis of 623 patients

J.C. van Egmond, MD[1]
B. Hesseling, MSc[1]
H. Verburg, MD[1]
N.M.C. Mathijssen, PhD[1]

Acta Orthop. 2021 Oct;92(5):602-607

[1] Department of Orthopedic Surgery, Reinier de Graaf Groep, Delft, the Netherlands

ABSTRACT

Background and purpose

Early functional outcome after total knee arthroplasty (TKA) has been described before, but without focus on the presence of certain functional recovery patterns. We investigated patterns of functional recovery during the first three months after TKA and determined characteristics for non-responders in functional outcome.

Patients and methods

All primary TKA in a fast-track setting with complete Patient Reported Outcome Measures (PROMs) preoperatively, at six weeks, and three months postoperatively were included. Included PROMs were Oxford Knee Score (OKS), Knee disability and Osteoarthritis Outcome Score Physical Function Short-Form (KOOS-PS), and EuroQol 5 dimensions (EQ-5D) including the self-rated health Visual Analogue Scale (VAS). Patients with improvement on OKS less than the minimal clinical important difference (MCID) were determined as non-responders at that time point. Characteristics between groups of responders and non-responders in functional recovery were tested for differences: we defined four groups a priori, based on the responder status at each time point.

Results

623 patients were included. At six weeks OKS, KOOS-PS, and EQ-5D self-rated health VAS were statistically significant improved compared with preoperative scores. The mean improvement was clinically relevant at six weeks for KOOS-PS and at three months for OKS. Patient characteristics in non-responders were higher BMI and worse scores on EQ-5D items: mobility, self-care, usual activities, and anxiety/depression.

Interpretation

Both statistically significant and clinically relevant functional improvement was found in most patients during the first three months after primary TKA. Presumed modifiable patient characteristics in non-responders on early functional outcome were BMI and anxiety/depression.

INTRODUCTION

Most arthroplasty research has focused on long-term functional outcomes and survival of the prosthesis. These outcomes have frequently been used for quality assessments and performance outcomes of the prosthesis itself.

Because around 20% of patients remain unsatisfied after total knee arthroplasty (TKA),[1,2] studying early functional outcome patterns more closely might provide important information to further optimize rehabilitation and patient satisfaction.

In a recent article of van Egmond et al. three distinct recovery trajectories were found after TKA, using preoperative, six months, and 12 months postoperative Oxford Knee Scores (OKS), of which two trajectories at six months had approximately the same trajectory and subsequently diverged.[3] Relatively similar patterns have seen in total hip arthroplasty (THA).[4]

Several studies on early function, pain, and quality of life outcomes after TKA have been published.[5-10] Moreover, Canfield et al. concluded that most improvement in function and pain is gained during the first six months postoperatively.[11]

Although functional rehabilitation in TKA and THA patients before six months has been studied,[12,13] the question remains whether differences in functional recovery patterns exist before the six-month mark in TKA patients.

We expect that rehabilitation might be further optimized with knowledge of early functional rehabilitation patterns. Therefore, the primary objective of this study was to determine patterns in functional outcome at six weeks and three months after primary TKA. Secondary objectives were a non-responder analysis and to determine characteristics for non-responders in early functional recovery.

PATIENTS AND METHODS

This is a retrospective exploratory cohort study. Data, all prospectively collected, were gathered from the digital PROMs database of our institution.

Patients

As standard procedure in our institution, during the study period from January 2015 to August 2017, all patients with primary TKA were asked to complete Patient Reported Outcome Measures (PROMs) preoperatively, and received digital PROMs questionnaires at six weeks and three months postoperatively (OnlinePROMs, Amsterdam, the Netherlands).

All patients who underwent primary TKA with fast-track recovery at our institution during the study period were eligible for inclusion. Patients with completed PROMs at

all three time points were included for analysis. In patients with bilateral TKA during the inclusion period only the results of the first TKA were analyzed.

Measurements

Included PROMs were OKS, Knee disability and Osteoarthritis Outcome Score Physical Function Short-Form (KOOS-PS), and EuroQol 5 dimensions (EQ-5D-3L).

The EQ-5D-3L questionnaire comprises five questions on the dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The second part of the EQ-5D contains a self-rated health score on a visual analogue scale (VAS) from 0 to 100, where 0 represents the worst imaginable health and 100 the best imaginable health. The EQ-5D self-rated health VAS was used from every administration to determine general health improvement.[14]

The KOOS-PS score ranges from 0 to 100%, where 0% represents no difficulty in physical functioning.[15] The minimal clinically important difference (MCID) is 4% for KOOS-PS, while a moderate improvement is stated at 32%.[16]

The OKS is based on 12 questions regarding pain and function of the knee. Total score ranges from 0 to 48 with higher scores indicating better function and less pain.[17] Anchor-based methods showed that a change in score of approximately nine points on the OKS indicates a meaningful improvement at the group level.[18] Missing data were handled according to the specific questionnaire rules.[19]

For non-responder analysis we used the OKS, mainly to ensure our results could be compared our previous study. Moreover, we find the OKS to cover a broader range of functional outcome than the KOOS-PS. Patients were rated as responders based on MCID of the OKS; an improvement on OKS above the MCID of nine points labelled patients as responders. Both at six weeks and three months improvement was determined. Consequently, four groups were formed including: (1) responder at six weeks, responder at three months; (2) non-responder at six weeks, responder at three months; (3) non-responder at six weeks, non-responder at three months; and (4) responder at six weeks, non-responder at three months.

Statistics

Normally distributed outcomes were presented as mean and 95% confidence interval (CI). Not normally distributed outcomes were presented as median, total, and interquartile range (IQR).

Repeated measures ANOVA was used to determine changes in outcome over time for OKS, KOOS-PS, and EQ-5D self-rated health VAS separately, using all three time points. If there was a statistically significant change over time, a priori planned post-hoc ANOVA analysis was performed to compare preoperative scores with six weeks, and scores at six weeks with three months to determine at which point in time the scores improved.[20]

For responder analysis only the OKS was used to determine whether a patient was a responder. Groups of responders and non-responders were compared and tested for differences on their characteristics using chi-square, Kruskal-Wallis, and ANOVA. If there was an overall statistically significant difference between the groups, a priori planned post-hoc Mann-Whitney U analysis with Bonferroni correction was performed to test which groups differed.

Characteristics of interest were dichotomized for analysis; age (≤75 vs. >75), ASA (class I-II vs. III-IV), and EQ-5D scores (no problems vs. moderate-to-severe problems).

For statistical analyses IBM SPSS statistics version 25 (IBM Corp. Armonk, NY: IBM Corp.) was used. A p-value of 0.05 or lower was considered statistically significant.

Ethics, funding, and potential conflicts of interest

This study did not fall under the scope of the research with human subjects act according to the local ethical committee since this study placed no additional burden on the patient. This study was conducted according to the Declaration of Helsinki (version 64, October 2013). No funding was received for this study. The authors have no conflicts of interest to declare.

RESULTS

623 patients with unilateral primary TKA in a fast-track setting were included (Table 1). Median age was 70 years, and 420 (67%) patients were female. 437 patients (70%) were classified as ASA 2. Median BMI was 29 [IQR 26-36] for the total group.

Demographics	623 TKA
Age, median [IQR] (range)	70 [64-77] (32-93)
Female sex	420 (67)
Smoking yes	64 (10)
ASA score	
I	100 (16)
II	437 (70)
III	86 (14)
BMI	
Normal weight (<25)	100 (16)
Overweight (25-30)	267 (43)
Obesity (>30)	256 (41)
LOS, median [IQR] (range)	2 [2-3] (0-9)

LOS= length of stay by hospital nights.

Table 1. *Patient demographics (N = 623). Values are count (%) unless otherwise specified*

Primary outcome

Both the function scores (OKS and KOOS-PS) and EQ-5D self-rated health VAS improved during the first three months as presented in Table 2. Since all scores were not normally distributed the median, total range, and IQR were presented.

Item	Preoperative	6 weeks	3 months
OKS	23 [17-28] (2-45)	30 [25-36] (4-48) [a]	35 [29-41] (9-48) [b]
KOOS-PS	51 [42-62] (15-100)	40 [34-46] (0-100) [a]	35 [28-44] (0-100) [b]
EQ-5D VAS	71 [60-81] (3-100)	75 [60-86] (0-100) [a]	79 [65-88] (6-100) [b]

[a] *Significant improvement between preoperative and 6 weeks, Wilks' λ <0.001*
[b] *Significant improvement between 6 weeks and 3 months, Wilks' λ <0.001*

Table 2. *Median function scores at the 3 time points. Values are median [IQR] (range)*

Repeated-measures ANOVA of both function scores and EQ-5D self-rated health VAS over the three-months postoperative period showed statistically significant improvement. For OKS, KOOS-PS, and EQ-5D self-rated health VAS the Wilks' λ was <0.001 for the preoperative to six weeks and from six weeks to three months as well.

The improvement on KOOS-PS at 6 weeks postoperative was 11% which is clinically relevant. At three months, compared with preoperatively, an improvement of 16% was found (Figure 1).

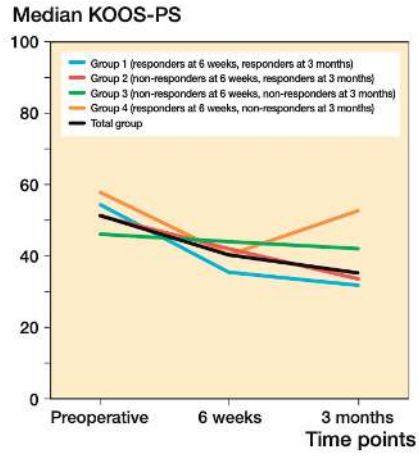


Figure 1. *Median KOOS-PS course in 3 months*

The OKS improved seven points during the first six weeks, which is statistically significant but not clinically relevant. At three months a statistically significant and clinically relevant improvement of 12 points was found (Figure 2).

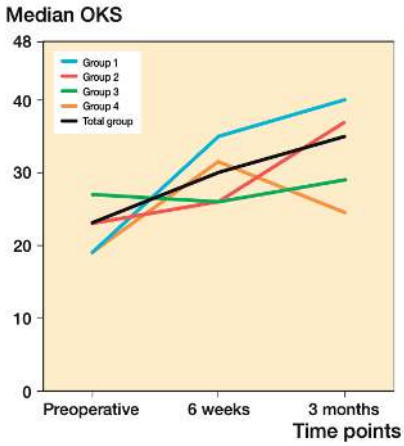


Figure 2. *Median OKS course in 3 months*

The EQ-5D self-rated health VAS showed improvement both at six weeks and three months postoperative of respectively four and eight points compared to preoperative levels (Figure 3).

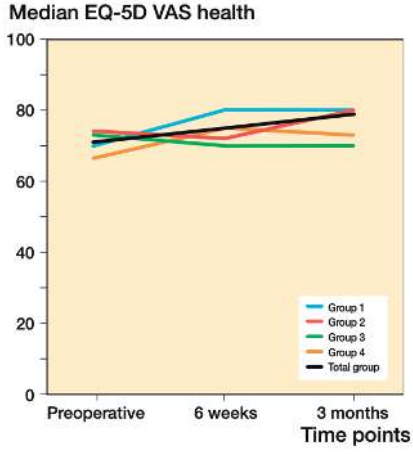


Figure 3. *Median EQ-5D VAS health course in 3 months*

SECONDARY OUTCOME

Responder analysis was performed based on MCID of OKS at six weeks and three months postoperatively, compared with preoperative scores. The percentage of responders improved from 44% at six weeks to 67% at three months.

Factor		Group 1	Group 2	Group 3	Group 4	
Total number		218 (41)	119 (23)	177 (33)	14 (3)	
Age	≤75 years	142 (65)	90 (76)	121 (68)	10 (71)	0.3[a]
	>75 years	76 (35)	29 (24)	56 (32)	4 (29)	
BMI	<25	26 (12)	16 (13)	42 (24)	1 (7)	0.02[b]
	25-30	101 (46)	55 (46)	71 (40)	3 (21)	
	>30	91 (42)	48 (40)	64 (36)	10 (71)	
Smoking	yes	21 (10)	11 (9)	19 (11)	1 (7)	1.0[a]
	no	197 (90)	108 (91)	158 (89)	13 (93)	
ASA	I-II	197 (90)	102 (86)	155 (88)	11 (79)	0.4[b]
	III-IV	21 (10)	17 (14)	22 (12)	3 (21)	
Preoperative EQ-5D						
- Mobility						
No problems		8 (4)	2 (2)	18 (10)	0 (0)	0.004[b]
Some problems in walking or confined to bed		210 (96)	117 (98)	159 (90)	14 (100)	
- Self-care						
No problems		165 (76)	101 (84)	151 (85)	7 (50)	0.001[b]
Some problems or unable to wash or dress		53 (24)	18 (15)	26 (15)	7 (50)	
- Usual activities						
No problems		32 (15)	18 (15)	50 (28)	0 (0)	0.001[b]
Some problems or unable to perform usual activities		186 (85)	101 (84)	127 (72)	14 (100)	
- Pain/ discomfort						
No pain or discomfort		16 (7)	10 (8)	25 (14)	1 (7)	0.1[b]
Moderate or extreme pain or discomfort		202 (93)	109 (92)	152 (86)	13 (93)	
- Anxiety/ depression						
Not anxious or depressed		173 (79)	91 (76)	137 (77)	4 (29)	<0.001[b]
Moderate or extremely anxious or depressed		45 (21)	28 (24)	40 (23)	10 (71)	
VAS health	median	70	74	73	67	0.3[c]
	IQR	60-81	60-82	60-82	50-79	
	range	11-100	25-100	13-100	3-100	

Group 1: responder at 6 weeks, responder at 3 months
Group 2: non-responder at 6 weeks, responder at 3 months
Group 3: non-responder at 6 weeks, non-responder at 3 months
Group 4: responder at 6 weeks, non-responder at 3 months
[a] Chi-square
[b] Kruskall-Wallis
[c] ANOVA

Table 3. *Responder analysis. Values are count (%) unless otherwise specified*

The predefined four groups comprised: (1) responder at six weeks, responder at three months (41%); (2) non-responder at six weeks, responder at three months (23%); (3) non-responder at six weeks, non-responder at three months (33%); and (4) responder at six weeks, non-responder at three months (3%).

Groups one and two were determined as responders versus groups three and four as non-responders.

There was a statistically significant difference between the groups regarding BMI and EQ-5D items: mobility, self-care, usual activities, and anxiety/depression (Table 3). In the planned post-hoc analysis group one and two were mostly comparative (Table 4). On EQ-5D anxiety/depression, group four differed from the other groups (Table 4). Finally, the distribution of normal and high BMI was different between groups 1 and 2 compared with group four (Table 3). The post-hoc pairwise analysis presented in Table 4 showed a statistically significant difference between groups three and four for BMI.

Item	Group 1 vs. 2	Group 1 vs. 3	Group 1 vs. 4	Group 2 vs. 3	Group 2 vs. 4	Group 3 vs. 4
BMI	1.0	0.2	0.4	0.8	0.3	0.05
EQ-5D						
Mobility	1.0	0.03	1.0	0.008	1.0	0.6
Self-care	0.3	0.1	0.1	1.0	0.01	0.008
Usual activities	1.0	0.004	1.0	0.03	1.0	0.06
Anxiety/depression	1.0	1.0	<0.001	1.0	<0.001	<0.001
Group 1-4: see table 3						

Table 4. *Post-hoc pairwise analysis*

The median OKS in group one improved from 19 preoperative to 40 at three months and group two improved from 23 to 37 (Table 5). This is in contrast to groups three and four where median OKS at three months showed only minimal improvement from 27 preoperative to 29 at three months for group three, and 19 to 25 for group four (Table 5).

Group	Preoperative	6 weeks	3 months
1	19 [14-24] (3-36)	35 [30-40] (12-48)	40 [34-44] (21-48)
2	23 [19-27] (3-37)	26 [22-31] (11-42)	37 [34-42] (16-48)
3	27 [22-31] (5-45)	26 [21-31] (5-46)	29 [24-34] (9-47)
4	19 [16-25] (9-28)	32 [27-36] (19-39)	25 [20-28] (15-33)
Group 1-4: see table 3			

Table 5. *OKS per group for each time-point. Values are median [IQR] (range)*

DISCUSSION

The primary goal of this study was to determine patterns in early functional outcome after primary TKA. The most important finding was the statistically significant and clinically relevant early improvement of both function scores at six weeks and three months postoperatively for the sample as a whole. Moreover, we examined four a priori defined subgroups. Patient characteristics for non-responders were higher BMI and worse scores on EQ-5D items: mobility, self-care, usual activities, and anxiety/depression.

With the knowledge that subgroups in TKA recovery exist, based on this study and previous studies, we have to use this knowledge to further improve rehabilitation and outcomes. For example, expectation management can be used in patients at risk for non-responding. Recently, preoperative education and expectation modification was found to increase fulfillment of expectations and concomitant higher satisfaction.[21] Therefore more individual rehabilitation might be needed instead of the usual generic type. Preoperative education and the outpatient physical therapist might play a major role in this, as patients are admitted relatively shortly to the hospital.

In addition, further studies are needed on how to identify non-responding patients preoperatively and provide better selection criteria. Further research is also needed to find what will help non-responding patients preoperatively and during the postoperative rehabilitation. There might, for example, be a need for more support or guidance in the rehabilitation by a physical therapist.

Besides the improvement on both function scores, there was also a statistically significant improvement in EQ-5D self-rated health VAS. This is in line with the findings of Larsen et al. who found improved health related quality of life scores in knee arthroplasty patients with no or mild pain and good function.[6] To the best of our knowledge, no MCID has been determined for EQ-5D self-rated health VAS, therefore it is unknown if the improvement was clinically relevant as well. In this study the EQ-5D self-rated health VAS was used instead of the index score of the EQ-5D, because we were not interested in estimating quality-adjusted life years (QALYs). Moreover, index scores are not comparable internationally, as converting EQ-5D to an index score is referenced nationally.

Our findings were also in accordance with Husted et al. who found a median OKS three months postoperatively of 32 and 31 in the group of discharge on day of surgery and not discharged on day of surgery, respectively.[10] We found in our analysis of fast-track TKA patients a median OKS at three months of 35 (IQR 29-41).

We used the OKS for non-responder analysis, as this validated score was previously used in the study by van Egmond et al.[3] Therefore, our results would be more easily compared with the results from that study. Moreover, we find the OKS covers a broader range of functional outcome than the KOOS-PS. Characteristics of interests were dichotomized including age (≤75 vs. >75), ASA (1-2 vs. 3-4), and EQ-5D (no problems vs. moderate-to-severe problems), and BMI was divided into 3 groups, to prevent small group sizes in analysis.

The post hoc pairwise analysis in Table 4 shows a statistically significant BMI between groups three and four. However, Table 3 presents an obvious difference in percentages of high and normal BMI between groups one and two compared with group four. Even though these differences did not reach statistical significance, we find these differences large enough to be of clinical relevance.

In our non-responder analysis, non-responders differed on the EQ-5D items mobility, self-care, usual activities, and anxiety/depression, compared with the other groups. In several studies, poor mental health is related to poor functional outcome.[22-24] Other studies are less distinct and did not find a relationship between anxiety and suboptimal outcomes.[25] Nevertheless, previous studies showed that psychological support might lead to lower incidence of pain, anxiety/depression, and improve faster recovery.[26,27] Preoperative analysis of the presence of these factors and concomitant treatment might be an effective way to improve the satisfaction rate of TKA. Currently we perform no preoperative screening for psychological status in our institution. This might be feasible with the Pain Catastrophizing Scale (PCS) or Hospital Anxiety and Depression Scale (HADS).[28] The recently published systematic review by Sorel et al. is promising and described various interventions with good effect on postoperative pain, quality of life, and function for psychological distress in TKA patients.[27] Therefore further studies are needed to identify these patients preoperatively and to examine in which way adequate therapy can be provided in this setting.

A major strength of this study is the relatively large number of included patients. However, there are some limitations of this study.

The most important is the retrospective design with all its known forms of bias. However, all data was collected prospectively and validated questionnaires have been used.

Furthermore, the results were based on single institutional data, which might make the results less generalizable. Given that our results were comparable to previously published studies from other countries, we feel this is a minor limitation.

First multinomial logistic regression analysis was performed to test for patient characteristics in the four determined groups. Because errors occurred due to small group sizes, these analyses were not valid. Therefore, descriptive statistics were performed resulting in a more exploratory study. No causal relations can be drawn from our non-responder analysis. However, this is the first study that presents patterns in early functional outcome after TKA. New studies are needed to confirm and further define our findings.

We used PROMs to determine early functional recovery after TKA. Previous studies concluded that improvement in PROMs do not correlate with objectively assessed function.[29,30] We are aware that our findings based on PROMs might not fully represent objective function. However, as the subjective PROMs relate to how patients themselves experience their function, we regard this as a highly valuable outcome.

Finally, no PROMs data was available at further time points up to one year to present a detailed course of functional outcomes during the first postoperative year.

In conclusion, orthopedic surgeons and patients can expect improved functional outcomes early after TKA surgery at six weeks postoperatively and substantial improvement at three months. Concomitant health status improvement was detected as well in

this early postoperative phase. Modifiable patient characteristics for non-responders on early functional outcome were BMI and anxiety/depression. Preoperative treatment of these factors might improve postoperative outcomes.

ACKNOWLEDGEMENT

The authors would like to thank all patients for completing the questionnaires.

AUTHOR CONTRIBUTION

JE designed the study, performed data collection, data-analysis and he wrote and revised the manuscript. BH supported data-analysis and critically reviewed the manuscript. HV operated several of the included patients, and critically reviewed the manuscript. NM designed the study, supported data-analysis and critically reviewed the manuscript.

REFERENCES

1. Baker PN, van der Meulen JH, Lewsey J, Gregg PJ, National Joint Registry for E, Wales. The role of pain and function in determining patient satisfaction after total knee replacement. Data from the National Joint Registry for England and Wales. J Bone Joint Surg Br. 2007;89(7):893-900.
2. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KD. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clin Orthop Relat Res. 2010;468(1):57-63.
3. van Egmond JC, Hesseling B, Melles M, Vehmeijer SBW, van Steenbergen LN, Mathijssen NMC, et al. Three distinct recovery patterns following primary total knee arthroplasty: Dutch arthroplasty register study of 809 patients. Knee Surg Sports Traumatol Arthrosc. 2021;29(2):529-39.
4. Hesseling B, Mathijssen NMC, van Steenbergen LN, Melles M, Vehmeijer SBW, Porsius JT. Fast Starters, Slow Starters, and Late Dippers: Trajectories of Patient-Reported Outcomes After Total Hip Arthroplasty: Results from a Dutch Nationwide Database. J Bone Joint Surg Am. 2019;101(24):2175-86.
5. Castorina S, Guglielmino C, Castrogiovanni P, Szychlinska MA, Ioppolo F, Massimino P, et al. Clinical evidence of traditional vs fast track recovery methodologies after total arthroplasty for osteoarthritic knee treatment. A retrospective observational study. Muscles Ligaments Tendons J. 2017;7(3):504-13.
6. Larsen K, Hansen TB, Soballe K, Kehlet H. Patient-reported outcome after fast-track knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2012;20(6):1128-35.
7. Schotanus MGM, Bemelmans YFL, Grimm B, Heyligers IC, Kort NP. Physical activity after outpatient surgery and enhanced recovery for total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2017;25(11):3366-71.
8. Jakobsen TL, Kehlet H, Husted H, Petersen J, Bandholm T. Early progressive strength training to enhance recovery after fast-track total knee arthroplasty: a randomized controlled trial. Arthritis Care Res (Hoboken). 2014;66(12):1856-66.
9. Andersen LO, Gaarn-Larsen L, Kristensen BB, Husted H, Otte KS, Kehlet H. Subacute pain and function after fast-track hip and knee arthroplasty. Anaesthesia. 2009;64(5):508-13.
10. Husted CE, Husted H, Ingelsrud LH, Nielsen CS, Troelsen A, Gromov K. Are functional outcomes and early pain affected by discharge on the day of surgery following total hip and knee arthroplasty? Acta Orthop. 2020:1-5.
11. Canfield M, Savoy L, Cote MP, Halawi MJ. Patient-reported outcome measures in total joint arthroplasty: defining the optimal collection window. Arthroplast Today. 2020;6(1):62-7.
12. Klapwijk LC, Mathijssen NM, Van Egmond JC, Verbeek BM, Vehmeijer SB. The first 6 weeks of recovery after primary total hip arthroplasty with fast track. Acta Orthop. 2017;88(2):140-4.
13. Van Egmond JC, Verburg H, Mathijssen NM. The first 6 weeks of recovery after total knee arthroplasty with fast track. Acta Orthop. 2015;86(6):708-13.
14. Devlin NJ, Parkin D, Browne J. Patient-reported outcome measures in the NHS: new methods for analysing and reporting EQ-5D data. Health Econ. 2010;19(8):886-905.
15. Perruccio AV, Stefan Lohmander L, Canizares M, Tennant A, Hawker GA, Conaghan PG, et al. The development of a short measure of physical function for knee OA KOOS-Physical Function Shortform (KOOS-PS) - an OARSI/OMERACT initiative. Osteoarthritis Cartilage. 2008;16(5):542-50.
16. Singh JA, Luo R, Landon GC, Suarez-Almazor M. Reliability and clinically important improvement thresholds for osteoarthritis pain and function scales: a multicenter study. J Rheumatol. 2014;41(3):509-15.

17. Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. J Bone Joint Surg Br. 1998;80(1):63-9.
18. Beard DJ, Harris K, Dawson J, Doll H, Murray DW, Carr AJ, et al. Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. J Clin Epidemiol. 2015;68(1):73-9.
19. Murray DW, Fitzpatrick R, Rogers K, Pandit H, Beard DJ, Carr AJ, et al. The use of the Oxford hip and knee scores. J Bone Joint Surg Br. 2007;89(8):1010-4.
20. Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology. A Practical Guide. Cambridge University Press. 2003.
21. Tolk JJ, Janssen RPA, Haanstra TM, van der Steen MC, Bierma-Zeinstra SMA, Reijman M. The influence of expectation modification in knee arthroplasty on satisfaction of patients: a randomized controlled trial. Bone Joint J. 2021;103-B(4):619-26.
22. Melnic CM, Paschalidis A, Katakam A, Bedair HS, Heng M, Committee MGBAP-ROW. Patient-Reported Mental Health Score Influences Physical Function After Primary Total Knee Arthroplasty. J Arthroplasty. 2021 Apr;36(4):1277-1283.
23. Sorel JC, Veltman ES, Honig A, Poolman RW. The influence of preoperative psychological distress on pain and function after total knee arthroplasty: a systematic review and meta-analysis. Bone Joint J. 2019;101-B(1):7-14.
24. Hafkamp FJ, de Vries J, Gosens T, den Oudsten BL. The Relationship Between Psychological Aspects and Trajectories of Symptoms in Total Knee Arthroplasty and Total Hip Arthroplasty. J Arthroplasty. 2021;36(1):78-87.
25. Wood TJ, Gazendam AM, Kabali CB, Hamilton Arthroplasty G. Postoperative Outcomes Following Total Hip and Knee Arthroplasty in Patients with Pain Catastrophizing, Anxiety, or Depression. J Arthroplasty. 2021 Jun;36(6):1908-1914.
26. Tristaino V, Lantieri F, Tornago S, Gramazio M, Carriere E, Camera A. Effectiveness of psychological support in patients undergoing primary total hip or knee arthroplasty: a controlled cohort study. J Orthop Traumatol. 2016;17(2):137-47.
27. Sorel JC, Overvliet GM, Gademan MGJ, den Haan C, Honig A, Poolman RW. The influence of perioperative interventions targeting psychological distress on clinical outcome after total knee arthroplasty. Rheumatol Int. 2020;40(12):1961-86.
28. Mercurio M, Gasparini G, Carbone EA, Galasso O, Segura-Garcia C. Personality traits predict residual pain after total hip and knee arthroplasty. Int Orthop. 2020;44(7):1263-70.
29. Luna IE, Kehlet H, Peterson B, Wede HR, Hoevsgaard SJ, Aasvang EK. Early patient-reported outcomes versus objective function after total hip and knee arthroplasty: a prospective cohort study. Bone Joint J. 2017;99-B(9):1167-75.
30. Fransen BL, Mathijssen NMC, Slot K, de Esch NHH, Verburg H, Temmerman OPP, et al. Gait quality assessed by trunk accelerometry after total knee arthroplasty and its association with patient related outcome measures. Clin Biomech (Bristol, Avon). 2019;70:192-6.

Chapter 5

Three distinct recovery patterns following primary total knee arthroplasty: Dutch arthroplasty register study of 809 patients

J.C. van Egmond, MD[1]
B. Hesseling, MSc[1]
M. Melles, PhD[2,3]
S.B.W. Vehmeijer, MD, PhD[1]
L.N. van Steenbergen, PhD[4]
N.M.C. Mathijssen, PhD[1]
J.T. Porsius, PhD[5,6]

Knee Surg Sports Traumatol Arthrosc. 2021 Feb;29(2):529-539

[1] Department of Orthopedic Surgery, Reinier de Graaf Groep, Delft, the Netherlands
[2] Faculty of Industrial Design Engineering, Delft University of Technology, Delft, the Netherlands
[3] Department of Public and Occupational Health, Amsterdam Public Health Research Institute, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[4] Dutch Arthroplasty Register (Landelijke Registratie Orthopedische Implantaten/LROI), Hertogenbosch, the Netherlands
[5] Integrated Brain Health Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, USA
[6] Department of Rehabilitation Medicine and the Department of Plastic and Reconstructive Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

ABSTRACT

Purpose

Total knee arthroplasty (TKA) is usually effective, although not all patients have satisfactory outcomes. This assumes distinct recovery patterns might exist. Little attention has been paid to determine which patients have worse outcomes. This study attempts to distinguish specific recovery patterns using the Oxford knee score (OKS) during the first postoperative year. The secondary aim was to explore predictors of less favorable recovery patterns.

Methods

Analysis of patients in the Dutch Arthroplasty Register (LROI) with unilateral primary TKA. Data collected up to one year postoperative was used. To identify subgroups of patients based on OKS, latent class growth modeling (LCGM) was used. Moreover, multivariable multinomial logistic regression analysis was used to explore predictors of class membership.

Results

809 Patients completed three OKS during the first year postoperative and were included. LCGM identified three groups of patients; 'high risers' (most improvement during first 6-months, good 12-month scores 77%), 'gradual progressors' (continuous improvement during the first year 13%) and 'non responders' (initial improvement and subsequent deterioration to baseline score 10%). Predictors of least favorable class membership (OR, 95%CI) are EQ-5D items: VAS health score (0.83, 0.73–0.95), selfcare (2.22, 1.09–4.54) and anxiety/depression (2.45, 1.33–4.52).

Conclusion

Three recovery patterns after TKA were distinguished; 'high risers', 'gradual progressors' and 'non responders'. Worse score on EQ-5D items VAS health, selfcare, and anxiety/depression were correlated with the least favorable 'non responders' recovery pattern.

INTRODUCTION

Approximately 20% of patients reported being dissatisfied with the results of total knee arthroplasty (TKA).[1,2] To improve preoperative consultation and postoperative rehabilitation, better understanding of the differences in recovery patterns and the patient characteristics which are associated with pattern membership is needed.

A valuable statistical method to obtain insight into recovery patterns is latent class growth modeling (LCGM).[3] LCGM is a very suitable method when studying the results of TKA based not only on absolute or relative outcomes, but on the trajectory leading up to these outcomes.

Previous studies using LCGM to analyze pain and function trajectories during the first years after TKA were based on data from single institutions, and demonstrated considerable heterogeneity in recovery after TKA.[4-7]

However, it is still unclear yet whether this heterogeneity is best characterized by two or more than two distinct trajectories. In addition, there is limited information regarding predictors for distinct recovery trajectories. Therefore, trajectories of TKA recovery needs to be investigated in a large nationwide database. The findings will be more generalizable in comparison to single institutional data.

This present study will be the first that investigated TKA recovery trajectories in a large nationwide sample of patients from an arthroplasty registry. The primary objective was to characterize subgroups of patients after TKA according to their Oxford knee score (OKS). The second objective was to determine which patient characteristics were associated with a negative trajectory class membership. The outcome of this study will increase insight into recovery trajectories after primary TKA and might provide indications to further improve and personalize quality of care.

MATERIALS AND METHODS

Data were retrieved from the Dutch Arthroplasty Register (Landelijke Registratie Orthopedische Implantaten: LROI). The LROI started collecting patient-related outcome measures (PROMS) in 2014.[8] The registry includes 99% of all arthroplasties performed in general hospitals, university hospitals and private clinics in the Netherlands.[9,10]

All data obtained from the LROI database were prospectively collected. All patients with primary unilateral TKA for osteoarthritis who were operated between January 2014 and December 2016 were included.

The OKS[11] determined preoperatively, and 6- and 12-months postoperatively were collected. Patients were excluded when the OKS was not completed at all these three time points. Data were also retrieved on the following patient characteristics: age, sex,

smoking, American Society of Anaesthesiologists (ASA), Charnley score, body mass index (BMI) and any previous surgery. Previous surgery includes arthroscopy, osteotomy, anterior cruciate ligament repair, meniscectomy, osteosynthesis, patella realignment or synovectomy. Furthermore, the following additional PROMS were retrieved: Numeric Rating Scale (NRS) for pain, and EuroQol-5D-3L (EQ-5D).[12]

All data were registered as part of routine clinical care, and the present study placed no additional burden on the patient. Therefore, no ethical approval was necessary according to the Dutch Medical Research Involving Human Subjects Act (WMO). All data were handled in line with the Helsinki Declaration.

Statistical analysis

To clean the data and provide descriptive statistics of the overall sample IBM SPSS version 25 (IBM Corp. Armonk, NY: IBM Corp.) was used. To distinguish trajectories, latent class growth analysis (LCGA) and growth mixture modeling (GMM) analysis were performed in Mplus Version 8.1 (Los Angeles, CA: Muthén & Muthén). A p-value of 0.05 or less was considered statistically significant.

Outcome

The trajectories were based on reported problems with the operated knee, which were determined by means of the OKS. The OKS is based on 12 questions regarding pain and function of the knee. Total score ranges from 0 to 48 with higher scores indicating better function and less pain.[11]

Model selection

In this present study LCGM was used. One advantage of LCGM lies in the assumption that there are two or more unobserved subgroups with each their own intercept and slope (i.e., starting point and change over time), as opposed to conventional growth modeling which assumes a single population with one intercept and one slope. Another advantage is that it allows each subgroup to demonstrate a unique pattern of change over time; the subgroups do not need to display the same overall shape for recovery pattern.

Within LCGM, LCGA and GMM also differ from each other: where LCGA assumes there is no variability in growth factors within groups, GMM does allow within-group variability in growth factors.

Based on previous studies it was presumed that 2 to 4 classes could be identified.[4-7] Starting with a conventional growth model to assess the overall degree of heterogeneity between patients; in this model the intercept and slope variance was estimated as well as the covariance in the sample as a whole.[13] For a full exploration of distinct trajectories, 1-class to 6-class LCGA and GMM models were fitted and compared to the results of the conventional growth model. In all models, a latent basis model was specified for

the growth pattern preventing to force a predefined shape of recovery trajectory, such as a linear shape, onto the data.[14,15] This also allowed to estimate the amount of change between the preoperative measurement and the 12 months measurement (i.e., the estimated mean slopes in the models), while also estimating how much of that change occurred at 6 months (i.e., the estimated factor loading of the 6 months measurement).

In both the LCGA and GMM models, the pattern of change and the means of the growth factors were estimated per class. The free residual variances were estimated for the overall model only. In the LCGA models, variance and covariance are naturally restricted to zero. In the GMM models, variance and covariance were only estimated for the overall model, not per class.

There are no definitive decision criteria for the optimal number of classes. However, model specification and selection should be guided by theory, previous empirical findings, and initial examinations of the data.[14-16]

Model selection was based on a combination of indices of fit[15], including the following four indices: (1) visual inspection of the plots and parsimony, interpretability and clinical meaningfulness of the model; (2) the relative fit statistics Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC) and Adjusted BIC, where lower values indicate a better fit; (3) entropy, where higher values indicate a higher confidence in the correct classification of individuals; and (4) the Bootstrapped Likelihood Ratio Test (BLRT). Based on these criteria, a final model was chosen to further explore patient characteristics associated with the different trajectories of recovery. All models were run with 500 random starting values and 20 final iterations, and subsequently rerun with 2000 random starting values and 400 final iterations to ensure that the optimal solution was found. Common procedures were followed to check whether models were local solutions.[17]

The r3step procedure in Mplus was used to perform univariable and multivariable multinomial logistic regression analyses, in which the smaller subgroups of patients were compared to the largest group of patients.

Predictors

After selecting the final model, preoperative patient characteristics across the different classes were compared. Characteristics of interest included age (dichotomized into ≤ 75 years and > 75 years), sex, smoking, Charnley score, BMI (normal, overweight and obese), ASA (dichotomized into ASA I–II and III–IV) and previous surgery on the affected joint. Moreover, EQ-5D scores (depression, self-care, pain, daily activities, and VAS health score) were compared.[18] EQ-5D scores were dichotomized (no problems vs. moderate-to-severe problems) if group sizes became too small for subgroup analysis.

RESULTS

Patient characteristics

Complete preoperative OKS as well as 6- and 12-months postoperative OKS were available for 809 patients and were included in the analysis. Table 1 presents all patient characteristics for the whole group as well as for each class in the final model.

Selection of final model

The conventional one-class growth model showed a large amount of variability in preoperative OKS and longitudinal change. Although the fit statistics of LCGA and GMM models continued to improve up to a 6-class model, this started to flatten out above the 3-class model. (Table 2) In addition, group sizes became very small in models with more than 3-classes, and eventually the additional classes were not considered clinically relevant, since additional groups were slight variations of the 3-class model.

The smaller classes were more heterogeneous in the LCGA models than in the GMM models; because of this heterogeneity and the worse fit statistics of LCGA, was continued with the GMM models.

Based on a parsimonious solution, and on the combination of distinct trajectories, entropy and class sizes, the 3-class GMM model was chosen as final model (Fig. 1). In all models, the largest class was the most homogeneous and the other classes were more heterogeneous (Fig. 2). This 3-class model had an entropy of 0.868, and the average posterior class probability of all classes was above 0.70, which indicates good class separation (see appendix for additional information).[15,19]

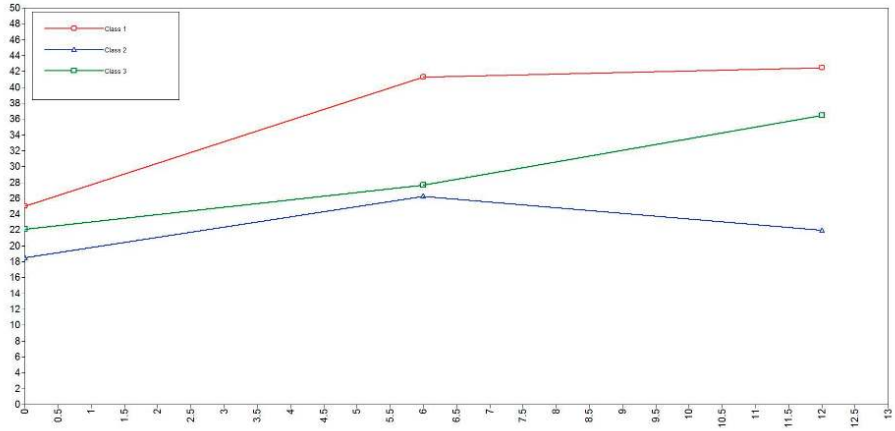


Figure 1. *Trajectories patterns of GMM 3-class model. x-axis: time in months, y-axis: OKS score. Class 1, red, 'high risers', 623 patients, 77%. Class 2, green, 'gradual progressor', 108 patients, 13.4%. Class 3, blue, 'non responder', 78 patients, 9.6%*

	Entire sample *(n=809)*	High risers *(n=623, 77%)*	Gradual progressors *(n=108, 13.4%)*	Non responders *(n=78, 9.6%)*
Age, mean (SD) years	67.2 (8.1)	67.3 (7.8)	66.6 (9.1)	67.5 (9.1)
[95% CI]	[66.7 - 67.8]	[66.7 - 67.9]	[64.9 - 68.4]	[65.4 - 69.5]
Sex				
Male	296 (37%)	230 (37%)	43 (40%)	23 (30%)
Female	513 (63%)	393 (63%)	65 (60%)	55 (70%)
Smoking				
No	741 (93%)	575 (94%)	95 (89%)	71 (93%)
Yes	54 (7%)	37 (6%)	12 (11%)	5 (7%)
ASA score				
I-II	674 (83%)	530 (85%)	89 (82%)	55 (70%)
III-IV	134 (17%)	92 (15%)	19 (18%)	23 (30%)
BMI				
Normal weight (BMI 20-25)	143 (18%)	118 (19%)	16 (15%)	9 (12%)
Overweight (BMI 25-30)	354 (44%)	277 (45%)	45 (42%)	32 (41%)
Obese (BMI >30)	306 (38%)	223 (36%)	47 (43%)	36 (47%)
Previous surgery on affected knee				
No	524 (66%)	399 (65%)	73 (69%)	52 (67%)
Yes	274 (34%)	215 (35%)	33 (31%)	26 (33%)
Charnley score				
A	397 (49%)	308 (49%)	52 (48%)	37 (48%)
B1	234 (29%)	184 (30%)	32 (30%)	18 (23%)
B2	150 (19%)	111 (18%)	20 (19%)	19 (25%)
C	25 (3%)	18 (3%)	4 (4%)	3 (4%)
Pain at rest, mean (SD)	5.49 (2.42)	5.28 (2.42)	6.02 (2.32)	6.29 (2.36)
[95% CI]	[5.27 - 5.70]	[5.03 - 5.52]	[5.44 - 6.59]	[5.65 - 6.92]
Pain during activity, mean (SD)	7.54 (1.72)	7.40 (1.77)	7.79 (1.66)	8.20 (1.12)
[95% CI]	[7.39 - 7.70]	[7.22 - 7.58]	[7.38 - 8.20]	[7.90 - 8.50]
EQ-5D item 'Mobility'				
No problems	47 (5%)	40 (6%)	4 (4%)	3 (4%)
Some problems in walking about	754 (94%)	575 (93%)	104 (96%)	75 (96%)
Confined to bed	3 (1%)	3 (1%)	0 (0%)	0 (0%)
EQ-5D item 'Self-Care'				
No problems	692 (86%)	548 (88%)	89 (83%)	55 (71%)
Some problems washing or dressing	108 (13%)	68 (11%)	18 (17%)	22 (28%)
Unable to wash or dress	4 (1%)	3 (1%)	0 (0%)	1 (1%)
EQ-5D item 'Usual Activities'				
No problems	136 (17%)	109 (18%)	17 (16%)	10 (13%)
Some problems performing usual activities	628 (78%)	489 (79%)	84 (78%)	55 (70%)
Unable to perform usual activities	41 (5%)	22 (3%)	6 (6%)	13 (17%)
EQ-5D item 'Pain / Discomfort'				
No pain or discomfort	56 (7%)	45 (7%)	6 (5%)	5 (6%)
Moderate pain or discomfort	568 (71%)	452 (73%)	77 (72%)	39 (50%)
Extreme pain or discomfort	181 (22%)	123 (20%)	24 (23%)	34 (44%)
EQ-5D item 'Anxiety / Depression'				
Not anxious or depressed	638 (79%)	509 (82%)	82 (76%)	47 (60%)
Moderate anxious or depressed	146 (18%)	97 (16%)	22 (20%)	27 (35%)
Extremely anxious or depressed	22 (3%)	14 (2%)	4 (4%)	4 (5%)
EQ-5D VAS health score, mean (SD)	70.07 (17.77)	71.54 (17.52)	66.84 (17.66)	62.89 (17.77)
[95% CI]	[68.83 - 71.32]	[70.14 - 72.95]	[63.340 - 70.27]	[58.83 - 66.96]

All values are presented as n (%) unless otherwise specified
Abbreviation: BMI body mass index

Table 1. *Descriptive of the entire sample and of the three separated trajectories*

Fit statistics								Model parameters				
Class	LL	BIC	AIC	Adjusted BIC	BLRT	Entropy	Number of free parameters		Factor loading OKST1	Intercept (S.E.)	Slope (S.E.)	Patients per class N (%)
1 class	-7956.796	15967.104	15929.537	15941.699	-	-	8	Class 1	0.888	23.94 (0.257)	15.70 (0.303)	809 (100%)
2 class	-7847.715	15766.963	15710.613	15728.856	p <0.001	0.911	12	Class 1	1.453	18.74 (0.876)	4.88 (1.027)	98 (12,1%)
								Class 2	0.866	24.61 (0.275)	17.31 (0.306)	711 (87.9%)
3 class	-7802.348	15649.355	15574.222	15598.546	p <0.001	0.868	16	Class 1	0.931	24.97 (0.315)	17.49 (0.357)	623 (77.0%)
								Class 2	2.371	18.73 (1.151)	3.17 (0.901)	78 (9.6%)
								Class 3	0.368	22.41 (0.807)	14.10 (0.962)	108 (13.4%)
4 class	-7771.111	15603.443	15509.527	15539.931	p <0.001	0.860	20	Class 1	0.919	25.27 (0.328)	17.90 (0.457)	584 (72.2%)
								Class 2	3.698	15.31 (3.130)	2.20 (0.865)	36 (4.4%)
								Class 3	0.322	22.49 (0.994)	16.39 (1.899)	68 (8.4%)
								Class 4	1.023	20.76 (1.230)	9.28 (2.659)	121 (15.0%)
5 class	-7734.763	15580.138	15467.439	15503.924	p <0.001	0.848	24	Class 1	0.917	25.57 (0.336)	18.46 (0.399)	496 (61.3%)
								Class 2	0.853	19.69 (1.015)	6.64 (1.249)	63 (7.8%)
								Class 3	0.957	22.62 (0.828)	12.71 (0.872)	161 (19.9%)
								Class 4	0.314	22.39 (1.147)	17.44 (1.743)	57 (7.0%)
								Class 5	6.406	15.59 (1.657)	1.23 (0.481)	32 (4.0%)
6 class	-7712.834	15551.565	15420.082	15462.648	p <0.001	0.863	28	Class 1	0.542	22.52 (0.728)	15.64 (0.822)	134 (16.6%)
								Class 2	0.927	22.51 (0.332)	18.51 (0.483)	500 (61.8%)
								Class 3	1.272	22.22 (1.165)	10.84 (1.570)	85 (10.5%)
								Class 4	5.506	15.41 (2.000)	1.50 (0.745)	31 (3.8%)
								Class 5	-0.108	24.25 (2.081)	18.88 (2.342)	9 (1.1%)
								Class 6	0.682	19.45 (1.221)	6.62 (1.666)	50 (6.2%)

LL = loglikelihood, BIC = Bayesian Information Criterion, AIC = Akaike Information Criterion, BLRT = Bootstrapped Likelihood Ratio Test, S.E. = Standard Error

Table 2. *Fit statistics of GMM model*

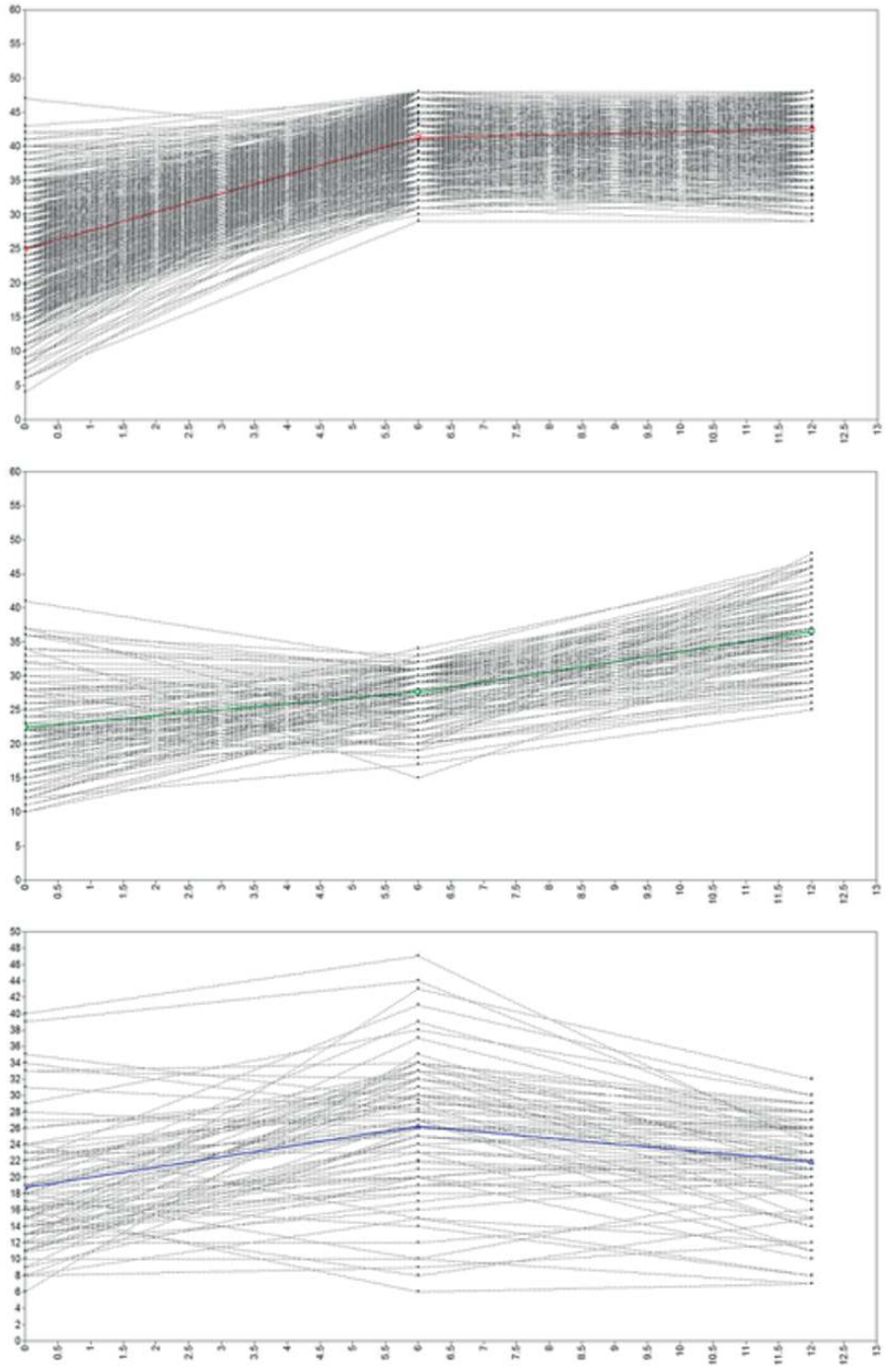


Figure 2. *Individual group plots for each class. High risers, gradual progressors, non responders*

The largest group was labelled as 'high risers', since this group continued to improve after most of the improvement on OKS was obtained during the first six months. The middle group was labelled as 'gradual progressors' due to the subsequent improvement on OKS after a medium improvement during the first six months. The smallest group was labelled as 'non responders', since this patient group showed a deterioration in OKS after an initial improvement during the first six months after surgery. Table 3 presents preoperative and 6-month and 12-month postoperative OKS for each class.

OKS	Entire sample (n=809)	High risers (n=623)	Gradual progressors (n=108)	Non responders (n=78)
Preoperative	23.94 (7.30) [23.44-24.44]	24.93 (7.00) [24.38-25.38]	22.27 (6.90) [20.95-23.58]	18.35 (7.37) [16.69-20.01]
6 months postoperative	37.89 (7.90) [37.34-38.43]	41.25 (4.47) [40.90-41.61]	27.01 (4.04) [26.24-27.78]	26.05 (8.40) [24.15-27.94]
12 months postoperative	39.64 (7.84) [39.10-40.18]	42.46 (4.45) [42.11-42.81]	36.37 (5.50) [35.32-37.42]	21.65 (5.99) [20.30-23.00]
All OKS are presented as mean (±SD) [95% CI]				

Table 3. *OKS of entire sample and the three separated trajectories at the three time points*

Univariable analysis

For the univariable analysis, the largest group 'high risers' was chosen as the reference group. The following variables were significant (OR, 95% CI) for class membership of 'non responders': ASA ≥ III (2.65, 1.47–4.79) and low scores on the EQ-5D items self-care (3.65, 2.00–6.68), anxiety/depression (3.43, 1.96–5.98) and VAS health score (0.97, 0.96–0.99).

For the 'gradual progressors' the following variables were significant (OR, 95% CI) for class membership: smoking (2.23, 0.99–4.99) and the EQ-5D item VAS health score (0.98, 0.97–1.00).

Multivariable analysis

In the multivariable analysis all covariates were simultaneously entered. The largest group, 'high risers', was chosen as the reference group. Smoking was significant for the 'gradual progressors' group. The 'non responders' group was significantly associated with the EQ-5D items: self-care, and anxiety/depression, and VAS health score, whereas ASA ≥ III was no longer significant in multivariable analysis. (Table 4).

	Non responders vs. high risers		Gradual progressors vs. high risers	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age >75 years vs. ≤75 years	0.97 (0.44 – 2.16)	0.941	0.99 (0.38 – 2.55)	0.976
Sex (female)	1.51 (0.78 – 2.91)	0.221	0.82 (0.47 – 1.44)	0.493
Smoking	1.23 (0.42 – 3.65)	0.706	2.80 (1.14 – 6.92)	**0.025**
ASA III-IV vs. I-II	1.97 (0.99 – 3.93)	0.054	1.36 (0.57 – 3.24)	0.493
BMI				
Normal weight	1.0	-	1.0	-
Overweight (BMI 25 – 30)	1.58 (0.57 – 4.41)	0.380	1.28 (0.49 – 3.38)	0.613
Obese (BMI >30)	1.69 (0.59 – 4.81)	0.326	1.98 (0.73 – 5.35)	0.178
Previous surgery to the affected knee	1.05 (0.56 – 1.98)	0.882	1.04 (0.56 – 1.93)	0.910
Charnley score				
A	1.0	-	1.0	-
B1	0.67 (0.33 – 1.36)	0.265	0.94 (0.47 – 1.88)	0.849
B2	1.10 (0.53 – 2.30)	0.793	0.86 (0.38 – 1.94)	0.721
C	0.73 (0.19 – 2.85)	0.654	1.04 (0.27 – 3.99)	0.961
EQ-5D item 'Self-Care'				
No problems	1.0	-	1.0	-
Some problems or unable to wash or dress	2.22 (1.09 – 4.54)	**0.029**	1.63 (0.73 – 3.66)	0.236
EQ-5D item 'Usual Activities'				
No problems	1.0	-	1.0	-
Some problems or unable to perform usual activities	0.92 (0.35 – 2.42)	0.858	1.27 (0.54 – 2.99)	0.582
EQ-5D item 'Pain / Discomfort'				
No pain or discomfort	1.0	-	1.0	-
Moderate or extreme pain or discomfort	0.78 (0.27 – 2.20)	0.633	2.89 (0.14 – 58.82)	0.489
EQ-5D item 'Anxiety / Depression'				
Not anxious or depressed	1.0	-	1.0	-
Moderately or extremely anxious or depressed	2.45 (1.33 – 4.52)	**0.004**	1.26 (0.66 – 2.43)	0.482
EQ-5D VAS health score (per 10 points)	0.83 (0.73 – 0.95)	**0.005**	0.89 (0.77 – 1.04)	0.152

Table 4. *Multivariable analysis*

DISCUSSION

The most important finding of the present study was the identification of three subgroups with distinct recovery trajectories based on OKS after TKA. Of the subgroups, the 'high risers' could be interpreted as having the most favorable trajectory and 'non responders' as having the least favorable trajectory. Based on these present findings, as on those of previously conducted trajectory studies, patients after TKA cannot be regarded as one group and various trajectories exist.

The identification of a 'non responders' class in the present study is in line with previous studies that showed that at least one trajectory was unfavorable for pain or functional outcome.[5-7]

However, another group (gradual progressors) was identified with a distinctly less favorable recovery pattern as well. Together, these two groups comprise up to 24% of the included patients. Unfortunately, this dataset did not include information on how satisfied patients were with the results of TKA. Presumably the slower recovery of the 'gradual progressors' may have been associated with less satisfaction with TKA. Future research might be able to improve the understanding of how 'gradual progressors' differ from 'non responders' and might assess the consequences for satisfaction with the outcome of TKA.

The present study showed a negative effect of psychological factors and preoperative pain scores on the outcome of TKA, which is similar to previously published studies.[4,19,20] In this present study, membership of a less favorable class membership (non responders or gradual progressors) was associated with worse EQ-5D scores on the item's anxiety and depression. While the EQ-5D-3L has not been designed for diagnosing anxiety or depression, both anxiety and depression have been labelled as risk factors. These are potentially modifiable preoperative factors that may be used to achieve better postoperative outcome and satisfaction. This suggestion is in line with the findings of Tristaino et al. and Singh et al. who showed that psychological support in TKA patients led to a lower incidence of anxiety and depression and faster recovery.[21,22]

The multivariable analysis included the ASA score, the Charnley score and the EQ-VAS. These three scores could theoretically be influenced by each other and could interfere with the multivariable analysis. However, since the multivariable analysis was explorative, all three parameters were included.

Age was pragmatically chosen to be dichotomized at age of 75, since literature is not clear on the age at which outcome of TKA deteriorates. However, the threshold of around 75 years has been used before in previous studies to dichotomize age groups.[23]

In the present study, obesity was not found to be a risk factor for less favorable class membership. This is in line with the study of Baker et al. who found no difference in OKS and EQ-5D between groups based on BMI.[24] These results are in contrast to the findings of Dowsey et al.[7] and Sing et al.[25], who showed obesity was a risk factor for less favorable class membership. This difference may be explained by a difference in follow-up time, since this present study investigated trajectories of the first postoperative year, whereas Dowsey et al. and Singh et al. have a follow-up of 5 years. Furthermore, this present study used OKS, whereas Dowsey et al. used the KSS; slight differences in the content of these questionnaires may lead to differences in the effect of BMI on the outcome scores.

An unexpected and important finding is that smoking was a significant characteristic of class membership for 'gradual progressors'. This is in contrast to previously published trajectory studies, which did not consider smoking a risk factor in TKA recovery, even though it is known that worse patient-related outcomes are found in smokers.[26] Moreover, it has been shown that smoking cessation before surgery may improve post-

operative outcomes.[27] Since the number of smoking patients in this present study was relatively small, however, this outcome should be interpreted with caution.

A strength of this study is the large group of patients (n=809), which to the best of our knowledge is the largest so far of all studies that attempted to identify distinct trajectories after TKA. Besides, using data from a national registry with a systematic approach increased the generalizability of these findings. This is a first step in better understanding heterogeneity in recovery after TKA.

There are several limitations that need to be addressed. The limitations mainly concern the fact that this is a retrospective analysis (although all data were prospectively collected), with all its known and unknown forms of bias and has missing data (patient characteristics).

Another limitation is that patients who did not complete all three OKS questionnaires were excluded from this analysis. These patients might have not completed all three OKS questionnaires due to, for example, revision surgery during their first year. As a result, 1.2% of all primary TKA of the study period were included, which nevertheless amounted to 809 patients (Table 5). The incompleteness of OKS data can only be partially explained by the fact that a subset of the patients had revision surgery within the first year. Additionally, although the LROI started registering PROMS in 2014, not all hospitals directly started collecting PROMS immediately. Methods of collecting PROMS also vary between hospitals which might have affect completeness of OKS. Besides, highly motivated and satisfied patients are likely more motivated to complete questionnaires, whereas TKA patients with complications would have been less likely to complete further OKS, although these patients would not represent the full 98%. Baseline characteristics between patients who completed OKS and those who did not or only partially completed OKS were statistically and clinically comparable. However, similarity of the groups cannot be based only on baseline patient characteristics.

A further limitation is that the intervals between the moments of completing OKS questionnaires were relatively long. Therefore, it is likely that different rehabilitation patterns and trajectories could be found if the OKS were determined more frequently or at other intervals.

The final limitation is that the LROI database does not include more detailed patient-related information, such as patient expectations, psychosocial questionnaires, and socio-economic status. Recently Zale et al. described the importance of psychosocial factors for orthopedic conditions.[28] Furthermore, implant properties (cruciate retaining, posterior stabilizing e.d.) were not analyzed; therefore, it is still unclear if these contribute to class membership or trajectory. However, considering that Dowsey et al.[7] found no relation between type of prosthesis and class membership in a multivariable logistic model, assuming that prosthesis type has no or little influence on trajectories.

Characteristics	No missing OKS *(n=809, 1.2%)*	1 or 2 missing OKS *(n=12.820, 18.4%)*	All OKS missing *(n=56.076, 80.4%)*
Age, mean (SD)	67.2 (8.1)	68.4 (8.7)	68.7 (9.1)
Sex			
Female	63.4%	62.4%	64.6%
Male	36.6%	37.6%	35.4%
BMI			
Underweight	0.1%	0.1%	0.2%
Normal weight	17.7%	16.5%	16.4%
Overweight	44.1%	41.8%	41.1%
Obesity	36.5%	38.3%	38.4%
Morbid obesity	1.6%	3.3%	4.0%
ASA			
I	13.7%	14.3%	14.7%
II	69.7%	70.0%	69.3%
III-IV	16.6%	15.7%	16.0%
Charnley score			
A	49.3%	45.3%	42.7%
B1	29.0%	32.8%	34.7%
B2	18.6%	18.9%	20.0%
C	3.1%	3.0%	2.6%
Smoking			
No	93.2%	91.0%	90.2%
Yes	6.8%	9.0%	9.8%
OKS: Oxford knee score			

Table 5. *Comparison of preoperative patient characteristics between patients with no, some and all OKS scores missing*

CONCLUSIONS

Three distinct recovery patterns were found after primary unilateral TKA, namely ‘high risers’, ‘gradual progressors’ and ‘non responders’. Predictors for class membership of ‘non responders’ are the EQ-5D items self-care and anxiety/depression and the VAS health score. This study provides surgeons with risk factors that may help them predict which patients will face less favorable recovery trajectories.

ACKNOWLEDGEMENTS

The authors would like to thank LROI for using the data. Moreover, we would like to thank the Van Rens Fonds for financially supporting this study.

AUTHOR CONTRIBUTION

JE performed data-analysis, he wrote and revised the manuscript for important intellectual content. BH supported data-analysis and critically reviewed the manuscript for important intellectual content. MM designed the study and critically reviewed the manuscript for important intellectual content. SV designed the study and critically reviewed the manuscript for important intellectual content and wrote the funding application. LS designed the study, provided data from the Dutch Arthroplasty Register (LROI) and critically reviewed the manuscript for important intellectual content. NM designed the study, supported data analysis and critically reviewed the manuscript for important intellectual content. JP designed the study, supported data analysis, critically reviewed the manuscript for important intellectual content and wrote the funding application. All authors approved the final version of the manuscript.

FUNDING

This study was funded by the Van Rens Fonds Foundation (VRF2017-005), The Netherlands.

REFERENCES

1. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KD. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clin Orthop Relat Res. 2010;468(1):57-63.
2. Baker PN, van der Meulen JH, Lewsey J, Gregg PJ, National Joint Registry for E, Wales. The role of pain and function in determining patient satisfaction after total knee replacement. Data from the National Joint Registry for England and Wales. J Bone Joint Surg Br. 2007;89(7):893-900.
3. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol. 2010;6:109-38.
4. Lindberg MF, Miaskowski C, RustoEn T, Rosseland LA, Cooper BA, Lerdal A. Factors that can predict pain with walking, 12 months after total knee arthroplasty. Acta Orthop. 2016;87(6):600-6.
5. Page MG, Katz J, Romero Escobar EM, Lutzky-Cohen N, Curtis K, Fuss S, et al. Distinguishing problematic from nonproblematic postsurgical pain: a pain trajectory analysis after total knee arthroplasty. Pain. 2015;156(3):460-8.
6. Dumenci L, Perera RA, Keefe FJ, Ang DC, Slover J, Jensen MP, et al. Model-Based Pain and Function Outcome Trajectory Types for Patients Undergoing Knee Arthroplasty: A Secondary Analysis from a Randomized Clinical Trial. Osteoarthritis Cartilage. 2019 Jun;27(6):878-884.
7. Dowsey MM, Smith AJ, Choong PFM. Latent Class Growth Analysis predicts long term pain and function trajectories in total knee arthroplasty: a study of 689 patients. Osteoarthritis Cartilage. 2015;23(12):2141-9.
8. Dutch Arthroplasty Register (in Dutch: LROI). Online LROI-Rapportage 2016: Blik op uitkomsten. http://wwwlroi-rapportage.nl/media/pdf/PDF%20Online%20LROI-Rapportage%202016pdf. Assessed 9 Jan 2020
9. van Steenbergen LN, Denissen GA, Spooren A, van Rooden SM, van Oosterhout FJ, Morrenhof JW, et al. More than 95% completeness of reported procedures in the population-based Dutch Arthroplasty Register. Acta Orthop. 2015;86(4):498-505.
10. Dutch Arthroplasty Register (in Dutch: LROI). Online LROI annual report 2017. https://www.lroi-rapportage.nl/media/pdf/PDF%20LROI%20annual%20report%202017.pdf. Accessed 11 Nov 2019
11. Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. J Bone Joint Surg Br. 1998;80(1):63-9.
12. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337-43.
13. Jung T, Wickrama K. An introduction to latent class growth analysis and growth mixture modeling. Soc Personal Psychol Compass. 2008;2(1):302-17.
14. Berlin KS, Parra GR, Williams NA. An introduction to latent variable mixture modeling (part 2): longitudinal latent class growth analysis and growth mixture models. J Pediatr Psychol. 2014;39(2):188-203.
15. Ram N, Grimm KJ. Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups. Int J Behav Dev. 2009;33(6):565-76.
16. van de Schoot R, Sijbrandij M, Depaoli S, Vermunt JK. The GRoLTS-Checklist: Guidelines for Reporting on Latent Trajectory Studies. Structural Equation Modeling: A Multidisciplinary Journal. 2017(24):451–67.
17. Wickrama KAS, Lee TK. Higher-Order Growth Curves and Mixture Modeling with Mplus: A Practical Guide. 2016.

18. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
19. Nagin DS. Group-Based Modeling of Development. Harvard University Press. 2005.
20. Vissers MM, Bussmann JB, Verhaar JA, Busschbach JJ, Bierma-Zeinstra SM, Reijman M. Psychological factors affecting the outcome of total hip and knee arthroplasty: a systematic review. Semin Arthritis Rheum. 2012;41(4):576-88.
21. Singh JA, Lewallen DG. Medical and psychological comorbidity predicts poor pain outcomes after total knee arthroplasty. Rheumatology (Oxford). 2013;52(5):916-23.
22. Tristaino V, Lantieri F, Tornago S, Gramazio M, Carriere E, Camera A. Effectiveness of psychological support in patients undergoing primary total hip or knee arthroplasty: a controlled cohort study. J Orthop Traumatol. 2016;17(2):137-47.
23. Kuperman EF, Schweizer M, Joy P, Gu X, Fang MM. The effects of advanced age on primary total knee arthroplasty: a meta-analysis and systematic review. BMC Geriatr. 2016;16:41.
24. Baker P, Petheram T, Jameson S, Reed M, Gregg P, Deehan D. The association between body mass index and the outcomes of total knee arthroplasty. J Bone Joint Surg Am. 2012;94(16):1501-8.
25. Singh JA, O'Byrne M, Harmsen S, Lewallen D. Predictors of moderate-severe functional limitation after primary Total Knee Arthroplasty (TKA): 4701 TKAs at 2-years and 2935 TKAs at 5-years. Osteoarthritis Cartilage. 2010;18(4):515-21.
26. Halawi MJ, Allen DA, Baron S, Savoy L, Williams VJ, Cote MP. Tobacco Smoking Independently Predicts Lower Patient-Reported Outcomes: New Insights on a Forgotten Epidemic. J Arthroplasty. 2019 Jul;34(7S):S144-S147.
27. Zhao S, Chen F, Wang D, Wang H, Han W, Zhang Y. Effect of preoperative smoking cessation on postoperative pain outcomes in elderly patients with high nicotine dependence. Medicine (Baltimore). 2019;98(3):e14209.
28. Zale EL, Ring D, Vranceanu AM. The Future of Orthopaedic Care: Promoting Psychosocial Resiliency in Orthopaedic Surgical Practices. J Bone Joint Surg Am. 2018;100(13):e89.

APPENDIX

MATERIALS AND METHODS

Difference between conventional growth models, LCGA and GMM

As described in the method section, LCGA and GMM differ from conventional growth models in their assumptions of the underlying population. Conventional growth models assume that all patients are drawn from a single population and, therefore, using one intercept (initial status) and one slope (change over time) sufficiently describes overall growth in that population. LCGA and GMM assume there are two or more unobserved subgroups and that each subgroup has its own intercept and slope to reflect the growth.

LCGA and GMM also differ from each other. Where LCGA assumes there is no variability in growth factors within groups, GMM does allow within-group variability in growth factors. More detailed explanation on both approaches can be found in the papers by Jung and Wickrama and Berlin et al.[1,2]

Model specification

Model specification and selection should be guided on theory, previous empirical findings and initial examinations of the data.[2-4] The study started with a conventional growth model to assess the overall degree of heterogeneity between patients; in this model the intercept and slope variance was estimated as well as the covariance in the sample as a whole (see Jung and Wickrama[1]).

Both LCGA and GMM models were fitted with 1-class to 6-class and compared with the results to the conventional growth model. The pattern of change and the means of the growth factors were estimated per class in both the LCGA and GMM models. The free residual variances were estimated for the overall model only. In the LCGA models, variance and covariance are naturally restricted to zero. In the GMM models, variance and covariance were only estimated for the overall model, not per class. All models were run with 500 random starting values and 20 final iterations, and subsequently rerun with 2000 random starting values and 400 final iterations to ensure the optimal solution was found.

Model selection

As advised by Ram and Grimm[3] model selection was based on a combination of:

1) visual inspection of the plots and parsimony, interpretability and clinical meaningfulness of the model (for example, a model with a higher number of classes may have a better fit, but may be less meaningful or more difficult to interpret compared to a model with a lower number of classes with worse fit statistics);

2) the relative fit statistics Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC) and Adjusted BIC (lower values indicate a better fit);
3) entropy, where a higher entropy indicates a higher confidence in the correct classification of individuals;
4) Bootstrapped Likelihood Ratio Test (BLRT).

Based on these criteria one final model was chosen to further explore patient- and surgical characteristics associated with the different trajectories of recovery.

RESULTS

Selection of the final model

The conventional one-class growth model showed a large amount of variability in preoperative OKS scores and longitudinal change. Subsequently, LCGA and GMM models were ran from one to six classes. In both the LCGA and GMM models, the BIC, adjusted BIC and AIC all continued to improve up to the six-class model. After the three-class models, the improvement of fit statistics started to flatten out. The entropy (Table 3) was sufficiently high (>0.80 for all models)[3], although it decreased somewhat for every class added to the models.

In both the LCGA and GMM models the largest class was always the most homogeneous. The smaller classes were more heterogeneous in the LCGA models than in the GMM models; because of this and the worse fit statistics, the study continued with the GMM models.

A clearly different type of trajectory emerged from each new added class up to the 3-class GMM model. After that, each new class was a slight variation on these three distinct trajectories. In addition, some classes became so small that clinical meaningfulness was limited.

For these reasons, the 3-class GMM model was chosen as the final model.

REFERENCES

1. Jung T, Wickrama KAS (2008) An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. Social and Personality Psychology Compass 2:302-317
2. Berlin KS, Parra GR, Williams NA (2014) An introduction to latent variable mixture modeling (part 2): longitudinal latent class growth analysis and growth mixture models. J Pediatr Psychol 39:188-203
3. Ram N, Grimm KJ (2009) Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups. Int J Behav Dev 33:565-576
4. van de Schoot R, Sijbrandij M, Winter SD, Depaoli S, Vermunt JK (2017) The GRoLTS-Checklist: Guidelines for Reporting on Latent Trajectory Studies. Structural Equation Modeling 24:451-467

Part III

Optimizing fast-track protocols for total knee arthroplasty

Chapter 6

Optimal dose of intrathecal isobaric bupivacaine in total knee arthroplasty

J.C. van Egmond, MD[1]
H. Verburg, MD[1]
E.A. Derks, MD[2]
P.N.J. Langendijk, PharmD[3]
C. Içli, BSc[1]
N.T. van Dasselaar, MD, PhD[2]
N.M.C. Mathijssen, PhD[1]

Can J Anaesth. 2018 Sep;65(9):1004–1011

[1] Department of Orthopedic Surgery, Reinier de Graaf Groep, Delft, the Netherlands
[2] Department of Anesthesiology, Reinier de Graaf Groep, Delft, the Netherlands
[3] Department of Pharmacy, Reinier de Graaf Groep, Delft, the Netherlands

ABSTRACT

Purpose

Early mobilization is an important aspect of fast-track protocols and intrathecal bupivacaine is often used in primary total knee arthroplasty (TKA). Although the optimal dose is not known, conventional doses leave patients unable to mobilize for two to four hours. The dose of an intrathecally administered local anesthetic should therefore be optimized to achieve immediate postoperative mobilization. This study determined the median effective dose (ED) of intrathecal bupivacaine for primary unilateral TKA.

Methods

Between April 2016 and February 2017 all patients who qualified for unilateral primary TKA were eligible for inclusion. In this dose-finding study, the up-and-down method by Dixon and Massey was used, which is a sequential allocation model. Patients received a dose of isobaric bupivacaine according to the outcome of the preceding patient with an initial starting dose of 5 mg. The dose was increased or decreased by steps of 0.5 mg, depending on the outcome of the preceding patient. During surgery, patients were closely monitored for indications of pain. Time points of regaining motor and sensory functions were determined.

Results

Twenty-five patients were included. Mean (SD) age was 70.1 (8.8) year old, median [IQR] body mass index was 29.5 [27.3-30.9 $kg \cdot m^{-2}$], and 48% were female. In 11 patients the dose was inadequate; of these, nine patients needed additional anesthesia during surgery, and in four of these nine patients a conversion to general anesthesia was required. The median ED was 3.5 (95% confidence interval [CI], 3.1 to 4.0) mg of intrathecal bupivacaine. The calculated ED50 was 3.4 (95% CI, 2.7 to 4.0) mg; the calculated ED95 was 5 (95% CI, 3.7 to 8.0) mg.

Conclusion

In this small study with tight control over operative duration, the median effective dosage of intrathecal isobaric bupivacaine for primary unilateral TKA was 3.5 mg and the ED95 was 5 mg. Reduction of conventional dosages of intrathecal bupivacaine is feasible at centers using fast-track arthroplasty protocols.

INTRODUCTION

During the last decades, fast-track protocols have been introduced for total knee arthroplasty (TKA), which have reduced the length of hospital stay without an increase of complications and readmissions.[1,2] Early mobilization is an important aspect of these fast-track protocols.[3] Therefore, they create new challenges in anesthesia protocols requiring dose optimization to allow immediate postoperative mobilization.[4,5]

In fast-track TKA, intrathecal anesthesia is preferred over general anesthesia because of lower mortality and morbidity rates.[6-9] Moreover, spinal anesthesia yields lower postoperative pain scores and less nausea and vomiting after TKA.[10,11]

Current dosages of intrathecal bupivacaine interfere with immediate postoperative mobilization and often leave patients unable to mobilize for two to four hours after surgery, which prolongs hospital stay.[3] Awad et al. found significantly earlier recovery room discharge after TKA with low-dose (5 mg) isobaric bupivacaine in combination with a femoral and sciatic nerve block compared with their standard 10mg dosage.[12]

We presume it might be feasible to reduce the dosage of bupivacaine to optimize the rehabilitation after primary TKA.

METHODS

The study was approved by the Institutional Review Board METCZWH (HagaZiekenhuis, Den Haag, the Netherlands, March 2016) and was registered in EudraCT (2016-000082-23). All included patients gave their written informed consent before enrolment.

Patients

All consecutive patients between April 2016 and February 2017 who qualified for unilateral primary TKA at Reinier de Graaf Hospital (Delft, the Netherlands) were eligible for inclusion. Inclusion criteria were: American Society of Anesthesiologists physical status I, II, or III, sufficient command of the Dutch language, willingness to participate, and being competent to decide.

Patients were excluded in cases of hypersensitivity to local anesthetics or any of the other excipients of bupivacaine and in cases with contraindications to intrathecal anesthesia. All patients were operated on by a single orthopedic surgeon (H.V.) and the same anteromedial approach and prosthesis (NexGen® LPS-High Flex Fixed Bearing Knee prosthesis; Zimmer®, Warsaw, IN, USA) was used in all patients. A tourniquet was not used on any of the patients during surgery.

Measurements

The primary outcome of this present study was the median effective dose (ED) of isobaric bupivacaine in primary TKA to allow immediate postoperative mobilization as well as adequate anesthesia during surgery. The up-and-down method as described by Dixon and Massey was used.[13,14] This is a sequential allocation model in which patients received a dose of isobaric bupivacaine according to the outcome of the preceding patient. A starting dose of the test sequence was set to 5 mg bupivacaine.

According to Gautier et al. intrathecal administration of 8 mg bupivacaine at level L3-4 will lead to a motor blockade of 100-225 min and a sensory blockade of 90-190 min.[15] Nevertheless, the mean surgery time for TKA is shorter; a duration (standard deviation, SD) of 83 (18) min was described by Lozano et al.[16]

To determine the dose of bupivacaine adequate for most patients, a threshold at the 95th percentile of mean surgery time for TKA was defined from our surgery statistics. In 2015, the mean duration of primary TKA surgery was 71 min at our institution. Nevertheless, surgery times ranged between 45 and 144 min. The 95th percentile of mean surgery time was 101 min. According to the Summary of Product Characteristics, the mean onset time of the sensory blockade is 15 min. This time was added to the mean surgery time; therefore, a threshold at 116 min after injecting intrathecal anesthesia was used. When no sensory blockage was reached within 15 min after administration, the start of surgery was postponed.

An adequate dose (no pain during surgery and regaining motor and sensory functions after 116 min) led to a decrease of 0.5 mg bupivacaine and an inadequate dose (pain during surgery) led to a 0.5 mg increase of bupivacaine for the subsequent patient (Fig. 1).

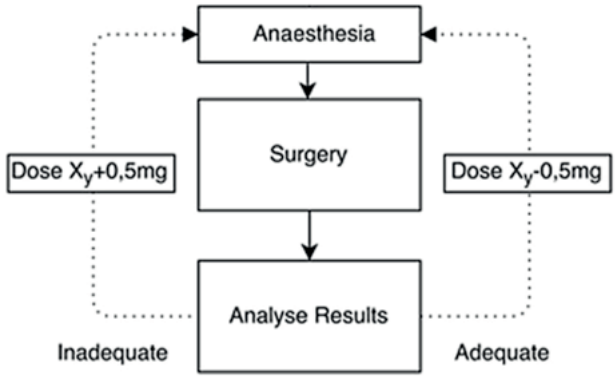


Figure 1. *Dose determination chart based on the up-and-down method by Dixon and Massey. Adequate = no pain during surgery, regaining motor and sensory functions after 116 min. Inadequate = patients were in pain during surgery*

To test the diminution of spinal blockade, patients received repetitive questions and tests with ten-minute intervals regarding sensory and motor functions from start of surgery (Fig. 2). During surgery, the heart rate and blood pressure were monitored to determine if the patient was in pain; since patients received propofol infusion to induce light sedation some were not always able to answer questions regarding pain during surgery. No pre-defined limits of heart rate or blood pressure were used. Changes in one or both were judged by the anesthesiologist and he/ she decided if the patient was in pain. Postoperatively, a pinprick test was performed by a trained investigator at dermatome L5 and S1 to test regained sensory functions. A small sharp wooden stick was used to prick the skin at the dorsum of both feet and the patient was asked if he/she experienced this as a sharp sensation. Moreover, the modified Bromage scale (grade 0 = no weakness; grade 1 = inability to raise extended leg; grade 2 = inability to flex knee; grade 3 = inability to move any joint in legs) was used to test motor functions.[17] If patients reached full recovery of the motor blockade (Bromage grade 0) and full recovery of the sensory blockade (positive pinprick test at S1 dermatome) after the threshold of 116 min after administration of anesthesia, the dose was adequate.

The single surgeon and his assistant, the patient, and the investigator (who performed the per- and postoperative tests) were all blinded to the used dosage of bupivacaine. Based on the outcome of the preceding patient, the dosage of the subsequent patient was determined by one of the researchers (N.M.) who only informed the anesthesiologist of the dose to be administered.

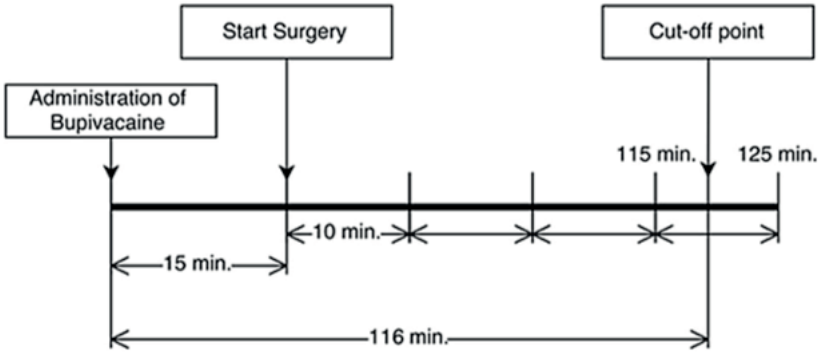


Figure 2. *Test interval time frame. Cut-off point is the predefined threshold of 116 min after administrating intrathecal anesthesia*

Anesthesia

All patients were admitted on the day of surgery. At admission, participants received 400 mg celecoxib, 1 g of paracetamol, and 600 mg of gabapentin on the ward. Furthermore, in the preoperative holding area, patients received dexamethasone 0.15 mg×kg^{-1} iv [18,19] as well as antibiotic prophylaxis; 0.5% isobaric bupivacaine (Marcaine® spinal 5 mg mL^{-1}; Aspen, Gorinchem, the Netherlands) was administered intrathecally at the L2-L3 or L3-L4 intervertebral space by an experienced anesthesiologist. The spinal block was performed in a dedicated block room. The patient was in a sitting position when the bupivacaine was administered and was put in supine position two minutes after injecting isobaric bupivacaine. Cerebrospinal fluid was aspirated before and after injection. Opiates were not administered to rule out possible side effects such as nausea, vomiting, or sedation, which might prolong the length of stay after surgery.[20,21]

All included patients received standard additional local infiltration anesthesia with 300 mg ropivacaine and 3 mg epinephrine around the knee joint during the end of surgery, conforming to our fast-track regimen. Propofol was continually administered for sedation and to allow a single shot of 15 mg esketamine iv without unwanted side effects. Esketamine was administered to prevent postoperative pain.[22,23] Propofol was given by target-controlled infusion (TCI), which is often used in anesthesia to control the concentration of selected drugs in the plasma or at the site of its effect. In our protocol, patients received propofol 1-2 μg×mL^{-1} set as target concentration administered through a TCI DiprifusorTM pump (Carefusion, Basingstoke, UK) using the Marsh model.[24]

If a patient showed signs of insufficient anesthesia during surgery, he/she received general anesthesia; the patient was then treated with propofol, remifentanil, and a laryngeal mask.

Statistical analysis

At least six independent pairs of patients with sufficient/insufficient anesthesia should provide reliable estimates of median ED using the up-and-down method by Dixon and Massey.[25] A group of 20 to 30 patients was sufficient to have six independent pairs of patients with response/no response. Therefore, a sample size of 25 patients was chosen for this study. Dixon and Massey's method was used to calculate the median ED with the 95% confidence interval (CI).[13,14] The average of the dose of the ''fail/success'' pair was chosen. The data were further analyzed; the ED50 and ED95 were calculated by the MASS package.[26] With the BOOT package, 1.000 bootstrap resamples were generated to determine the CI of the ED50 and ED95.[27] For statistical analysis, IBM SPSS statistics for Windows version 21 (IBM SPSS, Armonk, NY, USA) and R for Windows version 3.2.4 Revised (R Foundation for Statistical Computing, Vienna, Austria) were used.

RESULTS

Between April 2016 and February 2017, a total of 118 patients were eligible for inclusion. Twenty-five patients were included. Thirty-five patients were excluded because of contraindications to intrathecal anesthesia (anticoagulant use, spinal herniation/stenosis), eight patients were excluded for logistical reasons, five patients were excluded because of expected prolonged surgery time because of removal of plate osteosynthesis of previously performed osteotomy, and 45 patients were not willing to participate (Fig. 3).

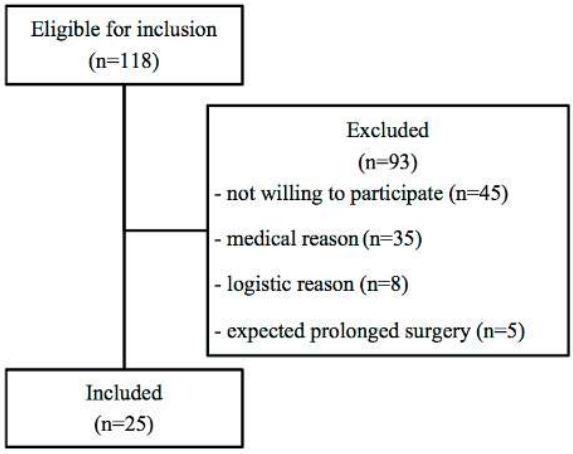


Figure 3. *Flowchart of patients*

The mean (SD) age of the included patients was 70.1 (8.8) year old, 12 (48%) patients were female, and in 15 patients (60%) the left knee was operated on. The mean (SD) height was 174 (9) cm [range, 158-191] and the median [interquartile range (IQR)] body mass index (BMI) was 29.5 [27.3 - 30.9] (Table 1).

Doses varied between 5.0 mg and 2.5 mg of bupivacaine. In 11 patients the dose was inadequate and the subsequent patient received an increased dose. Of these 11 patients, nine required additional intravenous analgesia and four of the nine patients also required a conversion to general anesthesia. The mean (SD) duration of sensory blockade in the total group was 118 (45) min. The mean (SD) motor blockade was 111 (24) min in all patients without general anesthesia (n = 21; Table 2). In all patients with sufficient intrathecal anesthesia during surgery, motor function was regained prior to sensory function.

The data sequence of adequate and inadequate doses is shown in Fig. 4. The median dose of bupivacaine resulting in adequate analgesic blockade at the threshold of 116 min was 3.5 mg (95% CI, 3.1 to 4.0). The ED50 and ED95 were, respectively, 3.4 (95% CI, 2.7 to 4.0) mg and 5.0 (95% CI, 3.7 to 8.0) mg.

	n= 25	25th-75th percentile	Range
Age, years	70.1 (8.8)		52 - 85
Gender, female	12 (48%)		
Side, left	15 (60%)		
Length, cm	174 (9)		158 - 191
BMI [median]	29.5 (IQR 3.3)	27.3-30.9	23.2 - 39.2
ASA 1	4 (16%)		
2	17 (68%)		
3	4 (16%)		

All values are presented as mean (standard deviation) or as n (%). BMI was not normally distributed; therefore, the 25th and 75th percentiles are presented
ASA = American Society of Anesthesiologists; BMI = body mass index

Table 1. *Patient characteristics*

	Total	Without additional anesthesia
Motor blockade	111 (24) (*n*=21)	115 (17) (*n*=16)
Sensory blockade	118 (45) (*n*=25)	141 (25) (*n*=16)

All values are mean (standard deviation)
Missing cases: no further motor blockade tests were performed after general anesthesia

Table 2. *Mean duration of blockade (minutes)*

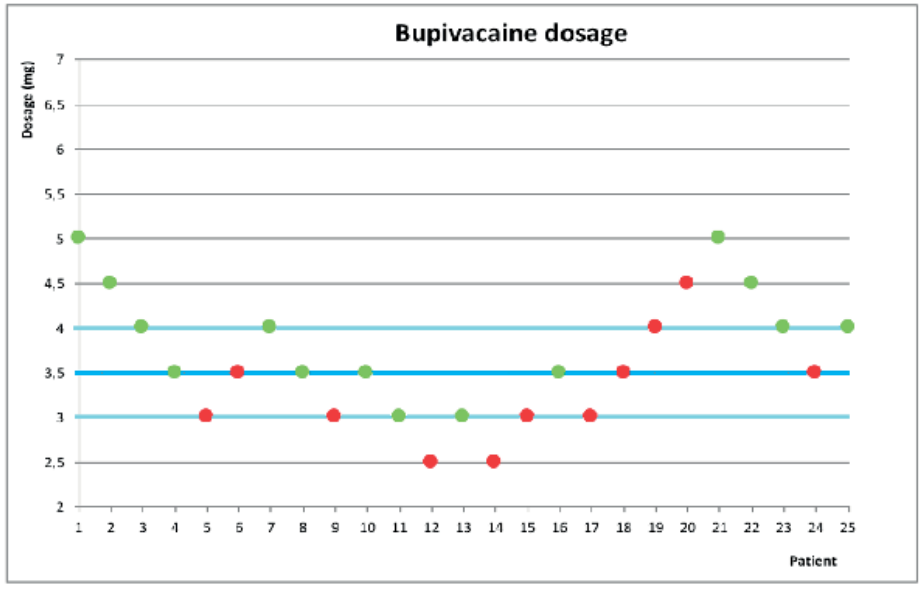


Figure 4. *Graphic of bupivacaine dosage during the study; each rhomb equals a patient.*
Green dot = adequate dosage; red dot = inadequate dosage

DISCUSSION

The goal of this dose-finding study was to determine the median ED of intrathecal bupivacaine that preserved adequate anesthesia during surgery. The outcome of this study might validate adjustments to the current anesthesia protocols, which might further optimize fast-track protocols.

The median ED in our study was 3.5 (95% CI, 3.1 to 4.0) mg bupivacaine, which is much less compared with the amount normally given in our hospital (6-8 mg) and the amounts of bupivacaine used in many previous studies. For example, the recent study of Harsten et al., which compared general anesthesia with spinal anesthesia for TKA, 15 mg bupivacaine was administered.[28] This study showed an overall favorable outcome for general anesthesia; however, no optimal dose of bupivacaine was used. Lowering the dosage could change the immediate postoperative outcomes in favor of spinal anesthesia.[29]

In the study of Awad et al. patients were randomized to 5 mg or 10 mg intrathecal bupivacaine in combination with a femoral and sciatic nerve block, and they found earlier post anesthesia care unit discharge and fewer voiding problems in the 5 mg group. In our study, voiding was not examined; therefore, no urine retention tests were presented. Based on the findings of Awad et al., lower doses of bupivacaine reduce the risk of urine retention. This needs to be examined in new studies.[12]

The results of our study are consistent with the recent study by Mathijssen et al. (unpublished data), which examined the median effective dose of bupivacaine in total hip arthroplasty (THA). In this study a median dose of 5.7 mg (95% CI 5.2 to 6.1) bupivacaine was sufficient for adequate anesthesia during primary unilateral THA surgery and allowed immediate postoperative mobilization.

No dose adjustments were made for bodyweight or height since no hard evidence has been found that this influences spinal anesthesia outcomes. One study has described that the duration of spinal blockade in obese patients appears to be prolonged.[30] Even though our patient group contained a wide variation of BMIs, we presume this had no influence on our outcomes. Moreover, of the 11 patients in whom the dosage was insufficient and the four patients who needed general anesthesia, the mean BMI was equal to that of the sufficient group (however, these numbers are small).

No dose adjustments were made for age, although age might affect motor blockade duration in which older patients requires less bupivacaine.[31] Since the mean age of our study population was not extensively spread and representative for the national age for TKA as found by the Dutch arthroplasty register, no subdivision based on age was made and the outcome was analyzed as one group.[32]

The predefined dose of bupivacaine was not diluted to maintain baricity. Various studies have shown that dosage is a more important factor than volume and concentra-

tion of local anesthetics when administered intrathecally and volume does not influence the maximal spread or sensory or motor blockade.[33,34]

There are some limitations of this study that need to be addressed.

First, we did not determine the exact moment of recurring motor and sensory functions. As practiced by other studies, a ten-minute interval for testing pinprick sensation is adequate to assess regained sensory functions.[35,36] Bhat et al. have shown that a ten-minute interval for the assessment of motor functions with the Bromage scale can be used.[37]

Second, the results of this study can only be used for primary unilateral TKA, since the dosage is determined on a threshold of the 95th percentile surgery time of primary unilateral TKA in a large teaching hospital. In complicated cases, revisions, or bilateral TKA, dose adjustments may be necessary.

Third, a substantial number of patients were excluded or refused to participate in this study (Fig. 3). Patients refused to contribute for various reasons, mostly because of fear of pain during surgery. A significant number of patients were excluded from intrathecal anesthesia because of anticoagulant medication, which was an exclusion criterion in this study. Although a substantial number of the eligible patients were excluded, we expected no bias since we included a representative patient group.

Fourth, no postoperative pain scores were reported. Moreover, no time to first postoperative mobilization was registered. Therefore, the clinical implications of our study are somewhat uncertain. Now that we have presented that lower dosages of bupivacaine are feasible, further studies are needed to determine the clinical effects on time to postoperative mobilization, incidence of urine retention, pain scores, and length of hospital stay. This is particularly true in teaching hospitals, where the duration of surgery can be highly variable.

Finally, no direct estimation of the ED95 can be made using the up-and-down method of Dixon and Massey. Therefore, the ED95 was calculated rather than directly observed.

In conclusion, the current dose of 10 mg of bupivacaine in primary TKA can be reduced. Using a lower dose of intrathecal isobaric bupivacaine is feasible in primary, well-planned unilateral TKA in conjunction with a preoperative multimodal analgesic regimen and perioperative sedation using propofol. For patients who are not good candidates for propofol, the intraoperative course might be quite different. The lower dosage of bupivacaine provided sufficient anesthesia in many patients, but the procedures had to be well planned regarding logistics and time management. In this small study with tight control over operative duration, the median effective dosage of intrathecal isobaric bupivacaine for primary unilateral TKA was 3.5 mg (95% CI, 3.1 to 4.0); the calculated ED95 was 5 mg (95% CI, 3.7 to 8.0).

The results of this present study might lead to the justification of lower doses of bupivacaine for intrathecal anesthesia in primary TKA. Consequently, the fast-track program can be further optimized.

ACKNOWLEDGEMENT

The authors thank all the patients as well as Nicole de Esch, Yvonne van Limburg, and Brechtje Hesseling, MSc., of the Orthopedic Department at the Reinier the Graaf Groep, Delft, the Netherlands, for their help with including patients for this study.

AUTHOR CONTRIBUTIONS

Jeroen C. van Egmond performed the data analysis and perioperative measurements and wrote and revised the manuscript. Hennie Verburg operated all of the included patients, designed the study, and critically reviewed the manuscript. Eveline A. Derks performed the spinal anesthesia in all patients and critically reviewed the manuscript. Pim N.J. Langendijk designed the study and critically reviewed the manuscript. Caner Içli performed most of the perioperative measurements and critically reviewed the manuscript. Nick T. van Dasselaar designed the study and critically reviewed the manuscript. Nina M.C. Mathijssen designed the study, supported data analysis, determined dosages, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

REFERENCES

1. Dowsey MM, Kilgour ML, Santamaria NM, Choong PF. Clinical pathways in hip and knee arthroplasty: a prospective randomised controlled study. Med J Aust 1999; 170: 59-62.
2. Barbieri A, Vanhaecht K, Van Herck P, et al. Effects of clinical pathways in the joint replacement: a meta-analysis. BMC Med 2009; 7: 32.
3. Husted H, Hansen HC, Holm G, et al. What determines length of stay after total hip and knee arthroplasty? A nationwide study in Denmark. Arch Orthop Trauma Surg 2010; 130: 263-8.
4. Tarkkila P, Huhtala J, Tuominen M. Home-readiness after spinal anaesthesia with small doses of hyperbaric 0.5% bupivacaine. Anaesthesia 1997; 52: 1157-60.
5. Turnbull ZA, Sastow D, Giambrone GP, Tedore T. Anesthesia for the patient undergoing total knee replacement: current status and future prospects. Local Reg Anesth 2017; 10: 1-7.
6. Pugely AJ, Martin CT, Gao Y, Mendoza-Lattes S, Callaghan JJ. Differences in short-term complications between spinal and general anesthesia for primary total knee arthroplasty. J Bone Joint Surg Am 2013; 95: 193-9.
7. Basques BA, Toy JO, Bohl DD, Golinvaux NS, Grauer JN. General compared with spinal anesthesia for total hip arthroplasty. J Bone Joint Surg Am 2015; 97: 455-61.
8. Wong PB, McVicar J, Nelligan K, Bleackley JC, McCartney CJ. Factors influencing the choice of anesthetic technique for primary hip and knee arthroplasty. Pain Manag 2016; 6: 297-311.
9. Memtsoudis SG, Sun X, Chiu YL, et al. Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. Anesthesiology 2013; 118: 1046-58.
10. Gonano C, Leitgeb U, Sitzwohl C, Ihra G, Weinstabl C, Kettner SC. Spinal versus general anesthesia for orthopedic surgery: anesthesia drug and supply costs. Anesth Analg 2006; 102: 524-9.
11. Sansonnens J, Taffe P, ADS Study Group. Higher occurrence of nausea and vomiting after total hip arthroplasty using general versus spinal anesthesia: an observational study. BMC Anesthesiol 2016; 16: 44.
12. Awad IT, Cheung JJ, Al-Allaq Y, Conroy PH, McCartney CJ. Low-dose spinal bupivacaine for total knee arthroplasty facilitates recovery room discharge: a randomized controlled trial. Can J Anesth 2013; 60: 259-65.
13. Dixon WJ, Massey FJ Jr. Introduction to Statistical Analysis. NY: McGraw-Hill; 1969. p. 344.
14. De Jonge H. Inleiding tot de Medische Statistiek II - Klassieke Methoden. Verhandeling van het Nederlands Instituut voor Praeventieve Geneeskunde XLVIII; 1960. Available from URL: https://publications.tno.nl/publication/34610624/gx31hc/jonge-1960-klassieke.pdf (accessed April 2018).
15. Gautier P, De Kock M, Huberty L, Demir T, Izydorczic M, Vanderick B. Comparison of the effects of intrathecal ropivacaine, levobupivacaine, and bupivacaine for caesarean section. Br J Anaesth 2003; 91: 684-9.
16. Lozano LM, Tio M, Rios J, et al. Severe and morbid obesity (BMI ≥ 35 kg/m(2)) does not increase surgical time and length of hospital stay in total knee arthroplasty surgery. Knee Surg Sports Traumatol Arthrosc 2015; 23: 1713-9.
17. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand Suppl 1965; 16: 55-69.
18. De Oliveira GS, Jr Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2011; 115: 575-88.

19. Lunn TH, Andersen LO, Kristensen BB, et al. Effect of high-dose preoperative methylprednisolone on recovery after total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. Br J Anaesth 2013; 110: 66-73.
20. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta Orthop 2011; 82: 679-84.
21. Jia XF, Ji Y, Huang GP, Zhou Y, Long M. Comparison of intrathecal and local infiltration analgesia by morphine for pain management in total knee and hip arthroplasty: a meta-analysis of randomized controlled trial. Int J Surg 2017; 40: 97-108.
22. Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. Anesth Analg 2005; 100: 475-80.
23. Remerand F, Le Tendre C, Baud A, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. Anesth Analg 2009; 109: 1963-71.
24. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth 1991; 67: 41-8.
25. Dixon WJ. The Up-and-Down method for small samples. J Am Stat Assoc 2012; 60: 967-78.
26. Venables WN, Ripley BD. Modern applied Statistics with S. 4th ed. NY: Springer; 2002.
27. Davison AC, Hinkley DV. Bootstrap Methods and their Applications. Cambridge: Cambridge University Press; 1997.
28. Harsten A, Kehlet H, Ljung P, Toksvig-Larsen S. Total intravenous general anaesthesia vs. spinal anaesthesia for total hip arthroplasty: a randomised, controlled trial. Acta Anaesthesiol Scand 2015; 59: 298-309.
29. Hansen TB. Fast track in hip arthroplasty. EFORT Open Rev 2017; 2: 179-88.
30. Kim HJ, Kim WH, Lim HW, et al. Obesity is independently associated with spinal anesthesia outcomes: a prospective observational study. PloS ONE 2015; 10: e0124264.
31. Chen M, Chen C, Ke Q. The effect of age on the median effective dose (ED50) of intrathecally administered plain bupivacaine for motor block. Anesth Analg 2014; 118: 863-8.
32. LROI-Rapportage. Orthopedische Implantaten in Beeld. 2014. Available from URL: https://www.lroi.nl/base/downloads/lroi- jaarrapportage-2014.pdf (accessed April 2018).
33. Bengtsson M, Malmqvist LA, Edstrom HH. Spinal analgesia with glucose-free bupivacaine–effects of volume and concentration. Acta Anaesthesiol Scand 1984; 28: 583-6.
34. Sheskey MC, Rocco AG, Bizzarri-Schmid M, Francis DM, Edstrom H, Covino BG. A dose-response study of bupivacaine for spinal anesthesia. Anesth Analg 1983; 62: 931-5.
35. Malinovsky JM, Renaud G, Le Corre P, et al. Intrathecal bupivacaine in humans: influence of volume and baricity of solutions. Anesthesiology 1999; 91: 1260-6.
36. Liu S, Kopacz DJ, Carpenter RL. Quantitative assessment of differential sensory nerve block after lidocaine spinal anesthesia. Anesthesiology 1995; 82: 60-3.
37. Bhat SN, Himaldev MU. Comparison of efficacy and safety of ropivacaine with bupivacaine for intrathecal anesthesia for lower abdominal and lower limb surgeries. Anesth Essays Res 2013; 7: 381-5.

Chapter 7

Perioperative systemic corticosteroids in primary unilateral total knee arthroplasty: a systematic review

J.C. van Egmond, MD[1]
F.W. van de Graaf, MD, PhD[2]
C.D. Niehot, BSc[3]
H. Verburg, MD[1]
N.M.C. Mathijssen, PhD[1]

(submitted)

[1] Department of Orthopedic Surgery, Reinier de Graaf Groep, Delft, the Netherlands
[2] Department of Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands
[3] Medical library, Erasmus University Medical Center, Rotterdam, the Netherlands

ABSTRACT

Background

Fast-track protocols have been developed to improve postoperative recovery and consequently reduce the length of hospital stay (LOS) after total knee arthroplasty (TKA). Main reasons for prolonged hospital stay are postoperative nausea and vomiting (PONV) and pain. Having a positive effect on both PONV and pain, perioperative administration of corticosteroids might improve rehabilitation and reduce LOS after TKA. In this systematic review, the effect of different corticosteroid dosages on PONV, pain, and LOS are delineated.

Patients and Methods

A systematic search for articles comparing dosage effects of corticosteroids regarding PONV, pain, and LOS after primary unilateral TKA was conducted using EMBASE, PubMed publisher, MEDLINE, Cochrane, Google scholar, and Web-of-Science for articles published form inception to March 17, 2022.

Results

16 studies were included involving 2352 TKA procedures. Most studies showed reduced pain scores in corticosteroid groups and some described better pain reduction in high-dose groups. All studies showed reduced PONV in the corticosteroid groups. LOS was similar in most studies comparing placebo and perioperative corticosteroids. Only one study reported increased infection rates and intramuscular venous thrombosis in the corticosteroid group.

Conclusion

Current literature on corticosteroids use in TKA is highly variable in type, dosage, and timing of administering medication. Overall, corticosteroids mostly reduce pain and PONV with limited effects on LOS after TKA. Only minimal statistically significant and clinically relevant benefits were found in perioperative high-dose corticosteroids compared to low-dose. Given the short follow-up in most studies, it is not possible to evaluate safety of high-dose corticosteroids.

INTRODUCTION

During the last decades fast-track protocols have been implemented to optimize rehabilitation after total knee arthroplasty (TKA). As a result, length of hospital stay (LOS) has been decreased and even TKA in an outpatient setting is feasible in selected patients.[1] However, optimizing analgesia and rehabilitation after TKA is challenging.[2]

Main reasons for prolonged hospital admission after TKA are postoperative nausea and vomiting (PONV), orthostatic intolerance, fatigue, and pain.[3,4] These symptoms are the result of a surgical stress response.[5] Adequately managing of these symptoms will lead to reduced LOS, improved patient satisfaction, and will further optimize fast-track rehabilitation.[1,6-8]

One of the most potent pharmacological interventions in reducing the surgical stress response are corticosteroids.[7,9] Corticosteroids have an anti-inflammatory effect by inhibiting the cyclooxygenase-2 (COX-2) signaling pathway which lead to a reduced local and systemic inflammatory response.[10] Corticosteroids have a proven beneficial effect on PONV and pain.[11-13] Therefore, interest has been raised for the use of corticosteroids in arthroplasty surgery.

However, despite the promising results of corticosteroids on pain and PONV, there are still concerns regarding the possible side effects of corticosteroids, including hyperglycemia, gastrointestinal hemorrhage, and particularly the risk of infection, preventing further implementation in daily clinical use. Moreover, uncertainty remain concerning the optimal timing, frequency, and dosage of corticosteroids.[12]

We hypothesized that the effect of corticosteroids is dose-depended, therefore high-dose of corticosteroids would improve early recovery and reduce LOS, pain, and PONV to a larger extend than low-dose corticosteroids in primary unilateral TKA.

In this systematic review, the dose-effect relationship of perioperative systemic corticosteroids administration with PONV, pain, and LOS after primary unilateral TKA, as well as the occurrence of adverse events was investigated.

METHODS

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/prospero), prior to the start of the systematic review, with registration number CRD42021235773.

Search strategy

This systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and the PRISMA-S extension to

the PRISMA Statement for Reporting Literature Searches in Systematic Reviews.[14,15] A systematic search was developed in Embase.com and then translated to other databases. The search was carried out on March 17, 2022 in the databases Embase.com, MEDLINE ALL via Ovid, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials via Wiley. Additionally, a search was performed in Google Scholar from which the 200 most relevant references were downloaded using the software Publish or Perish. Detailed search strings are presented in appendix 1.

The following elements were used: 1) total knee arthroplasty, 2) corticosteroids, and 3) perioperative.

The searches in EMBASE, MEDLINE, and Web of Science were limited to exclude conference papers and animal-only articles. The results were deduplicated using the Bramer method.[16] No study registries were searched, but Cochrane Central retrieves the contents of ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform.

Inclusion and exclusion criteria were defined a priori. Studies comparing dose-effect relationship of corticosteroids and placebo vs. corticosteroids (dexamethasone, methylprednisolone, hydrocortisone, betamethasone) regarding PONV, pain, and LOS after primary unilateral TKA were included. Manuscripts were required to report one or more of the following outcomes: LOS, pain, PONV, or adverse events. Non-English written articles were excluded. Further exclusion criteria were local or intra-articular injection of corticosteroids, revision arthroplasty, unicompartmental knee arthroplasty, and bilateral TKA.

Article selection and data extraction

Potential eligible articles were reviewed independently by two investigators (JE and FG) according to pre-agreed criteria. Discrepancies were resolved by consensus or by consulting a third reviewer (NM). Finally, citation tracking was performed by manually screening the reference lists of eligible studies by one reviewer (JE). No authors were contacted to provide full-text articles, since all included articles were obtained full-text.

The following data were extracted from the included studies: number of participants, duration of follow-up, type of corticosteroid used, corticosteroid dosages used, LOS, postoperative pain, PONV, and adverse events.

Risk of bias assessment

The Cochrane Collaborations Risk of Bias Tool 2 was used to assess the methodological quality of the included studies.[17] All domains were independently assessed for possible bias by two reviewers (JE and FG).

Data analysis

Quantitative synthesis was not realized due to the presence of conceptual heterogeneity among the included studies. A narrative synthesis was therefore performed.

RESULTS

The initial search resulted in 3134 articles. After removal of duplicate studies, 1879 were screened based on title and abstract, resulting in 31 eligible studies for full-text review. Finally, 16 articles were included for analysis.[18-33] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for systematic reviews is presented in figure 1.[34]

Citation tracking was performed by manually screening the reference lists of eligible studies and no additionally studies were identified as relevant.

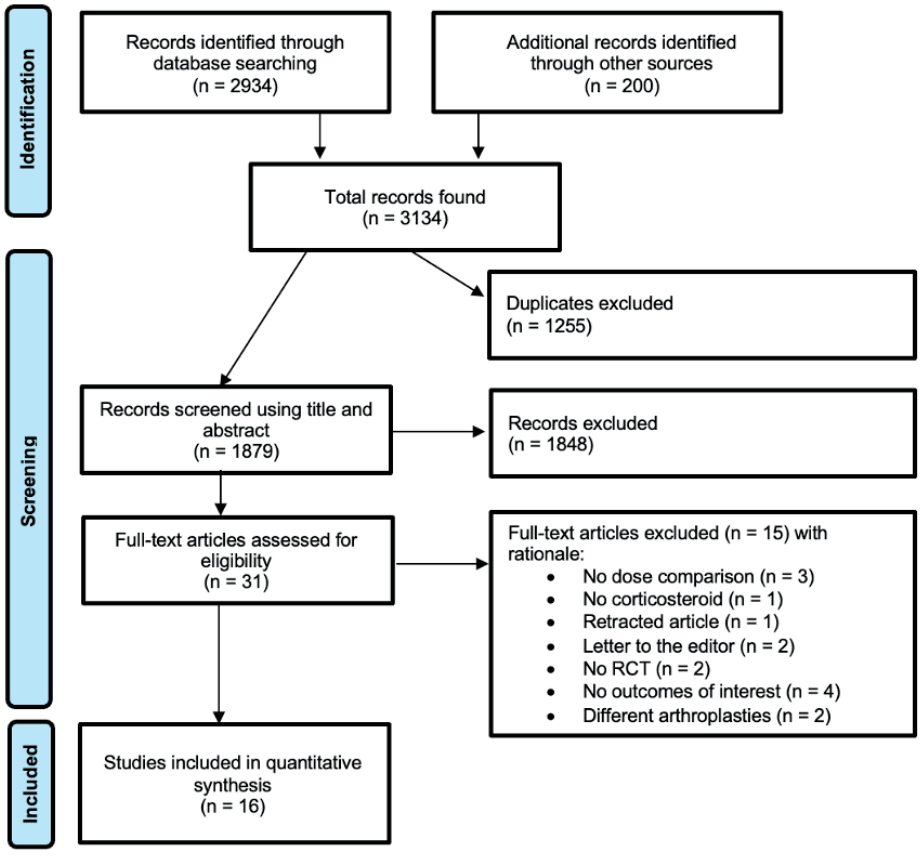


Figure 1. *PRISMA flowchart*

Author, Year	Surgery	Patients	Control	Intervention(s)	Primary outcome	Follow-up
Backes et al., 2013 **(18)**	TKA/THA	73/47	Placebo	10mg dexamethasone i.v. preoperative 10mg dexamethasone i.v. pre- and postoperative	LOS, length of ambulation, ROM, cumulative hydromorphone PCA use, daily hydrocodone consumption, patient pain scores, daily rescue anti-emetic consumption, and nausea/ vomiting scores	6 months
Chan et al., 2020 **(19)**	TKA	138	Placebo	16mg dexamethasone i.v.	postoperative pain score	1 year
Cheng et al., 2019 **(20)**	TKA	60	Placebo	125mg methylprednisolone i.v.	rest pain and pain on movement	1 year
Dissanayake et al., 2018 **(21)**	TKA/THA	81/83	Placebo	8mg dexamethasone i.v. pre- and postoperative	length of stay	6 weeks
Gasbjerg et al., 2022 **(22)**	TKA	485	Placebo	24mg dexamethasone preoperative 24mg dexamethasone pre- and postoperative	total opioid consumption in milligrams of intravenous morphine equivalents 0-48 hours after the end of surgery.	90 days
Kim et al., 2020 **(23)**	TKA	184	Placebo	10mg dexamethasone i.v. preoperative 0.1mg/kg^{-1} dexamethasone i.v. preoperative 0.2mg/kg^{-1} dexamethasone i.v. preoperative	pain and nausea visual analogue scale	1 week
Koh et al., 2013 **(24)**	TKA	269	Placebo	10mg dexamethasone	incidence of PONV	1 year
Lei et al., 2022 **(25)**	TKA	192	Placebo	20mg dexamethasone i.v. preoperative 10mg dexamethasone i.v. pre- and postoperative	postoperative pain level	3 months
Li et al., 2019 **(26)**	TKA	112	Placebo	100mg hydrocortisone i.v. pre- and postoperative 100mg hydrocortisone i.v. pre- and 4x postoperative	level of IL-6 and CRP at 12 hours, 24 hours, 48 hours, and 72 hours after operation	30 days
Lindberg et al., 2017 **(27)**	TKA	70	Placebo	125mg methylprednisolone i.v.	change in knee-extension strength from baseline to 48 hours postoperatively	2 days
Lunn et al., 2011 **(28)**	TKA	48	Placebo	125mg methylprednisolone i.v.	pain during walking 24 hours after surgery	30 days
Nielsen et al., 2022 **(29)**	TKA	88	-	0.3mg/kg^{-1} dexamethasone i.v. preoperative 1.0mg/kg^{-1} dexamethasone i.v. preoperative	proportion of patients experiencing moderate-to-severe pain (VAS >30) during a 5 m walk 24 h postoperatively	90 days

Author, Year	Surgery	Patients	Control	Intervention(s)	Primary outcome	Follow-up
Tammachote et al., 2020 **(30)**	TKA	100	Placebo	0.15mg/kg^{-1} dexamethasone i.v. preoperative	pain level determined by a visual analog scale, and the amount of morphine consumption (mg) 48 hours post-TKA	12 weeks
Wu et al., 2018 **(31)**	TKA	150	Placebo	10mg dexamethasone i.v. preoperative 10mg dexamethasone i.v. pre- and postoperative	n.a.	3 months
Xu B. et al., 2018 **(32)**	TKA	120	Placebo	10mg dexamethasone i.v. pre- and postoperative	n.a.	3 days
Xu H. et al., 2018 **(33)**	TKA	182	Placebo	20mg dexamethasone i.v. preoperative 20mg dexamethasone i.v. preoperative and 2x 10mg dexamethasone postoperative	n.a.	3 months

Table 1. *Detailed description of included studies*

Abbreviations: TKA total knee arthroplasty, THA total hip arthroplasty, LOS length of hospital stay, ROM range of motion, PONV postoperative nausea and vomiting, n.a. not applicable
Dose equivalents: 125mg methylprednisolone = 25mg dexamethasone, 100mg hydrocortisone = 4mg dexamethasone

Description of included studies

The 16 included studies contained 2352 TKA. Table 1 presents an overview of all included studies. In two studies both TKA and THA were included of which we only analyzed TKA outcomes in this systematic review.[18,21] Pain was reported in all studies,[18-33] PONV in 12 studies,[18,21-26,28,30-33] and LOS in 11 studies[18,20,21,26-33]. Adverse events were reported in all studies with varied length of follow-up from 3 days up to 1 year.[18-33]

All, except one study, included a placebo group and compared placebo to one or two intervention groups.[18-28,30-33] In nine studies low-dose and high-dose corticosteroids were compared.[18,19,22,23,25,26,29,31,33] In 12 studies dexamethasone was used in the intervention group.[18,19,21-25,29-33] Three studies used methylprednisolone[20,27,28] and one study used hydrocortisone[26]. Since all corticosteroids have their own specific potential, the equivalent dose of dexamethasone was calculated to assist in the interpretation of the results. The following calculation was used: methylprednisolone 125mg has a dose equivalent of 25mg dexamethasone and hydrocortisone 100mg has a dose equivalent of 4mg dexamethasone.

Primary outcomes

Pain

All studies utilized a visual analogue scale (VAS) to evaluate pain scores. Moreover, some studies used morphine consumption as outcome measurement. In 14 studies a reduction of postoperative pain was found.[18-20,22-26,28-33] In two studies, Lindberg et al. and Dissanayake et al., no difference in postoperative pain was found between placebo and corticosteroids.[21,27] In six of the nine studies which compared high-dose and low-dose of corticosteroids, a better pain relief was found in high-dose corticosteroids groups.[19,22,26,29,31,32]

PONV

Various ways were used to report PONV in different studies. Most studies used self-reported outcomes. In 12 studies PONV was analyzed.[18,21-26,28,30-33] In all studies reduced PONV was reported in the intervention groups. In one study, the group receiving high-dose corticosteroid had significantly less PONV compared to low-dose and placebo.[31] In two studies no difference was found between dosage and effect of corticosteroids on PONV.[25,33]

Length of stay

In two studies LOS was a primary outcome, in which Backes et al. found a dose depended significant reduction of LOS[18], and Dissanayake et al. found no difference between placebo and corticosteroid groups.[21] In the study of Li et al. a significant reduced LOS was

described; however, this was not dose depended.26 In the other eight studies reporting LOS no difference was detected.[20,27-33]

Secondary outcome

Adverse events

Length of follow-up varied widely between the included studies with follow-up periods ranging from 3 days up to 1 year. No adverse events were found for gastrointestinal bleeding. In one study, increased infection rates and intramuscular venous thrombosis were found in the corticosteroid groups.[31] In seven studies blood glucose levels were reported[18,19,21,23,25,26,33] and in three of these seven studies increased blood glucose levels were found postoperative in the corticosteroid group.[18,19,21]

Risk of bias assessment

The results for the assessment of risk of bias can be found in Figure 2. Three studies had an overall low risk of bias.[22,27,29] Twelve studies (75%) were assessed with a moderate risk of bias.[18-20,23-26,28,30-33] This was mainly due to a lack of prespecified outcomes and analysis plan, Cochrane Risk of Bias domain 5. One study was rated as high risk of bias for excluding 52 of the 218 patients after randomization.[21]

Figure 2. *Cochrane traffic light risk of bias plot by individual domains for all included studies*

DISCUSSION

In this systematic review we provided a critical analysis of perioperative intravenous corticosteroid use in primary unilateral TKA in relation to LOS, postoperative pain, PONV, and adverse events. In general, studies showed that corticosteroids reduce mostly pain and PONV after primary TKA with limited effects on LOS. Furthermore, only minimal statistically significant and clinically relevant benefits were found in perioperative high-dose corticosteroids compared to low-dose as well as in multiple doses compared to single preoperative dose.

In the past years, a number of systematic reviews regarding the perioperative use of systemic corticosteroid administration in arthroplasty have been published.[2,35,36] Most of these systematic reviews included RCTs with both THA and TKA and analyzed these as one group.[35,36] However, it is undesirable to investigate these two different types of arthroplasty as a single group considering the fact that recovery for THA and TKA are clearly different.[37] Sufficient analgesic treatment is challenging in TKA[2] and functional improvement is less and more slowly in the first year after TKA compared to THA.[37] Therefore, and in contrast to other systematic reviews, we included only studies providing separate data for TKA.

Risk of bias assessment of the included studies was generally moderate, which is in line with previous systematic reviews.[2,35] The quality of this systematic review is naturally limited by the included studies. Despite methodological impairment, limited follow-up impedes strong conclusions regarding implementation of high dose corticosteroids in fast-track arthroplasty recovery.

The use of corticosteroids in arthroplasty has two major concerns.

First is the presumed high risk of periprosthetic joint infections due to the immunosuppressive effects of corticosteroids. As stated in the article of Backes et al. the absence of proof does not prove absence of risk.[18] Recent literature showed no increased infection risk in low-dose and high-dose corticosteroids.[38-40] One of these studies contained over 18 thousand arthroplasties with low-dose corticosteroids and showed no increased infection risk.[38] Furthermore, high-dose corticosteroids in arthroplasty does not result in higher complication rates.[39] However, most studies have a lack of statistical power and follow-up to determine uncommon adverse events as the risk of infection.

Secondly is the risk of hyperglycemia in diabetic patients.[41] Hyperglycemia has been frequently described after administrating corticosteroids even in non-diabetic patients. Interestingly in the study of Backes only an increase in blood glucose was found in diabetic patients.[18] It remain unclear what effects transient hyperglycemia might have on the postoperative outcomes and complications. Remarkably, Diabetes Mellitus (DM) is an exclusion criterion in most studies examining corticosteroids in an arthroplasty setting. Since DM is relatively common in patients with osteoarthritis an advice regard-

ing corticosteroids in these patients or an alternative for corticosteroids is needed, otherwise these patients are treated insufficiently.[42]

Inflammatory mediators are involved in nociceptive processing and PONV.[43] Corticosteroids reduce the CRP peak after TKA.[44] The study of Wasko et al. reported increased levels of C-reactive protein (CRP) after TKA, up to 96 hours postoperatively.[45] The half-life of Dexamethasone is 36-54 hours and the maximum effect is to be expected in the first 24-48 hours.[12] Consequently, a single dose of dexamethasone will not be sufficient in reducing CRP levels during the first 4 postoperative days. This is illustrated by the non-randomized study of Samona et al. in which 8mg dexamethasone showed effective pain control only in the first 24 hours postoperative compared to placebo.[46] Therefore, the reasoning to investigate multiple doses at different times in the perioperative phase, as was utilized by several included studies, is valid.

Even though most studies demonstrated statistically significant improvement in terms of pain scores (VAS) it is more important to interpret these outcomes in terms of clinical relevance. To achieve this some articles searched for a minimal clinically important difference. For PONV no validated questionnaires are available.

In two studies no reduction in postoperative pain was found. However, in these studies pain was no primary outcome measure and were therefore possibly underpowered.

Recently Jørgensen et al. described an increased opioid use in TKA and THA and high usage of opioids after one year in 17.6% and 10.2% respectively.[47] The use of opioid-sparing pain medication should be further improved due to the negative side effects of opioids and to prevent long-term opioid dependence.[48] In the RCT of Gasbjerg et al. significant reduction in morphine consumption was found by two doses of 24mg dexamethasone in TKA.[22] However, in this study only the first 48 hours after surgery were analyzed, therefore no long-term effects of corticosteroids on opioid consumption were presented.

Despite improvement in pain and PONV, which are both symptoms that prolong hospital stay, most included studies showed no reduced LOS. We presume this might be due to the fact that LOS is dependent to multiple factors including factors which are not influenced by corticosteroids. Therefore, LOS might not be a valid outcome measure to determine the effectiveness of corticosteroids.

Although insomnia is less frequent described, it is a common side effect of corticosteroids. Lunn et al. demonstrated significant increase of insomnia the first night after high-dose methylprednisolone.[28] However, this is not found in other studies.[20,26,29]

There are some limitations of this study. First, quality of the included studies was moderate. A high risk of bias was found in one study and the remaining studies had some concerns which might affect their validity. Secondly, outcomes were difficult to compare since dosing, type, and timing regimens for the administered corticosteroids varied greatly. Since different types of corticosteroids have been used with all their own

specific potency and half-life, this might cause the varying dosing regimens between studies.[12] Finally, with the short follow-up of most of the included studies we were unable to determine safety aspects of high-dose corticosteroids in TKA.

CONCLUSIONS

Current literature on perioperative use of systemic corticosteroids in TKA is highly variable in type, dosage, and timing of administration. Overall, corticosteroids reduce mostly pain and PONV with limited effects on LOS after TKA. Only minimal statistically significant and clinically relevant benefits were found in perioperative high-dose corticosteroids compared to low-dose. Moreover, in multiple doses compared to a single preoperative dose only minimal benefits were found. Given the short follow-up in most studies, it is difficult to conclude that high-dose corticosteroids are safe in use. Further research is needed regarding effect and safety aspects before implementation of high-dose corticosteroids in fast-track TKA protocols.

AUTHORS CONTRIBUTION

JE designed the study, supported data collection and data analysis and he wrote and critically reviewed the manuscript. FG supported data analysis and critically reviewed the manuscript. CN supported formulating and executing the search strategy and critically reviewed the manuscript. HV designed the study and critically reviewed the manuscript. NM designed the study, supported data analysis and critically reviewed the manuscript. All authors approved the final version of the manuscript.

REFERENCES

1. Vehmeijer SBW, Husted H, Kehlet H. Outpatient total hip and knee arthroplasty. Acta Orthop. 2018;89(2):141-4.
2. Kehlet H, Joshi GP. The systematic review/meta-analysis epidemic: a tale of glucocorticoid therapy in total knee arthroplasty. Anaesthesia. 2020;75(7):856-60.
3. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta Orthop. 2011;82(6):679-84.
4. Coenders MJ, Mathijssen NMC, Vehmeijer SBW. Three and a half years' experience with outpatient total hip arthroplasty. Bone Joint J. 2020;102-B(1):82-9.
5. Brekke AC, Amaro EJ, Posey SL, Engstrom SM, Polkowski GG, Schoenecker JG. Do Corticosteroids Attenuate the Peri-Operative Acute Phase Response After Total Knee Arthroplasty? J Arthroplasty. 2019;34(1):27-35.
6. Si HB, Yang TM, Zeng Y, Zhou ZK, Pei FX, Lu YR, et al. Correlations between inflammatory cytokines, muscle damage markers and acute postoperative pain following primary total knee arthroplasty. BMC Musculoskelet Disord. 2017;18(1):265.
7. Steinthorsdottir KJ, Kehlet H, Aasvang EK. Surgical stress response and the potential role of preoperative glucocorticoids on post-anesthesia care unit recovery. Minerva Anestesiol. 2017;83(12):1324-31.
8. Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. Br J Anaesth. 2000;84(1):6-10.
9. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med. 2005;353(16):1711-23.
10. Falkenstein E, Tillmann HC, Christ M, Feuring M, Wehling M. Multiple actions of steroid hormones--a focus on rapid, nongenomic effects. Pharmacol Rev. 2000;52(4):513-56.
11. Sculco PK, Pagnano MW. Perioperative solutions for rapid recovery joint arthroplasty: get ahead and stay ahead. J Arthroplasty. 2015;30(4):518-20.
12. Salerno A, Hermann R. Efficacy and safety of steroid use for postoperative pain relief. Update and review of the medical literature. J Bone Joint Surg Am. 2006;88(6):1361-72.
13. De Oliveira GS, Jr., Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011;115(3):575-88.
14. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
15. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. J Med Libr Assoc. 2021;109(2):174-200.
16. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc. 2016;104(3):240-3.
17. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
18. Backes JR, Bentley JC, Politi JR, Chambers BT. Dexamethasone reduces length of hospitalization and improves postoperative pain and nausea after total joint arthroplasty: a prospective, randomized controlled trial. J Arthroplasty. 2013;28(8 Suppl):11-7.

19. Chan TCW, Cheung CW, Wong SSC, Chung AYF, Irwin MG, Chan PK, et al. Preoperative dexamethasone for pain relief after total knee arthroplasty: A randomised controlled trial. Eur J Anaesthesiol. 2020;37(12):1157-67.
20. Cheng BLY, So EHK, Hui GKM, Yung BPK, Tsui ASK, Wang OKF, et al. Pre-operative intravenous steroid improves pain and joint mobility after total knee arthroplasty in Chinese population: a double-blind randomized controlled trial. Eur J Orthop Surg Traumatol. 2019;29(7):1473-9.
21. Dissanayake R, Du HN, Robertson IK, Ogden K, Wiltshire K, Mulford JS. Does Dexamethasone Reduce Hospital Readiness for Discharge, Pain, Nausea, and Early Patient Satisfaction in Hip and Knee Arthroplasty? A Randomized, Controlled Trial. J Arthroplasty. 2018;33(11):3429-36.
22. Gasbjerg KS, Hagi-Pedersen D, Lunn TH, Laursen CC, Holmqvist M, Vinstrup LO, et al. Effect of dexamethasone as an analgesic adjuvant to multimodal pain treatment after total knee arthroplasty: randomised clinical trial. BMJ. 2022;376:e067325.
23. Kim JK, Ro DH, Lee HJ, Park JY, Han HS, Lee MC. Efficacy of Systemic Steroid Use Given One Day After Total Knee Arthroplasty for Pain and Nausea: A Randomized Controlled Study. J Arthroplasty. 2020;35(1):69-75.
24. Koh IJ, Chang CB, Lee JH, Jeon YT, Kim TK. Preemptive low-dose dexamethasone reduces postoperative emesis and pain after TKA: a randomized controlled study. Clin Orthop Relat Res. 2013;471(9):3010-20.
25. Lei Y, Huang Z, Huang Q, Pei F, Huang W. Dose optimization of intravenous dexamethasone for total knee arthroplasty: when two is not better than one. Arch Orthop Trauma Surg. 2022;142(4):665-72.
26. Li D, Zhao J, Yang Z, Kang P, Shen B, Pei F. Multiple Low Doses of Intravenous Corticosteroids to Improve Early Rehabilitation in Total Knee Arthroplasty: A Randomized Clinical Trial. J Knee Surg. 2019;32(2):171-9.
27. Lindberg-Larsen V, Bandholm TQ, Zilmer CK, Bagger J, Hornsleth M, Kehlet H. Preoperative methylprednisolone does not reduce loss of knee-extension strength after total knee arthroplasty A randomized, double-blind, placebo-controlled trial of 61 patients. Acta Orthop. 2017;88(5):543-9.
28. Lunn TH, Kristensen BB, Andersen LO, Husted H, Otte KS, Gaarn-Larsen L, et al. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. Br J Anaesth. 2011;106(2):230-8.
29. Nielsen NI, Kehlet H, Gromov K, Troelsen A, Husted H, Varnum C, et al. High-dose steroids in high pain responders undergoing total knee arthroplasty: a randomised double-blind trial. Br J Anaesth. 2022;128(1):150-8.
30. Tammachote N, Kanitnate S. Intravenous Dexamethasone Injection Reduces Pain From 12 to 21 Hours After Total Knee Arthroplasty: A Double-Blind, Randomized, Placebo-Controlled Trial. J Arthroplasty. 2020;35(2):394-400.
31. Wu Y, Lu X, Ma Y, Zeng Y, Bao X, Xiong H, et al. Perioperative multiple low-dose Dexamethasones improves postoperative clinical outcomes after Total knee arthroplasty. BMC Musculoskelet Disord. 2018;19(1):428.
32. Xu B, Ma J, Huang Q, Huang ZY, Zhang SY, Pei FX. Two doses of low-dose perioperative dexamethasone improve the clinical outcome after total knee arthroplasty: a randomized controlled study. Knee Surg Sports Traumatol Arthrosc. 2018;26(5):1549-56.
33. Xu H, Zhang S, Xie J, Lei Y, Cao G, Pei F. Multiple Doses of Perioperative Dexamethasone Further Improve Clinical Outcomes After Total Knee Arthroplasty: A Prospective, Randomized, Controlled Study. J Arthroplasty. 2018;33(11):3448-54.

34. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
35. Lex JR, Edwards TC, Packer TW, Jones GG, Ravi B. Perioperative Systemic Dexamethasone Reduces Length of Stay in Total Joint Arthroplasty: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Arthroplasty. 2021;36(3):1168-86.
36. Yue C, Wei R, Liu Y. Perioperative systemic steroid for rapid recovery in total knee and hip arthroplasty: a systematic review and meta-analysis of randomized trials. J Orthop Surg Res. 2017;12(1):100.
37. O'Brien S, Bennett D, Doran E, Beverland DE. Comparison of hip and knee arthroplasty outcomes at early and intermediate follow-up. Orthopedics. 2009;32(3):168.
38. Vuorinen MA, Palanne RA, Makinen TJ, Leskinen JT, Huhtala H, Huotari KA. Infection safety of dexamethasone in total hip and total knee arthroplasty: a study of eighteen thousand, eight hundred and seventy two operations. Int Orthop. 2019;43(8):1787-92.
39. Jorgensen CC, Pitter FT, Kehlet H, Lundbeck Foundation Center for Fast-track H, Knee Replacement Collaborative G. Safety aspects of preoperative high-dose glucocorticoid in primary total knee replacement. Br J Anaesth. 2017;119(2):267-75.
40. Toner AJ, Ganeshanathan V, Chan MT, Ho KM, Corcoran TB. Safety of Perioperative Glucocorticoids in Elective Noncardiac Surgery: A Systematic Review and Meta-analysis. Anesthesiology. 2017;126(2):234-48.
41. Wasfie TJ, Groton J, Cwalina N, Hella JR, Barber K. Efficacy of Preoperative Usage of Dexamethasone in Diabetic Patients Undergoing Total Hip or Knee Arthroplasty for Control of Nausea and Vomiting. Am Surg. 2021;87(3):336-40.
42. Capozzi JD, Lepkowsky ER, Callari MM, Jordan ET, Koenig JA, Sirounian GH. The Prevalence of Diabetes Mellitus and Routine Hemoglobin A1c Screening in Elective Total Joint Arthroplasty Patients. J Arthroplasty. 2017;32(1):304-8.
43. Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin. 2007;45(2):27-37.
44. Smith C, Erasmus PJ, Myburgh KH. Endocrine and immune effects of dexamethasone in unilateral total knee replacement. J Int Med Res. 2006;34(6):603-11.
45. Wasko MK, Bobecka-Wesolowska K, Tomasiuk R, Kowalczewski J. Measurement of the inflammatory response in the early postoperative period after hip and knee arthroplasty. Clin Chem Lab Med. 2015;53(11):1785-92.
46. Samona J, Cook C, Krupa K, Swatsell K, Jackson A, Dukes C, et al. Effect of Intraoperative Dexamethasone on Pain Scores and Narcotic Consumption in Patients Undergoing Total Knee Arthroplasty. Orthop Surg. 2017;9(1):110-4.
47. Jorgensen CC, Petersen M, Kehlet H, Aasvang EK. Analgesic consumption trajectories in 8975 patients 1 year after fast-track total hip or knee arthroplasty. Eur J Pain. 2018.
48. Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The Opioid Crisis: a Comprehensive Overview. Curr Pain Headache Rep. 2018;22(3):16.

APPENDIX I – SEARCH STRINGS USED IN DIFFERENT DATABASES

EMBASE

('dexamethasone'/de OR 'prednisolone'/de OR 'steroid'/exp OR 'glucocorticoid'/exp OR (corticosteroid* OR dexametha* OR predniso* OR prediso* OR methylprednisо* OR methylfluorpredniso* OR hexadecadrol* OR steroid* OR glucocortic* OR hydrocortiso*):ab,ti,kw) AND ('perioperative period'/exp OR 'preoperative period'/exp OR 'postoperative period'/exp OR (((surger* OR surgic*) NEAR/3 (recover*)) OR fast-track* OR preoperati* OR pre-operati* OR postoperati* OR post-operati* OR perioperativ* OR peri-operative* OR post-surg* OR postsurg* OR pre-surg* OR presurg* OR peri-surg* OR perisurg*):ab,ti,kw) AND ('knee surgery'/de OR 'knee arthroplasty'/exp OR 'knee prosthesis'/exp OR (knee OR knees OR tkr OR tka):ab,ti,kw) NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) NOT ([Conference Abstract]/lim)

MEDLINE

("Glucocorticoids"/ OR exp "Prednisolone"/ OR exp "Dexamethasone"/ OR exp "Steroids"/ OR (corticosteroid* OR dexametha* OR predniso* OR prediso* OR methylprednisо* OR methylfluorpredniso* OR hexadecadrol* OR steroid* OR glucocortic* OR hydrocortiso*).ab,ti,kf.) AND (exp "Perioperative Period"/ OR (((surger* OR surgic*) ADJ3 (recover*)) OR fast-track* OR preoperati* OR pre-operati* OR postoperati* OR post-operati* OR perioperativ* OR peri-operative* OR post-surg* OR postsurg* OR pre-surg* OR presurg* OR peri-surg* OR perisurg*).ab,ti,kf.) AND ("Knee Prosthesis"/ OR "Arthroplasty, Replacement, Knee"/ OR ((exp "Knee"/ AND exp "Specialties, Surgical"/) OR exp "Knee"/su) OR (knee OR knees OR tkr OR tka).ab,ti,kf.) NOT (exp animals/ NOT humans/) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt.

Web-of-Science

TS=(((corticosteroid* OR dexametha* OR predniso* OR prediso* OR methylprednisо* OR methylfluorpredniso* OR hexadecadrol* OR steroid* OR glucocortic* OR hydrocortiso*)) AND ((((surger* OR surgic*) NEAR/2 (recover*)) OR fast-track* OR preoperati* OR pre-operati* OR postoperati* OR post-operati* OR perioperativ* OR peri-operative* OR post-surg* OR postsurg* OR pre-surg* OR presurg* OR peri-surg* OR perisurg*)) AND ((knee OR knees OR tkr OR tka)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man))) AND DT=(Article OR Review OR Letter OR Early Access)

Cochrane

((corticosteroid* OR dexametha* OR predniso* OR prediso* OR methylpredniso* OR methylfluorpredniso* OR hexadecadrol* OR steroid* OR glucocortic* OR hydrocortiso*):ab,ti,kw) AND ((((surger* OR surgic*) NEAR/3 (recover*)) OR fast NEXT track* OR preoperati* OR pre NEXT operati* OR postoperati* OR post NEXT operati* OR perioperativ* OR peri NEXT operative* OR post NEXT surg* OR postsurg* OR pre NEXT surg* OR presurg* OR peri NEXT surg* OR perisurg*):ab,ti,kw) AND ((knee OR knees OR tkr OR tka):ab,ti,kw)

Google Scholar

Corticosteroid|dexamethason|prednisol|prednison|predisol|methylprednison|steroid|glucocorticoid| corticosteroids|steroids|glucocorticoids “fast track”| preoperative| postoperative| perioperative| “post surgery”|postsurgery|”pre surgery”|presurgery knee|knees|tkr|tka

Chapter 8

Preoperative carbohydrate drink in fast-track primary total knee arthroplasty: a randomized controlled trial

J.C. van Egmond, MD[1,2]
N.H.H. de Esch, BSc[1,2]
H. Verburg, MD[1,2]
N.T. van Dasselaar, MD, PhD[3]
N.M.C. Mathijssen, PhD[1,2]

(submitted)

[1] Department of Orthopedic Surgery, Reinier de Graaf Groep, Delft, the Netherlands
[2] Department of Orthopedic Surgery, Reinier Haga Orthopedisch Centrum, Zoetermeer, the Netherlands
[3] Department of Anesthesiology, Reinier de Graaf, the Netherlands

ABSTRACT

Background

A key component in fast-track total knee arthroplasty (TKA) is early mobilization. Preoperative fasting might cause orthostatic hypotension and -intolerance which both can interfere with early mobilization. It was hypothesized that consuming a carbohydrate drink 2-3 hours prior to surgery is a viable option to reduce orthostatic hypotension and -intolerance, and as a result, improve rehabilitation.

Methods

A randomized controlled trial in which all consecutive unilateral primary TKA patients were assessed for inclusion. Exclusion criteria were American Society of Anesthesiologists (ASA) class above 3, older than 80 years of age, and Diabetes Mellitus. Patients were distributed in two groups. The control group was allowed to eat till 6 hours and drink clear fluids till 2 hours before surgery (standard treatment). The intervention group consumed, additionally to the standard treatment, a carbohydrate drink 2-3 hours before surgery. Blood pressure was measured both lying and standing as a measure for orthostatic hypotension, during first time postoperative mobilization on day of surgery.

Results

A total of 168 patients were included. Prevalence of orthostatic hypotension in the control- and intervention group was 24 patients (34%) and 14 patients (19%) respectively, (p=0.046). Prevalence of orthostatic intolerance was 13 patients (19%) in the control group and 9 patients (13%) in the intervention group (p=0.317). No drink related adverse events occurred.

Conclusion

Preoperative carbohydrate drinks reduce the incidence of postoperative orthostatic hypotension during first time mobilization. The results of this present study might improve postoperative rehabilitation with early mobilization.

INTRODUCTION

During the last decades, fast-track rehabilitation protocols have been widely implemented, which improved quality of care, patient outcomes, and safely reduced length of hospital stay after total knee arthroplasty (TKA).[1,2] One of the key elements in fast-track protocols is early mobilization.[3,4] This can be interfered by orthostatic hypotension and -intolerance which is frequently observed; up to 42% of patients after total hip arthroplasty (THA) suffer from this.[5-7] Orthostatic hypotension and -intolerance can be due to various causes, including hypovolemia, opioids, anemia, anesthesia residual effects, and leaves patients unable to mobilize.[5] Therefore, prevention of orthostatic hypotension and -intolerance might improve early mobilization.[8,9]

Historically, patients were instructed not to eat or drink after midnight before surgery.[10] This fasting period was maintained to prevent pulmonary aspiration of gastric contents during anesthesia. Literature showed that reduced fasting times are feasible, therefore, the current policy is 2 hours fasting for liquids and 6 hours fasting for solid food before surgery.[11-15]

Preoperative carbohydrate drinks reduce anxiety, nausea, vomiting, and increase well-being in non-orthopedic surgery.[16-22] Moreover, consuming a carbohydrate drink 2-3 hours preoperatively, was not associated with increased intake related complications.[13,23,24]

In THA small positive effects regarding pain and well-being were found for preoperative oral carbohydrate intake.[25]

The hypothesis of this present study was that consuming a carbohydrate drink 2-3 hours prior to TKA, is a good and feasible option to decrease postoperative orthostatic hypotension and -intolerance.

METHODS

A prospective, randomized controlled trial was conducted. The study was initially performed in the Reinier de Graaf Hospital, Delft, the Netherlands and due to the merger of hospitals continued in the Reinier Haga Orthopedisch Centrum, Zoetermeer, the Netherlands.

All consecutive patients scheduled for a primary unilateral TKA between December 2019 and December 2021 were assessed for inclusion. Patients with risk factors for pulmonary aspiration were excluded. Therefore, exclusion criteria were: age above 80 years, and American Society of Anesthesiologists (ASA) class >3. Additionally, patients with Diabetes Mellitus (DM) were excluded, since fasting and oral carbohydrate drinks might have greater influence on these patients. Moreover, an insufficient command of

Dutch language was an exclusion criterion. Patients with previous bariatric surgery or medical treatment for hypertension were not excluded.

All TKAs were performed in a fast-track setting. Two groups were compared, a control group with current fasting times, and an intervention group in which patients consumed a carbohydrate drink 2-3 hours before surgery.

Primary objective was to compare the number of patients with postoperative orthostatic hypotension and -intolerance between both groups during first time mobilization after TKA. Secondary objectives were comparing prevalence of nausea, vomiting, and length of stay between both groups.

Patients were randomized into the control- or intervention group by a digital program Castor EDC (Amsterdam, the Netherlands).[26] Randomization was performed by variable block randomization in the proportions 4, 6 and 8.

Treatment

Patients in the control group were allowed to drink clear liquids until 2 hours before surgery and to eat 6 hours before surgery. Patients in the intervention group consumed 2 bottles of 200ml (total 400ml) carbohydrate drink (Nutrica Preop; Numico, Zoetermeer, the Netherlands) 2-3 hours before surgery. This is a clear, non-carbonated, isomolar carbohydrate drink.

All patients were admitted on the day of surgery. Preoperatively patients received dexamethasone 0.15mg/kg confirming our protocol.[27,28] All patients were operated with either spinal- of general anesthesia. In spinal anesthesia 0,5% isobaric bupivacaine (Marcaine spinal 5mg/mL; Aspen, Gorinchem, the Netherlands) admitted intrathecally. In general anesthesia a larynx mask was used, no muscle relaxant was administrated. Opiates were not administered to rule out possible side effects such as nausea, vomiting, or sedation, which might interfere measurements.[8,29] All patients received additional local infiltration anesthesia with 300mg ropivacaine around the knee joint during end of surgery, conforming to our fast-track regimen. Esketamine (15 mg) was administered to prevent postoperative pain.[30,31]

Measurements

Primary objective was to compare the number of patients in both groups with orthostatic hypotension and -intolerance during first time postoperative mobilization on day of surgery. To determine orthostatic hypotension the blood pressure was measured; once in supine position and three times (after 1, 3, and 5 minutes) in standing position. This was performed by a trained outcome assessor which was not blinded. Orthostatic hypotension was defined as a systolic blood pressure decrease of at least 20mmHg or a diastolic blood pressure decrease of at least 10mmHg within three minutes of standing compared

to supine position.[32] Orthostatic intolerance was determined by the researcher in case of dizziness, feeling of heat, sweating or syncope during mobilization.

Secondary objectives were prevalence of nausea, vomiting, and length of stay in both groups. During first time postoperative mobilization, patients were asked if they had nausea or vomiting. If patients were unable to mobilize this was noted including the reason why. Finally, length of hospital stay was determined.

Power

Power calculation was based on the primary objective, the reduction of orthostatic hypotension and -intolerance. Since it was hypothesized that consuming a preoperative drink will reduce orthostatic hypotension and -intolerance, a superiority design was chosen. A reduction in the number of patients with orthostatic hypotension of 20% was assumed to be clinically relevant.

Based on the results of the study of Lindberg et al. the prevalence of orthostatic intolerance is 40% after total hip arthroplasty.[7] We assumed this would be comparable for TKA.

When using an alpha of 0.05 and power of 80% a sample size of 73 patients per group were needed. When taking a loss to follow-up of 15% into account, a total of 84 patients per group was needed.

Statistics

For statistical analyses, IBM SPSS statistics version 28 (IBM Corp. Armonk, NY: IBM Corp.) was used. A p-value of 0.05 or lower was considered to be statistically significant. Data analysis was performed by per protocol analysis. Descriptive statistics were used for data analysis. Taking distribution of the data into account chi-square was used for categorical variables and Mann-Withney U test for continuous variables.

Ethics

The protocol for this randomized controlled trial was approved by the regional Ethical Committee METC-LDD (Z19.025/NL70848.098.19) and was registered in the Netherlands Trial Register (NL7996). All data were handled according to the Helsinki Declaration (version 64, October 2013). All patients signed informed consent.

RESULTS

A total of 395 patients were assessed for inclusion of which 164 patients (168 TKA) were included. The control- and intervention group comprised 85 and 83 TKA respectively. Most patients were excluded based on DM (66 patients), age >80 years (65 patients), and

not willing to participate (61 patients). After inclusion, 1 TKA in the control group and 3 TKAs in the intervention group were excluded before surgery. The study flowchart is presented in figure 1.

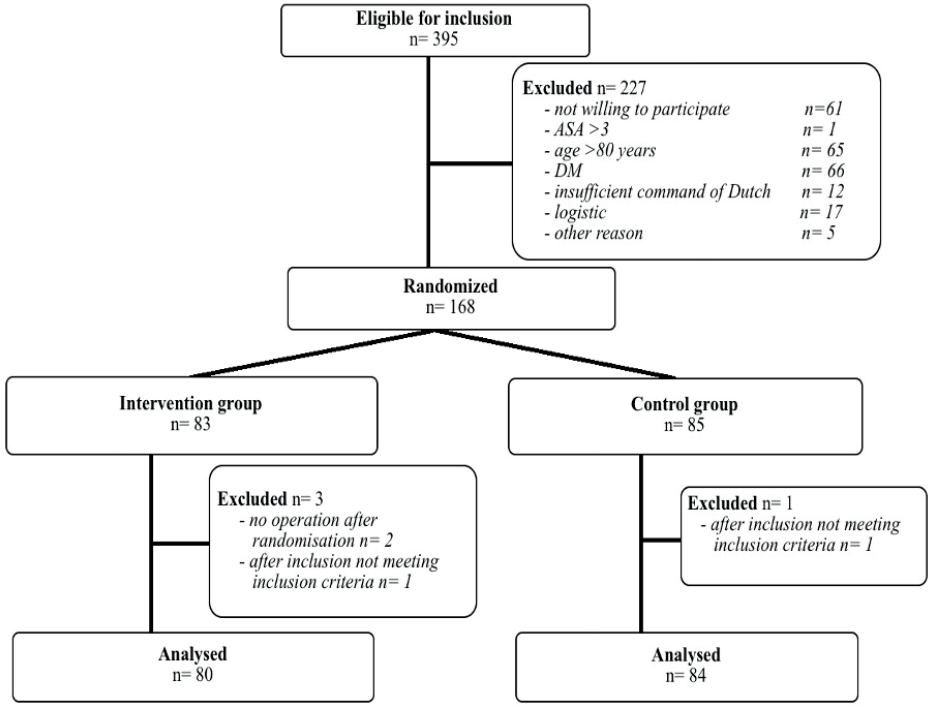


Figure 1. *Study flowchart*

Table 1 presents the baseline patient characteristics of the participating patients. Median age was 69 years (25-80) and 101 (62%) patients were female. Most patients were classified as ASA 2 (117 patients (71%)). Median BMI was 28.7 (19.1-46.1).

Median dose of intrathecal bupivacaine was 10mg which was comparable for both groups. The median fasting time in the control group was 12 hours (2.4-19.1) and in the intervention group 5 hours (3.4-6.8).

Early mobilization, and therefore blood pressure measurements, was not possible in 7 patients of the control group and 4 patients in the intervention group due to wound leakage or sensomotoric impairment. In 2 patients, 1 in each group, the patient had mobilized before the blood pressure measurements took place and were therefore excluded for analysis. Patients with an insufficient dose of dexamethasone, less than 0.15mg/kg, were excluded for analysis which were 5 patients in the control group and 3 patients in the intervention group.

	Total *(n=164)*	**Control group** *(n=84)*	**Intervention group** *(n=80)*
Age, years, median (IQR) *[range]*	69 (11) [25 - 80]	70 (9) [25 - 80]	68 (11) [52 - 80]
Females, n (%)	101 (61.6%)	52 (61.9%)	49 (61.3%)
Side left, n (%)	77 (47%)	43 (51.2%)	34 (42.5%)
ASA class, n (%)			
I	16 (9.8%)	8 (9.5%)	8 (10.0%)
II	117 (71.3%)	54 (64.3%)	63 (78.8%)
III	31 (18.9%)	22 (26.2%)	9 (11.3%)
BMI, median (IQR) *[range]*	28.7 (5.8) [19.1 - 46.1]	27.7 (6.0) [19.2 - 38.8]	29.4 (5.8) [22.5 - 46.1]

All data were presented as (median, Interquartile Range (IQR), [range]) or (n, %)
Abbreviations: ASA American Society of Anesthesia, BMI Body Mass Index

Table 1. *Patient demographics*

Primary outcome

A total of 142 patients, 70 control group and 72 intervention group, were analyzed for postoperative orthostatic hypotension and -intolerance. Orthostatic hypotension was present in 24 patients (34%) in the control group and in 14 patients (19%) in the intervention group (p=0.046). (Table 2)

Orthostatic intolerance occurred in 13 patients (19%) in the control group and in 9 patients (13%) in the intervention group (p=0.317).

	Total *(n=142)*	**Control group** *(n=70)*	**Intervention group** *(n=72)*	**P** †
Orthostatic hypotension, n (%)	38 (26.8%)	24 (34.3%)	14 (19.4%)	0.046
Orthostatic intolerance, n (%)	22 (15.5%)	13 (18.6%)	9 (12.5%)	0.317
Nausea, yes, n (%)	7 (4.9%)	3 (4.3%)	4 (5.6%)	0.727
Vomiting, yes, n (%)	4 (2.8%)	2 (2.9%)	2 (2.8%)	0.977
LOS, nights, median (IQR) *[range]*	2 (1) [0 - 6]	2 (1) [0 - 5]	2 (1) [1 - 6]	0.917
Anesthesia technique, n (%)				0.316
Spinal anesthesia	126 (89%)	64 (91.4%)	62 (86.1%)	
General anesthesia	16 (11%)	6 (8.6%)	10 (13.9%)	
Surgery time, minutes, median (IQR) *[range]*	85 (28) [48-155]	84 (28) [58-155]	86 (31) [48-128]	0.903
Time to mobilize, hours, median (IQR) *[range]*	3.8 (1.3) [1.6 – 7.9]	3.7 (1.0) [1.6 – 6.4]	3.9 (1.6) [1.6 – 7.9]	0.296

All data were presented as (median, Interquartile Range (IQR), [range]) or (n, %)
† Chi-square test in categorical data, Mann-Whitney U test in continuous data
Abbreviations: LOS length of hospital stay

Table 2. *Primary and secondary outcomes*

Secondary outcomes

Mean time between surgery and first mobilization was 3.8 hours (1.6-7.9). The median length of hospital stay was 2 nights (0-6) for both groups (p=0.917). (Table 2) No difference was found for nausea between the control and intervention group, 3 patients (4.3%) and 4 patients (5.6%) respectively (p=0.727). In both groups 2 patients vomited early after surgery.

None of the patients disliked the carbohydrate drink, a single patient had troubles with the amount of fluid. No drink related adverse events occurred during the study.

DISCUSSION

The primary goal of our study was to investigate the effect of a carbohydrate drink on the prevalence of orthostatic hypotension and -intolerance during first time mobilization after unilateral primary TKA. The number of patients with orthostatic hypotension and -intolerance in the intervention group were lower compared to the control group.

Despite the reduction in orthostatic hypotension by consuming a carbohydrate drink preoperatively, still 19% of the patients in the intervention group experienced orthostatic hypotension which might interfere early mobilization. Moreover, orthostatic intolerance found in 13% of the patients in the intervention group. Since orthostatic hypotension and -intolerance are multifactorial symptoms,[5] other interventions besides adding a carbohydrate drink might be successful and need to be further studied. Previously midodrine has been studied in THA with no statistical effect.[33] In addition, high dose glucocorticoids did not reduce orthostatic hypotension in THA.[7]

In previous studies, preoperative carbohydrate drinks in THA have only minor or no influence on postoperative well-being.[25,34] This might partially be explained by the small patient groups (60 patients) which make both studies possibly underpowered to determine well-being. In this present study well-being was not investigated.

To the best of our knowledge no literature is available of the prevalence of orthostatic intolerance after TKA. In THA prevalence of orthostatic intolerance has been reported up to 40%.[7] We presume that the prevalence of 34% orthostatic hypotension in the control group found in this present study is in line with previous reported numbers in THA.

Previously Husted et al. and Bundgaard-Nielsen et al. showed that orthostatic intolerance is one of the reasons for prolonged hospital stay.[8,35] The importance of our present study was further stressed by the article of Farley et al. which stated that postoperative hypotension is a modifiable factor to reduce length of hospital stay after THA.[9] Therefore, further research is needed to reduce orthostatic hypotension and -intolerance in joint arthroplasty.

The exclusion criteria were mostly based on patient characteristics that were thought to be associated with increased intake related risks and are therefore debatable. Excluding patients of 80 years and older was arbitrary since literature is not clear regarding the risk of age on gastric emptying.[36]

The exclusion of patients with DM was not based on increased intake related risks with preoperative carbohydrate drinks, since it was found this was safe to administer 180 minutes before surgery in DM patients.[37] The reason for exclusion of DM patients was that the effect of preoperative carbohydrate drink might differ between patients with and without DM which eventually could bias the results.

The effects of dexamethasone on orthostatic hypotension and -intolerance are unclear, although this might influence the measurements.[7] In our study dexamethasone was in the majority of patients administered according to our protocol. We excluded patients for analysis in which less than 0.15mg/kg dexamethasone was administrated as prescribed in our protocol.

In the study of Harsten et al. general anesthesia showed less symptoms of orthostatic hypotension and -intolerance compared to spinal anesthesia.[38] However, in this study high dose of spinal anesthesia (15mg) was used which is notably higher than the dosage used in our study (median 10mg). We presumed that type of anesthesia has only minor influence on the outcome, which makes our findings more generalizable.

There are some limitations to this study, which need to be addressed.

First, patients and outcome assessors were not blinded and were aware of treatment allocation. Since the primary outcome was an objective measurement (blood pressure) it was presumed that blinding does not influence the outcome.

Due to merger of hospitals the study has been continued in another hospital. No changes were made at the study protocol and therefore the change of hospital has no influence on the results. In addition, the COVID-19 pandemic has led to a delay of the study due to cancelled surgery programs.

Despite randomization the baseline characteristics were different for BMI and ASA between the control- and treatment group. More ASA 2 patients and higher median BMI was present in the intervention group. We presume that the difference in baseline characteristics has only minor influence on the outcome.

Patients who used medication (diuretics or ACE inhibitors) for hypertension were instructed not to use this medication at the day of surgery. This is thought to have only minor influence on postoperative blood pressure and no influence on orthostatic hypotension and -intolerance.[5,39]

Finally, the time of carbohydrate drink intake was preoperatively determined. Due to some logistical reasons, the surgery schedule changed and not all patients took the carbohydrate drink exact 2-3 hours before surgery. Median time between carbohydrate

drink and surgery was 5 (3.4-6.8) hours which was a significantly reduced fasting period compared to the control group ($p < 0.001$).

CONCLUSION

Preoperative carbohydrate drinks reduce the incidence of postoperative orthostatic hypotension during first time mobilization. No drink related adverse events occurred in our selected patient group. The results of this present study might improve post-operative rehabilitation with early mobilization. Further studies are needed to further decrease postoperative orthostatic hypotension and -intolerance and thereby improve fast-track recovery.

FUNDING

This work was supported by the research commission Reinier de Graaf (Wetenschappelijke Advies Raad: WAC).

AUTHORS CONTRIBUTION

JE designed the study, supported data collection, data analysis, and he wrote and critically reviewed the manuscript. NE supported data collection and critically reviewed the manuscript. HV designed the study, operated several of the included patients, and critically reviewed the manuscript. ND designed the study and critically reviewed the manuscript. NM designed the study, supported data analysis, and critically reviewed the manuscript.

REFERENCES

1. Barbieri A, Vanhaecht K, Van Herck P, Sermeus W, Faggiano F, Marchisio S, et al. Effects of clinical pathways in the joint replacement: a meta-analysis. BMC Med. 2009;7:32.
2. Dowsey MM, Kilgour ML, Santamaria NM, Choong PF. Clinical pathways in hip and knee arthroplasty: a prospective randomised controlled study. Med J Aust. 1999;170(2):59-62.
3. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, et al. What determines length of stay after total hip and knee arthroplasty? A nationwide study in Denmark. Arch Orthop Trauma Surg. 2010;130(2):263-8.
4. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. JAMA Surg. 2017;152(3):292-8.
5. Jans O, Kehlet H. Postoperative orthostatic intolerance: a common perioperative problem with few available solutions. Can J Anaesth. 2017;64(1):10-5.
6. Jans O, Bundgaard-Nielsen M, Solgaard S, Johansson PI, Kehlet H. Orthostatic intolerance during early mobilization after fast-track hip arthroplasty. Br J Anaesth. 2012;108(3):436-43.
7. Lindberg-Larsen V, Petersen PB, Jans O, Beck T, Kehlet H. Effect of pre-operative methylprednisolone on orthostatic hypotension during early mobilization after total hip arthroplasty. Acta Anaesthesiol Scand. 2018;62(7):882-92.
8. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta Orthop. 2011;82(6):679-84.
9. Farley KX, Anastasio AT, Premkumar A, Boden SD, Gottschalk MB, Bradbury TL. The Influence of Modifiable, Postoperative Patient Variables on the Length of Stay After Total Hip Arthroplasty. J Arthroplasty. 2019;34(5):901-6.
10. Maltby JR. Fasting from midnight--the history behind the dogma. Best Pract Res Clin Anaesthesiol. 2006;20(3):363-78.
11. Ljungqvist O, Soreide E. Preoperative fasting. Br J Surg. 2003;90(4):400-6.
12. Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. Cochrane Database Syst Rev. 2003(4):CD004423.
13. Hellstrom PM, Samuelsson B, Al-Ani AN, Hedstrom M. Normal gastric emptying time of a carbohydrate-rich drink in elderly patients with acute hip fracture: a pilot study. BMC Anesthesiol. 2017;17(1):23.
14. Li L, Wang Z, Ying X, Tian J, Sun T, Yi K, et al. Preoperative carbohydrate loading for elective surgery: a systematic review and meta-analysis. Surg Today. 2012;42(7):613-24.
15. Nygren J, Thorell A, Jacobsson H, Larsson S, Schnell PO, Hylen L, et al. Preoperative gastric emptying. Effects of anxiety and oral carbohydrate administration. Ann Surg. 1995;222(6):728-34.
16. Hausel J, Nygren J, Thorell A, Lagerkranser M, Ljungqvist O. Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. Br J Surg. 2005;92(4):415-21.
17. Nygren J, Thorell A, Ljungqvist O. Are there any benefits from minimizing fasting and optimization of nutrition and fluid management for patients undergoing day surgery? Curr Opin Anaesthesiol. 2007;20(6):540-4.
18. Savluk OF, Kuscu MA, Guzelmeric F, Gurcu ME, Erkilinc A, Cevirme D, et al. Do preoperative oral carbohydrates improve postoperative outcomesin patients undergoing coronary artery bypass grafts? Turk J Med Sci. 2017;47(6):1681-6.

19. Cakar E, Yilmaz E, Baydur H. The Effect of Preoperative Oral Carbohydrate Solution Intake on Patient Comfort: A Randomized Controlled Study. Journal of perianesthesia nursing: official journal of the American Society of PeriAnesthesia Nurses. 2017;32(6):589-99.
20. De Jonghe B, Fajardy A, Merian-Brosse L, Fauconnier A, Chouillard E, Debit N, et al. Reducing preoperative fasting while preserving operating room scheduling flexibility: feasibility and impact on patient discomfort. Acta Anaesthesiol Scand. 2016;60(9):1222-9.
21. Noba L, Wakefield A. Are carbohydrate drinks more effective than preoperative fasting: A systematic review of randomised controlled trials. J Clin Nurs. 2019;28(17-18):3096-116.
22. Liu B, Wang Y, Liu S, Zhao T, Zhao B, Jiang X, et al. A randomized controlled study of preoperative oral carbohydrate loading versus fasting in patients undergoing elective craniotomy. Clin Nutr. 2019;38(5):2106-12.
23. Awad S, Varadhan KK, Ljungqvist O, Lobo DN. A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. Clin Nutr. 2013;32(1):34-44.
24. de Andrade Gagheggi Ravanini G, Portari Filho PE, Abrantes Luna R, Almeida de Oliveira V. Organic Inflammatory Response to Reduced Preoperative Fasting Time, with a Carbohydrate and Protein Enriched Solution; a Randomized Trial. Nutr Hosp. 2015;32(2):953-7.
25. Harsten A, Hjartarson H, Toksvig-Larsen S. Total hip arthroplasty and perioperative oral carbohydrate treatment: a randomised, double-blind, controlled trial. Eur J Anaesthesiol. 2012;29(6):271-4.
26. Castor EDC. Castor Electronic Data Capture 2019 [27 Aug. 2019]. Available from: https://castoredc.com.
27. De Oliveira GS, Jr., Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011;115(3):575-88.
28. Lunn TH, Andersen LO, Kristensen BB, Husted H, Gaarn-Larsen L, Bandholm T, et al. Effect of high-dose preoperative methylprednisolone on recovery after total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. Br J Anaesth. 2013;110(1):66-73.
29. Jia XF, Ji Y, Huang GP, Zhou Y, Long M. Comparison of intrathecal and local infiltration analgesia by morphine for pain management in total knee and hip arthroplasty: A meta-analysis of randomized controlled trial. Int J Surg. 2017;40:97-108.
30. Li Z, Chen Y. Ketamine reduces pain and opioid consumption after total knee arthroplasty: A meta-analysis of randomized controlled studies. Int J Surg. 2019;70:70-83.
31. Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. Anesth Analg. 2005;100(2):475-80.
32. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology. 1996;46(5):1470.
33. Jans O, Mehlsen J, Kjaersgaard-Andersen P, Husted H, Solgaard S, Josiassen J, et al. Oral Midodrine Hydrochloride for Prevention of Orthostatic Hypotension during Early Mobilization after Hip Arthroplasty: A Randomized, Double-blind, Placebo-controlled Trial. Anesthesiology. 2015;123(6):1292-300.
34. Ljunggren S, Hahn RG. Oral nutrition or water loading before hip replacement surgery; a randomized clinical trial. Trials. 2012;13:97.

35. Bundgaard-Nielsen M, Jans O, Muller RG, Korshin A, Ruhnau B, Bie P, et al. Does goal-directed fluid therapy affect postoperative orthostatic intolerance?: A randomized trial. Anesthesiology. 2013;119(4):813-23.
36. de Leon A. The aging digestive tract: what should anesthesiologists know about it? Minerva Anestesiol. 2016;82(12):1336-42.
37. Gustafsson UO, Nygren J, Thorell A, Soop M, Hellstrom PM, Ljungqvist O, et al. Pre-operative carbohydrate loading may be used in type 2 diabetes patients. Acta Anaesthesiol Scand. 2008;52(7):946-51.
38. Harsten A, Kehlet H, Toksvig-Larsen S. Recovery after total intravenous general anaesthesia or spinal anaesthesia for total knee arthroplasty: a randomized trial. Br J Anaesth. 2013;111(3):391-9.
39. Hajjar I. Postural blood pressure changes and orthostatic hypotension in the elderly patient: impact of antihypertensive medications. Drugs Aging. 2005;22(1):55-68.

Part IV

General discussion and appendices

Chapter 9

General discussion and future perspectives

Fast-track programs aim to improve postoperative recovery by reducing surgical stress, providing effective pain treatment, and initiating early mobilization.[1,2] These multimodal treatment protocols result in rapid functional recovery and shorter convalescence with a concomitant reduction in postoperative length of hospital stay without increased morbidity and mortality.[3,4]

During the last decade, more and more hospitals have implemented fast-track recovery protocols for orthopaedic procedures, including total hip arthroplasty (THA) and total knee arthroplasty (TKA).[5] The recent COVID-19 pandemic has led to further interest in outpatient arthroplasty surgery, given the limited inpatient capacity.[6,7] Therefore, optimizing fast-track protocols in primary TKA is of great importance.

The main objective of this thesis was to investigate opportunities for further optimization of perioperative care for primary TKA patients. This was attempted by exploring TKA patients' experiences in the first postoperative period, by analysing recovery patterns after TKA, and finally by identifying possible improvements in current fast-track protocols.

Part I - Opening the black box

Patients' experiences during the first weeks after hospital discharge have not been studied extensively. Therefore, we opened this 'black box' in *Chapter 2* and *Chapter 3*. Both chapters report on studies in which patients were asked to report their personal experiences of fast-track TKA. Both studies showed that postoperative physical therapy outside the hospital varied widely in the duration, intensity, and treatment modalities of the therapy sessions. Previously, Klapwijk et al. (2017) reported similar findings for THA.[8] Preoperative physical therapy was found not to be effective.[9] However, postoperative rehabilitation by a physical therapist is very common.[10] Since various treatment modalities have been used in physical therapy, it is difficult to identify the most effective ones.[11,12] That is why standardized postoperative physiotherapy strategies are needed to determine the effectiveness of physical therapy, as is being done in the PaTIO study in the Netherlands.[13] However, recently published studies concluded that physical therapy might not be necessary for all patients after arthroplasty. These studies suggested that unsupervised exercises are safe and effective for most patients.[14-16] Future studies should identify which patients need postoperative physical therapy and what the most effective treatment modality is for this group.

Recent publications on patients' experiences after fast-track TKA had outcomes that were comparable to our findings in *Chapter 2* and *Chapter 3* regarding short hospital stay and the need for individualized information. It was concluded that patients appreciate the short duration of hospital stay, although some felt uncertain about discharge and being left on their own.[17] Moreover, patients would like to have more individualized information, mostly regarding the wound, exercises, sleep, and pain medication.[17-20]

Further improvements of fast-track protocols should address these information needs of arthroplasty patients. We assume that telemedicine will be a solution in the near future which can meet these needs by providing information and easily accessible video consultations with a specialist. Recent studies showed encouraging outcomes.[21,22]

In both studies (*Chapter 2* and *Chapter 3*), a considerable number of patients (40%) complained of pain and the formation of haematomas caused by the daily injections of low-molecular-weight heparin (LMWH). Further research is required regarding the duration and need for LMWH injections. Other, possibly oral anticoagulant options may be considered as well[23], since some patients experience subcutaneous injections on a daily basis for six weeks as stressful. Nowadays, patients mobilize shortly after surgery, and this early mobilisation may reduce the risk of deep vein thrombosis and pulmonary embolism. Therefore, it has been suggested that the duration of LMWH prophylaxis can be safely reduced.[24,25] Petersen et al. (2018) found that in fast-track TKA and THA, thromboprophylaxis only in hospital was safe and led to a 90-day incidence of venous thromboembolism of 0.40%.[26] The authors stated that prolonged thromboprophylaxis might only be indicated for a length of hospital stay of more than five days and for specific high-risk patients.[26] Two studies in the Netherlands are under way regarding thrombosis prophylaxis. In these studies, patients with a high risk of thrombosis will be randomized for oral anticoagulants or LMWH. Patients with a low risk of thrombosis will be randomized for LMWH only in hospital or four weeks of LMWH. The outcome of these studies may lead to a change in thrombosis prophylaxis protocols.

Finally, we found that a reasonable percentage of patients (20%) were very uncertain about wound healing, and other studies had the same findings.[27] Extensive patient information seems necessary and might help to reduce concerns regarding wound healing, which might further improve patient satisfaction. The use of applications for smartphones or tablets could be helpful for providing coaching and patient-specific information and must be investigated further.[28,29] Moreover, these applications might be helpful in wound care, as patients could send pictures of the wound to a physician.[30] In a recent randomized clinical trial, the use of an application which provided patient-specific information about pain medication and exercises contributed to reduced opiate use during the initial period at home after TKA.[31] This finding shows the potential of using applications in rehabilitation and postoperative recovery. We assume that an application will meet the needs for individualized patient information. Moreover, such an application might also be used to easily collect data of patient recovery for research purposes.

Future perspectives part I

Based on our own studies in *Chapter 2, Chapter 3,* and on the literature, we can formulate the following research perspectives for the near future:

Sleep

In both studies (*Chapter 2* and *Chapter 3*), patients reported that sleep was impaired during the first weeks postoperatively. Besides, previous research showed that sleep is often disturbed during hospitalization.[32] Sleep deprivation might lead to a delay in rehabilitation and induce hyperalgesia.[33-35] Further studies seem to be required on the effects of insomnia and options to improve sleep after implant surgery.[36]

Physical therapy

Until now, there is no standard nation-wide treatment protocol for out-of-hospital physical therapists regarding rehabilitation after arthroplasty. This results in various treatment strategies, which are partly suboptimal. Hopefully, the physical therapy profession will acknowledge this problem and will improve their guidelines in cooperation with orthopaedic surgeons.[37] A further transition in physical therapy is expected with the increased use of telerehabilitation/mobileHealth.[9] Moreover, physical therapy might need adjustments to be more patient specific. Finally, since it is questionable if all patients need physical therapy[14-16], high-risk patients need to be identified for referral to a physical therapist.

Thrombosis prophylaxis

Until now, it still is unclear whether LMWH prophylaxis after discharge is needed and for which period of time.[26,38] The lack of reliable evidence regarding thrombosis prophylaxis is emphasized by the different recommendations in the available guidelines.[39] Since patients mobilize directly after the operation, the classic concept of postoperative immobilization and concomitant risk of deep vein thrombosis after TKA is no longer valid. Oral treatment options (aspirin, dabigatran) need to be further explored since evidence is emerging that oral options are effective as well.[15,23,40-42]

Smartphone applications

The use of smartphone applications is expected to be the future with regard to providing patients with better information regarding the surgery, wound treatment, and rehabilitation, and recent papers about this topic are promising.[29,31,43] Since the orthopaedic arthroplasty patient population mostly consists of older patients, the demand for such an application is still rather low, however, we believe that this demand will increase fast during the next decade given the increased use of smartphones among the elderly. Based on the study of Freiman et al., outpatient visits might not be replaced by telemedicine and presently patients still want to consult the orthopaedic surgeon or physician assistant in person, but that may also change rapidly over the coming years.[44]

Part II – Recovery after total knee arthroplasty

It has been known that not all patients recover similarly and achieve the same functional improvement and pain relief after TKA. Approximately 10 to 20% of patients remain dissatisfied after TKA.[45-47] This suggests that rehabilitation after TKA might need to be tailored according to the specific needs of the patient. Further progress is possible if we can identify the rehabilitation patterns and associated characteristics of patients in order to improve rehabilitation and thereby improve satisfaction.

In *Chapter 4,* we studied functional outcomes during the first three months after TKA. The functional outcomes gradually improved, and this gain was both statistically significant as well as clinically relevant. In our study, four distinct recovery patterns were identified. In the non-responder group, more patients had a higher BMI and worse scores on the EQ-5D items mobility, self-care, usual activities, and anxiety/depression than in the responder group, and these differences were statistically significant. Since BMI and anxiety/depression are modifiable factors, postoperative outcomes might be improved by preoperative counselling and treatment. The first step is to preoperatively identify the patients with risk factors for being non-responders. This identification might be feasible with the Pain Catastrophizing Scale (PCS) or the Hospital Anxiety and Depression Scale (HADS).[48,49] The next step is to offer these patients an evidence-based treatment. Promising results were described by Tristaino et al. (2016) and Sorel et al. (2020), who showed that preoperative psychological support improved recovery.[50-52]

In *Chapter 5,* a retrospective analysis of 809 TKA cases was performed based on national data from the Dutch arthroplasty registry (LROI: Landelijke Registratie Orthopedische Implantaten). Three distinct recovery patterns were identified: 'high risers', 'gradual progressors', and 'non-responders'. Moreover, patient characteristics were identified for unfavourable trajectory class membership, which were the EQ-5D items self-care, anxiety/depression, and VAS health score. Although this study was a retrospective analysis of prospectively collected data, it provides important information about distinct recovery trajectories and could be helpful to further improve tailored fast-track recovery protocols. Recently, Hamilton et al. (2021) performed a comparable study in the United Kingdom with almost similar outcomes regarding trajectories and risk factors for non-responding patients.[53] Since both studies used functional outcomes registered in national data bases, these findings are highly generalizable. Risk factors in both studies were psychosocial factors such as expectations of pain and anxiety/depression, limited function, and poor coping strategies. The acquired knowledge of risk factors for an unfavourable trajectory might enable preoperative patient selection using specific questionnaires and might offer opportunities for preoperative interventions. Further research is needed to identify effective preoperative treatment options for these patients.

Future perspectives part II

Based on our own studies in *Chapter 4*, *Chapter 5,* and on the literature, we can formulate the following research perspectives for the near future:

Personalized care

Based on the findings of *Chapter 4* and *Chapter 5,* there are different rehabilitation patterns or trajectories in TKA patients. This finding is in line with previous research that also found distinct recovery patterns in THA patients.[54,55]

Current fast-track protocols are based on the 'one-size-fits-all' principle. However, the reality is more complex. Therefore, fast-track protocols need to be more tailored to accommodate the specific needs of individual patients. Further studies are necessary to design more personalized rehabilitation protocols that are more effective than the presently used general one.

Preoperative interventions

Functional outcomes during the first year after surgery have been explored and risk factors for non-responders have been defined. Since some of these factors are modifiable, postoperative outcome might be improved by means of preoperative counselling and related treatment. Preoperative interventions such as a standard check for Diabetes Mellitus (DM) and preoperative treatment of DM might further improve rehabilitation and reduce complications.[56]

Another risk factor for complications in arthroplasty is frailty.[57,58] Various validated frailty scores are available for arthroplasty, and these scores can successfully identify frail patients who are at risks for adverse events.[59-61] Preoperatively identifying frail patients using specific frailty instruments has the protentional to improve patient outcomes.[58] Moreover, it might be justifiable to invite all frail patients for a standard preoperative consultation with the geriatrician.

A reduced length of hospital stay is not feasible for all patients, nor is performing TKA or THA in an outpatient setting. It is assumed that a reduced hospital stay is preferred for selected patients.[62,63] Nowadays, preoperative selection criteria are available to safely include patients for arthroplasty in an outpatient setting.[64] Patients are thought to be good candidates for outpatient arthroplasty if they have no severe medical conditions, live close to the hospital, and have support at home.[62]

With all these available instruments and scoring systems for risk factors, the question remains who should initiate the screening and treatment. It seems to be clear that the orthopaedic surgeons should organise this process to obtain an optimal result.

Satisfaction

Much work has been done and many ideas and interventions have been designed to improve the satisfaction rate among TKA patients. Still, 10 to 20% of the patients remain dissatisfied about the outcome after TKA.[47] No specific single factor has been found to explain this dissatisfaction.[65] Dissatisfaction was associated with unfulfilled expectations, young age, and complications of the procedure.[66,67] Improved preoperative counselling regarding patients' expectations resulted in improved satisfaction rates.[68] Finally, since the patients' satisfaction often differs from the orthopaedic surgeons' evaluation, both will have to be matched to achieve an optimal outcome.[69,70]

Part III – Optimizing fast-track protocols for total knee arthroplasty

To further improve fast-track protocols, the third part of the thesis described different studies that examined the effectiveness of optimal dosage of intrathecal bupivacaine, the effects of perioperative high-dose corticosteroids, and the preoperative use of carbohydrate drinks.

Fast-track protocols require changes in care of all specialists involved with TKA patients. Anaesthesia and analgesia have evolved, although further changes are needed to optimize the perioperative pathway.[71] The high dose of bupivacaine that is routinely used in spinal anaesthesia interferes with early mobilization after TKA due to prolonged postoperative impairment of motor and sensory functions. Since early (same day) mobilisation is a key component of fast-track recovery, it was hypothesized that reducing the dose of intrathecal bupivacaine would improve mobilisation and postoperative rehabilitation.

Chapter 6 concludes that the intrathecal dosage of bupivacaine can safely be reduced. An ED95 of 5.0mg (95% CI 3.7-8.0) was found, which is significantly less than the routinely used dosage of 15mg. We concluded that reducing the intrathecal dose of bupivacaine might improve rehabilitation and reduce the length of hospital stay as well as reduce voiding problems, although this latter finding was not within the scope of the present study. Further research is needed to determine the effects of a reduced dosage of intrathecal bupivacaine on rehabilitation, length of hospital stay, and complications such as urine retention. Moreover, previous studies that compared general anaesthesia and spinal anaesthesia may no longer be valid, since these studies used high dosages of spinal anaesthesia. When lower dosage spinal anaesthesia is compared with general anaesthesia, this might result in different conclusions about the type of anaesthesia that is optimal in fast-track arthroplasty.

Besides the optimization of spinal anaesthesia, other local anaesthetic options need to be investigated. For instance, early mobilization has been improved by means of Local Infiltration Anaesthesia (LIA).[72] Recent investigations regarding motor-sparing nerve blocks and alternatives such as iPACK showed promising results, indicating that these

approaches might be useful additions in multimodal analgesia.[73-76] Recently, Jørgensen et al. (2018) described an increased opioid use after TKA and THA and high usage of opioids after one year in 17.6% and 10.2%, respectively.[77] In view of the negative side effects of opioids and to prevent an 'opioid epidemic', the use of opioid-sparing pain medication should be further improved.

Common causes of a delayed hospital discharge after TKA include pain, nausea, and vomiting.[78] These symptoms result from a surgical stress response and include an inflammatory-immunological response which currently receives a lot of attention. Since the perioperative administration of corticosteroids has a positive effect on postoperative nausea, vomiting, and pain, corticosteroids might improve rehabilitation and reduce the length of hospital stay after TKA. High-dose corticosteroids were thought to reduce this inflammatory-immunological response even more than low-dose corticosteroids, thus improving early recovery.[79] The question remains if high-dose corticosteroids may further enhance recovery and facilitate a safe outpatient setting.[80]

A systematic review reported in *Chapter 7* examined the assumed positive effects of high-dose corticosteroids in fast-track TKA. In total 16 studies on the perioperative use of systemic corticosteroids in TKA were included. These studies vary widely in type, dosage, and timing of administration systemic corticosteroids. Overall, corticosteroids reduce pain, postoperative nausea, vomiting, and length of hospital stay after TKA. Only minimal statistically significant and clinically relevant benefits were found for high-dose perioperative corticosteroids compared to low-dose perioperative corticosteroids. Moreover, multiple perioperative doses were found to have only minimally greater clinical benefits than a single preoperative dose. Given the short follow-up in most studies, it is difficult to conclude that high-dose corticosteroids are safe in use. Further research is needed regarding the effects, the dosage, and the safety aspects before high-dose corticosteroids can be implemented in fast-track TKA protocols.

Preoperative fasting does not only result in discomfort for the patient but might also inhibit early mobilization due to orthostatic intolerance and orthostatic hypotension. In THA, postoperative orthostatic intolerance and orthostatic hypotension were found in 40% of the patients.[81,82] Jans et al. (2017) concluded that orthostatic intolerance is a multifactorial problem, as illustrated in figure 1.[83]

It was assumed that preoperative carbohydrate drinks reduce the hypovolemia component and reduce orthostatic intolerance and orthostatic hypotension. Previous studies investigating preoperative carbohydrate drinks in various types of surgery showed promising results for postoperative orthostatic intolerance.[84] In THA, only minor advantages have been found.[81,82] No previous studies were performed on the effects of preoperative carbohydrate drinks in TKA.

The prospective randomized controlled trial reported in *Chapter 8* showed a lower incidence of orthostatic hypotension in the intervention group, which preoperatively

received a carbohydrate drink. Although the incidence of orthostatic hypotension was lower, still 19% of these patients had orthostatic hypotension. Since orthostatic intolerance and orthostatic hypotension is a multifactorial symptom, a preoperative carbohydrate drink might not be the only solution. Further studies are needed to reduce orthostatic intolerance and hypotension, since these symptoms are frequently reported and possibly modifiable reasons for prolonged hospital stay.[78, 85, 86]

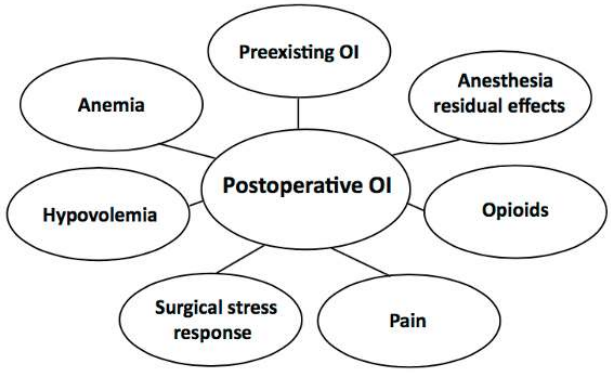


Figure 1. *Proposed mechanisms for postoperative Orthostatic Intolerance (OI) (Jans et al. 2017)*

Future perspectives part III

Based on our own studies in *Chapter 6, Chapter 7*, *Chapter 8,* and on the literature, we can formulate the following research perspectives for the near future:

Anaesthesia

Chapter 6 showed that a lower dose of intrathecal bupivacaine is feasible. However, this study did not explore clinical implications, such as length of stay, bladder retention, and time to mobilize, which should therefore be investigated in further research. Moreover, new promising local anaesthesia methods for multimodal analgesia have been studied with favourable outcomes.[73-76] To improve postoperative pain control and to reduce opioid consumption, these new methods need to be further examined.

Glucocorticoids

It has been thought that the surgical stress response after TKA prohibits early recovery after surgery since this response results in fatigue, nausea, and pain. Adequately managing these symptoms will further optimize fast-track rehabilitation and lead to reduced length of hospital stay and improved patient satisfaction.[87-89]

Recently, high doses of dexamethasone have been of interest to reduce the surgical stress response. *Chapter 7* showed that, due to the highly variable usage of corticoste-

roids in terms of timing, dosage, and type of corticosteroids, the outcomes of different studies are difficult to compare. Moreover, further research is needed to find a more specific treatment for reducing the surgical stress response. Instead of using corticosteroids, there might be a role for specific medication that interferes with the cascade, for instance IL-6 blockers.

Postoperative orthostatic intolerance

The results in *Chapter 8* regarding the implementation of a preoperative carbohydrate drink was a first step in reducing postoperative orthostatic intolerance. The incidence of 13% in our intervention group is in accordance with the findings of other studies.[90] Various interventions have been examined, including the use of corticosteroids, but unfortunately without success.[91] Further research is needed since postoperative orthostatic intolerance is a multifactorial and presumably modifiable problem that hampers with early postoperative mobilisation and prolongs hospital stay.[92]

Limitations

In this thesis, most of the factors have been studied that influence length of hospital stay as stated in the article of Kehlet et al.[92] However, we did not study all the possible factors that might influence early postoperative mobilisation, length of stay, and fast-track recovery. One of the important factors not included in this thesis is preoperative anaemia. In fast-track protocols, the detection of preoperative anaemia and the reduction of perioperative blood loss is very important. Studies have shown that preoperative anaemia is a modifiable risk factor for prolonged hospital stay, blood transfusions, readmissions, and mortality.[93-96] Postoperative anaemia is mostly treated with blood transfusion, which is associated with risks of adverse events.[97] Various treatments are available to reduce perioperative blood loss, and recently there has been increasing interest in the use of tranexamic acid (TXA), with very favourable results. In a recent consensus statement, the use of TXA is recommended since it is both efficient and safe to use.[98] However, the most optimal dosage and way of administration (oral, topical, intravenous) is still unclear.

Recommendations for further research

It becomes more and more evident that good functioning and satisfied patients are not achieved by the use of good implants and well performed surgery alone. The final outcome depends on multiple factors and on the entire perioperative trajectory.

Although many improvements have been realised in fast-track recovery during the last decade, further research and improvements are needed. The ‘black-box’ of early recovery has been opened, but the ‘box’ has not been completely explored yet. There

are still options for further improvement of fast-track protocols. As stated by Husted: "First doing it better, then doing it quicker".[99]

Roughly two decades ago, fast-track was first introduced. The short-term outcomes are encouraging, but no long-term outcomes have been fully explored.[100] Further research should prove that fast-track recovery with short length of hospital stay does not compromise long-term outcomes of arthroplasty.

More clinical research is needed for thrombosis prophylaxis, physical therapy, the deployment of eHealth, and more tailored recovery, which are all aspects that need further improvement.

Finally, the next focus of research should be on preoperative optimisation of patients. Referring to the old principle 'better-in-better-out', the literature shows improved postoperative outcomes after preoperative optimization. Known factors of great importance are anaemia, Diabetes Mellitus, BMI, anxiety/depression, and frailty.

Conclusion and clinical implications of this thesis

This thesis opens the 'black box' regarding the first weeks after fast-track primary unilateral TKA. Based on our findings, fast-track protocols need to be improved regarding anticoagulation, physical therapy, and personalised information and coaching.

This research identified four distinct recovery patterns in the first months and three distinct recovery patterns in the first year after primary TKA. These patterns were related to specific patient characteristics and revealed that BMI and anxiety/depression are presumably modifiable risk factors for non-responders in primary TKA. A more tailored rehabilitation than the usual general one might improve rehabilitation and satisfaction rates.

Based on our dose finding study, a reduction in dosage of intrathecal anaesthesia might be helpful to improve early mobilization. Moreover, minimal evidence is available for high-dose corticosteroids to reduce the surgical stress response in order to optimize early postoperative recovery. Finally, reducing the fasting period by supplying patients with a carbohydrate drink shortly before surgery reduced orthostatic hypotension.

But the surgeon should always keep in mind that to improve fast-track, the focus should be "first better and then faster".

REFERENCES

1. Husted H, Solgaard S, Hansen TB, Soballe K, Kehlet H. Care principles at four fast-track arthroplasty departments in Denmark. Dan Med Bull. 2010;57(7):A4166.
2. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, et al. What determines length of stay after total hip and knee arthroplasty? A nationwide study in Denmark. Archives of orthopaedic and trauma surgery. 2010;130(2):263-8.
3. Husted H, Jensen CM, Solgaard S, Kehlet H. Reduced length of stay following hip and knee arthroplasty in Denmark 2000-2009: from research to implementation. Archives of orthopaedic and trauma surgery. 2012;132(1):101-4.
4. Malviya A, Martin K, Harper I, Muller SD, Emmerson KP, Partington PF, et al. Enhanced recovery program for hip and knee replacement reduces death rate. Acta orthopaedica. 2011;82(5):577-81.
5. Hansen TB. Fast track in hip arthroplasty. EFORT open reviews. 2017;2(5):179-88.
6. Gleicher Y, Peacock S, Peer M, Wolfstadt J. Transitioning to outpatient arthroplasty during COVID-19: time to pivot. CMAJ. 2021;193(13):E455.
7. Ding BTK, Ng J, Tan KG. Enhanced Recovery after Surgery for Knee Arthroplasty in the Era of COVID-19. J Knee Surg. 2022;35(4):424-33.
8. Klapwijk LC, Mathijssen NM, Van Egmond JC, Verbeek BM, Vehmeijer SB. The first 6 weeks of recovery after primary total hip arthroplasty with fast track. Acta orthopaedica. 2017;88(2):140-4.
9. Joice MG, Bhowmick S, Amanatullah DF. Perioperative Physiotherapy in Total Knee Arthroplasty. Orthopedics. 2017;40(5):e765-e73.
10. Sarpong NO, Lakra A, Jennings E, Cooper HJ, Shah RP, Geller JA. Same-Day Physical Therapy Following Total Knee Arthroplasty Leads to Improved Inpatient Physical Therapy Performance and Decreased Inpatient Opioid Consumption. J Arthroplasty. 2019;34(12):2931-6.
11. Peter WF, Nelissen RG, Vlieland TP. Guideline recommendations for post-acute postoperative physiotherapy in total hip and knee arthroplasty: are they used in daily clinical practice? Musculoskeletal Care. 2014;12(3):125-31.
12. Pozzi F, Snyder-Mackler L, Zeni J. Physical exercise after knee arthroplasty: a systematic review of controlled trials. Eur J Phys Rehabil Med. 2013;49(6):877-92.
13. Groot L, Gademan MGJ, Peter WF, van den Hout WB, Verburg H, Vliet Vlieland TPM, et al. Rationale and design of the PaTIO study: PhysiotherApeutic Treat-to-target Intervention after Orthopaedic surgery. BMC Musculoskelet Disord. 2020;21(1):544.
14. Austin MS, Urbani BT, Fleischman AN, Fernando ND, Purtill JJ, Hozack WJ, et al. Formal Physical Therapy After Total Hip Arthroplasty Is Not Required: A Randomized Controlled Trial. The Journal of bone and joint surgery American volume. 2017;99(8):648-55.
15. Jakobsen TL, Jakobsen MD, Andersen LL, Husted H, Kehlet H, Bandholm T. Quadriceps muscle activity during commonly used strength training exercises shortly after total knee arthroplasty: implications for home-based exercise-selection. J Exp Orthop. 2019;6(1):29.
16. Hamilton DF, Beard DJ, Barker KL, Macfarlane GJ, Tuck CE, Stoddart A, et al. Targeting rehabilitation to improve outcomes after total knee arthroplasty in patients at risk of poor outcomes: randomised controlled trial. BMJ. 2020;371:m3576.
17. Specht K, Agerskov H, Kjaersgaard-Andersen P, Jester R, Pedersen BD. Patients' experiences during the first 12 weeks after discharge in fast-track hip and knee arthroplasty - a qualitative study. Int J Orthop Trauma Nurs. 2018;31:13-9.
18. Sjoveian AKH, Leegaard M. Hip and knee arthroplasty - patient's experiences of pain and rehabilitation after discharge from hospital. Int J Orthop Trauma Nurs. 2017;27:28-35.

19. Hardy A, Gervais-Hupe J, Desmeules F, Hudon A, Perreault K, Vendittoli PA. Comparing ERAS-outpatient versus standard-inpatient hip and knee replacements: a mixed methods study exploring the experience of patients who underwent both. BMC Musculoskelet Disord. 2021;22(1):978.
20. Groeneveld BS, Dekkers T, Mathijssen NMC, Vehmeijer SBW, Melles M, Goossens RHM. Communication Preferences in Total Joint Arthroplasty: Exploring the Patient Experience Through Generative Research. Orthop Nurs. 2020;39(5):292-302.
21. Moore MR, Galetta MS, Schwarzkopf R, Slover JD, Force Writing C. Patient Satisfaction and Interest in Telemedicine Visits Following Total Knee and Hip Replacement Surgery. Telemed J E Health. 2022 online ahead of print.
22. Petersen W, Karpinski K, Backhaus L, Bierke S, Haner M. A systematic review about telemedicine in orthopedics. Archives of orthopaedic and trauma surgery. 2021;141(10):1731-9.
23. Rondon AJ, Shohat N, Tan TL, Goswami K, Huang RC, Parvizi J. The Use of Aspirin for Prophylaxis Against Venous Thromboembolism Decreases Mortality Following Primary Total Joint Arthroplasty. The Journal of bone and joint surgery American volume. 2019;101(6):504-13.
24. Husted H, Otte KS, Kristensen BB, Orsnes T, Wong C, Kehlet H. Low risk of thromboembolic complications after fast-track hip and knee arthroplasty. Acta orthopaedica. 2010;81(5):599-605.
25. Jorgensen CC, Kehlet H, Lundbeck Foundation Centre for Fast-track Hip and Knee replacement collaborative group. Early thromboembolic events ≤1week after fast-track total hip and knee arthroplasty. Thrombosis research. 2016;138:37-42.
26. Petersen PB, Kehlet H, Jorgensen CC, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Safety of In-Hospital Only Thromboprophylaxis after Fast-Track Total Hip and Knee Arthroplasty: A Prospective Follow-Up Study in 17,582 Procedures. Thromb Haemost. 2018;118(12):2152-61.
27. Naylor JM, Harmer AR, Heard RC, Harris IA. Patterns of recovery following knee and hip replacement in an Australian cohort. Aust Health Rev. 2009;33(1):124-35.
28. Saunders R, Seaman K, Emery L, Crompton D, Lynch C, Penjor D, et al. My hip journey: A qualitative study of patients' experiences of an eHealth program for patient preparation and recovery from hip replacement surgery. J Clin Nurs. 2021 Online ahead of print.
29. Timmers T, Janssen L, van der Weegen W, Das D, Marijnissen WJ, Hannink G, et al. The Effect of an App for Day-to-Day Postoperative Care Education on Patients With Total Knee Replacement: Randomized Controlled Trial. JMIR Mhealth Uhealth. 2019;7(10):e15323.
30. Scheper H, Derogee R, Mahdad R, van der Wal RJP, Nelissen R, Visser LG, et al. A mobile app for postoperative wound care after arthroplasty: Ease of use and perceived usefulness. Int J Med Inform. 2019;129:75-80.
31. Pronk Y, Peters M, Sheombar A, Brinkman JM. Effectiveness of a Mobile eHealth App in Guiding Patients in Pain Control and Opiate Use After Total Knee Replacement: Randomized Controlled Trial. JMIR Mhealth Uhealth. 2020;8(3):e16415.
32. Tranmer JE, Minard J, Fox LA, Rebelo L. The sleep experience of medical and surgical patients. Clin Nurs Res. 2003;12(2):159-73.
33. Cremeans-Smith JK, Millington K, Sledjeski E, Greene K, Delahanty DL. Sleep disruptions mediate the relationship between early postoperative pain and later functioning following total knee replacement surgery. J Behav Med. 2006;29(2):215-22.
34. Krenk L, Jennum P, Kehlet H. Sleep disturbances after fast-track hip and knee arthroplasty. Br J Anaesth. 2012;109(5):769-75.

35. Shen SP, Wang YJ, Zhang Q, Qiang H, Weng XS. Improved Perioperative Sleep Quality or Quantity Reduces Pain after Total Hip or Knee Arthroplasty: A Systematic Review and Meta-Analysis. Orthop Surg. 2021;13(4):1389-97.
36. Wang Y, Liu Y, Li X, Lv Q, Xia Q, Wang X, et al. Prospective assessment and risk factors of sleep disturbances in total hip and knee arthroplasty based on an Enhanced Recovery After Surgery concept. Sleep Breath. 2021;25(3):1231-7.
37. Schneider M, Kawahara I, Ballantyne G, McAuley C, Macgregor K, Garvie R, et al. Predictive factors influencing fast track rehabilitation following primary total hip and knee arthroplasty. Archives of orthopaedic and trauma surgery. 2009;129(12):1585-91.
38. Jorgensen CC, Petersen PB, Reed M, Kehlet H. Recommendations on thromboprophylaxis in major joint arthroplasty - many guidelines, little consensus? J Thromb Haemost. 2019;17(2):250-3.
39. Flevas DA, Megaloikonomos PD, Dimopoulos L, Mitsiokapa E, Koulouvaris P, Mavrogenis AF. Thromboembolism prophylaxis in orthopaedics: an update. EFORT open reviews. 2018;3(4):136-48.
40. Feng W, Wang X, Huang D, Lu A. Ranking the efficacy of anticoagulants for the prevention of venous thromboembolism after total hip or knee arthroplasty: A systematic review and a network meta-analysis. Pharmacol Res. 2021;166:105438.
41. Hamilton SC, Whang WW, Anderson BJ, Bradbury TL, Erens GA, Roberson JR. Inpatient enoxaparin and outpatient aspirin chemoprophylaxis regimen after primary hip and knee arthroplasty: a preliminary study. J Arthroplasty. 2012;27(9):1594-8.
42. Gesell MW, Gonzalez Della Valle A, Bartolome Garcia S, Memtsoudis SG, Ma Y, Haas SB, et al. Safety and efficacy of multimodal thromboprophylaxis following total knee arthroplasty: a comparative study of preferential aspirin vs. routine coumadin chemoprophylaxis. J Arthroplasty. 2013;28(4):575-9.
43. Backer HC, Wu CH, Schulz MRG, Weber-Spickschen TS, Perka C, Hardt S. App-based rehabilitation program after total knee arthroplasty: a randomized controlled trial. Archives of orthopaedic and trauma surgery. 2021;141(9):1575-82.
44. Freiman S, Schwabe MT, Barrack RL, Nunley RM, Clohisy JC, Lawrie CM. Telemedicine for patients undergoing arthroplasty : access, ability, and preference. Bone Joint J. 2021;103-B(7 Supple B):98-102.
45. Kahlenberg CA, Nwachukwu BU, McLawhorn AS, Cross MB, Cornell CN, Padgett DE. Patient Satisfaction After Total Knee Replacement: A Systematic Review. HSS J. 2018;14(2):192-201.
46. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KD. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clin Orthop Relat Res. 2010;468(1):57-63.
47. Dunbar MJ, Richardson G, Robertsson O. I can't get no satisfaction after my total knee replacement: rhymes and reasons. Bone Joint J. 2013;95-B(11 Suppl A):148-52.
48. Mercurio M, Gasparini G, Carbone EA, Galasso O, Segura-Garcia C. Personality traits predict residual pain after total hip and knee arthroplasty. Int Orthop. 2020;44(7):1263-70.
49. Larsen DB, Laursen M, Edwards RR, Simonsen O, Arendt-Nielsen L, Petersen KK. The Combination of Preoperative Pain, Conditioned Pain Modulation, and Pain Catastrophizing Predicts Postoperative Pain 12 Months After Total Knee Arthroplasty. Pain Med. 2021;22(7):1583-90.
50. Tristaino V, Lantieri F, Tornago S, Gramazio M, Carriere E, Camera A. Effectiveness of psychological support in patients undergoing primary total hip or knee arthroplasty: a controlled cohort study. J Orthop Traumatol. 2016;17(2):137-47.

51. Sorel JC, Veltman ES, Honig A, Poolman RW. The influence of preoperative psychological distress on pain and function after total knee arthroplasty: a systematic review and meta-analysis. Bone Joint J. 2019;101-B(1):7-14.
52. Sorel JC, Overvliet GM, Gademan MGJ, den Haan C, Honig A, Poolman RW. The influence of perioperative interventions targeting psychological distress on clinical outcome after total knee arthroplasty. Rheumatol Int. 2020;40(12):1961-86.
53. Hamilton DF, Shim J, Howie CR, Macfarlane GJ. Patients follow three distinct outcome trajectories following total knee arthroplasty. Bone Joint J. 2021;103-B(6):1096-102.
54. Porsius JT, Mathijssen NMC, Klapwijk-Van Heijningen LCM, Van Egmond JC, Melles M, Vehmeijer SBW. Early recovery trajectories after fast-track primary total hip arthroplasty: the role of patient characteristics. Acta orthopaedica. 2018;89(6):597-602.
55. Hesseling B, Mathijssen NMC, van Steenbergen LN, Melles M, Vehmeijer SBW, Porsius JT. Fast Starters, Slow Starters, and Late Dippers: Trajectories of Patient-Reported Outcomes After Total Hip Arthroplasty: Results from a Dutch Nationwide Database. The Journal of bone and joint surgery American volume. 2019;101(24):2175-86.
56. Shohat N, Goswami K, Tarabichi M, Sterbis E, Tan TL, Parvizi J. All Patients Should Be Screened for Diabetes Before Total Joint Arthroplasty. J Arthroplasty. 2018;33(7):2057-61.
57. Tram MK, O'Connor CM, Qian AS, Tram JT, Tetreault MW. Frailty Is Associated With Increased 30-Day Adverse Events and Hospitalization Costs After Primary Total Hip Arthroplasty. J Arthroplasty. 2022 Online ahead of print.
58. Lemos JL, Welch JM, Xiao M, Shapiro LM, Adeli E, Kamal RN. Is Frailty Associated with Adverse Outcomes After Orthopaedic Surgery?: A Systematic Review and Assessment of Definitions. JBJS Rev. 2021;9(12).
59. Seilern Und Aspang J, Zamanzadeh RS, Schwartz AM, Premkumar A, Martin JR, Wilson JM. The Age-Adjusted Modified Frailty Index:An Improved Risk Stratification Tool for Patients Undergoing Primary Total Hip Arthroplasty. J Arthroplasty. 2022 Online ahead of print.
60. Chen Y, Qin J. Modified Frailty Index Independently Predicts Postoperative Delirium and Delayed Neurocognitive Recovery After Elective Total Joint Arthroplasty. J Arthroplasty. 2021;36(2):449-53.
61. Meyer M, Parik L, Leiss F, Renkawitz T, Grifka J, Weber M. Hospital Frailty Risk Score Predicts Adverse Events in Primary Total Hip and Knee Arthroplasty. J Arthroplasty. 2020;35(12):3498-504 e3.
62. Kolisek FR, McGrath MS, Jessup NM, Monesmith EA, Mont MA. Comparison of outpatient versus inpatient total knee arthroplasty. Clin Orthop Relat Res. 2009;467(6):1438-42.
63. Gromov K, Kjaersgaard-Andersen P, Revald P, Kehlet H, Husted H. Feasibility of outpatient total hip and knee arthroplasty in unselected patients. Acta orthopaedica. 2017;88(5):516-21.
64. Meneghini RM, Ziemba-Davis M, Ishmael MK, Kuzma AL, Caccavallo P. Safe Selection of Outpatient Joint Arthroplasty Patients With Medical Risk Stratification: the "Outpatient Arthroplasty Risk Assessment Score". J Arthroplasty. 2017;32(8):2325-31.
65. Verhaar J. Patient satisfaction after total knee replacement-still a challenge. Acta orthopaedica. 2020;91(3):241-2.
66. Ayers DC, Yousef M, Zheng H, Yang W, Franklin PD. The Prevalence and Predictors of Patient Dissatisfaction 5-years Following Primary Total Knee Arthroplasty. J Arthroplasty. 2022 Online ahead of print.

67. Gunaratne R, Pratt DN, Banda J, Fick DP, Khan RJK, Robertson BW. Patient Dissatisfaction Following Total Knee Arthroplasty: A Systematic Review of the Literature. J Arthroplasty. 2017;32(12):3854-60.
68. Tolk JJ, Janssen RPA, Haanstra TM, van der Steen MC, Bierma-Zeinstra SMA, Reijman M. The influence of expectation modification in knee arthroplasty on satisfaction of patients: a randomized controlled trial. Bone Joint J. 2021;103-B(4):619-26.
69. Mark-Christensen T, Kehlet H. Assessment of functional recovery after total hip and knee arthroplasty: An observational study of 95 patients. Musculoskeletal Care. 2019;17(4):300-12.
70. Choi YJ, Ra HJ. Patient Satisfaction after Total Knee Arthroplasty. Knee Surg Relat Res. 2016;28(1):1-15.
71. Turnbull ZA, Sastow D, Giambrone GP, Tedore T. Anesthesia for the patient undergoing total knee replacement: current status and future prospects. Local and regional anesthesia. 2017;10:1-7.
72. Seangleulur A, Vanasbodeekul P, Prapaitrakool S, Worathongchai S, Anothaisintawee T, McEvoy M, et al. The efficacy of local infiltration analgesia in the early postoperative period after total knee arthroplasty: A systematic review and meta-analysis. Eur J Anaesthesiol. 2016;33(11):816-31.
73. Feng JE, Ikwuazom CP, Umeh UO, Furgiuele DL, Slover JD, Macaulay W, et al. Adductor Canal Blocks Reduce Inpatient Opioid Consumption While Maintaining Noninferior Pain Control and Functional Outcomes After Total Knee Arthroplasty. J Arthroplasty. 2021;36(6):1980-6.
74. Mingdeng X, Yuzhang A, Xiaoxiao X, Yucheng A, Xin W, Dianming J. Combined application of adductor canal block and local infiltration anesthesia in primary total knee arthroplasty: an updated meta-analysis of randomized controlled trials. Archives of orthopaedic and trauma surgery. 2021 Online ahead of print.
75. Balocco AL, Claes E, Lopez A, Van Herreweghe I. Selective periarticular blocks for postoperative pain after hip and knee arthroplasty. Curr Opin Anaesthesiol. 2021;34(4):544-52.
76. Layera S, Aliste J, Bravo D, Saadawi M, Salinas FV, Tran Q. Motor-sparing nerve blocks for total knee replacement: A scoping review. J Clin Anesth. 2021;68:110076.
77. Jorgensen CC, Petersen M, Kehlet H, Aasvang EK. Analgesic consumption trajectories in 8975 patients 1 year after fast-track total hip or knee arthroplasty. Eur J Pain. 2018 Online ahead of print.
78. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta orthopaedica. 2011;82(6):679-84.
79. Zhuo Y, Yu R, Wu C, Huang Y, Ye J, Zhang Y. The role of perioperative intravenous low-dose dexamethasone in rapid recovery after total knee arthroplasty: a meta-analysis. J Int Med Res. 2021;49(3):1-18.
80. Kehlet H, Lindberg-Larsen V. High-dose glucocorticoid before hip and knee arthroplasty: To use or not to use-that's the question. Acta orthopaedica. 2018;89(5):477-9.
81. Harsten A, Hjartarson H, Toksvig-Larsen S. Total hip arthroplasty and perioperative oral carbohydrate treatment: a randomised, double-blind, controlled trial. Eur J Anaesthesiol. 2012;29(6):271-4.
82. Ljunggren S, Hahn RG. Oral nutrition or water loading before hip replacement surgery; a randomized clinical trial. Trials. 2012;13:97.
83. Jans O, Kehlet H. Postoperative orthostatic intolerance: a common perioperative problem with few available solutions. Can J Anaesth. 2017;64(1):10-5.
84. Bilku DK, Dennison AR, Hall TC, Metcalfe MS, Garcea G. Role of preoperative carbohydrate loading: a systematic review. Ann R Coll Surg Engl. 2014;96(1):15-22.

85. Farley KX, Anastasio AT, Premkumar A, Boden SD, Gottschalk MB, Bradbury TL. The Influence of Modifiable, Postoperative Patient Variables on the Length of Stay After Total Hip Arthroplasty. J Arthroplasty. 2019;34(5):901-6.
86. Bundgaard-Nielsen M, Jans O, Muller RG, Korshin A, Ruhnau B, Bie P, et al. Does goal-directed fluid therapy affect postoperative orthostatic intolerance?: A randomized trial. Anesthesiology. 2013;119(4):813-23.
87. Si HB, Yang TM, Zeng Y, Zhou ZK, Pei FX, Lu YR, et al. Correlations between inflammatory cytokines, muscle damage markers and acute postoperative pain following primary total knee arthroplasty. BMC Musculoskelet Disord. 2017;18(1):265.
88. Steinthorsdottir KJ, Kehlet H, Aasvang EK. Surgical stress response and the potential role of preoperative glucocorticoids on post-anesthesia care unit recovery. Minerva Anestesiol. 2017;83(12):1324-31.
89. Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. Br J Anaesth. 2000;84(1):6-10.
90. Kurkis GM, Dennis DA, Johnson RM, Mejia M, Yazdani-Farsad Y, Jennings JM. Incidence and Risk Factors of Orthostasis After Primary Hip and Knee Arthroplasty. J Arthroplasty. 2022.
91. Lindberg-Larsen V, Petersen PB, Jans O, Beck T, Kehlet H. Effect of pre-operative methylprednisolone on orthostatic hypotension during early mobilization after total hip arthroplasty. Acta Anaesthesiol Scand. 2018;62(7):882-92.
92. Kehlet H, Thienpont E. Fast-track knee arthroplasty -- status and future challenges. Knee. 2013;20 Suppl 1:S29-33.
93. Jans O, Jorgensen C, Kehlet H, Johansson PI, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. Transfusion. 2014;54(3):717-26.
94. Pujol-Nicolas A, Morrison R, Casson C, Khan S, Marriott A, Tiplady C, et al. Preoperative screening and intervention for mild anemia with low iron stores in elective hip and knee arthroplasty. Transfusion. 2017;57(12):3049-57.
95. Munoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia. 2017;72(2):233-47.
96. Mathew KK, Vakharia RM, Salem HS, Sodhi N, Anis HK, Roche MW, et al. Is Iron Deficiency Anemia a Risk Factor for Poorer Outcomes in Primary Total Knee Arthroplasty? J Arthroplasty. 2020;35(5):1252-6.
97. Friedman R, Homering M, Holberg G, Berkowitz SD. Allogeneic blood transfusions and postoperative infections after total hip or knee arthroplasty. The Journal of bone and joint surgery American volume. 2014;96(4):272-8.
98. Wainwright TW, Gill M, McDonald DA, Middleton RG, Reed M, Sahota O, et al. Consensus statement for perioperative care in total hip replacement and total knee replacement surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Acta orthopaedica. 2020;91(1):3-19.
99. Husted H. Fast-track hip and knee arthroplasty: clinical and organizational aspects. Acta Orthop Suppl. 2012;83(346):1-39.
100. Pagnotta G, Rich E, Eckardt P, Lavin P, Burriesci R. The Effect of a Rapid Rehabilitation Program on Patients Undergoing Unilateral Total Knee Arthroplasty. Orthop Nurs. 2017;36(2):112-21.

Appendices

- Summary
- Nederlandse samenvatting
- List of publications
- PhD Portfolio
- Dankwoord
- About the author

SUMMARY

Primary Total Knee Arthroplasty (TKA) is an orthopaedic surgery that is frequently and successfully performed worldwide. When conservative treatment of knee osteoarthritis fails, TKA is a good option for alleviating pain and limitations. Historically, patients who had undergone TKA were admitted at the hospital for several weeks, where their treatment mainly consisted of bed rest.

During the last few decades, perioperative treatment has been greatly improved due to fast-track protocols. These protocols are focused on improved rehabilitation by reducing surgical stress, providing effective pain treatment, and initiating early mobilization. To achieve fast-track recovery, current care requires adjustments, even in the treatment protocols of various specialties involved in the care of TKA patients, including nurses, physical therapists, orthopaedic surgeons, and anaesthesiologists.

The implementation of fast-track protocols improved rehabilitation after TKA and concomitantly reduced the length of hospital stay. Currently, the mean length of hospital stay after TKA has decreased to only one or two nights after surgery, and in selected patients, TKA is even feasible in day care. Fast-track recovery protocols result in safe perioperative care.

During the last decade, there has been a continued interest in implementing fast-track protocols after TKA. However, the challenge remains to further optimize perioperative care for patients who underwent primary TKA, since 15 to 20% of TKA patients remains dissatisfied.

The main objective of this thesis was to investigate how perioperative care for TKA patients can be further optimized. This was attempted by obtaining a more detailed insight into the first postoperative period, by analysing recovery patterns after TKA, and finally by identifying possible changes in current fast-track protocols.

This thesis was subdivided into three parts:

1. the early postoperative phase after primary TKA in a fast-track setting
2. recovery after fast-track TKA
3. possible improvements in perioperative care of fast-track TKA protocols

Part I – Opening the black box

Chapter 2 presented a qualitative study in which 20 patients were interviewed about their experiences after TKA and total hip arthroplasty (THA). Patients reported complaints of inability to sleep during the first postoperative weeks. Moreover, patients who lived alone needed more care and, therefore, would stay hospitalized for a longer period. Finally, patients reported various treatments by out-of-hospital physical therapists.

To investigate and measure the burden of complaints described in *Chapter 2*, a quantitative study was performed, which was presented in *Chapter 3.* In this study, 30

patients were included, who completed a diary that comprised various questionnaires regarding pain, quality of life, and functioning during the first six postoperative weeks. Moreover, questions were posted regarding wound care, physical therapy, medication, readmission, and use of aids. Of the 30 included patients, 28 were positive regarding the short length of hospital stay. Pain scores gradually decreased and quality of life and functioning gradually improved during the first six postoperative weeks. Patients reported a high variance of treatment modalities, intensity, and duration of physical therapy. We presumed that these variations resulted from a lack of standardized physical therapy protocols. A total of nine patients reported clinical consultations during their first six postoperative weeks, which were mostly due to concerns about the wound and about inability to sleep. Complaints about the daily low-molecular-weight heparin injections increased during the six weeks.

Part II – Recovery after total knee arthroplasty

Rehabilitation and outcomes of TKA varied between patients, 15 to 20% of whom dissatisfied with their outcome. Therefore, it was presumed that distinct recovery patterns might exists. The functional outcomes after TKA during the first three postoperative months were explored in *Chapter 4.* In this study, patient-reported outcomes (PROMs) of 623 patients were analysed. The PROMs comprised various international validated questionnaires (Oxford knee score (OKS), Knee disability and Osteoarthritis Outcome Score Physical Function Short-Form (KOOS-PS), and EuroQol 5 dimensions (EQ-5D)). Improvements of function scores were both statistically significant and clinically relevant in this early phase of rehabilitation. We defined four distinct recovery patterns. Responders and non-responders were distinguished based on the OKS. Characteristics of non-responders were a higher BMI and worse scores on the EQ-5D items mobility, selfcare, activities, and anxiety/depression. Both BMI and anxiety/depression were presumed to be modifiable preoperative risk factors for an unfavourable recovery pattern.

In *Chapter 5,* recovery after TKA was assessed during the first postoperative year. A total of 809 TKA procedures were retrospectively analysed to detect distinct recovery patterns. Data were gathered from the Dutch national arthroplasty registry (Landelijke Registratie Orthopedische Implantaten: LROI) to present a more generalized outcome. Using latent class growth modelling (LCGM), three distinct recovery trajectories were identified: ‘high risers’, ‘gradual progressors’, and ‘non-responders’. Low scores on the EQ-5D items VAS health, self-care, and anxiety/depression were correlated with a less favourable class membership.

Part III – Optimizing fast-track protocols for total knee arthroplasty

Since early mobilization is a key component of fast-track protocols, prolonged immobilization due to sensory and motor dysfunction of the legs is undesirable. It was presumed

that reducing the dosage of spinal anaesthesia would result in faster recovery of motor and sensory functions. *Chapter 6* presented a prospective dose-finding study which examined the feasibility of lowering the bupivacaine dosage. This study was performed according to the sequential allocation model as described by Dixon and Massey, in which each patient received a dosage based on the outcome of the preceding patient. A total of 25 patients were included. A median dosage (ED50) of 3.5mg (95% CI 3.1-4.0) was found. The ED95 was determined at 5.0mg (95% CI 3.7-8.0) and was considered optimal, indicating that the dosage should be significantly lower than the currently admitted dosage of 15mg.

Reasons for delayed discharge or prolonged length of stay include pain, nausea, and vomiting. These factors have been shown to be reduced by dexamethasone. Successful outcomes of perioperative administrating dexamethasone in arthroplasty have been published, but dosage effects remain unclear. *Chapter 7* presented a systematic review investigating the effects of dosage on pain, nausea, vomiting, length of hospital stay, and complications. In total, 16 studies were included, which varied widely in type, dosage, and timing of administration. Overall, corticosteroids reduced pain, nausea, vomiting, and length of hospital stay after TKA. High doses of perioperative corticosteroids showed only minimally clinically relevant benefits of than low doses. Given the short follow-up in most studies, it is difficult to conclude that high doses of corticosteroids are safe in use.

Most TKA patients complain about the preoperative fasting period. Besides the inconvenience of fasting, preoperative fasting might even lead to postoperative orthostatic hypotension and orthostatic intolerance, which impede postoperative mobilisation. To optimize postoperative mobilization, it was assumed that rehabilitation might be improved by reducing the fasting period. Literature showed that a reduced fasting period is safe and that preoperative carbohydrate drinks reduce anxiety and improve patient well-being. In *Chapter 8,* a prospective randomized controlled trial was described in which patients were randomized between an intervention group and a control group. The intervention group received a carbohydrate drink (400cc) 2 to 3 hours before surgery. The control group was treated according to the current fasting protocol, which means no food 6 hours preoperative and no drinks 2 hours preoperative. A total of 168 patients were included. Orthostatic hypotension was lower in the intervention group than in the control group. No adverse events related to the preoperative drinks were noted. Finally, no differences were found regarding orthostatic intolerance, length of stay, nausea, and vomiting.

NEDERLANDSE SAMENVATTING

Het plaatsen van een totale knieprothese (TKP) is een succesvolle en wereldwijd frequent uitgevoerde orthopedische operatie. Wanneer de conservatieve behandelingen niet meer helpen bij gevorderde knie artrose, dan is een TKP een goede behandeling voor pijn en functiebeperkingen. Vroeger bedroeg de opnameduur na een TKP enkele weken, die met name bestond uit bedrust.

Gedurende het laatste decennium is de perioperatieve behandeling enorm veranderd door het gebruik van fast-track protocollen. Fast-track protocollen zijn gericht op een verbeterd en versneld herstel door het verminderen van de chirurgische stressrespons, effectieve pijnstilling en vroeg mobiliseren. Dit vereist veranderingen in de zorg en behandeling van alle betrokken specialismen rondom een TKP-operatie, waaronder die van verpleegkundigen, fysiotherapeuten, orthopedisch chirurgen en anesthesiologen.

De implementatie van fast-track protocollen heeft de postoperatieve zorg na een TKP verbeterd en de opnameduur aanzienlijk verkort. De routine opnameduur na een TKP is nu gereduceerd tot één of twee nachten, waarbij in geselecteerde patiënten een TKP ook in dagbehandeling mogelijk is gebleken. Daarnaast leiden fast-track protocollen tot een veilige perioperatieve zorg.

Er is in het laatste decennium een toenemende interesse in het implementeren van fast-track protocollen na een TKP. Echter 15-20% van de patiënten is na een TKP niet geheel tevreden of ontevreden. Het blijft dus een uitdaging om de perioperatieve zorg voor patiënten die een TKP-operatie ondergaan verder te verbeteren.

Het doel van dit proefschrift was te onderzoeken hoe de perioperatieve zorg rondom een TKP-operatie verder kan worden verbeterd. Dit wilden we bereiken door meer inzicht te geven in de vroege postoperatieve periode, door herstel trajecten te analyseren en tot slot door mogelijke aanpassingen in fast-track protocollen te onderzoeken.

Drie aspecten van perioperatieve zorg in fast-track TKP werden onderzocht:

1. de vroege postoperatieve periode na een primaire TKP met fast-track
2. herstel na een TKP-operatie
3. mogelijke aanpassingen van fast-track TKP protocollen

Deel I – Openen van de ‘zwarte doos’

Hoofdstuk 2 beschrijft een kwalitatieve studie, waarin 20 patiënten werden geïnterviewd naar hun ervaringen na een TKP of totale heupprothese (THP). Patiënten gaven aan de eerste paar weken slecht te slapen. Verder gaven patiënten die alleen wonen aan meer hulp in huis nodig te hebben en wilden daarom voor het gevoel liever nog enkele dagen langer in het ziekenhuis verblijven. Tot slot beschreven patiënten wisselende ervaringen en behandelingen van de fysiotherapeut buiten het ziekenhuis.

Om de klachten van patiënten, die beschreven zijn in *Hoofdstuk 2*, in maat en getal uit te kunnen drukken werd er een kwantitatieve studie uitgevoerd die is beschreven in *Hoofdstuk 3.* Hiervoor werden 30 patiënten gevraagd zes weken lang dagelijks een dagboek in te vullen met daarin verschillende vragenlijsten over onder andere pijn, kwaliteit van leven en functioneren. Daarnaast werd er gevraagd naar wondzorg, fysiotherapie, medicatie, doktersconsulten en het gebruik van hulpmiddelen. Van de 30 patiënten waren 28 patiënten positief over het korte verblijf in het ziekenhuis. De pijn nam geleidelijk af en de kwaliteit van leven scores verbeterden geleidelijk gedurende de eerste zes weken. Patiënten beschreven verschillende ervaringen met fysiotherapie wat betreft inhoud, intensiteit en duur van de behandelingen. Mogelijk wordt deze variatie veroorzaakt door het ontbreken van gestandaardiseerde en gevalideerde fysiotherapeutische protocollen dan wel behandelrichtlijnen. In totaal gaven negen patiënten aan een extra doktersconsult gehad te hebben gedurende de eerste zes weken, vaak ten gevolge van onzekerheid over de wond en het niet kunnen slapen. Klachten van de dagelijkse injecties met Low-Moleculair-Weight-Heparin namen toe gedurende de zes weken.

Deel II – Herstel na totale knie prothesiologie

Het herstel en de uitkomsten van een TKP verschillen per patiënt, waarbij een aanzienlijk percentage van de patiënten (15-20%) niet geheel tevreden of ontevreden is na de operatie. Wij vermoedden daarom dat er verschillende herstelpatronen zouden zijn. Een verkennend onderzoek naar functionele uitkomsten in de eerste drie maanden na een TKP is beschreven in *Hoofdstuk 4.* In dit hoofdstuk werden de zogenoemde 'patient gerapporteerde uitkomsten' (PROMs) van 623 geopereerde patiënten gebruikt. De PROMs bestonden uit verschillende internationaal gevalideerde vragenlijsten (Oxford knee score (OKS) Knee disability and Osteoarthritis Outcome Score Physical Function Short-Form (KOOS-PS), en EuroQol 5 dimensions (EQ-5D)). De functie scores verbeterden in deze vroege fase van herstel zowel statistisch significant als klinisch relevant. Wij vonden vier verschillende herstel trajecten. Responders en non-responders werden gedefinieerd op basis van de Oxford knee score. Karakteristieken van de non-responders waren een hoger BMI en slechte uitkomsten op de EQ-5D items mobiliteit, zelfzorg, activiteiten en angst/depressie op basis van preoperatief ingevulde vragenlijsten. Zowel BMI als angst/depressie zijn mogelijk preoperatief beïnvloedbare factoren voor een ongunstig herstelpatroon.

In *Hoofdstuk 5* werd het herstel gedurende het eerste jaar na een TKP geanalyseerd. In totaal zijn 809 patiënten met een TKP geanalyseerd om verschillende herstel trajecten te identificeren. Data werd verkregen vanuit de database van de Landelijke Registratie Orthopedische Implantaten (LROI). Middels latent class growth modeling (LCGM) werden drie groepen patiënten geïdentificeerd, namelijk: 'high risers', 'gradual progressors' en 'non-responders'. Specifieke patiënt karakteristieken die kenmerkend zijn voor een

ongunstig herstel patroon zijn lage scores op beoordeling van eigen gezondheid, problemen in zelfzorg en hoge scores op angst en depressie.

Deel III – Optimaliseren van fast-track protocollen bij een totale knieprothese

Omdat vroeg mobiliseren na de TKP-operatie een hoofdcomponent is van een fast-track herstel, is langdurige postoperatieve immobilisatie als gevolg van afwezige sensibiliteit en motoriek in de benen door de gebruikte anesthesie onwenselijk. Dit leidde tot de hypothese dat een vermindering van de dosis intrathecale bupivacaine bij spinale anesthesie zal leiden tot sneller herstel van motoriek en sensibiliteit. *Hoofdstuk 6* beschrijft een prospectieve studie waarin de haalbaarheid naar het verlagen van de dosis bupivacaine werd onderzocht. Dit onderzoek werd uitgevoerd volgens de sequentiële allocatie methode van Dixon en Massey. Hierin ontving de patiënt een dosis die gebaseerd was op de uitkomsten van de dosis van de vorige patiënt. In totaal werden er 25 patiënten geïncludeerd. Er werd een mediane dosis (ED50) van 3.5mg (95% CI 3.1-4.0) gevonden. De ED95 werd berekend op 5.0mg (95% CI 3.7-8.0) en werd beschouwd als de optimale dosis, wat een evident lagere dosering is dan de regulier gebruikte dosis van 15mg.

Redenen voor een vertraagd ontslag of verlengde opname zijn pijn, misselijkheid en braken. Dexamethason is een medicijn dat dit tegen kan gaan maar de optimale dosis is nog onbekend. Daarvoor werd een systematic review verricht die in *Hoofdstuk 7* is beschreven, naar het effect van dosis corticosteroïden op pijn, misselijkheid, braken, opnameduur en complicaties. Er werden in totaal 16 artikelen geïncludeerd. De studies zijn onderling zeer moeizaam vergelijkbaar gezien er verschillende doseringen en toedieningstijden zijn gebruikt met daarnaast ook verschillende soorten corticosteroïden. Over het algemeen werd er minder pijn, misselijkheid en braken, en een verkorte opnameduur gezien in de groepen die corticosteroïden kregen toegediend. Er was echter maar een minimaal verschil tussen lage en hoge doseringen steroïden. Daarnaast is het door de korte duur van de studies niet te concluderen dat het gebruik van corticosteroiden veilig is.

Patiënten klagen vaak over het nuchter zijn voor een operatie. Naast dat nuchter zijn vervelend is voor de patiënt, kan dit mogelijk ook bijdragen aan postoperatieve orthostatische hypotensie en -intolerantie. De postoperatieve orthostatische hypotensie en -intolerantie zorgt ervoor dat patiënten na de operatie niet kunnen mobiliseren. Om de postoperatieve mobilisatie te verbeteren werd onderzocht of het drinken van een koolhydraat verrijkte drank voor de operatie een verbetering zou zijn. Uit eerder onderzoek is gebleken dat het verkorten van de periode van nuchter zijn veilig is, de angst vermindert en het welbevinden van de patiënt verbetert. In *Hoofdstuk 8* wordt een prospectief gerandomiseerd onderzoek gerapporteerd waarin patiënten werden verdeeld over twee groepen. De interventiegroep kreeg 2-3 uur vooraf aan de operatie een

koolhydraat verrijkt drankje (totaal 400cc) en de controlegroep werd behandeld middels het standaard geldende nuchter beleid wat betekende minimaal 6 uur voor de operatie geen eten en tot 2 uur voor de operatie alleen heldere vloeistof. In totaal werden 168 patiënten geïncludeerd. Orthostatische hypotensie was verminderd in de interventiegroep ten opzichte van de controlegroep. Er werden geen bijwerkingen waargenomen die te maken hadden met het koolhydraat verrijkte drankje. Tot slot werden er geen verschillen gevonden in orthostatische intolerantie, opnameduur, misselijkheid en braken.

LIST OF PUBLICATIONS

In this thesis:

1. *Jeroen C. van Egmond, Hennie Verburg, Stephan B.W. Vehmeijer, Nina M.C. Mathijssen* **Early follow-up after primary total knee and total hip arthroplasty with rapid recovery: focus groups** Acta Orthop. Belg. 2015 Sep; 81 (3): 447-53
2. *Jeroen C. van Egmond, Hennie Verburg, Nina M.C. Mathijssen* **The first 6 weeks of recovery after total knee arthroplasty with fast track** Acta Orthopaedica 2015; 86 (6): 708-13
3. *Jeroen C. van Egmond, Brechtje Hesseling, Hennie Verburg, Nina M.C. Mathijssen* **Short-term functional outcome after fast-track primary total knee arthroplasty: analysis of 623 patients** Acta Orthopaedica 2021 Oct; 92 (5): 602-607
4. *Jeroen C. van Egmond, Brechtje Hesseling, Marijke Melles, Stephan B.W. Vehmeijer, Liza N. van Steenbergen, Nina M.C. Mathijssen, Jarry T. Porsius* **Three distinct recovery patterns following primary total knee arthroplasty: Dutch arthroplasty register study of 809 patients** Knee Surg Sports Traumatol Arthrosc. 2021 Feb; 29 (2): 529-539
5. *Jeroen C. van Egmond, Hennie Verburg, Eveline A. Derks, Pim N.J. Langendijk, Caner Içli, Nick T. van Dasselaar, Nina M.C. Mathijssen* **Optimal dose of intrathecal isobaric bupivacaine in total knee arthroplasty** Can. J. of Anaesth. 2018 Sep; 65 (9): 1004-1011
6. *Jeroen C. van Egmond, Floyd W. van de Graaf, Christa D. Niehot, Hennie Verburg, Nina M.C. Mathijssen* **Perioperative systemic corticosteroids in primary unilateral total knee arthroplasty: a systematic review** (submitted)
7. *Jeroen C. van Egmond, Nicole H.H. de Esch, Hennie Verburg, Nick T. van Dasselaar, Nina M.C. Mathijssen* **Preoperative carbohydrate drink in fast-track primary total knee arthroplasty: a randomized controlled trial** (submitted)

Other publications:

1. *T. Duivenvoorden, P. van Diggele, M. Reijman, P.K. Bos, J.C. van Egmond, S.M.A. Bierma-Zeinstra, J.A.N. Verhaar* **Adverse events after closing-wedge or opening-wedge High Tibial Osteotomy: a study of 412 patients** Knee Surg Sports Traumatol Arthrosc. 2017 March; 25(3):895-901
2. *J.C. van Egmond, S. J.M. Breugem, M. Driessen, D.J. Bruijn* **Platelet-Rich-Plasma injection seems to be effective in treatment of plantar fasciitis: a case series** Acta Orthop. Belg. 2015 Jun;81(2):315-320

3. *J.C. van Egmond, V. Eggerding, F.Th.G. Rahusen, T. Gosens* **Complications of using calcium sulfate/hydroxyapatite in opening wedge high tibial osteotomy: a critical appraisal of the literature** Nederlands Tijdschrift voor Orthopedie, March 2017; 24(1):26-28
4. *J.C. van Egmond, H. Verburg, B. Hesseling, N.M.C. Mathijssen* **The correlation of shoe size and component size of primary total knee arthroplasty** J Knee Surg. 2020 Mar; 33(3):260-264
5. *L.C.M. Klapwijk, N.M.C. Mathijssen, J.C. van Egmond, B.M. Verbeek, S.B.W. Vehmeijer* **The first 6 weeks of recovery after primary total hip arthroplasty with fast-track: a diary study of 94 patients** Acta Orthopaedica 2018 Feb;88(2):140–144
6. *J.T. Porsius, N.M.C. Mathijssen, L.C.M. Klapwijk-Heijningen, J.C. van Egmond, M. Melles, S.B.W. Vehmeijer* **Early recovery trajectories after fast-track primary total hip arthroplasty: The role of patient characteristics** Acta Orthopaedica 2018 Dec;89(6):597-602
7. *J.C. van Egmond, P.D. de Rooij* **Hernia Spigeli -dubbel zeldzaam-** Nederlands Tijdschrift voor Heelkunde 2018;27(6):54-55
8. *J.C. van Egmond, C.A. Selles, B.I. Cleffken, G.R. Roukema, K.H. van der Vlies, N.W.L. Schep* **Plate fixation for unstable displaced distal radius fractures in children** Journal of Wrist surgery 2019 Oct;8(5):384-387
9. *J.C. van Egmond, N.G.M. Hunfeld, B.J.A. Rijnders, J.A.N. Verhaar* **Persistent candida arthritis successfully treated with micafungin instillation and surgery. A case report** Med Mycol Case Rep. 2019 Dec 17;27:29-31
10. *C.R. Quispel [§], J.C. van Egmond [§], M.M. de Bruin, A. Spekenbrink-Spooren, H. Verburg, J.H. Pasma* **No effect of fixation type on early and late mortality after total knee arthroplasty: a Dutch arthroplasty register study** Knee Surg Sports Traumatol Arthrosc. 2022 Apr;30(4):1231-1238
    [§]both authors contributed equally

PHD PORTFOLIO

Name PhD student: Jeroen Cornelis van Egmond
PhD period: 2013 - 2022
Department: Orthopedic Surgery

Promotor: Prof.dr. J.A.N. Verhaar
Co-promotor: Dr. N.M.C. Mathijssen

PhD training

		Year	ECTS
Courses			
	Good Clinical Practice (GCP)	2021	1.5
	Integrity course	2021	0.3
	Introduction epidemiology	2021	1.0
Oral Presentations			
	at home after TKA - ROGO dag, Rotterdam, the Netherlands *(awarded best oral presentation)*	2015	1.0
	at home after TKA - Wetenschapsdag, Delft, the Netherlands	2015	1.0
	Patient experiences after fast-track THA - European Hip Society, Munich, Germany	2016	1.0
	Optimal dose of intrathecal bupivacaine in primary TKA - Wetenschapsdag, Delft, the Netherlands	2017	1.0
	Optimal dose of intrathecal bupivacaine in primary TKA - NOV, Rotterdam, the Netherlands	2018	1.0
	The correlation of shoe size and implant size of primary TKA - ROGO dag, Rotterdam, the Netherlands	2018	1.0
	Trajectories of patient-reported outcomes after unilateral primary total knee arthroplasty - EKS, Valencia, Spain *(awarded best oral presentation)*	2019	1.0
	Trajectories of patient-reported outcomes after unilateral primary total knee arthroplasty - ISAR, Leiden, the Netherlands	2019	1.0
	Hersteltrajecten na TKP: zijn we allemaal gelijk? - ROGO dag, Tilburg, the Netherlands	2020	1.0
	Optimalisatie van fast-track totale knie prothesiologie - Wetenschapscafé Renier de Graaf, Delft, the Netherlands	2021	1.0
	Preoperative carbohydrate drink in primary total knee arthroplasty - Dutch Knee Society, Utrecht, the Netherlands	2022	1.0
Poster Presentations			
	Complications of using calcium sulfate/hydroxyapatite in opening wedge high tibial osteotomy: a critical appraisal of the literature - Tilburg, the Netherlands	2015	1.0
	The first 6 weeks after THA in a fast-track setting - European Hip Society, Munich, Germany	2016	1.0
	The correlation of shoe size and implant size of primary TKA - European Knee Society, London, England	2017	1.0
	Optimal dose of intrathecal bupivacaine in primary TKA - EFORT, Vienna, Austria	2017	1.0
	Trajectories of patient-reported outcomes after unilateral primary total knee arthroplasty - EFORT, Lisbon, Portugal	2019	1.0
	No effect of fixation type on early and late mortality after total knee arthroplasty: a Dutch arthroplasty register study - EFORT, Vienna, Austria (virtual meeting)	2021	1.0

PhD Portfolio

(Inter)National Conferences			
	2nd Luxembourg Osteotomy Congress, Luxembourg	2013	0.5
	NOV annual meeting, 's Hertogenbosch, the Netherlands	2016	0.5
	EHS, Munich, Germany	2016	0.5
	NOV autumn meeting, Veldhoven, the Netherlands	2016	0.5
	NOV annual meeting, 's Hertogenbosch, the Netherlands	2017	0.5
	EKS, London, England	2017	0.5
	EFORT, Vienna, Austria	2017	0.5
	NOV annual meeting, 's Hertogenbosch, the Netherlands	2018	0.5
	NOV autumn meeting, Rotterdam, the Netherlands	2018	0.5
	EKS, Valencia, Spain	2019	0.5
	EFORT, Lisbon, Portugal	2019	0.5
	ISAR, Leiden, the Netherlands	2019	0.5
	NOV annual meeting, 's Hertogenbosch, the Netherlands	2020	0.5
	WAC, Munich, Germany (virtual meeting)	2021	0.5
	EFORT, Vienna, Austria (virtual meeting)	2021	0.5
	NOV annual meeting, 's Hertogenbosch, the Netherlands	2021	0.5
	NOV annual meeting, 's Hertogenbosch, the Netherlands	2022	0.5
Lecturing			
	Erasmus Anatomy Research Project (EARP) as teacher	'10-'14	4.0
	Erasmus Anatomy Research Project (EARP) as a guest speaker	2018	0.3
	Erasmus Anatomy Research Project (EARP) as a guest speaker	2019	0.3
	Erasmus Anatomy Research Project (EARP) as a guest speaker	2021	0.3
Other			
	Supervising Casper Quispel; No effect of fixation type on early and late mortality after total knee arthroplasty: a Dutch arthroplasty register study	2020	4.0
	Member of the science and innovation committee of the Dutch Orthopedic Association	2021	3.0
	Peer reviewer BMC Musculoskeletal Disorders	'21-'22	2.0

DANKWOORD

Dit proefschrift zou nooit tot stand zijn gekomen zonder hulp van anderen. Alle patiënten die bereid waren om deel te nemen aan de verschillende studies in dit proefschrift verdienen uiteraard het eerste woord van dank. Daarnaast wil ik iedereen enorm bedanken die een bijdrage heeft geleverd aan dit proefschrift, met een aantal in het bijzonder.

Promotor, prof.dr. J.A.N. Verhaar, beste professor, allereerst hartelijk dank voor de mogelijkheid voor het starten van een promotietraject in de Orthopedie. Wij kwamen bij u met een plan en u was gelijk enthousiast. Met hier en daar bijsturen heeft u mij de regie laten behouden en de onderzoeken laten starten zoals wij hadden voorgesteld. Heel veel dank voor het vertrouwen en uw kritische reviews. Geniet van uw wel verdiende pensioen!

Co-promotor, dr. N.M.C. Mathijssen, beste Nina, wat na onze ontmoeting op de Summerclass in 2013 begon met het opzetten van een "onderzoekje" om de wachttijd tot mijn co-schappen te overbruggen is nu gekomen tot dit proefschrift. Daarnaast ook allebei een black belt! Hoe gek kan het lopen. Zonder al jouw hulp had ik het nooit gered en daarvoor kan ik je niet genoeg bedanken. Je stond altijd voor me klaar. Door jou opbouwende kritiek heb ik heel veel kunnen leren. Enorm bedankt en ik hoop nog veel met je te mogen samenwerken.

Bijna co-promotor, drs. H. Verburg, beste Hennie, ook al is mijn proefschrift eerder klaar dan dat van jou, zie ik je toch als mijn co-promotor! Je altijd positieve energie en enthousiasme heeft mij enorm gemotiveerd. Ik ben je heel dankbaar dat je mij kennis hebt laten maken met de orthopedie, onderzoek doen en fast-track. Met de out-of-the-box ideeën, van dagboek tot schoenmaat, hebben wij iedere keer iets moois neer kunnen zetten die de wetenschap op een andere tegel liet staan. De dubbelrol die je had als co-auteur en opleider heb je perfect vervuld! Ik heb mij hierdoor optimaal kunnen ontwikkelen als mens, onderzoeker en dokter.

De overige leden van mijn promotiecommissie. Hartelijk dank voor uw tijd en bereidheid om in mijn commissie plaats te nemen. In het bijzonder prof.dr. S.M.A. Bierma-Zeinstra, prof.dr. R.J. Stolker en prof.dr. T.P.M. Vliet Vlieland voor het lezen en de kritiek op mijn proefschrift.

De paranimfen Floyd van de Graaf en Willem Rinkel. Wat fijn dat jullie aan mijn zijde staan deze dag.

Dr. F.W. van de Graaf, Floyd, maatje, gozert, met EARP hebben wij een mooie tijd gehad op de snijzaal. Jij hebt mij als digibeet veel moeten leren, maar we hebben ieder jaar iets moois neergezet. Bedankt voor jouw Rotterdamse kritiek, blik op problemen, maar vooral op oplossingen! Je hebt een hart van goud. Het was altijd fijn ontspannen tijdens het leren koken met je. Ook nog samen een artikel geschreven en nu allebei een PhD! Veel succes als generalist (huisarts) met een chirurgische inslag!

Dr. W.D. Rinkel, Willem, kapitein! Ook met jou goede herinneringen op de snijzaal en daarbuiten. Het is mooi te zien hoe jij naar de wereld kijkt. Je bent daarin inspirerend voor mij. Van imker tot klassieke auto's, je verbaast me iedere keer. Ik kijk uit naar nog vele zeiltochten.

De co-auteurs van de verschillende artikelen; Marijke Melles, Eveline Derks, Pim Langendijk en Christa Niehot, allen hartelijk dank voor jullie hulp bij het schrijven van de artikelen. Enorm bedankt voor jullie hulp en advies. Leuk om multidisciplinair naar de revalidatie van TKP-patiënten te kijken. In het bijzonder dr. van Dasselaar, bedankt voor uw hulp bij de verschillende studies. Dit toont maar weer eens hoe multidisciplinair de fast-track is en net als deze promotie een team effort!

Dr. Ir. Liza van Steenbergen en Anneke van Spekenbrink-Spooren, veel dank voor de fijne samenwerking met de LROI. Jullie hulp en snelle reacties hebben tot twee mooie artikelen geleid.

Dr. Ir. J.H. Pasma, beste Jantsje, de eerste ontmoetingen waren vooral digitaal via ZOOM en mail, maar de samenwerking was top! De LROI-studie ging als een trein en beloofde veel goeds. Dank voor al je (statistische) hulp.

Prof.dr. Kleinrensink, beste Gert-Jan, de basis van een chirurgisch vak is natuurlijk de anatomie. Desondanks helaas in dit proefschrift geen anatomische studie. Maar naast de anatomie kan de fysiotherapie ook een belangrijke basis leggen blijkt maar weer. Mede door uw passie voor anatomie en onderwijs heb ik een prachtige tijd gehad op de snijzaal. Enorm bedankt voor al het vertrouwen en steun door de jaren heen. Daarbij ook bedankt voor de kans om mij breder te ontwikkelen bij EARP (Erasmus Anatomy Research Project). Acta non verba! Geniet van uw pensioen!

Opleiders, dr. Bloem, dr. Gosens en dr. Bos, ontzettend veel dank voor de beslissing en het vertrouwen om mij aan te nemen voor het Dedicated Schakeljaar en daarna voor de opleiding tot Orthopedisch Chirurg.

Nicole, jij zet jezelf nooit op de voorgrond en werkt enorm hard. Jouw precisie, volharding en Excel bestanden hebben de inclusies geholpen. Zonder jouw hulp was dit proefschrift nooit gelukt. Enorm bedankt voor al je hulp en inzet. En natuurlijk de gezelligheid en moederlijke gesprekken niet te vergeten!

Brechtje, enorm bedankt voor jouw (statische) hulp. Of het nu SPSS, M-plus of cross-tabulation was, overal wist je een antwoord op. Er gaat geen syntax voorbij dat ik niet aan je denk! Door jouw hulp is een schoenmaat nu niet zomaar een maat en het herstel na TKP een trajectorie! Je systematisch werken en niet opgeven was een voorbeeld voor mij.

Roos en Rianne bedankt voor jullie hulp bij Castor en de inclusies. Het is superfijn samenwerken met jullie en jullie stonden altijd klaar voor me. Succes met alles verder!

Jarry, bedankt voor je hulp, ondanks de fysieke afstand (Delft-Harvard, Boston, USA) was de samenwerking top! Bedankt voor alle analyses en statistische hulp. Het artikel schrijven was een “trajectory” op zich!

Dr. Vehmeijer, beste Stephan, bedankt voor je hulp bij de verschillende artikelen. Jouw visie en kennis van fast-track hebben mij enorm geholpen.

Wetenschappelijke Advies Commissie (WAC) van het Reinier de Graaf, hierbij wil ik jullie danken voor de sponsering van diverse trials.

Maatschap orthopedie Delft; dr. Bloem, drs. Verburg, drs. Niesten, dr. Vehmeijer, drs. van Linge, drs. Hoelen, dr. Kraan en drs. van der Linden. Bedankt voor alle mogelijkheden die ik bij jullie heb gekregen voor de onderzoeken in het Reinier de Graaf en later in het Orthopedisch centrum en het tot stand komen van dit proefschrift.

Maurits en Caner, bedankt voor jullie hulp bij het verzamelen van de data. Veel succes bij jullie verdere orthopedische carrière.

Het secretariaat orthopedie Delft; Petra, Wendy, Suzanne en Janet bedankt voor al jullie hulp en gezelligheid.

Het secretariaat orthopedie van het EMC; Simone en Annet bedankt voor al jullie hulp en gezelligheid, veel dank ook voor het regelen van alle Teams sessies!

Jan Hermans, ik mag van geluk spreken dat ik bij jou in de praktijk een van mijn stages heb mogen lopen. Naast het opdoen van kennis en kunde van het prachtige vak fysiotherapie heb ik veel meer van je mogen leren. Bedankt voor al het vertrouwen en de kansen die je mij gegeven hebt. Dit heeft bijgedragen aan de basis voor mijn verdere stappen.

Chirurgen en A(N)IOS van het Maasstad ziekenhuis, bedankt voor jullie gezelligheid en enthousiasme. Ik heb met jullie een hele leuke en leerzame tijd gehad als startende dokter. In het bijzonder wil ik bedanken drs. Klaassen voor de mogelijkheden die ik heb gekregen in het Maasstad Ziekenhuis. Het was een hele mooie en leerzame tijd. De perfecte plek om te starten als ANIOS en later door te stromen in de vooropleiding. Bedankt voor uw steun, begeleiding en vertrouwen!

Collega AIOS van het Erasmus MC, Reinier de Graaf en Reinier Haga Orthopedisch Centrum, bedankt voor de leuke tijd, het samenwerken en lachen. Hoop in de toekomst nog vaak met jullie te mogen werken!

De Dekzwabbers; Willem, Bram, Laurens, Marc en Ralph, de jaarlijkse zeiltochten waren een heerlijke ontspanning en hield de vaart erin!

Ronald, broer(tje), vriend, ik heb veel handigheid op kunnen doen bij de verschillende klussen met jou, zoveel verschilt ons werk dus toch ook weer niet! Ik ben trots op je!

Pa en ma, bedankt voor alle kansen die ik heb gekregen en al jullie steun en vertrouwen. Niet alleen tijdens het maken van dit proefschrift, maar ook tijdens de studie en in

alle keuzes die ik gemaakt heb. Jullie stonden altijd voor me klaar en daarvoor kan ik jullie niet genoeg bedanken.

Lieve Willemijn, je hebt me altijd gesteund en tijd gegund voor dit proefschrift, maar me ook soms laten beseffen om ook te ontspannen. Dankjewel dat je mij in evenwicht houdt.

ABOUT THE AUTHOR

Jeroen Cornelis van Egmond was born on July 15th, 1987 in Bergschenhoek, the Netherlands. In 2004 after graduating from high school (HAVO) at the Melanchthon College in Schiebroek, he started studying Physical Therapy at the Academy of Rotterdam. He obtained his bachelor's degree in 2008. During one of his internships in Gent, Belgium his curiosity and enthusiasm were aroused for surgery and Medicine. Therefore, he started a one-year high school course at VAVO Rijnmond College to meet the admission requirements to study Medicine.

In 2009 Jeroen started to study Medicine at the Erasmus University Rotterdam. During his study, he worked as a physical therapist in a private practice. Besides, he worked as a physical therapist in a Dutch league baseball team (Neptunus Rotterdam) for several years. His musculoskeletal experience as a physical therapist was probably the reason for his interests in Orthopedic surgery. During his study, he was closely involved with an extra-curricular anatomy education, also known as EARP (prof. dr. G.J. Kleinrensink). He did his final rotations in orthopedic surgery (dedicated schakeljaar) and obtained his medical degree in 2016. Hereafter he stared as a not in training resident at the department of general surgery at the Maasstad hospital (drs. R.A. Klaassen) in Rotterdam.

In 2017 he continued his residency at the department of general surgery at the Maasstad hospital (drs. R.A. Klaassen) as a part of his residency training program in Orthopedic surgery. In 2018 he persecuted his residency at the Orthopedics Department of Erasmus University Medical Center (dr. P.K. Bos) in Rotterdam. In 2019 he continued his residency at the Orthopedic department of the Reinier de Graaf hospital (dr. G.A. Kraan) in Delft and in 2020 at the Reinier Haga Orthopedisch Centrum in Zoetermeer (dr. G.A. Kraan). In 2021 he joins the science committee of the Dutch Orthopedic federation (Nederlandse Orthopaedische Vereniging (NOV), Commissie Wetenschap en Innovatie (CWI)), and returned at the Orthopedic Department of Erasmus University Medical Center (dr. P.K. Bos) to finish his residency. In October 2022 he finished his residency and started with a fellowship in Elisabeth-TweeSteden hospital in Tilburg.

During his last years of Medicine, he started with scientific research at the Reinier de Graaf hospital in Delft, resulting in a PhD program supervised by professor dr. J.A.N. Verhaar and dr. N.M.C. Mathijssen. He presented most of his studies at various international congresses and was awarded for best oral presentation on EKS (European Knee Society) in 2019.