Prognostics of outcome of total knee replacement: on patient selection and intraoperative issues

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Prognostics of Outcome of Total Knee Replacement

on Patient Selection and Intraoperative Issues

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on Patient Selection and Intraoperative Issues

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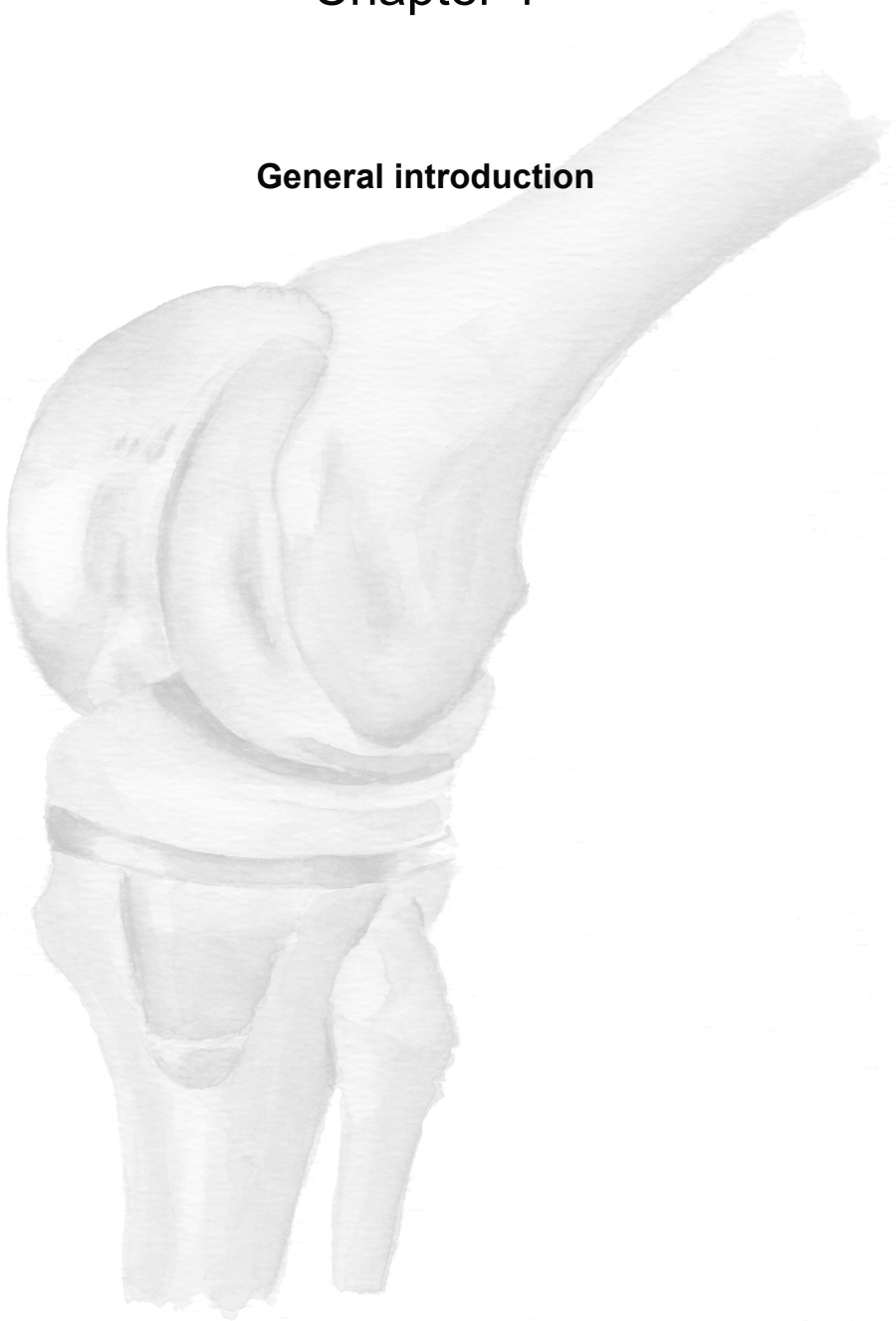
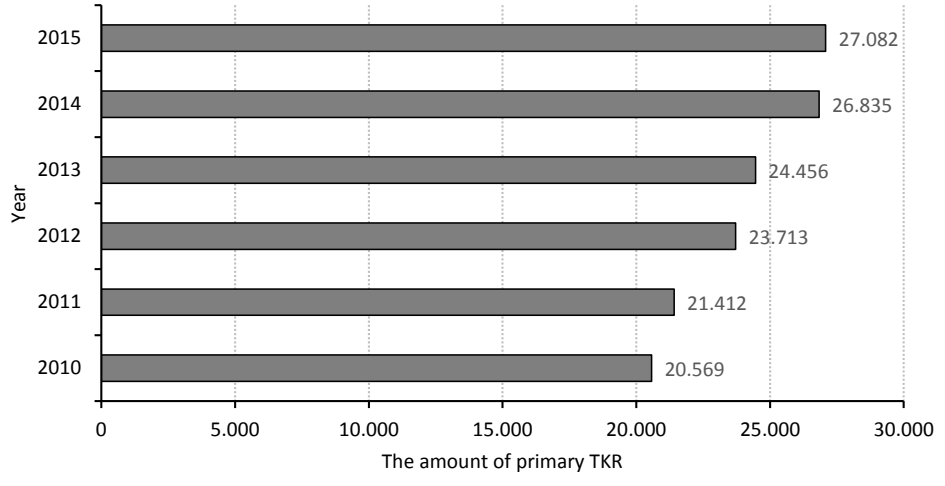
Chapter 1

General introduction



Osteoarthritis (OA) of the knee is a degenerative disease concerning the entire knee joint including the cartilage and its underlying bone, the ligaments, and other soft tissues.[1] The lifetime risk of developing symptomatic OA of the knee is almost 50%.[2] The one-year prevalence in the Netherlands of OA of the knee is almost 550.000 patients (www.volksgezondheidenzorg.info). As for treatment options; the vast majority of patients will have conservative treatment that will be patient specific. For mid-stage OA, besides conservative treatment, surgical options could be performed like osteotomies. For end-stage OA a total knee replacement (TKR) is the treatment of choice. In the Netherlands about 28.000 TKR's are performed annually.[3] TKR is an effective treatment in terms of improving knee function, reducing pain and improving quality of life.[4,5] The number of TKR's performed worldwide, and also in the Netherlands, is still rising.[3,6] According to the latest report of the Dutch Arthroplasty Registry, the LROI, in 2015 over 27.000 primary TKR's were performed (Figure 1.1), which is about 26% more compared to 2010.[3]

Figure 1.1: The amount of primary TKR registered within the LROI in the years 2010-2015 (With permission from LROI)



In 1891 the first attempt to resurface the knee joint was performed by a German surgeon, dr. Th. Gluck. He implanted a hinged knee prosthesis made of ivory.[7,8]

The subsequent versions following this prosthesis, several decades later, made of metal and plastic components, suffered from high rates of loosening due to the constraint character of these hinged types of implants. Again decades later, in the 1970s, the development of total knee replacement had a boost due to, amongst others, Gunston who used an implant with two separate tibial and femoral condylar components. Yamamoto in Japan was the first to develop a total condylar (non-hinged) type of design in the 1970s, which was followed, probably parallel, in the USA by Insall in the mid-seventies.[7,9] New issues on implant design were the use of implants of a single-piece femoral component covering both condyles, as well as the use of a monoblock resurfacing tibial component. Furthermore poly-methyl-methacrylate (PMMA) was used for fixation of the components (i.e. bone cement). In the 1970s different groups in Japan, the United States, United Kingdom, and Germany made efforts to improve TKR design. For the 1980s and the 1990s issues like patello-femoral joint replacement, resection of the anterior and/or posterior cruciate ligament, metal-backing, fixed or mobile bearing inserts and improvements in contact surfaces (like femoro-tibial congruency) are examples of issues surgeons and engineers encountered, discussed and tried to solve.[7] Although changes of the TKR systems became smaller, compared to the early 1970s, names of the TKR's changed frequently, even after minor adjustments, mainly for marketing reasons. Furthermore these design ameliorations, neither the ones of this millennium, improved final clinical outcome for patients a lot, while some of these new designs resulted in worse clinical outcome.[10]

Success of joint replacement surgery is traditionally evaluated by survival of the implant or revision rates.[11] Furthermore outcome measures such as range of motion and the presence of (anterior) knee pain were recorded. In the last decade a shift has occurred towards patient reported outcomes (PROM's). Although these PROM's are considered by some to give a good representation of patients' satisfaction and functional gain, one should be aware that they also present only the perceived outcome of the pre-, intra- and postoperative complexity of TKR.[12]

Literature about short- and midterm follow-up shows that not all patients are satisfied with the result of their TKR. Satisfaction rates after TKR are lower than rates after

total hip replacement (THR).[13-19] Literature on long-term follow-up patient satisfaction is scarce.[20,21] Within this thesis, patient satisfaction and quality of life at long-term follow-up (i.e. ten years or more after surgery) after TKR and THR is evaluated in a cohort from the TACTICS trial **(chapter 2)**. This trial is a randomized controlled study on the effect of leukocyte depleted red blood cell transfusions versus transfusions packed cells containing leucocytes after TKR and THR surgery.[22] Surgery was performed in 2000/2001 with the last clinical (i.e. PROM's) follow-up in 2012/2013.

An important issue to address before considering TKR surgery is the indication for the operation (i.e. patient selection). One of the reasons for unsatisfied patients after TKR could be that the decision to perform TKR was erroneous. The question of which patients should and which patients should not have a TKR, has been addressed by others as well.[23,24] The indication to perform TKR and the selection of which patient will benefit most from surgery appears to be very important in the outcome of TKR.[12,18,25 ,26] In **chapter 3 and 4** two studies investigating the indication for TKR are reported.

The overall global population in the Western part and parts of Asia is aging.[27] Patients with and without total joint replacement (TKR or THR) in the past become increasingly older as well. Patients of 85 years-old and older are considered the oldest old. Whether this oldest old patients regained their functional level and health status after a total joint replacement in the past is compared to oldest old without total joint replacement. In **chapter 5** a study using the Leiden 85+ database is reported.

The second part of this thesis focuses on more medical technical aspects that possibly can improve outcome of TKR. These are related to TKR design and materials, but also patient blood management.[7,28,29] Tranexamic acid, vacuum drainage systems, EPO administration etcetera, have all been investigated for its use in reducing blood loss during and after TKR.[30] Topical application of a fibrin sealant to reduce blood loss during and after TKR surgery has been investigated since the late 1990s.[31] Some literature has been published in the years after, however all studies were performed in small patient groups and focused on transfusion frequency and hemoglobin loss as primary outcomes, and not on patient reported outcome measures nor on functional gain for these patients.[32,33] Furthermore, since

transfusion rates have dramatically decreased during the last ten years due to restrictive protocols, different outcome metrics are needed, with focus on functionality for patients and not on the transfusion rate as such.[34] **Chapter 6** reports the results of a large randomized study using fibrin sealant focusing on functional outcome after TKR.

A TKR related issue on functional outcome might be preservation or resection of the posterior cruciate ligament (PCL). Advocates of PCL retention pose that retaining the PCL is important to remain an as natural movement pattern of the knee as is possible in TKR.[35] Furthermore, retention of the PCL might yield a better sense after TKR, due to mechanoreceptors for proprioception and kinesthesia within the PCL.[36,37] Sacrificing the PCL subtracts one factor that might complicate adequate ligament balancing, sacrificing the PCL could also prevent paradoxal femoral rollback.[38,39] A systematic review and meta-analysis on this topic is reported in **chapter 7** of this thesis.

Prosthetic joint infection is a feared complication after TKR. Mild hypothermia, defined as a body temperature between 34.0 and 36.0 ^{o}C, during surgery is associated with an increased risk of infection in primary TKR and THR.[40] Warming of the patient has become routine practice. Clean laminar airflow in operating rooms is considered to reduce risk of infection too. A forced-air warming blanket might disrupt laminar airflow and could potentially increase infection risk.[41] We performed a randomized, non-inferiority trial, to evaluate the prevention of hypothermia in patients who received warming by a forced-air blanket or an active self-heating blanket. Results are reported in **chapter 8**.

The aims of this thesis are related to clinical outcome of Total Knee Replacement

1. *Investigating patient satisfaction and quality of life at least ten years after total knee or hip replacement (Chapter 2).*
2. *Patient characteristics that are most probably related to the indication for TKR surgery by Dutch orthopedic surgeons were studied (Chapter 3) as well as international differences (9 countries) for the indication of TKR (chapter 4).*
    a. Three patient related variables were chosen; age of the patient (old versus young age), severity of radiological knee osteoarthritis (OA) and severity of pain.
    b. International comparison was done using a large database from the OARSI/OMERACT initiative, with characteristics of over 1.900 patients with either knee or hip OA were recorded from nine different countries (including the Netherlands).
3. *Age as a predictor for outcome was studies in oldest-old patients who received total joint replacement in the past (chapter 5).*
    a. To this end the Leiden 85+ database was used. A well-documented cohort of oldest-old patients from the Leiden area who were included around the start of this millennium and have annual follow-up moments.

The second part of the thesis focuses on medical technical aspects of TKR, related to both the patient in general as well as to the TKR implant.

4. *Evaluation of the use of an intraoperative topical fibrin sealant on the surgical field on functional outcome (extension of the leg) after TKR (Chapter 6).*
5. *A meta-analysis on the functional, clinical and radiological outcome of TKR after retention or sacrifice of the PCL (Chapter 7).*
6. *A randomized, non-inferiority trial analyzing the prevention of hypothermia in patients who received forced-air warming or active self-heating (Chapter 8).*

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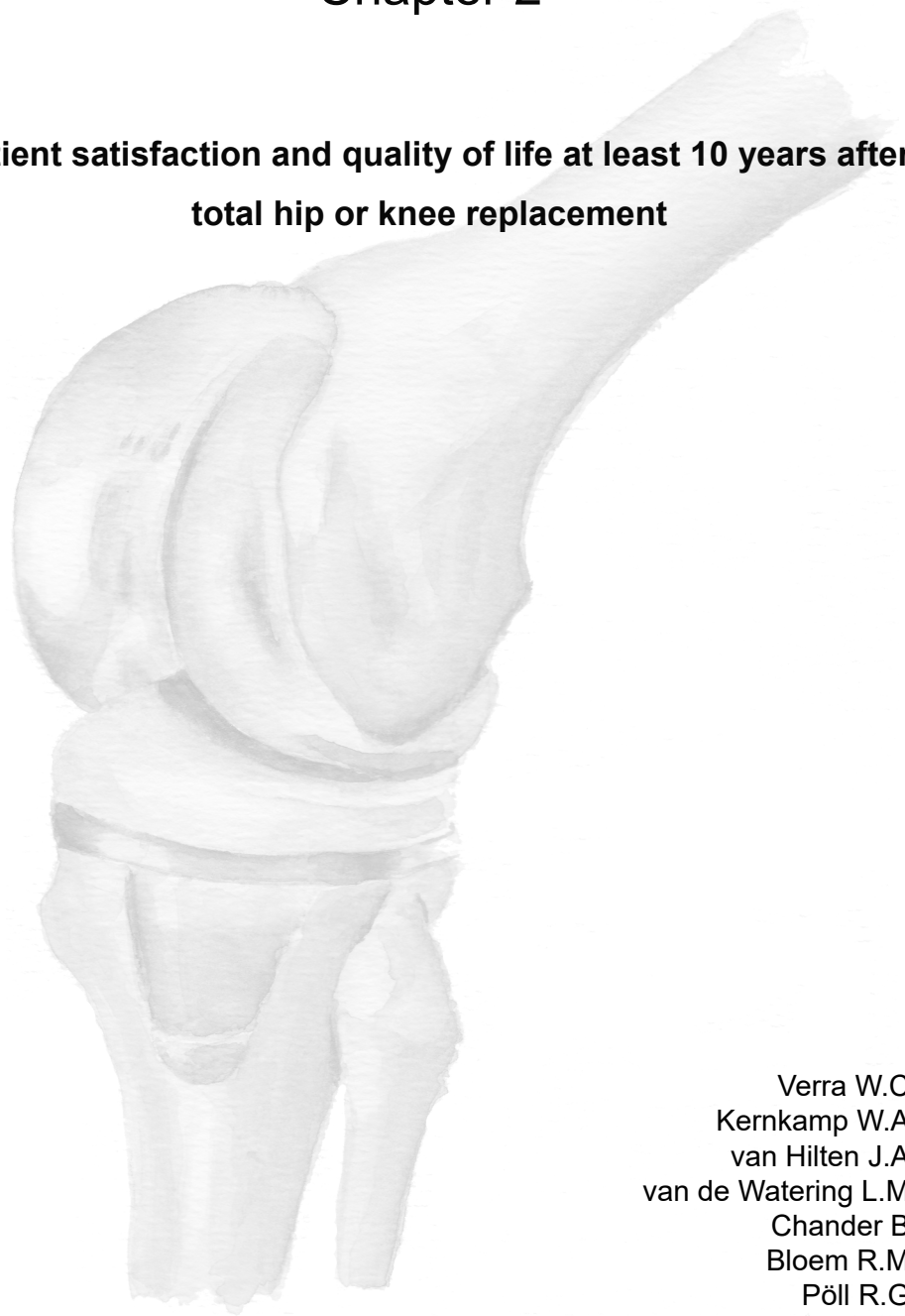
Chapter 2

Patient satisfaction and quality of life at least 10 years after total hip or knee replacement



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Abstract

Introduction. Total hip and knee replacement (THR and TKR respectively) are reliable and successful interventions in terms of relieving pain and improving joint function. Paucity exists on long-term data concerning patient satisfaction and patient related outcome measures (PROM's) after THR or TKR. We studied the long-term patient satisfaction and PROM's at least 10 years after THR and TKR.

Methods. A cohort of THR and TKR patients from a randomized clinical trial was used. At least 10 years after primary joint replacement, patient satisfaction was evaluated by means of three questions:

1. Would you still consider surgery knowing now what a THR/TKR consisted of?
2. Would you recommend the surgery to friends or relatives?
3. How satisfied are you at this moment with the THR/TKR? (using visual analogue scale)

Furthermore the Oxford Hip/Knee scores, EQ5D scores and RAND36 scores were recorded.

Results. A total of 123 patients were available for analysis. Of the THR's 78% and of the TKR's 64% would reconsider to undergo the same surgery again. Also 94% of the THR's and 76% of the TKR's would recommend the surgery to a friend or relative and the mean score of satisfaction was 83.1 of the THR and 80.8 of the TKR patients. The scores indicated that both THR and TKR patients are very satisfied at more than 10 years of follow-up. Furthermore comparable function and quality of life scores 10 years after initial surgery were found in both groups.

Conclusion. We demonstrated that at a minimum of 10 years of follow-up both THR and TKR patients are very satisfied, although THR patients being slightly more satisfied compared to TKR patients.

Introduction

Total hip and knee replacement (THR and TKR respectively) have both shown to be reliable and successful surgical procedures in terms of relieving pain, improving function and improving quality of life.[1-3] Traditionally, clinical success of THR and TKR has been measured by implant survivorship, range of motion and outcome measures like joint stability. Next to these 'established' outcome variables patients' perceived health after arthroplasty is important as outcome variable too, this has more and more been investigated this last decade.[4,5] Patient satisfaction is a proxy for the overall success of the initial surgery. Literature shows that not all patients are satisfied with the results after THR or TKR.[6-9] A systematic review published in 2004 on health-related quality of life after THR and TKR was not able to identify studies with a follow-up period of more than 7 years.[10] The majority of recent literature on patient reported outcome measures (PROM's) and patient satisfaction report short-to mid-term outcomes.[11-13] Reports on long-term satisfaction as outcome are scarce.[14,15]

The aim of this study was to evaluate long-term patient satisfaction and patient reported outcome measures using validated questionnaires at least 10 years after THR or TKR.

Methods

Study population

Patients used for this study consisted of the orthopedic subset of patients from a multicenter randomized clinical trial aiming to assess the difference between packed red blood cell transfusion with and without leukocyte depletion in THR and TKR patients; the TACTICS trial.[16] Enrolment of the TACTICS trial took place in four hospitals between April 2001 and November 2002. The cohort consisted of 228 THR and 108 TKR patients. Ethics committee and Medical review board approval was obtained from the Leiden university medical center (Protocol P11.050). Written informed consent was obtained from all participants.

The study was carried out on 336 THR and TKR patients between January 2012 and January 2013 when patients had at least a follow-up time of 10 years. All medical

records in the participating hospitals were reviewed to check if patients were still alive and/or had complications in the course of the follow-up since inclusion (i.e. since index operation). Contact addresses and death or alive status were also checked with information from the general practitioner. All patients were contacted about the study and received questionnaires. Informed consent for this follow-up study was received from all participants too.

Outcome measures

Three 'anchor questions' with respect to outcome were posed regarding patient satisfaction:

1. Knowing now what your hip/knee replacement surgery did for you, would you still have undergone this surgery?
2. Would you recommend this surgery to a friend or relative if he/she had the same symptoms as you had before your hip/knee surgery?
3. At this moment, how satisfied are you with the outcome of your hip/knee replacement?

The first two questions had a binary (yes or no) answer; the third question used a visual analogue scale (VAS) ranging from 0 to 10 cm with a 100-point subdivision scale. Zero indicated a very dissatisfied score and ten indicated a highly satisfied score.

Furthermore, function and quality of life questionnaires were recorded: the validated Dutch version of the modified Oxford hip and knee score (OHS and OKS respectively), the validated Dutch version of the EQ5D and the general health status RAND36.[17-22]

The OHS and OKS each consist of 12 questions to describe hip or knee pain and physical function. Each question is answered on a five-point Likert scale, and the overall score is calculated by summarizing the responses to each of the 12 questions. The total score ranges from 0-48, with a higher score indicating greater disability. The Oxford score uses a four band grading scale for determination of the joint function (0-19 may indicate severe joint problems, 20-29 may indicate moderate joint problems, 30-39 may indicate mild to moderate joint problems, and 40-48 may

indicate satisfactory joint function).[17,18,22,23] The EQ5D questionnaire has 5 items. It contains the domains of mobility, self-care, usual activity, pain/distress and depression/anxiety. It also contains one VAS-score about experienced 'health today' ranging from 0-100. The RAND-36 questionnaire has 36 items and the score ranges from 0-100. It focuses on physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mentally health. It is said to take up to 10 minutes to complete.[21,22]

Statistics

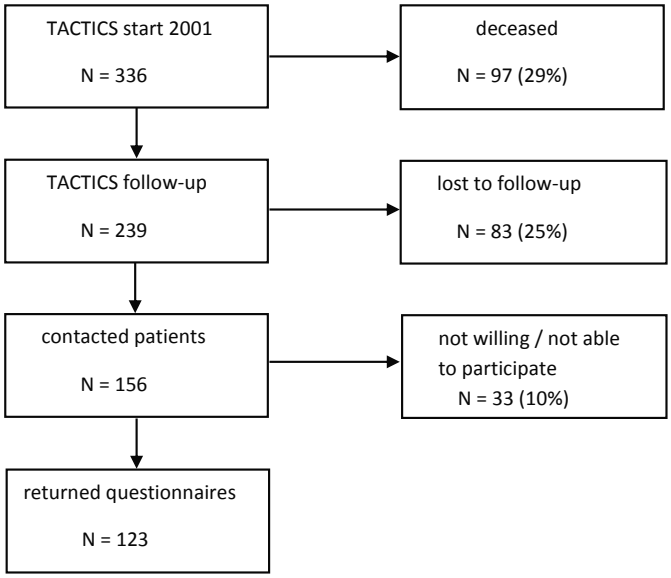
All data were entered and analyzed using SPSS Statistics (Version 21.0. Armonk, NY: IBM Corp). Data for THR and TKR were analyzed separately. Univariate qualitative comparison was calculated using Chi-square-tests. The Student's t-test was used for normally distributed quantitative parameters. Linear or logistic regression was applied to adjust for confounders (age and gender). A p-value of ≤0.05 was considered to be statistically significant.

Results

From the 336 originally included patients, 97 (29%) patients had died, 83 (25%) patients were lost to follow-up (due to several reasons including missing information from hospital records, from GP records or simply missing), 16 (5%) patients were not able to and 17 (5%) were not interested in participating. Overall, 123 (37%) patients were able to respond to the follow-up study of which 81 THR and 42 TKR patients (Figure 2.1). Baseline patient characteristics at follow-up of both responders and non-responders are presented in Table 2.1.

Table 2.2 shows an overview of data from the completed questionnaires of THR and TKR patients.

Figure 2.1: Follow-up study population



Outcomes at follow-up

First, the three anchor questions regarding patient satisfaction:

1. Knowing now what your hip/knee replacement surgery did for you, would you still undergo this surgery?
   Of the THR patients 78% (N=63) answered yes, 12% (N=10) answered no to this question, 8 participants did not answer this question. Of the TKR participants 64% (N=27) answered yes, 24% (N=10) answered no, 6 participants did not answer. More THR than TKR patients were willing to have their surgery again.
2. Would you recommend this surgery to a friend or relative if he/she had the same symptoms as you had before your surgery?
   Of the THR participants 94% (N=76) answered yes, 1 participant answered no, 4 participants did not answer this question. Of the TKR participants 76% (N=32) answered yes, 7% (N=3) answered no, 7 participants did not answer this question. More THR patients were willing to recommend their joint replacement to friends compared to TKR patients.

3. At this moment, how satisfied are you with your operation?
   For THR patients the mean score on the visual analogue score was 83.1 (95% CI 79.1 – 87.2) and for TKR patients the mean score was 80.8 (95% CI 74.6 – 86.9).

Table 2.1: Patient characteristics of responders and non-responders

	Responders (N = 123)		**Non-responders (N = 33)**	
	THR (N = 81)	**TKR (N = 42)**	**THR (N = 20)**	**TKR (N = 13)**
Gender female N(%)	62(77)	36(86)	16(80)	11(85)
Mean age years(SD[#])	78(9.9)	78(8.6)	80(10.5)	85(8.6)
	Indication for hip/knee replacement			
Primary replacement N(%)	59(73)	42(100)	15(75)	13(100)
Fracture N(%)	2(3)	0	2(10)	0
Other N(%)	1(1)	0	0	0
Unknown N(%)	19(23)	0	3(15)	0
Erythrocyte transfusions N(%)	35(43)	12(29)	7(35)	1(8)

[#] *SD: standard deviation. THR: Total hip replacement. TKR: Total knee replacement*

Oxford hip and knee score

Due to incomplete questionnaires, scores could not be calculated for eight patients. The mean OHS score was 40.0 (95% CI 38.1–42.0) and the mean OKS score was 35.5 (95%CI 32.3–38.7) (adjusted p=0.007) (Table 2.2). A satisfactory joint function (i.e. 40-48 points) was obtained by 63% of the THR patients, and by 40% of the TKR patients. The percentage of patients, who scored 0 to 19 points, indicating severe joint problems, was 2.7% for THR and 10% for TKR patients.

EQ5D

Mean score for the VAS "health today" was 72.9 (95% CI 69.0–76.5) for THR and 70.6 (95% CI 63.9–77.3) for TKR patients. The mean EQ5D score was 0.80 (95% CI 0.76–0.85) for THR patients and 0.76 (CI 0.69–0.83) for TKR patients.

Table 2.2: Completed questionnaires, Oxford hip/knee score and EQ5D

		THR (N = 81)	TKR (N = 42)
Satisfaction			
	1. Undergo surgery again?		
	yes	78%	64%
	no	12%	24%
	2. Recommend surgery?		
	yes	94%	76%
	no	1%	7%
	3. VAS[&] satisfaction		
	(95% confidence interval)	83.1 (79.1 -87.2)	80.8 (74.7 - 86.9)
OHS/OKS[$]			
	0-19 (severe arthritis)	2.7%	10%
	20-29 (moderate to severe)	4%	20%
	30-39 (mild to moderate)	30.7%	30%
	40-48 (satisfactory joint function)	62.7%	40%
	95% confidence interval	40 (38.1 - 42.0)	35.5 (32.3 - 38.7)
EQ5D			
	VAS[&] health today	72.9 (69.0 - 76.5)	70.6 (63.9 - 77.3)
	Total score	0.8 (0.76 - 0.85)	0.76 (0.69 - 0.83)

[$] *Oxford Hip Score / Oxford Knee Score.* [&] *Visual Analogue Scale*

RAND-36

The mean scores for THR and TKR patients for the health domains are shown in table 2.3. There were no significant differences comparing RAND-36 results for all domains between THR and TKR patients.

Table 2.3: Mean RAND-36 scores per domain

Domain [#]	Participants THR	Participants TKR
	THA (95% CI)	TKA (95% CI)
PCS	40.5 (37.8 – 43.1)	37.3 (33.5 – 41.1)
MCS	53.7 (51.3 – 56.0)	54.6 (50.7 – 58.1)
PF	37.0 (34.2 – 39.7)	35.2 (31.7 – 38.8)
RP	44.4 (41.4 – 47.3)	42.1 (38.0 – 46.1)
BP	49.6 (47.1 – 52.0)	47.7 (44.3 – 51.2)
GH	46.0 (44.0 – 48.1)	43.7 (40.6 – 46.8)
VT	53.0 (51.0 – 55.1)	52.7 (49.3 – 56.0)
SF	46.8 (43.9 – 49.7)	47.2 (43.3 – 51.1)
RE	46.7 (43.8 – 49.7)	45.7 (41.3 – 50.2)
MH	51.5 (49.4 – 53.6)	52.7 (50.1 – 55.4)

[#] PCS: physical component score, MCS: mental component score, PF: physical functioning, RP: role-functioning physical, BP: bodily pain, GH: general health perceptions, VT: vitality, SF: social role functioning, RE: emotional role functioning, MH: mental health.
THR: Total Hip Replacement. TKR: Total Knee Replacement. CI: confidence interval

Discussion

The present study showed high quality of life scores, high patient satisfaction and high willingness to undergo total hip or knee replacement again at a minimum 10 of years after primary surgery. The willingness to have surgery again and the recommendation of this procedure to friends or family was higher for THR than for TKR patients. This difference was also found earlier by our group, and is confirmed by others showing less satisfied TKR patients at mid-term follow-up.[24,25] Compared to a Dutch background population both patients who received THR and TKR have comparable function and quality of life scores at a minimum 10 years follow-up after initial surgery.[10,13,15,26,27]

THR and TKR are effective from a societal perspective over the entire lifespan, with costs that compare favorably to those of other medical interventions.[28,29] Although long-term implant survival in both THR and TKR has a mean survival at 10 years of at least 90%, these data are not well associated with perceived outcome after these procedures by the patient. Few studies have been published on THR and TKR

patients with long-term follow-up (i.e. >10 years); particularly knowledge of long-term patient satisfaction after such procedures is scarce. Recall bias might obscure negative experiences of the early postoperative period at long-term follow-up moments.

Loughead *et al*. evaluated patient satisfaction and PROM's in TKR patients showing good satisfaction and moderate functional limitations fifteen years after TKR.[14] Beverland *et al*. evaluated a cohort of THR and TKR patients ten years after surgery and found a much higher percentage 'very happy' patients after THR compared to TKR and a higher percentage of 'never happy' patients after TKR compared to THR.[15] Our study not only used three questions relating to patient satisfaction it also has three different validated questionnaires, enabling it to provide more elaborate long-term results.

If asked on the likelihood to reconsider surgery again for themselves or advice this to relatives/friends our study showed differences between THR (respectively 78% and 94%) and TKR (respectively 64% and 76%) patients. In both groups almost all (except for four patients) said to recommend surgery to a relative or friend. Initially this may seem contradictory, as this means there were patients who claim to be 'not satisfied', but do recommend surgery to a friend or relative. This might very well be due to a lack of power and is considered a type-II error. Meeting postoperative patient expectations is an important determinant of the subjective postoperative satisfaction.[30,31]

Unfortunately this study did not have detailed demographic or pre-and postoperative information about patient expectations. Both THR and TKR patients were highly satisfied given a mean score of over 80.0 for satisfaction on their joint replacement with THR patients being more satisfied compared to TKR patients. The latter was also found earlier in a different cohort of Dutch THR and TKR patients at a mean follow-up of 3 years. This is also substantiated by the higher Oxford hip compared to Oxford knee scores, thus THR patients have better pain reduction and a higher functionality compared to TKR patients.[11,12,27] This study has several strengths. Patients from the study cohort were both included from academic and non-academic hospitals yielding a diverse population of patients and participating orthopedic

surgeons. To our knowledge it is one of the most detailed studies to date to describe detailed long-term satisfaction and PROM's in THR and TKR patients using disease specific and generic quality of life questionnaires.

Since the Oxford hip and knee scores did not exist when this study started, no preoperative data could be collected. Thus no change scores (i.e. after the intervention) could be calculated nor different preoperative symptom states between patients could be taken into account in order to have a more valid comparison between groups [32,33] Another limitation might be that results are based on responders, in long-term follow-up studies response bias is an issue since non-responders may have different outcomes compared to responders. Responders in this study tended to be younger than non-responders.

Conclusion

We demonstrated that at a minimum of 10 years of follow-up both THR and TKR patients are on average very satisfied, THR patients being more satisfied compared to TKR patients.

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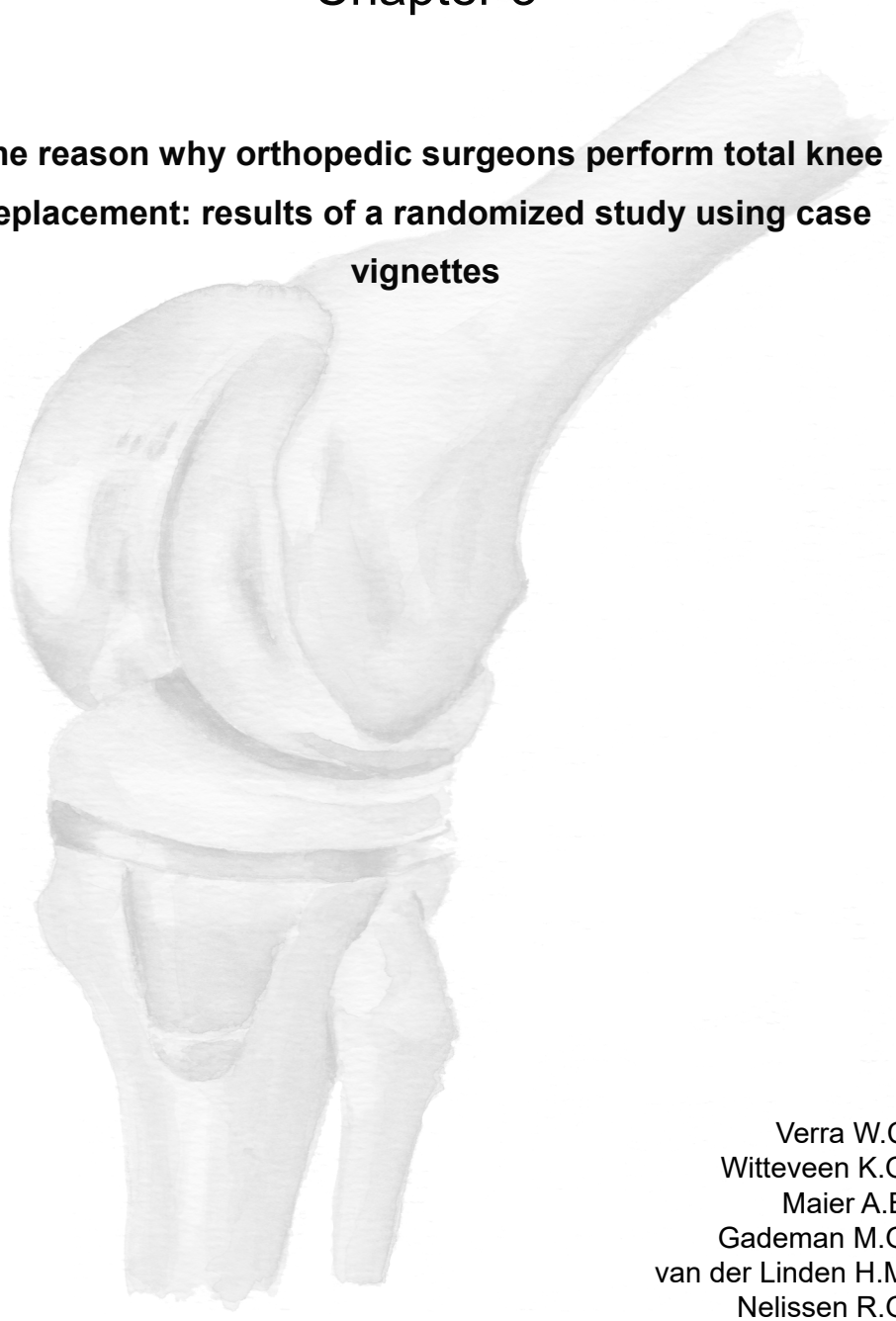
Chapter 3

The reason why orthopedic surgeons perform total knee replacement: results of a randomized study using case vignettes



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Abstract

Introduction. End-stage knee osteoarthritis (OA) results in total knee replacement (TKR) surgery. The decision to perform TKR is not well defined resulting in variation of indications among orthopedic surgeons. Non-operative treatment measures are often not extensively used. Aim of this study is to investigate factors influencing the decision to perform TKR by Dutch orthopedic surgeons.

Methods. Three case vignettes, each case divided into two versions, being identical except for information on age (younger and older age), pain (mild and severe pain) or radiological OA (low and high grade) were developed. A questionnaire including these three case vignettes was sent to all 599 Dutch orthopedic surgeons, who were randomized to either one of the two versions. The orthopedic surgeons were asked if TKR would be the next step in treatment. Furthermore from a list of patient factors they were asked how strong these factors would influence the decision to perform TKR.

Results. 54% of the orthopedic surgeons completed the questionnaire (N=326). Orthopedic surgeons indicated to perform TKR significantly more often at higher age (73.3% vs. 45.5%, $p<0.001$). In presence of mild pain orthopedic surgeons were slightly more reluctant to perform a TKR compared to severe pain (57.0% vs. 64.0%, n.s.). Mild radiological OA made surgeons more reluctant to perform TKR compared to severe OA (9.7% vs. 96.9%, $p<0.001$).

Conclusions. Old age and severe radiological OA are variables which are considered to be important in the decision to perform a TKR. Pain symptoms of moderate or severe pain are unequivocal when considering a TKR.

Introduction

Knee osteoarthritis (OA) is a major cause of disability and functional limitations which affects millions of people in our aging population worldwide.[1,2] A total knee replacement (TKR) is generally accepted to be an effective surgical treatment for end-stage knee OA.[3-5] No succinct criteria on the decision making (i.e. patient selection) on TKR are available, other than "enough pain".[4] The latter not only results in variation among orthopedic surgeons in their decision to perform a TKR, but also in a potentially large percentage of patients not receiving adequate conservative (i.e. non-operative) treatment for knee OA.[6-9] On the other hand, not all patients improve after TKR; a study from the Swedish arthroplasty register shows that 17-25% of the patients after primary TKR were not satisfied or were uncertain about the functionality of their TKR.[10] Since patient expectations on their TKR surgery are not entirely met, well-timed surgery and preoperative counseling seem to be important variables to be addressed, even more considering the high prevalence of TKR surgery, with about 22.000 cases in 2012 in a small country such as the Netherlands and 719.000 cases in the United States in 2010.[11,12] Pain and the degree of radiographic OA are considered important variables in the decision process to perform TKR surgery.[4,7,13,14] Preoperative pain is a strong predictor of postoperative outcome; patients with severe preoperative pain complaints had worse postoperative outcomes compared to those with less severe pain complaints.[15,16] On the contrary, patients with mild radiological OA showed little improvement of clinical symptoms compared to patients with severe radiological OA.[17] Most orthopedic surgeons consider a TKR in case of moderate to severe radiological OA but there is a well-known weak association between pain symptoms/functional impairment and radiological OA.[14,18] As for total hip replacement (THR), ranking determinants for their importance in the decision to perform surgery showed that radiological changes were of less importance than functional impairment, decreased range of motion and pain. Pain at rest, at night and/or pain during activities.[19]

This emphasizes the need to explore the variables being involved in the decision making process to perform TKR. The aim of this study was to evaluate how these factors influence the opinion of Dutch orthopedic surgeons in the decision to

recommend TKR surgery in a given patient. We have used case vignettes to mimic clinical practice; this has never been done before. We hypothesized that Dutch orthopedic surgeons would recommend TKR to patients with high grade radiological OA, high levels of pain and older age.

Materials and Methods

In April 2012 all 599 actively practicing orthopedic surgeons in the Netherlands who were member of the Dutch Orthopedic Association (NOV) were contacted by e-mail from the NOV to participate in the study. After two and four weeks a reminder was sent by e-mail to those who did not respond. All orthopedic surgeons were randomized into two groups, both groups filled out a different version of a case vignette (version A or B, see Appendix). Randomization lists were generated randomly by a computer.

Questionnaire

The web-based survey used in this study was partially based on questionnaires previously used in surveys among orthopedic surgeons studying different outcomes.[14,19,20] In addition, one part of the questionnaire was adapted from a study on geriatric oncology patients.[21] This study used case vignettes with different versions to explore the influence of older age on oncologists' cancer management.[21] The TKR indication questionnaire was designed and critically appraised by two experienced knee specialists (RN and EL). Before the final versions were distributed to the Dutch orthopedic surgeons a pilot-test was performed among a test-panel of twelve orthopedic surgeons and residents for final feedback. The software used to distribute the questionnaire was NetQ (NetQuestionnaires BV, Amsterdam, the Netherlands).

The questionnaire was divided into three parts: part one consisted of general information of the respondent (gender, employment location (university medical center, general hospital (private group or fixed salary) or specialized private clinic), number of TKR performed each year (<50, 50-100 or >100) and years of experience).

Part two consisted of either version A or B of three case vignettes (Appendix A). The

case vignettes of the version A and B were entirely identical except for information on: 1. age (old versus young age), 2. severity of pain (mild versus severe) and 3. radiological OA (mild versus severe radiological destruction). Case 1 version A described a 54-year-old patient versus version B an 86-year-old patient.

Case 2 version A described a patient with mild pain symptoms and version B a patient with severe pain symptoms. Case 3 version A showed a radiograph with mild radiological OA and version B showed a radiograph with severe radiological OA. A radiograph of the knee was present in all three case vignettes (see Appendix). The diagnosis in all cases was primary OA with no other abnormalities in other joints of the lower extremities. Orthopedic surgeons were asked for each case: Is a TKR the next step in your treatment? “yes or no”. A short explanation in writing of the chosen answer was mandatory.

Part three of the questionnaire contained factors that might affect the decision to perform TKR surgery. These fourteen decision modifying factors were extracted from current orthopedic literature including; high co-morbidity, severe osteoporosis, obesity, dementia, low quality of life due to the knee problems, old age, young age, ineffective conservative treatment, limited walking distance, dependent on activities of daily living (ADL) due to knee problems, moderate motivation of the patient, severe pain, severe radiological OA and mild radiological changes.[14,19] For this part of the questionnaire the respondents were instructed to select an answer on a five-point Likert-scale: strongly against surgery, against surgery, neutral, in favor of surgery and strongly in favor of surgery. The factors explored in the case vignettes of part two were also included in this part to evaluate their importance in relation to other modifying factors. It was not possible to return to the previous question.

Since no study patients were involved, official approval of an ethics board was not necessary.

Statistical analysis

For analysis of the case vignettes a Chi-squared test was used. The decision modifying factors of part three of the questionnaire were presented in a five-point Likert-scale. These factors were ranked in hierarchical order from most likely influencing the decision to perform TKR to most unlikely to perform TKR. ‘Strongly in

favor of surgery' and 'in favor of surgery together as well as 'strongly against surgery' and 'against surgery' were combined. We performed no sample size calculation since our sample size consisted of a fixed cohort (i.e. all actively practicing orthopedic surgeons member of the NOV). All analyses were performed using SPSS for Windows, version 20. Tests were two-tailed and p-values less than 0.05 were considered to be significant.

Results

Of the 599 questionnaires a total of 354 (59%) orthopedic surgeons responded after three mailings (Figure 3.1). Of the 354 responders 8 indicated not to participate in the questionnaire due to lack of experience in performing a TKR and 20 did not complete the whole questionnaire. Therefore 326 (54%) were included in the analysis. Group A (N=165) and B (N=161) had comparable general characteristics (Table 3.1).

Figure 3.1: Flow chart of participating orthopedic surgeons

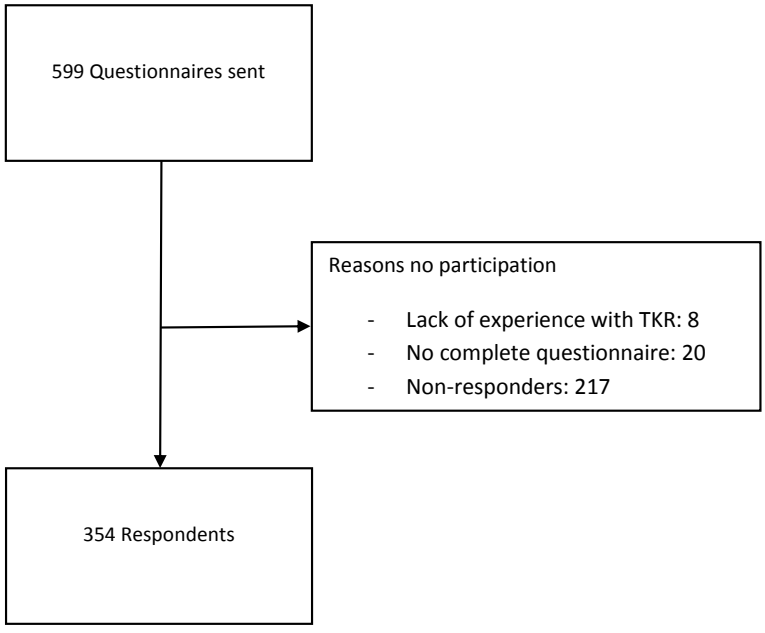


Table 3.1: General characteristics of the respondents, stratified by group (N=326)

Characteristics	Group		
	A	B	Total
	N=165	N=161	N=326
Gender			
Male N (%)	152 (92)	150 (93)	302 (93)
Working environment N (%)			
University medical center	17(10)	18 (11)	35 (11)
Private practice in general hospital	122 (74)	114 (71)	236 (72)
General hospital (fixed salary)	17 (10)	19 (12)	36 (11)
Specialized knee clinic	9 (6)	10 (6)	19 (6)
Number of knee replacements each year N (%)			
<50	50 (30)	59 (37)	109 (34)
50–100	91 (55)	86 (53)	177 (54)
>100	24 (15)	16 (10)	40 (12)
Years of experience median (IQR)	10 (5-19)	11 (4-20)	10 (5-10)

Values are displayed in frequency (N) and percentage (%) if not otherwise indicated.
IQR: interquartile range.

Case vignettes

Case 1, with difference in age, showed that orthopedic surgeons were willing to perform a TKR more often at higher chronological age (73% vs. 46%, p<0.0001). Case 2, with difference in severity of pain symptoms, showed no difference on the decision to perform a TKR between the cases with mild and severe pain (57% vs. 64%, n.s.). Case 3, with difference in radiological knee OA, showed that orthopedic surgeons were less likely to perform surgery in a patient with mild compared to severe radiological OA (10% vs. 97%, p<0.0001) (Table 3.2).

If a TKR was not recommended, valgus bracing of the knee, physiotherapy and unicompartimental knee prostheses were frequently proposed alternatives but heterogeneity between each of the three case vignettes and the two versions of the questionnaires was seen (Table 3.3-3.5).

Table 3.2: Differences in TKR recommendation, stratified by group based on case vignettes

	Group		
	A	**B**	
	N=165	N=161	**p-value**
Case 'Age'	54-year-old patient (46%)	86-year-old patient (73%)	<0.0001
Case 'Pain'	Mild pain symptoms (57%)	Severe pain symptoms (64%)	n.s.
Case 'ROA'	Mild radiological OA (10%)	Severe radiological OA (97%)	<0.0001

The percentages of orthopedic surgeons who do recommend a TKR in the case vignette.
Case 1 described a patient a young patient (group A) and old patient (group B). Case 2 described a patient with mild pain symptoms (group A) and severe pain symptoms (group B). Case 3 described a patient with mild radiological OA (group A) and severe radiological OA (group B).
** ROA: Radiological Osteoarthritis. n.s.: not significant.*

Decision modifying factors

The fourteen patients' characteristics and modifying factors were ranked in hierarchical order from most likely influencing the decision to perform TKR to least likely (Figure 3.2). The factors activities of daily life (ADL) dependency, low quality of life, presence of severe pain, limited walking distance, ineffective conservative treatment and severe radiological OA were positively associated with the decision of orthopedic surgeons to perform a TKR. On the other hand mild radiological OA, moderate motivation of the patient, high co-morbidity, dementia and young age urged the orthopedic surgeons less likely to perform a TKR. Presence of obesity was negatively associated with the decision of the orthopedic surgeons to perform a TKR, although one third of the respondents had a neutral opinion about obese patients considering a TKR. Old age and severe osteoporosis were of no clear influence in the decision to perform a TKR.

Table 3.3: Explanation not recommending a TKR, case 'Age'

Case 1 'Age'	**Group**	
	A (young)	**B** (old)
	N = 90	N = 43
High tibial osteotomy	37	-
Unicompartimental knee prosthesis	29	4
Valgus bracing of the knee	17	13
Intra-articular injection	7	11
Expand conservative treatment	6	7
Knee arthroscopy	6	1
Radiographs (long leg)	6	-
MRI	6	-
Physiotherapy	6	5
Patient too young	5	-
Patient too old	-	3
Lateral heel lift	2	-
Lack of information	1	1
Optimize the level of painkillers	1	1

Notes are given in multiple responses (N)

Discussion

The most important finding of the present study was that 'older age' and 'moderate to severe radiological OA' were important variables in the decision making process for TKR by Dutch orthopedic surgeons, while the 'level of pain' was not strongly associated with the indication to perform a TKR. While latter is generally considered an important factor to perform TKR. Furthermore we found that the factors 'depending on ADL', 'low quality of life', 'severe pain', 'limited walking distance', 'ineffective conservative treatment' and 'severe radiological OA' were associated with the decision of orthopedic surgeons to perform a TKR.

Table 3.4: Explanation not recommending a TKR, case 'Pain'

Case 2 'Pain'	**Group**	
	A (mild)	**B** (severe)
	N = 71	N = 58
Unicompartimental knee prosthesis	19	22
Valgus bracing of the knee	15	13
Physiotherapy	14	6
Intra-articular injection	11	3
Knee arthroscopy	3	11
High tibial osteotomy	3	7
Lack of information	1	7
No indication for TKR surgery	7	1
Expand conservative treatment	4	1
Optimize the level of painkillers	2	3
Radiographs (stress view)	-	4
MRI	2	1
Watchful waiting	3	-
Lateral heel lift	1	1
Meniscectomy	1	-

Notes are given in multiple responses (N).

Age

Respondents did not consider old age as a contraindication to perform a TKR, but high co-morbidity negatively influenced the decision to perform TKR. Therefore, we assume that a relatively good health status is essential for the decision to perform a TKR in aged patients, which is line with the literature.[20] The majority of orthopedic surgeons delayed recommendation of a TKR in the younger age groups (<55 years), probably due to a higher revision rate within this group and the unpredictable outcome after revision TKR.[22,23] Over 50% of the respondents recommended other

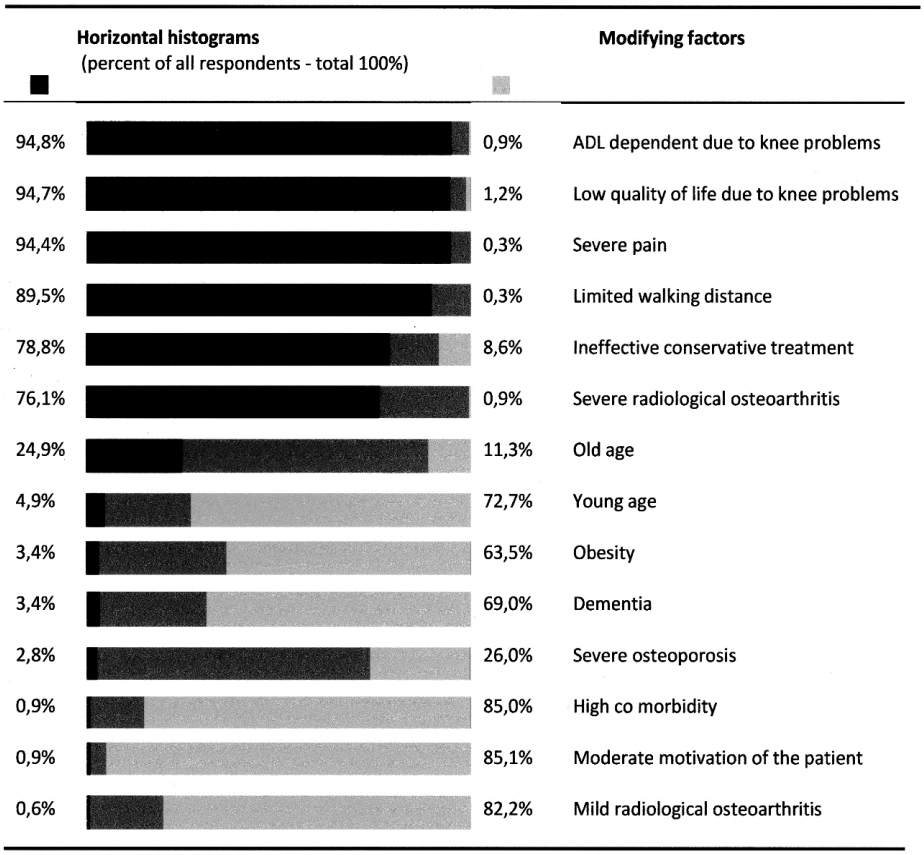
treatment options for this age group, like tibial osteotomy or unicompartimental knee prostheses.[20,24-26]

Table 3.5: Explanation not recommending a TKR, case 'Radiological OA'

Case 3 'Radiological OA'	**Group**	
	A (mild OA)	**B** (severe OA)
	N = 149	N = 5
Discrepancy: complaints vs ROA	47	*not applicable **
Intra-articular injection	32	
MRI	24	
Knee arthroscopy	19	
Additional diagnostic testing	17	
Expand conservative treatment	17	
Physiotherapy	12	
Valgus bracing of the knee	7	
Bone scintigraphy	5	
Lack of information	5	
Radiographs (stress view)	4	
Optimize the level of painkillers	4	
X-ray (long leg)	3	
Unicompartimental knee prosthesis	2	
High tibial osteotomy	1	
Expectations too high	1	
Rheumatoid arthritis screening	1	
Weight loss	1	

*Notes are given in multiple responses (N). * Only 5 respondents who did not recommend a TKR (3.6 % of total).*

Figure 3.2: Modifying factors affecting the decision to perform TKR (N= 326).



The black part of the bars represent the percentage of respondents who believed the modifying factor was a positive factor in the decision for surgery (in favor of surgery, strongly in favor of surgery). The dark gray part of the bars represents the percentage of surgeons who have a neutral opinion in considering a TKR related to this factor. The light gray part of the bars represent the percentage of surgeons who believe the factor was negatively affecting decision to perform TKR (against surgery, strongly against surgery).

Pain symptoms

Current literature highlights the importance of evaluating the pain level experienced by patients in the preoperative period since less severe pain experienced by patients (i.e. non-catastrophizing pain) predicts better postoperative outcome.[13,15,16] Differences in pain symptoms (pain at rest, pain at night and pain at activity) did not

affect the decision to recommend a TKR in the case vignettes. Based on these results we can conclude that OA patients presenting with knee pain in the Netherlands seem to undergo similar treatment, independent of their pain characteristics. However, severe pain is identified by 95% of the orthopedic surgeons as a very important variable in the decision to perform a TKR (part three of the study). The OA Research Society International and Outcome Measures in Rheumatology (OARSI-OMERACT) working group has shown that pain and function are weakly predictive in the surgeon's recommendation for TKR, which underlines our results.[7] Both results are conflicting with the importance of level of knee pain and function preoperatively which strongly affect the postoperative outcome of the patient (less severe knee OA obtain better outcome).[13,15,16]

Radiological OA

Our study showed that the degree of radiological knee OA is an important variable which influences the orthopedic surgeons' decision to perform TKR, as was found by others as well.[20] Although clear evidence exists on the discrepancy between presence of radiological OA and clinical symptoms, most orthopedic surgeons consider TKR surgery in presence of moderate to severe radiological OA.[5,14,27] The prevalence of knee OA is increasing, caused by both increasing life span, but also a growing group of people suffering from overweight and therewith negative metabolic changes on the cartilage as well as mechanical overuse of the knee joint.[28] This results in an increase of TKR surgery worldwide, with a predicted increase of over 700% until 2030 in the United States.[29] Not all patients with a TKR are satisfied. At one to five year follow-up about one fifth of patients with a TKR are not satisfied with their functional outcome.[10,30] This stresses the importance of preoperative prediction models on which patients will benefit from a TKR, in order not only to increase quality of life of patients but also to reduce national health care costs. With the implementation of patient reported outcome measures (PROM's) in national registries and the presence of option grids for patients based on prediction models for outcome, the indication for surgery, and thus the variation among orthopedic surgeons to recommend TKR is likely to decrease. Strengths of this study are the relatively large number of respondents, which gives a good reflection of the opinion

of the Dutch orthopedic surgeon. Second, case vignettes with each case developed in two versions are never used before in orthopedic questionnaire research, and are an effective method to analyse the symptoms (age, pain symptoms and radiological OA) determining the decision of an orthopedic surgeon to perform TKR. With the use of case vignettes a clinical setting was mimicked but this virtual setting might still be different from what orthopedic surgeons actually do in their own clinical practice (i.e. still artificial). Case vignettes do not provide all clinical information, which could affect the decision-making process. For that matter, the influence of conjoined factors in the decision making process, like young age and severe radiological OA and severe pain combined could not be determined. Another limitation is that an inability in the questionnaire existed to select no-or less experience with TKR surgery, which allows orthopedic surgeons to finish the questionnaire without noticing they had no or less experiences in knee surgery. However, the latter might also be a strong feature if it was a barrier for some respondents to start or complete the questionnaire. Finally, our results are limited to a health care system comparable to the Dutch system where surgeons do not receive fee-for-surgery payments or bonus plans (i.e. as an addition to fixed salary employment). These latter factors could also be of important influence in the decision to perform TKR surgery and were not investigated within this study.

Further clinical research is required to clarify the indication criteria of an orthopedic surgeon for TKR surgery, prediction models of both the symptom state of patients in presence of a certain functional deficit and radiological osteoarthritis and the education level of the orthopedic surgeon will be important variables in such a model. International implementation of the case vignette questionnaire would make cross-cultural differences in indication for TKR among surgeons visible and might define option grids among the different patient groups even better.

Conclusion

Older age and severe radiological osteoarthritis are variables resulting in the decision by the Dutch orthopedic surgeon to perform a TKR. Symptoms of moderate or severe pain are unequivocal when considering a TKR.

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Appendix – Case Vignettes

Case 1

Medical history

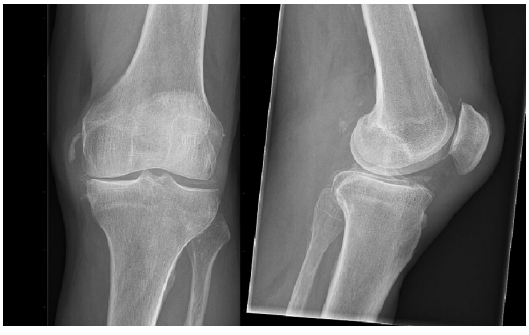
A 54 years-old *(Other version: 86 years-old)* woman was referred to the outpatient clinic with complaints of progressive knee pain, especially on the left side. No trauma was reported. Start-up pain and morning stiffness are present. She mentioned a VAS pain score of 7. There were no complaints of a locking knee and she is unable to walk more than 30 minutes. She wants to do many activities with her two grandchildren, but she is hindered because of the knee problems.

Conservative treatment

- Painkillers: 3 months NSAID's with no effect.
- Walking aids: A stick for long distance walks.
- Intra-articular injection: Twice, with a short-term effect.

Physical examination

Minimal varus deformity of the left knee with effusion. Knee-flexion 100 degrees. 5 degree of fixed flexion deformity. Collateral- and cruciate ligaments are stable. Patella no abnormalities.



Standing radiograph knee

Is a Total Knee Replacement the next step in your treatment?

Case 2

Medical history

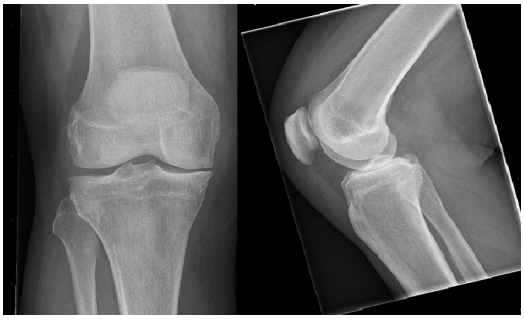
A 68 year old woman is referred to the outpatient clinic and is complaining about pain in both knees, more on the right side. Pain is presented during activities, almost every day. There is no pain at rest or at night while in bed. *(Other version: pain is constantly present including at rest and at night while in bed)* Start-up pain and morning stiffness are present. She is incapable of bicycling and has trouble with walking because of the knee problems. This causes great distress in her life.

Conservative treatment

- Painkillers: Minimal effect of NSAID's.
- Walking aids: Not applicable.
- Intra-articular injection: Few corticosteroid injections with short-term effect. She does not want the injections anymore.

Physical examination

Minimal varus deformity. Knee-flexion 110 degrees. 5 degree of fixed flexion deformity. Collateral- and cruciate ligaments are stable. Patella no abnormalities.



Standing radiograph knee

Is a Total Knee Replacement the next step in your treatment?

Case 3

Medical history

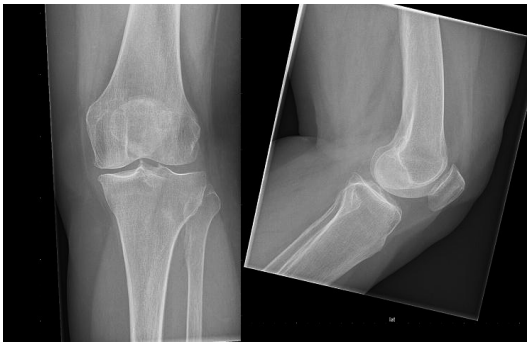
A 67 year old man with left sided knee pain is referred to the outpatient clinic. Pain at rest is present daily, and 2 or 3 times a week he has pain at night. Morning stiffness is present. Maximal walking distance is 1000 meters. It frustrates the patient that bicycling and working in the garden is no longer possible due to the knee problem.

Conservative treatment

- Painkillers: Paracetamol 4dd1 gram, if necessary diclofenac 50 mg.
- Walking aids: A stick when walking outdoors, for the last 3 months.
- Intra-articular injection: He is frightened of injections.

Physical examination

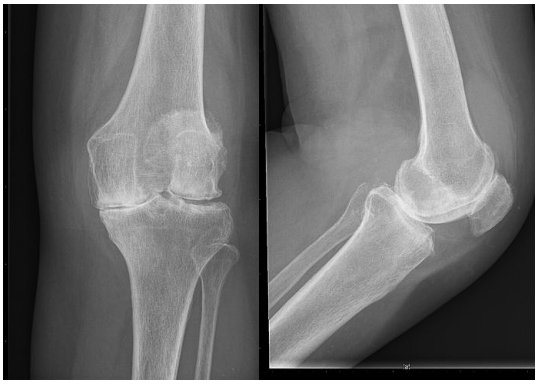
Minimal varus deformity and effusion. Knee-flexion 100 degrees. 10 degree of fixed flexion deformity. Collateral- and cruciate ligaments are stable. Patella-femoral crepitus.



Standing radiograph knee Case A

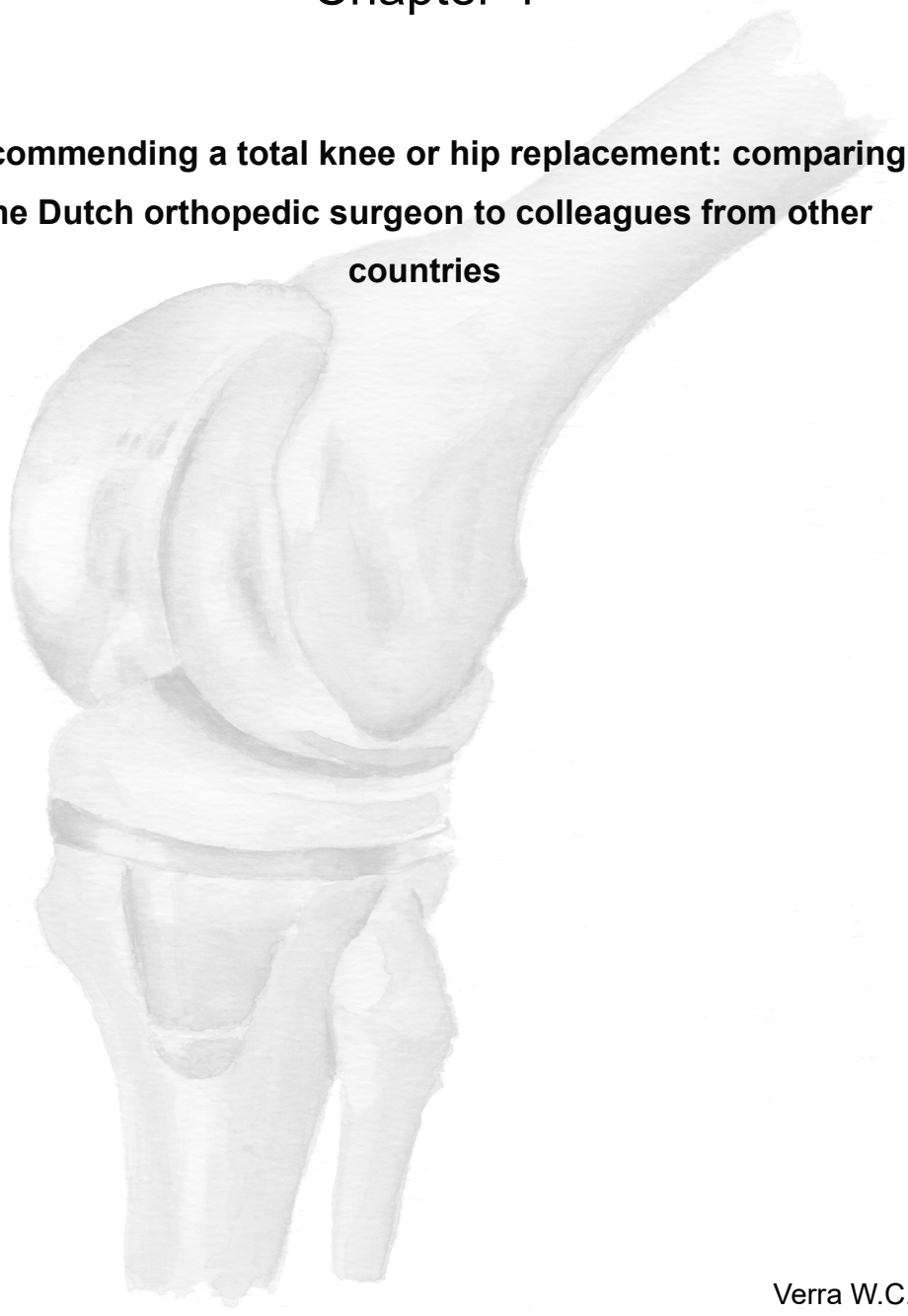
Is a Total Knee Replacement the next step in your treatment?

Radiograph of Case B:



Chapter 4

Recommending a total knee or hip replacement: comparing the Dutch orthopedic surgeon to colleagues from other countries



Verra W.C.
Nelissen R.G.

using data from the OARSI-OMERACT task force “total joint replacement as outcome

Introduction

Within the general population the number of individuals suffering from osteoarthritis (OA) is growing due to ageing.[1,2] OA is an important cause of disability, mortality and loss of function.[3-5] Reported prevalences worldwide of knee OA vary from 5% up to 30%, and of hip OA prevalences vary from 1% up to 18%.[1,6] OA occurs more often in females than in males and prevalences rise with increasing age.[6] In the Netherlands, the prevalence is about 850.000 cases of knee and hip OA (www.rivm.nl). Treatment of OA is either non-surgical or surgical, in that order. Several risks are related to surgical treatment, including postoperative infection, deep venous thrombosis and risk of significant blood loss. There are no clear guidelines for the recommendation of operative treatment. Indications for operative treatment, advocated in the literature, are the presence of radiological OA[7,8] in combination with sufficient pain and/or disability complaints from the patient.[9-11] Non-surgical treatment of OA consists of a broad array of different options from which many are proven effective.[12] In the Netherlands, the Dutch Orthopedic Association (NOV) has established guidelines on treatment modalities for OA. The first step is the use of a stepped care, non-surgical approach, before surgery is considered.[13,14]
In this study we compared the orthopedic surgeon's decision to recommend a patient with knee or hip OA for total joint replacement in the Netherlands with this decision of orthopedic surgeons from several other countries in the developed world.

Materials and methods

Data from the OARSI-OMERACT study on pain level and functional disability in knee or hip OA were used.[10] This study recorded indications for total joint replacement surgery (knee or hip) in 1.909 participants worldwide. Patients with OA of the knee or the hip were included and phenotyped using different characteristics and scores. Orthopedic surgeons were asked whether the patient was recommended for total knee/hip replacement (TKR/THR) or not. Inclusion took place between January 2008 and July 2009, patients with definite radiological OA of the knee or hip attending to an orthopedic outpatient clinic were included. In the Netherlands one academic and one general hospital participated in the study. The other participating countries were

Australia, Canada, Czech Republic, France, Germany, Sweden, United Kingdom and the United States.

Demographic and clinical parameters

In order to compare Dutch participants with participants from the other countries several characteristics were recorded including age, gender, and body-mass index (BMI) measured in kilograms per square meter. Furthermore, data on the presence of a joint replacement in the past were collected by self-report of the patient.

To evaluate pain experienced by the patient a specific questionnaire was used; the intermittent and constant OA pain score (ICOAP).[15,16] To assess clinical severity, the pain, stiffness and functional subscales of the Western Ontario and McMasters Universities OA Index (WOMAC), were used and results transformed to a 0-100 score where higher scores correspond with worse status.[17] To estimate the joint-related quality of life, the quality of life subset of the Knee/Hip disability and OA Outcome Score (KOOS/HOOS) was used in the translated and validated form.[18,19]

Statistical Analysis

For normal distributed variables, means with standard deviations were calculated for each country / group of countries. For non-parametric variables, medians with interquartile ranges were calculated for each country / group of countries. Logistic and linear regression analysis was used, adjusting outcome scores for age, gender and BMI. All analyses were performed using SPSS, version 17.0.

Results

Patient population

The study included 1.909 patients with OA (1.130 with knee OA and 779 with hip OA) who presented at the orthopedic outpatient clinic with complaints consistent with knee or hip OA.[10] From those presenting with knee OA the mean age was 67.5 (SD 10.4) years, mean BMI was 31.0 (SD 6.8) and 58% was female. From those patients presenting with hip OA the mean age was 65.0 (SD 11.4) years, mean BMI was 28.3 (SD 5.2) and 57% was female. From the patients with knee OA 536 (47%) were

recommended to have TKR. From the patients with hip OA 531 (68%) were recommended to have THR.

Table 4.1: Characteristics of patients who were recommended for total joint replacement

	NLD	**Other countries**
Knee (N)	(30)	(506)
Age mean (SD)	72.0 (9.8)	68.8 (9.5)
Gender Female N (%)	19 (63)	308 (61)
BMI mean (SD)	28.5 (4.4)	31.0 (6.3)
TJR in past yes N (%)	4 (13)	116 (23)
Hip (N)	(50)	(481)
Age mean (SD)	69.2 (10.4)	65.4 (10.4)
Gender Female N (%)	26 (52)	263 (60)
BMI mean (SD)	27.8 (3.8)	28.4 (4.8)
TJR in past yes N (%)	12 (24)	110 (23)

NLD = the Netherlands, TKR = total knee replacement, OA = osteoarthritis, SD = standard deviation, BMI = body mass index, TJR = total joint replacement, THR = total hip replacement.

Characteristics of patients indicated for total joint replacement

Table 4.1 shows characteristics of patients who were recommended for total joint replacement in the Netherlands and in the other countries (as a mean of the other countries). The mean age of Dutch patients was higher compared to the mean age in the other countries. BMI was slightly lower compared to the BMI abroad. Aforementioned is true both for TKR and THR, however differences are smaller in THR. THR was recommended relatively more common in the Netherlands compared to abroad (76% of patients with hip OA in the Netherlands versus 66% of the hip OA patients outside the Netherlands). TKR was recommended equally frequent in the Netherlands compared to abroad (45% of patients with knee OA in the Netherlands versus 46% of the knee OA patients outside the Netherlands).

Pain, function and joint-related quality of life

For TKR recommended patients perceived pain (ICOAP score) and KOOS-PS scores were similar in the Netherlands and abroad. The KOOS-QoL score was significantly higher in knee patients in the Netherlands compared to the other countries' KOOS quality of life score.

For THR recommended patients the same results were found, including a higher HOOS-QoL score too. Data are displayed in table 4.2.

Table 4.2: Pain, function and joint-related quality of life; Dutch patients vs. the other countries

	NLD	Other countries	P-value	95%-CI of difference
Knee (N)	(30)	(506)		
ICOAP total mean (se)	50.9 (4.0)	53.4 (0.96)	0.28	-16.8 - 4.8
KOOS-PS mean (se)	60.1 (1.5)	57.9 (0.85)	0.41	-4.7 - 10.1
KOOS-QoL mean (se)	63.8 (1.7)	77.0 (0.76)	<0.001	-20.2 - -6.6
Hip (N)	(50)	(481)		
ICOAP total mean (se)	56.2 (2.7)	58.0 (0.96)	0.93	-6.9 ; 6.3
HOOS-PS mean (se)	58.8 (2.2)	61.1 (0.69)	0.10	-8.2 ; 1.1
HOOS-QoL mean (se)	69.1 (1.8)	78.2 (0.77)	0.001	-14.6 ; -4.1

P-values and 95%-confidence intervals are adjusted for: age, gender and BMI.
NLD = the Netherlands, ICOAP = intermittent and constant OA pain score, a high score is worse pain.
KOOS-PS / HOOS-PS = Knee/Hip and OA Outcome Score – physical short form. QoL = quality of life subscore KOOS / HOOS.

Discussion

In this short, comparative study we compared the orthopedic surgeon's decision to recommend a patient with knee/hip OA for total joint replacement (i.e. TKR or THR) in the Netherlands with colleagues from other countries (including the United States,

Australia, Canada, Czech Republic, France, Germany, Sweden and the United Kingdom).

Because of the relatively low numbers of patients per country this study should be considered as a pilot for future studies. For patients presenting with OA of the knee, a comparable percentage of Dutch patients were recommended for total knee replacement (TKR) surgery compared to the other countries. Although Dutch patients had severe symptoms (pain and function impairment) and somewhat older age when being recommended for total joint replacement compared to the other countries, the Dutch patients had the highest (joint-related) quality of life scores within this multinational comparison both in knee and hip OA patients.

Total joint replacement is the end-stage treatment of OA, but the definition of end-stage is not a very succinct well-defined entity. Clear guidelines when to perform total joint replacement surgery and what treatment modalities have to be started first in symptomatic patients are not (yet) used on a routine basis. In the Netherlands the orthopedic association (NOV) has developed a guideline recommending conservative treatment as a first step in the management of knee/hip OA patients. In other countries this is recommended as well.[20-22] Although Dutch patients had severe symptoms (pain and function deterioration) when being indicated for total joint replacement, they still had the highest (joint-related) quality of life scores within this multi-national comparison of patients indicated for a TKR or THR. It might be argued that the Dutch population as a whole, has a high(er) quality of life score. For that matter, according to the Gallup World Poll the citizens of the Netherlands were considered to be the seventh happiest people in the world when the study was performed (http://worldhappiness.report).

We were able to use a large, well defined, database from an international multicenter study in which eight developed countries are represented worldwide.[10] To our knowledge this study is the first cohort that recorded whether a patient should have a total joint replacement or not, irrespective of the actual replacement of the joint took place. This reduces the chances on selection bias and offers the opportunity to get a clearer insight in the decision making process that leads to total joint replacement. No developing countries were included in the database. This could have given a

broader insight in the recommendation for total joint replacement in these countries. On the other hand, larger societal differences (i.e. access to joint replacement surgery, social class differences, waiting lists, etc.) between these countries could yield even more bias, a bias that is also present in the current comparison between Western countries. Another major limitation is the, before mentioned, limited group size of patients from all participating countries. For example in the Netherlands patients were included from one academic and one small general hospital. This should be taking into account before major conclusions can be drawn.

Endpoint was the recommendation to perform total joint replacement surgery, it was not recorded whether surgery took place or not, so data such as mean time between recommendation and surgery was not available. To learn more about the prognostic variables taken into account for the indication of orthopedic surgeons per country future studies could consist of questionnaires sent to orthopedic surgeons designed to find out what factor contribute to the recommendation to perform total joint surgery like the study reported in chapter 3 of this thesis.[11]

In conclusion, TKR is indicated equally frequent in Dutch OA patients compared to knee OA patients from eight other developed countries.

Dutch patients have the highest joint-related quality of life compared to other countries when being recommended for either TKR or THR, despite comparable pain and functional impairment of these joints. TKR and THR have no univocal success rate if patient reported outcomes (PROM's) are used as outcome measure, this is in contrast to good (high) survival rates in national registries.

An analysis into the complex decision on when to recommend TKR or THR using prognostic preoperative patient characteristics which might be associated to the different treatment modalities, would improve care of the patient with knee or hip OA. It would help the orthopedic surgeon when recommending TKR/THR, but might also help manage expectations from the patient before surgery.

Acknowledgements:

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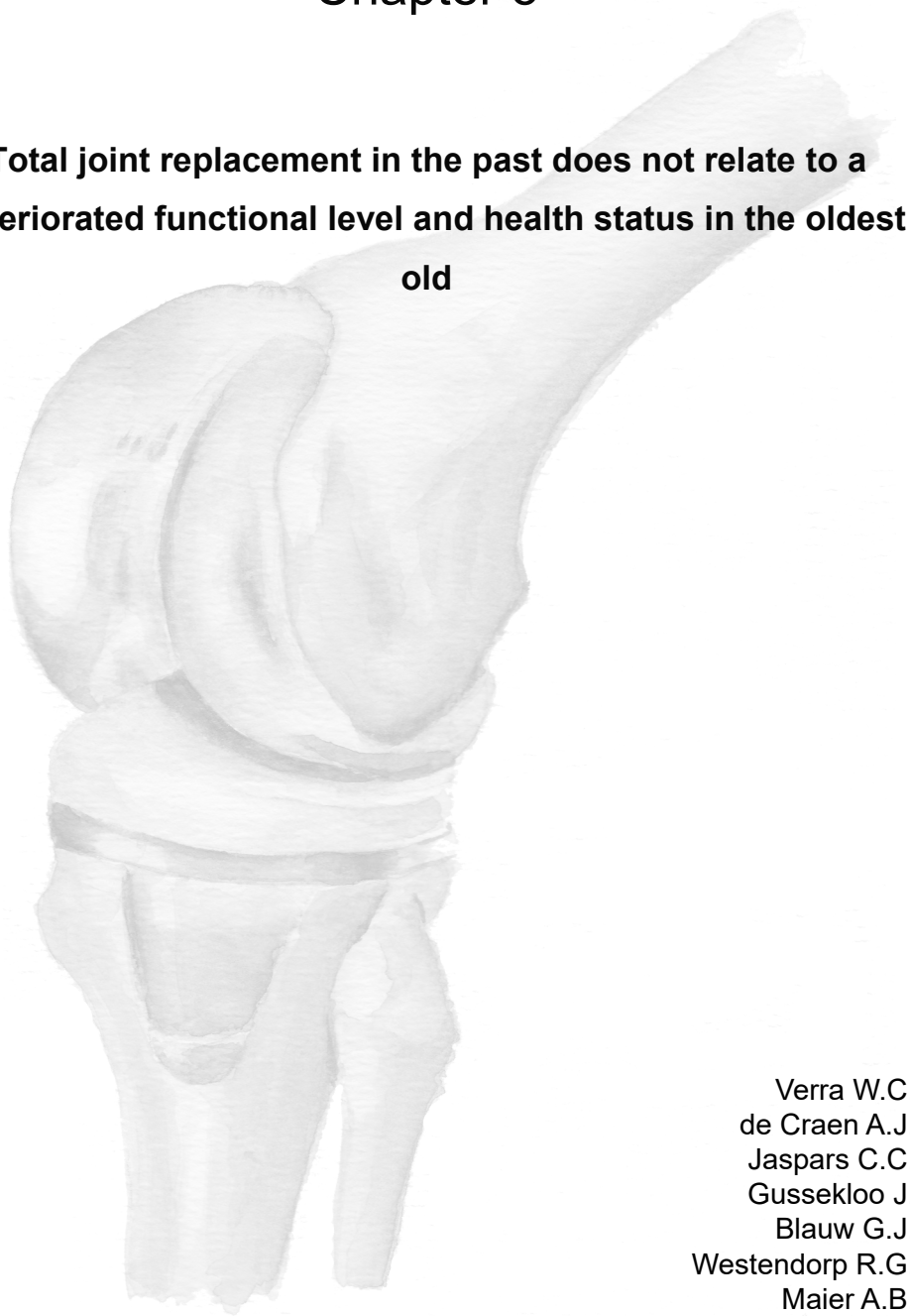
Chapter 5

Total joint replacement in the past does not relate to a deteriorated functional level and health status in the oldest old



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Abstract

Introduction. Total hip or knee replacement is effective in improving joint function, quality of life, and pain reduction. The oldest old population (i.e. 85 years and older) with joint replacements (TJR) is underrepresented in current literature. We compared health-related and functional characteristics of oldest olds with and without TJR.

Methods. Participants aged 85 years old and older were divided into a group with and without TJR. Data on comorbidity, physical and joint functioning, activities of daily living, quality of life, and mortality rate were recorded.

Results. A total of 38 out of 599 participants (6.3%) had received a TJR in the past. Participants with a TJR had slightly less comorbidities, walked slower (p=0.006), and complained more about hip-pain (p=0.007).

Mortality of those with a TJR was lower during the first 8-years of follow-up (p=0.04). All other characteristics were comparable between groups.

Conclusion. We conclude that subjects with a TJR performed equally well, besides showing a lower gait speed and a higher frequency of hip-pain. Except for the lower gait speed, having a TJR is not associated with poorer health.

Introduction

The population of oldest olds (i.e. 85 years old and older) is the fastest growing segment of the elderly population in the western society.[1] The health status decreases with increasing chronological age.[2] One of the major age-related diseases is osteoarthritis (OA), which is more common in females.[3-5] In subjects between 60 and 70 years of age, prevalences of symptomatic knee OA are reported of approximately 10% in males and 20% in females.[4] Prevalence of knee OA is comparable in subjects aged 80 years and older.[4,5] Symptomatic OA of the hip is present in approximately 5% of the 60 to 70 years old females and up to 18% in females of 80 years and older. In males, prevalences are slightly lower.[3,4] Due to the demographic changes, the number of total hip replacement (THR) and total knee replacement (TKR) procedures steadily increases.[6] Increasing age is associated with a higher complication and mortality rate after total joint replacement.[6] However, the results of total joint replacement in elderly patients have been proven effective in terms of pain reduction, functional improvement, and cost-effectiveness and show similar results compared to younger patients receiving total joint replacement.[7,8]

OA of the knee or the hip impairs physical activity.[4] Restriction of physical activity is associated with numerous detrimental effects on general health status, physical function, and quality of life.[4,9] Maintaining physical activity at older age is essential in order to maintain optimal health status. Treating OA, ultimately with a total joint replacement, influences function (i.e., flexion, extension, rotations) and quality of life positively.[8] However, in terms of improving physical activity level, the influence of a total joint replacement is less clear.[10] The long-term effects of receiving a total joint replacement have been underrepresented in the oldest old population.

In the present study, we compared a group of oldest old subjects with and without a total hip or knee replacement in their history. Since surgery is performed preferably on healthy subjects and based on the aforementioned positive effects of total joint replacement, we hypothesized that the group with total joint replacement would show better results on physical functioning, activities of daily living, joint complaints, and quality of life.

Methods

Participants

Data was used from the Leiden 85-plus Study, a community-based prospective follow-up study of the inhabitants of the city of Leiden, the Netherlands. All participants were included at the age of 85 years. There were no exclusion criteria. Follow-up visits were performed annually. Enrolment of the study took place between 1997 and 1999.[11] A total of 599 persons participated in the study, 87% of all eligible inhabitants. The Medical Ethical Committee of the Leiden University Medical Center approved the study. Informed consent was obtained from all participants.

In order to determine whether participants had received an elective TKR or THR, medical history concerning total joint replacement was obtained from the hospital charts and from information provided by general practitioners and nursing home physicians.

Participant Characteristics

Physical functioning was assessed at the participant's home, by the following items: if a participant was able to stand up and walk, gait speed, a five times stand-up test, hand grip strength, and a physical activity score. The ability to stand up and to walk was recorded dichotomously. Gait speed was determined using the six meter walking test.[12] Use of a walking aid was allowed. Gait speed was calculated using distance in meters and time in seconds (m/s). In the five times standup test participants were asked to stand up five times in a row, from sitting. Time was recorded in seconds. Hand grip strength, as a proxy of muscle strength, was measured with a Jamar hand dynamometer (Sammons Preston Inc. Bolingbrook, IL). Participants were asked to stand up and hold the dynamometer in the dominant hand. After one trial, participants were asked to squeeze three times. The maximum measurement was recorded in kilograms (kg).

To calculate the physical activity score (PAS), four items from the Time Spending Pattern questionnaire were selected to constitute physical exercise above routine daily physical activity: (a) walking for fun, (b) cycling for fun, (c) exercise alone or in groups or other physical activity, and (d) working in the garden.[13] Each item was

scored from 0 (no activity) to 3 (daily activity), and their sum score made up the Physical Activity Score (PAS).

Activities of daily living were measured using the Groningen Activity Restriction Scale (GARS).[14] The GARS assesses competence in abilities in nine personal basic activities of daily living (ADL) and nine instrumental activities of daily living (IADL). A summed score was calculated for basic IADL ranging from 9, indicating ability to perform all activities without assistance or undue effort, to 36 indicating disability. To assess joint complaints, participants were asked whether they experienced pain and stiffness of any knee or hip joint.

Quality of life was assessed with the Cantril ladder.[15] This quality of life-score uses a ten-point scale ranging from 0 “worst possible life” to 9 “best possible life.” Furthermore participants were asked to qualify their health status; results were dichotomized between good and poor.

Other Characteristics of Participants

Participants’ gender, demographics, socioeconomic status, marital status, and highest education were recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Chronic diseases identified from general practitioner and pharmacists’ records included cardiovascular disease (CVD), including myocardial infarction, angina pectoris, and hypertension. Furthermore, diabetes mellitus, obstructive pulmonary disease, Parkinson’s disease and arthritis (including rheumatoid arthritis and osteoarthritis) were recorded. Numbers of prescribed medicines were recorded from pharmacists’ records. Global cognitive performance was assessed with the Mini-Mental State Examination (MMSE).[16] Furthermore the 15-item Geriatric Depression Scale (GDS-15) was used to measure depressive symptoms.[17] This scale is developed to determine depression in the elderly and is filled in by the participants themselves. A score of six or more indicates the possible presence of depressive symptoms. Because of limited validity of the GDS-15 in people with moderate and severe cognitive impairment, it was completed only by people with MMSE scores of more than 18.

Statistics

For continuous data means with standard deviations and for non-parametric data medians with interquartile ranges were calculated. Differences between the two groups were calculated using the *t*-test when data was continuous, Mann-Whitney-*U* test for nonparametric data, and chi-square test when data was dichotomous. Linear or logistic regression was performed to adjust for gender.

Patient survival was analyzed using the Kaplan-Meier method. Cox regression analysis was used to compute a hazard ratio comparing subjects with a THR or TKR with subjects without a joint replacement. P-values less than 0.05 were considered to be significant. All statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago), version 17.

Results

From the 599 participants, 38 (6.3%) were identified with a total of 49 total joint replacements: 29 total hip replacements (THR) and 20 total knee replacements (TKR). The mean age of the subjects during their first primary joint replacement was 78.2 (SD 4.7) years. Characteristics of participants at 85 years are shown in Table 5.1. The prevalence of comorbidities was slightly lower in the group of participants with a joint replacement in the past compared to the group of participants without a total joint replacement. There were no statistically significant differences found between the two groups on any parameter except for the prevalence of arthritis. From the 38 participants, 28 had one total joint replacement. Five had 2 TKR's and three had 2 THR's, one had both a TKR and a THR, and one had a THR and 2 TKR's.

Physical Functioning, Activities of Daily Living, Joint Complaints, and Self-Reported Health

Table 5.2 shows the functional characteristics of the participants with and without joint replacement at age 85 years. In both groups, most of the participants were able to walk. Participants with a total joint replacement walked significantly slower compared to participants without joint replacement (p=0.006). All other tested items addressing physical functioning were similar between both groups.

Table 5.1: Baseline characteristics of participants aged 85 years with and without total joint replacement in the past

	Total joint replacement	
	Yes (N=38)	**No** (N=561)
Female N (%)	27 (71)	369 (66)
Widowed N(%)	23 (61)	322 (57)
Education: primary school only N (%)	22 (58)	331 (59)
Living situation		
Independent N (%)	25 (66)	304 (54)
Sheltered N (%)	5 (13)	155 (28)
Institutionalized N (%)	8 (21)	102 (18)
Clinical characteristics		
Body Mass Index mean (SD)	27.6 (4.5)	27.1 (4.5)
Mini Mental State Examination median (IQR)	27 (25-28)	26 (22-28)
Geriatric Depression Scale median (IQR)	1.5 (0-2)	2 (1-3)
Co-morbidity		
Stroke N (%)	1 (3)	47 (8)
CVD* N (%)	23 (61)	380 (68)
Diabetes Mellitus N (%)	3 (8)	82 (15)
Parkinson N (%)	0 (0)	11 (2)
COPD N (%)	1 (3)	64 (11)

*SD = standard deviation, IQR = Interquartile Range CVD = Cardiovascular Disease. COPD = Chronic Obstructive Pulmonary Disease * CVD included myocardial infarction, angina pectoris and hypertension.*

In terms of daily activities and self-reported health status, there were also no differences between both groups. The number of participants with a total joint replacement complaining about hip pain was significantly higher compared to the number of participants without a joint replacement (p=0.007). Within those participants complaining of hip pain, 11 had received at least one THR and four had received at least one TKR in the past. The number of participants complaining about knee pain differed between both groups; however, this result did not reach statistical significance (p=0.06). Within those complaining of knee pain, 8 participants had received at least one TKR and nine participants had at least one THR. Within those complaining about both knee and hip pain, 9 had received a TKR and 14 a THR.

From the participants with a THR (N=26), 42% complained about hip pain and 35% about knee pain. From the participants with a TKR (N=14), 29% complained about hip pain and 57% about knee pain.

Table 5.2: Health and functional characteristics of participants with and without a total joint replacement in the past

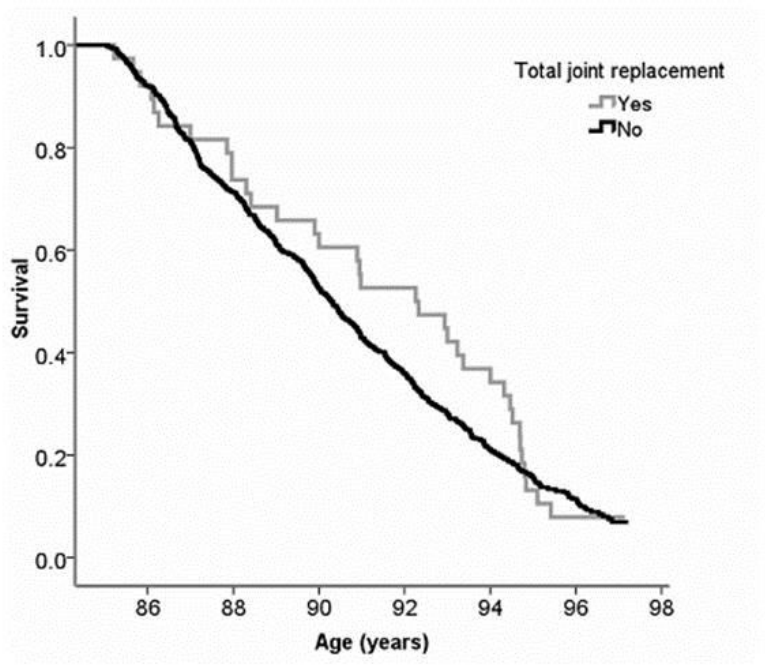
	Total joint replacement		**P-value**	
	Yes (N=38)	**No** (N=561)	**Crude**	**Gender adjusted**
Physical functioning				
Able to walk N (%)	34 (90)	492 (88)	0.75	0.69
Gait speed m/s, mean (SD)	0.42 (0.18)	0.53 (0.22)	0.003	0.006
5x stand up test sec, median (IQR)	15.9 (12.0-18.8)	13.6 (10.8-17.8)	0.31	0.31[¥]
Grip strength kg, mean (SD)	21.4 (9.0)	22.7 (8.9)	0.41	0.69
Physical activity score median (IQR)	3 (1 – 6)	3 (0 – 4)	0.12	0.11[¥]
GARS				
ADL median (IQR)	10.5 (9 – 14)	10 (9 – 15)	0.68	0.74[¥]
IADL median (IQR)	18.5 (13 – 25)	18 (12 – 27)	0.93	0.98[¥]
Joint complaints				
Pain hip N (%)	15 (40)	91 (16)	0.004	0.007
Pain knee N (%)	16 (42)	123 (22)	0.05	0.06
Stiffness hip N (%)	8 (21)	70 (13)	0.63	0.59
Stiffness knee N (%)	11 (29)	94 (17)	0.50	0.55
Self-reported status				
Cantril ladder mean (SD)	7.8 (1.5)	7.5 (1.8)	0.35	0.35
Self-reported health “good” N (%)	26 (88)	392 (70)	0.71	0.70

[¥] *Adjustment for gender after log transformation of non-parametric variables. SD = standard deviation. IQR = inter quartile range. GARS = Groningen Activity Restriction Scale. (I)ADL = (Instrumental) Activities of Daily Living.*

Survival

During a total follow-up period of 12 years (median 5.8 years, interquartile range 3.1–8.9 years), 542 (90.2%) participants died. Figure 5.1 shows the Kaplan-Meier survival curve of participants with and without joint replacement. During the first 10 years, mortality was attenuated in the group of participants with a joint replacement. When applying Cox regression to calculate a hazard ratio (HR) adjusted for gender, no significant differences in survival were found after follow-up of 12 years dependent on the history of joint replacement (HR of 0.86, 95%-CI [0.61,1.22], p=0.41). Cox regression up to eight years of follow-up showed a survival benefit of the participants with a joint replacement (HR of 0.60 (95%-CI [0.37, 0.98], p=0.04).

Figure 5.1: mortality of participants with and without a total joint replacement in the past



Discussion

Within the present study, characteristics of the oldest old with and without a total joint replacement in the past were compared. No differences in the prevalence of chronic, age-related diseases were found between the two groups except for the prevalence of arthritis. No differences in physical functioning were found except for a lower gait speed in the group with a total joint replacement. The group of oldest olds also complained more about joint pain. Furthermore, an attenuated mortality rate during follow-up was observed in this group.

Gait speed is considered to be an important predictor of functional status and (adverse) health events.[18,19] It is also related to functional activities, such as crossing the street.[19] A recently published study confirmed our results of lower gait speed in subjects with a total joint replacement.[19] That study showed slower gait speed in middle aged to elderly patients who received a THR about 2.5 years earlier.[19] More severe joint pain is associated with lower gait speed in patients with OA.[20] The group with total joint replacement complained more of joint pain; this could have contributed to the lower gait speed. It was not recorded whether the joint pain complaints came from the left, right, or both sides. A reason why oldest old participants with a joint replacement complained more about joint pain can be the presence of OA in the other joints. Since total joint replacement is the end-stage treatment of OA, other joints are likely to be affected by OA as well.[21,22]

With our data, we could not perform a cost-effectiveness analysis for total joint replacement in the oldest old. Literature on cost-effectiveness in the general OA population shows that both TKR and THR are (highly) cost-effective.[23,24] A smaller study shows cost-effective health outcomes of total knee or hip replacement in subjects aged 80 years or older.[25]

Reported quality of life did not differ between both groups in our cohort. This is in line with the results of several studies presented in a systematic review of the literature showing that subjects who received a TKR or THR performed similar in terms of health-related quality of life, as health-and age-matched controls.[26] Self-reported health status did also not differ between both groups in our cohort. There is evidence that self-reported health status improves after receiving a total joint placement in

middle-aged subjects.[27] To our knowledge, this is the first study reporting on self-reported health status in oldest old subjects with a total joint replacement compared to age-matched controls after follow-up of, on average, seven years.

The group of participants with a total joint replacement showed a trend towards a healthier phenotype, especially in terms of cardiovascular and pulmonary diseases and attenuated mortality rate, but differences did not reach significance. Elective surgery such as total joint replacement is preferably performed on subjects with a low number of comorbidities.[28,29] This could explain the difference in comorbidity and survival between both groups. Oldest olds with a poor physical condition might never have reached the age of 85 years and hence, were not included in our study. If these subjects were operated on despite their lesser health status, they probably died before inclusion in the study (i.e. before they reached the age of 85 years).

A limitation of the study is that no detailed information about the joint replacement surgery, such as surgical technique and prosthesis design, data from the hospital admission, and adverse events (i.e. complications) was available. The presence of a joint replacement was recorded in the study; however, the site of replacement was not consequently recorded. This data was not retrieved for all participants. Another limitation is the lack of information about the status of OA joints (i.e. radiological degree of OA) in lower extremities in both groups and the extent to which the TJR contributes to functional level. OA status can be graded based on the radiological appearance.[30,31] However, high-grade radiological OA is a modest indication for surgery since there is a poor correlation between radiological and clinical OA.[5] The most important factor in deciding to perform a total joint replacement is enough pain.[32]

Furthermore, the average age of participants with a joint replacement was higher compared to the general average age for receiving a THR being 70 to 75 years old, and for TKR being around 70 years old.[33,34] An explanation could be that, by retrospectively retrieving data on joint replacement, not all implants were identified. Another reason can be that a group of subjects with a joint replacement deceased before reaching the age of 85 years.

To our knowledge, this is the first study comparing an 85-year-old population who received a TKR or THR with their contemporaries who did not receive joint replacement surgery emphasizing on physical functioning, joint complaints, and reported health status. Current literature concerning total joint replacement in the oldest old patient is mostly observational, describing patient satisfaction and complications in cohorts of elderly patients who received a TKR or THR.[6,28] Some studies compare the outcome after surgery with a cohort of younger patients.[29,35] Several case-control studies have been published; however, controls were matched based on gender, comorbidity, and surgery type rather than based on age-matched comparison.[7,36] Another strength of our study is that the participants are part of a large longitudinal population-based cohort study with extensive measures for functioning and health with a follow-up of twelve years.

Future research should focus more on the growing oldest old population. Based on our study, we observed no differences in most clinical parameters in subjects aged 85 years with and without a joint replacement where those with a joint replacement walked slightly slower. Future studies should focus on gait parameters and physical functioning of the oldest old with and without joint replacement in order to further assess the impact of having a joint replacement at old age.

Conclusion

Oldest old participants with a joint replacement walked slower and complained more of joint pain compared to those without a joint replacement of the same age. Furthermore, the groups were comparable in terms of physical functioning, activities of daily living, and quality of life. Hence, having received a total knee or hip replacement is not associated with poorer functional level and health status except for a lower walking speed in those with a joint replacement, compared to subjects without a total joint replacement, which might be due to the direct effect of arthritis on gait parameters.

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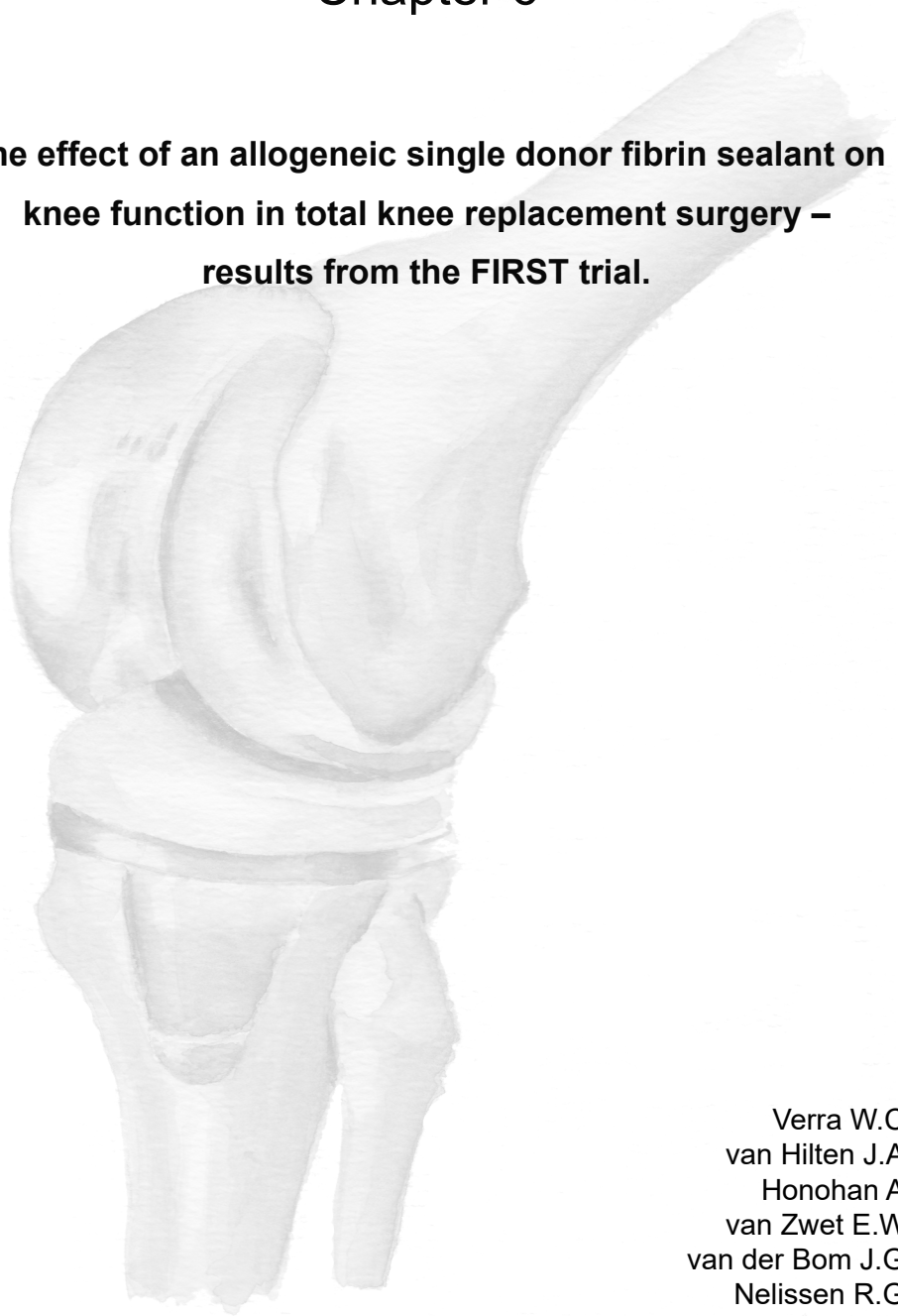
Chapter 6

The effect of an allogeneic single donor fibrin sealant on knee function in total knee replacement surgery – results from the FIRST trial.



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Abstract

Background. Total knee replacement (TKR) is increasingly performed in short term hospital stay, making same day mobilization an important issue after surgery. Little joint effusion, by reducing intra-articular blood loss, will enhance knee range of motion. The application of a topical fibrin sealant on the intraoperative bare bone and synovial tissue may contribute to better early full mobilization and thus improved functional outcomes. Since ambulation with a fully extended knee is less strenuous, we hypothesized that patients who received fibrin sealant would demonstrate improved early knee extension after six weeks compared to patients who received standard care.

Methods. A multicenter randomized controlled trial in a consecutive series of osteoarthritis patients scheduled for TKR surgery. Participants were randomized to receive fibrin sealant or not before closing the knee joint capsule. Primary outcome was change in knee extension angle (^{o}) at short term (2 weeks) follow-up (cExt). Secondary outcomes were 6 week extension angle, knee flexion angle, hemoglobin loss, blood transfusion rates, complication rates, the Knee Society Score, the KOOS and EQ5D scores.

Results. After six-week data were available from 250 patients an interim analysis was performed by an independent Data Safety Monitoring Board for safety and effectivity assessment. This interim analysis showed that sufficient patients were included to detect a cExt of 10^{o} between both groups. Inclusion was stopped but all, in the meantime, included patients were treated according to their randomization. A total of 466 patients were available for analysis.

Both groups were comparable in terms of baseline characteristics. The mean cExt was 0.2^{o} (95%CI -0.5 to 0.9). No differences in secondary outcomes were found.

Conclusions. No beneficial effects or side effects were found of a topically applied fibrin sealant during TKR surgery. These results discourage the clinical use of a fibrin sealant in TKR.

Introduction

The frequency of total knee replacement (TKR) for the treatment of osteoarthritis will increase in the coming years due to an aging population.[1] In the Netherlands the number of TKR increased by almost 25% between 2010 and 2015 to over 26.000 TKR's annually (www.lroi.nl). TKR is also increasingly performed in two-day or even one-day surgery, necessitating the need for immediate postoperative full ambulation and range of motion exercises. Since the latter is restricted by intra-articular blood loss, ways to control this loss are important for rapid patient recovery. The mobilization and weight bearing is less strenuous if full extension of the knee is present. On a more holistic patient level, these issues have also been shown to be related to patient blood management.[2-7] Earlier, our group demonstrated an average of 650-700 mL of overall (visible and non-visible) blood loss after TKR.[4] Reducing this blood loss will most likely benefit the TKR patient.

Theoretically, a fibrin sealant has the ability to reduce bleeding of surgically injured bone and synovial tissue by forming a sealing layer.[6] Several randomized studies report on the effect of fibrin sealant in reducing blood loss (i.e. hemoglobin level) and/or transfusion rates after TKR.[8-14] Since the introduction of modern transfusion trigger protocols transfusion rates have decreased tremendously and reducing transfusion frequency has therefore become a less relevant outcome after TKR. Outcome measures such as improvement of functioning and mobility are increasingly considered important, improving patient independence and satisfaction.

We designed a randomized controlled clinical trial to assess the effect of a topical applied allogeneic single donor fibrin sealant on functional knee recovery after TKR surgery. We hypothesized that patients who received this topical fibrin sealant intraoperatively would demonstrate improved clinical favorable early knee extension (primary endpoint) compared to patients who received standard care.

Methods

We conducted a single-blinded, multicenter randomized controlled trial at six orthopedic centers in the Netherlands. The study protocol was approved by the central medical ethics committee of the Leiden University Medical Center (P10.115) and registered at the Dutch Trial Registry (NTR2500). Local medical ethics committees approved the study protocol in all participating centers. A study independent monitor visited one of the centers to monitor legal-and protocol compliance.

Patients

Patients elected to undergo primary TKR between January 2011 and February 2013 for the treatment of primary osteoarthritis or rheumatoid arthritis were eligible to be included in the study. Exclusion criteria were age under eighteen years, ASA score >III, any coagulation disorders, no knowledge of the Dutch language, and unwillingness to participate. All patients provided written and signed informed consent before inclusion. Patients were randomized to receive either intra-articular topical Cryoseal™ fibrin sealant (CS) or standard care without an intra-articular hemostat.[15] A method of computer generated per-center randomization using permutated blocks with randomly differing block-sizes was used (ProMISe™ software; Leiden University Medical Center). Patients, all staff involved in data collection and data analysis and all authors were unaware of the treatment allocation.

Investigational Product

Cryoseal™ fibrin sealant (CS) is produced by Sanquin, the Netherlands.[15] CS is derived from one unit of fresh frozen plasma donated by a single donor. One unit of single-donor quarantined plasma yields between 10-15 mL CS from which two syringes were transported in a sealed bag. A fibrin sealant in general is composed of two main components, fibrinogen and thrombin that, when mixed together at 37°C results in a fibrin molecule clot.

Protocol of Surgery

All patients were operated on adhering to the study protocol. Type of anesthesia was not standardized. Tourniquet use during surgery was allowed; however, during the procedure the tourniquet was deflated in order to surgically coagulate injured vessels with electrocautery. Timing of deflation of the tourniquet was left to the orthopedic surgeons' preference. All participating hospitals were free to choose their own preferred brand and type of TKR implant. Cementation was left to the centers preference. The use of a drain was an important issue when the study was performed. We hypothesized that the use of drainage systems may interact with the effect of the CS. Orthopedic centers were therefore requested to perform the procedure either with or without vacuum drainage for all TKR procedures at that center.

For each randomized patient a cooling box was delivered to the operating room containing cooling elements and either CS or no CS. Before application the frozen CS was thawed at 40^{o}C for at least twenty minutes. The surgeon and scrub nurse were informed about the content of the box only immediately before application. Patients assigned to the CS group were treated with a maximum of 10 mL CS divided over two separate syringes, one with 5 mL and one with the remaining 3-5 mL. The use of at least 5 mL CS was mandatory. The CS was topically applied after placement of the implant on intra-articular tissues and bare bone surfaces. CS was applied with the use of a spray tip mounted on the syringe. The remaining 3-5 mL CS was used at the discretion of the surgeon. The knee was closed routinely. All unused CS and empty syringes were returned to the local blood transfusion department where the amount of CS applied to each patient was recorded. Standard care was considered TKR according to this protocol without the use of CS.

After surgery all patients received a low molecular weight heparin thrombosis prophylaxis during six weeks. All patients followed a regimen of full weight-bearing physical therapy.

Transfusion policy

Decisions regarding perioperative blood transfusion were made by the attending anesthesiologist and/or orthopedic surgeon, similar guidelines were in place in all participating hospitals. The transfusion protocol is presented in the Appendix.

Data collection

Data were transcribed onto Case Report Forms (CRF's) by research nurses who were unaware of the randomization result. All written data were transferred from the CRF to the secure web-based data management system (ProMISe^{TM}).

Outcomes

Primary outcome was the change in knee extension (cExt) angle (^{o}) at short term follow-up (i.e. after two weeks) compared to the preoperative knee extension. Secondary outcomes were the six week cExt, the knee flexion, perioperative blood (hemoglobin) loss, transfusion rates, postoperative pain, complications (superficial and deep infection, hematoma, and systemic complications), and total duration of hospital stay. Furthermore the Knee Society score and validated patient reported outcome scores; the Dutch versions of the Knee Injury and Osteoarthritis Outcome Score (KOOS)[16] and the EQ5-D[17] were recorded. Outcomes were recorded at baseline and 2- 6- and 52 weeks after surgery.

Sample size

A sample size calculation was performed for our primary outcome which is cExt two weeks after surgery. A difference between study arms of 10^{o} was expected and was also considered clinically relevant. Because of scarcity of data to base our calculations on, based on the date from a trial registered on clinicaltrials.gov (NCT00492219) a standard deviation of 35 degrees was assumed. The sample size needed to detect a difference of 10^{o} with a t-test assuming equal standard deviation in both groups of 35 is 259 per group (using the O'Brien-Fleming rule for one interim analysis. Because of the scarcity of data during development of the study protocol a re-estimation of the sample size was specified in the protocol after the first 250 inclusions were completed.

Interim analysis

According to the protocol a single interim analysis was conducted by an independent Data Safety Monitoring Board (DSMB) when 2-week follow-up data were available from 250 patients (because of overshoot this turned out to be N=262 included in interim analysis). The interim analysis was intended as both a safety assessment and superiority analysis as well as used to re-estimate the sample size.

Ultimately an interim analysis of the first 262 evaluable patients was performed. All (serious) adverse events were recorded. The DSMB judged whether an adverse event was possibly related to treatment with CS. The DSMB was blinded to group allocation when assessing the data. The standard deviation of cExt between baseline and 2 weeks was 7.7 according to the interim analysis. It was concluded that in the study protocol the standard deviation of the primary outcome was over-estimated. According to this new sample size calculation there was already enough power to stop inclusion. However, because the protocol stated at least 400 patients were to be included, it was decided to continue until this amount was reached. Ultimately over 400 patients were included because of overshoot of inclusion.

Statistics

Descriptive statistics are reported as number and percentage for categorical variables. Normally distributed continuous variables are reported as mean and standard deviation and non-normally distributed continuous variables as median and inter-quartile range.

Primary outcome

A repeated measure linear mixed model was used to assess the difference in cExt between patients randomized for Standard Care and CryoSeal fibrin sealant, adjusting for pre-operative knee extension angles (crude model). The model was adjusted for any misbalance in baseline characteristics between the randomized groups (Model 1). To investigate whether the CS effect was modified by the use of a drain, drain use and the interaction between drain use and CS versus standard care was added to the model (Model 2).

Secondary outcomes

For the secondary outcome change in knee extension after 6 week and for change in knee flexion, the same repeated measurement analysis of covariance was performed as for the primary outcome adjusting for preoperative knee flexion. EQ5D and VAS were compared by mean and interquartile range for both randomization groups pre-operatively and after six weeks of follow-up.

Analyses were carried out according to the intension-to-treat (ITT) principle. Difference in estimated mean differences between CS and Standard Care arms and their 95% confidence intervals were computed with the Standard care arm as a reference group. Statistical analysis was performed with computer software (SPSS 20.0 for Windows, SPSS Chicago, IL.). Statistical tests were two sided, a p-value of <0.05 was considered statistical significant.

Results

A total of 498 patients were randomized between January 2011 and February 2013. From these patients a total of twenty-four (twelve patients in each study arm) ultimately did not undergo TKR surgery or withdrew their informed consent (IC). A further four eligible patients (3 in CS arm and 1 in control arm) gave IC twice and were included by randomization for a second TKR at least three months later on the contra-lateral side. Eight patients who underwent TKR were excluded for analysis due to the missing cExt data pre- or postoperatively.

A total of 466 patients were available for analysis; 232 in the CS arm and 234 in the control arm (Figure 6.1). Due to random logistical reasons with the different clinics no exact total of patients who were eligible can be presented.

Figure 6.1: Flowchart of patient inclusion

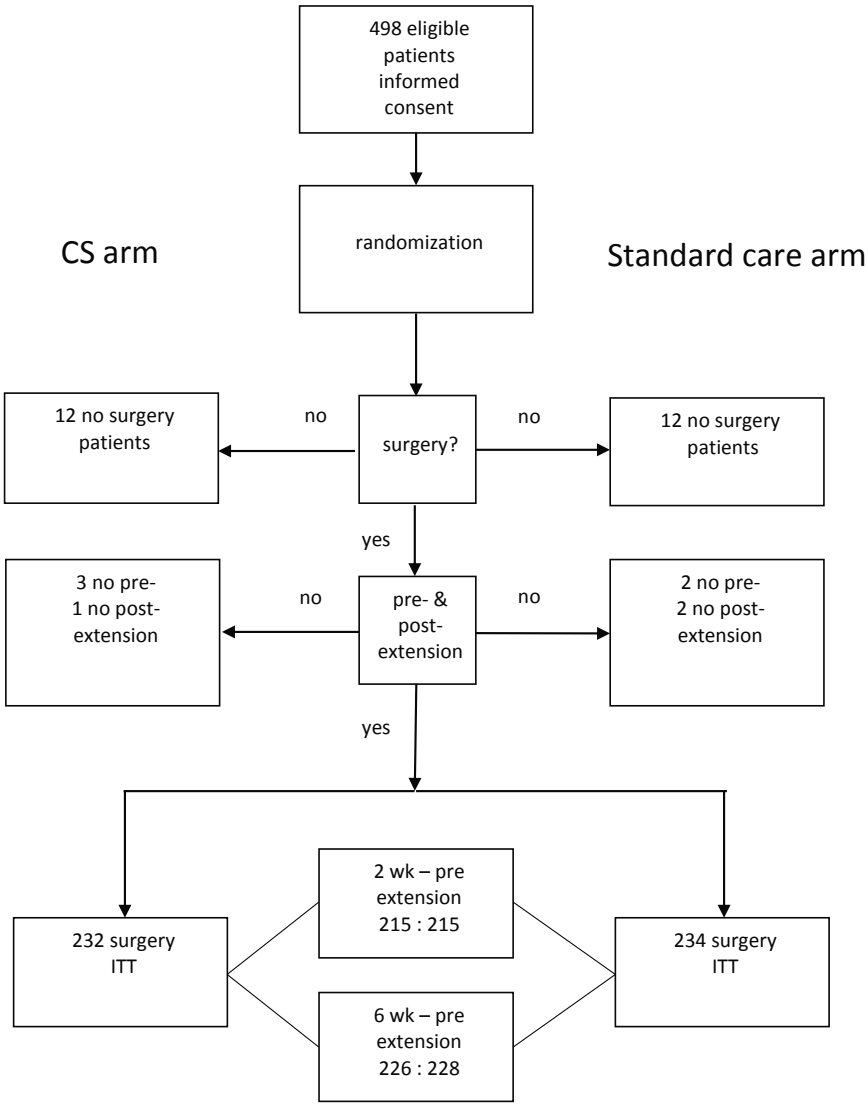

Table 6.1: Characteristics of participants

	Standard Care	CryoSeal
Baseline variables		
Number of patients	234	232
Females N (%)	152 (65)	148 (64)
Age years (SD)	68 (9)	68 (10)
Body mass index kg/m^2 (SD)	29 (5)	29 (5)
ASA score *N (%)*		
I	44 (19)	32 (14)
II or III	182 (78)	185 (80)
Associated co-morbidity *N (%)*		
Diabetes Mellitus	47 (20)	31 (13)
Type of OA *N (%)*		
Primary OA	215 (92)	203 (88)
Preoperative variables		
Hemoglobin g/dL mean (SD)	13.8 (1.3)	13.7 (1.4)
Pain score 0-10 median (IQR)	7 (5 to 8)	7 (5 to 8)
Knee extension angle ^{0} median (IQR)	-2.5 (0 to -5)	-5.0 (0 to -10)
Preoperative extension deficit ≤15^0 N (%)	26 (11)	37 (16)
Flexion angle ^{0} median (IQR)	110 (100 to 120)	110 (100 to 120)
Perioperative variables		
CS fibrin sealant use N (%)	1 (0.4)	211 (92)
Surgical time minutes (IQR)	75 (60 to 100)	76 (62 to 97)
Length of hospital stay days (IQR)	4 (3-4)	4 (3-4)
Drain system used N (%)	87 (38)	79 (34)
Drain production mL (IQR)	477 (312 to 730)	550 (325 to 760)
RBC transfusions N (%)	11 (4.7)	8 (3.4)
Cemented implant N (%)	200 (85)	197 (85)

N, number; SD, standard deviation; IQR, interquartile range; ASA, American Society of Anesthesiologists score; OA, osteoarthritis; RBC, Red Blood Cells.

Patient Characteristics

Table 6.1 shows pre-and perioperative characteristics of randomized patients. The only difference at baseline was a higher incidence of diabetes in the control arm.

Primary outcome

The results of the intention-to-treat (ITT)-analysis mean change in postoperative knee extension (cExt) for patients randomized for standard care and CS after 2 weeks are shown in table 6.2. The overall mean cExt at short term follow-up was comparable between CS (crude model: CS 2.0^{o} (95%CI 1.6^{o} to 2.5^{o}) and standard care 1.8^{o} (95% CI 1.4^{o} to 2.3^{o}); mean difference of 0.2^{o} (95%CI -0.5 to 0.9). Both arms were comparable after adjusting for diabetes (model 1). Also there was no interaction between drain usage and CS (model 2).

Table 6.2: Primary outcome, cExt, two weeks after TKR

		Mean cExt (95%-CI)
Model 1		
(adjusted for DM)	Standard care	1.2 (0.5 to 1.8)
	CS fibrin	1.0 (0.3 to 1.6)
Model 2		
(adjusted for drain)		
Drain +	Standard care	0.9 (0.1 to 1.7)
	CS fibrin	1.7 (0.7 to 2.6)
Drain -	Standard care	1.3 (0.6 to 2.1)
	CS fibrin	0.6 (-0.2 to 1.3)

cExt: mean change in extension, TKR: total knee replacement, 95%-CI: 95% confidence interval, DM: diabetes mellitus, CS: CryoSeal

Secondary outcomes

Both study arms showed equal improvement in cExt at 6 weeks compared to 2 weeks (Appendix table A). There was no difference in change in knee flexion in CS patients compared to standard care. Also there was no difference in length of hospital stay between both groups (median 4 days, IQR 3-4). The Knee Society

scores significantly improved after surgery, and comparing these scores between the groups did not yield a difference (Appendix Table B). The EQ5D VAS was also similar for both treatment groups. All subscales of the KOOS improved after the surgery, there were no differences between both groups (Appendix Figure A)

Complications

Postoperative (serious) adverse events were scored up to one year postoperatively. Table 6.3 shows the complications per treatment arm. Complication rates were low and similar for the two intervention arms.

Table 6.3: Complications

	Standard care	CS fibrin
Wound infection	5 (2.1)	8 (3.4)
Deep infection	1 (0.4)	3 (1.3)
Manipulation knee (OR)	3 (1.3)	0 (0)
Manipulation knee (ward)	3 (1.3)	1 (0.4)
Knee hematoma	1 (0.4)	4 (1.7)
Pneumonia	1 (0.4)	2 (0.9)
Urinary tract infection	4 (1.7)	3 (1.3)
Admission ICU	1 (0.4)	2 (0.9)
Cardial events	10 (4.2)	6 (2.6)
Respiratory events	4 (1.7)	1 (0.4)
Neurologic events	0 (0)	3 (1.3)

Complications are reported as number (between brackets is percentage of total of treatment group)

Discussion

Topical application of a fibrin sealant (CS) did not improve postoperative knee extension at short-term (2 weeks) follow-up after TKR compared to standard care. For this study a difference in extension angle of 10^{o} improvement or more was defined as clinically relevant.[18] However, this pre-defined clinical relevant knee extension appeared not feasible as in our cohort the median preoperative extension

deficit was only 5° (IQR 0° to 10°). Nonetheless the study results also accentuate that despite extensive surgery to a knee (TKR) which creates large bleeding surfaces, the intra-articular blood loss does not seem to interfere with short-term range of motion.

Two meta-analyses studied the effect of fibrin sealant in TKR surgery, both showing a reduction of postoperative blood loss in the fibrin sealant group with a subsequent decrease in postoperative drainage and red blood cell transfusion rates.[2,14] Both found no difference in complication rate between fibrin sealant and control groups. In contrast to our study Wang et al. showed in meta-analysis a significantly improved overall mean range of motion (i.e. flexion to extension) of 16° in patients (N=144) treated with a fibrin sealant compared to those who were not treated with fibrin.[14] However this pooled mean was based on a small number of patients from only 2 studies with significant heterogeneity.

Preventing blood loss perioperatively may include numerous strategies. Intraoperative strategies could include administration of pharmacological agents, i.e. tranexamic acid application, but also topical hemostats such as fibrin sealants.[3,6]

Since generic measures for patient blood management have reduced blood transfusion considerably, focus within blood management has also shifted towards improvement of quality of life and functionality of the patient.[4] Therefore we addressed the surgical bleeding area, since this has impact on early ambulation as well as knee mobility of the surgically treated joint.

An analysis of functional outcome as primary outcome (i.e. knee extension) has not been investigated in the context of patient blood management. Knee extension deficit was used as a primary outcome since ambulating with a flexed knee is more strenuous for the patient with subsequent more energy consumption in the postoperative period. A recent small study (N=48 knees) described the effect of fibrin sealant on blood loss and, for the first time in the literature, on early functional recovery defined by knee swelling, pain, range of motion and strength of knee extension.[12] Twenty-four patients receiving bilateral simultaneous TKR were analyzed with neither any benefit of fibrin sealant in this small patient sample. Another recent study evaluated the effect of topical application of fibrinogen in TKR in 200 patients, showing no difference in terms of blood loss or transfusion frequency.[19]

Small studies have been performed assessing the optimal dosage of fibrin sealant in TKR; 2 mL is considered too little while 5 mL was considered enough compared to 10 mL in a TKR study.[20,21]

We studied a large sample of TKR patients in a prospective randomized controlled trial, with the passive extension deficit of the knee as functional endpoint. This is the first RCT with sufficient power to measure a putative effect of fibrin sealant on functional recovery of the knee. We advocate, since patient blood management is well implemented in current clinical practice in the Netherlands, that knee extension is a clinically more relevant outcome measure than transfusion rates and hemoglobin loss. Transfusion rates in the Netherlands were already low, being 11% in a total of 2.500 TKR and total hip replacement patients study on patient blood management in 2010.[4,22] These have dropped even further to 4% in the current TKR study.

A limitation of our study is that we used standard care as control and also standard care with respect to the center's preference to the use of a postoperative drain. It was considered that interference of the clinical practice during the study period (use or non-use of drain system) would cause a larger bias than just accept center wide use or no use of a drain. The study protocol allowed several factors to the preference per center (i.e. not individual preference). Another limitation is that measurements of knee angle were performed using goniometry, which is considered to be imprecise. However, due to the large number of patients included, the randomized design and blinded analysis of the study data, even the small mean change in postoperative extension in outcomes could very well be clinically interpretable even more since inter-observer variability of range of motion measurements using a goniometer show good reliability in literature.[23]

Conclusion

This study demonstrated no beneficial effects or side effects of CS fibrin sealant on the functional postoperative recovery after total knee replacement surgery. There was no difference in change of knee extension after TKR between patient treated with topical fibrin sealant or with standard care. There was also no difference between these groups in change of other postoperative outcomes. These results discourage the clinical use of a fibrin sealant after TKR.

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Appendix Table A: Mean change in knee extension compared to the preoperative extension after 2 and 6 weeks in both drain and non-drain users

Model		Mean change extension angle (95% CI)		
		Overall (up to 6 weeks)	at 2 weeks	at 6 weeks
Crude model	Standard Care	2.0 (1.6 to 2.5)		
	CS	1.8 (1.4 to 2.3)		
Model 1	Standard Care	1.7 (1.2 to 2.3)	1.2 (0.5 to 1.8)	2.3 (1.7 to 2.8)
(adjusted for diabetes)	CS	1.5 (0.9 to 2.1)	1.0 (0.3 to 1.6)	2.1 (1.4 to 2.6)
Model 2				
(usage of drain)				
Drain +	Standard Care	1.5 (0.7 to 2.3)	0.9 (0.1 to 1.7)	2.0 (1.2 to 2.8)
	CS	2.2 (1.3 to 3.1)	1.7 (0.7 to 2.6)	2.8 (1.9 to 3.6)
Drain -	Standard Care	1.9 (1.2 to 2.6)	1.3 (0.6 to 2.1)	2.4 (1.7 to 3.1)
	CS	1.1 (0.5 to 1.8)	0.6 (-0.2 to 1.3)	1.7 (1.0 to 2.4)

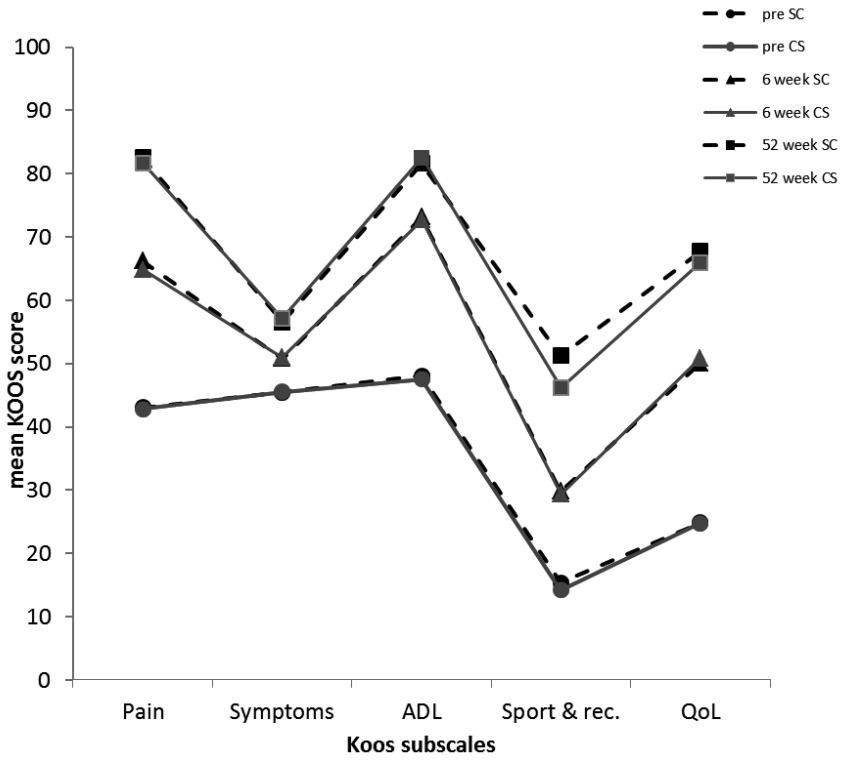
Data shown as mean cExt. angle (95%CI). Overall (up to 6 wk) and 2 and 6 week change in knee extension angle are shown as crude, adjusted (Model 1) and interaction between the drain and randomized groups (Model 2).

Appendix Table B: Knee Society Scores: Knee and Functional score

Knee Society Score	Pre		6 weeks		52 weeks	
	Standard	CS	Standard	CS	Standard	CS
Knee Score	51 (17)	51 (17)	80 (17)	78 (17)	92 (10)	90 (14)
Functional Score	47 (21)	46 (19)	59 (23)	56 (22)	77 (23)	76 (25)

Data shown as mean (standard deviation). CS, CryoSeal

Appendix Figure A: KOOS subscales preoperative and throughout follow-up



SC= Standard Care; CS= CryoSeal; ADL = activity and daily life; QoL = quality of life

Appendix <u>Transfusion protocol</u>

Patients younger than 60 years

Within 4 hours after surgery	More than 4 hours after surgery
Hb ≥ 4.0 mmol / l = 0 packed cell	Hb ≥ 4.0 mmol / l = 0 packed cell
3.0 - < 4.0 = 1 packed cell	3.5 - < 4.0 = 1 packed cell
< 3.0 = 2 packed cells	< 3.5 = 2 packed cells

Patients older than 60 years

Within 4 hours after surgery	More than 4 hours after surgery
Hb ≥ 4.5 mmol / l = 0 packed cell	Hb ≥ 5.0 mmol / l = 0 packed cell
4.0 - < 4.5 = 1 packed cell	4.5 - < 5.0 = 1 packed cell
< 4.0 = 2 packed cells	< 4.5 = 2 packed cells

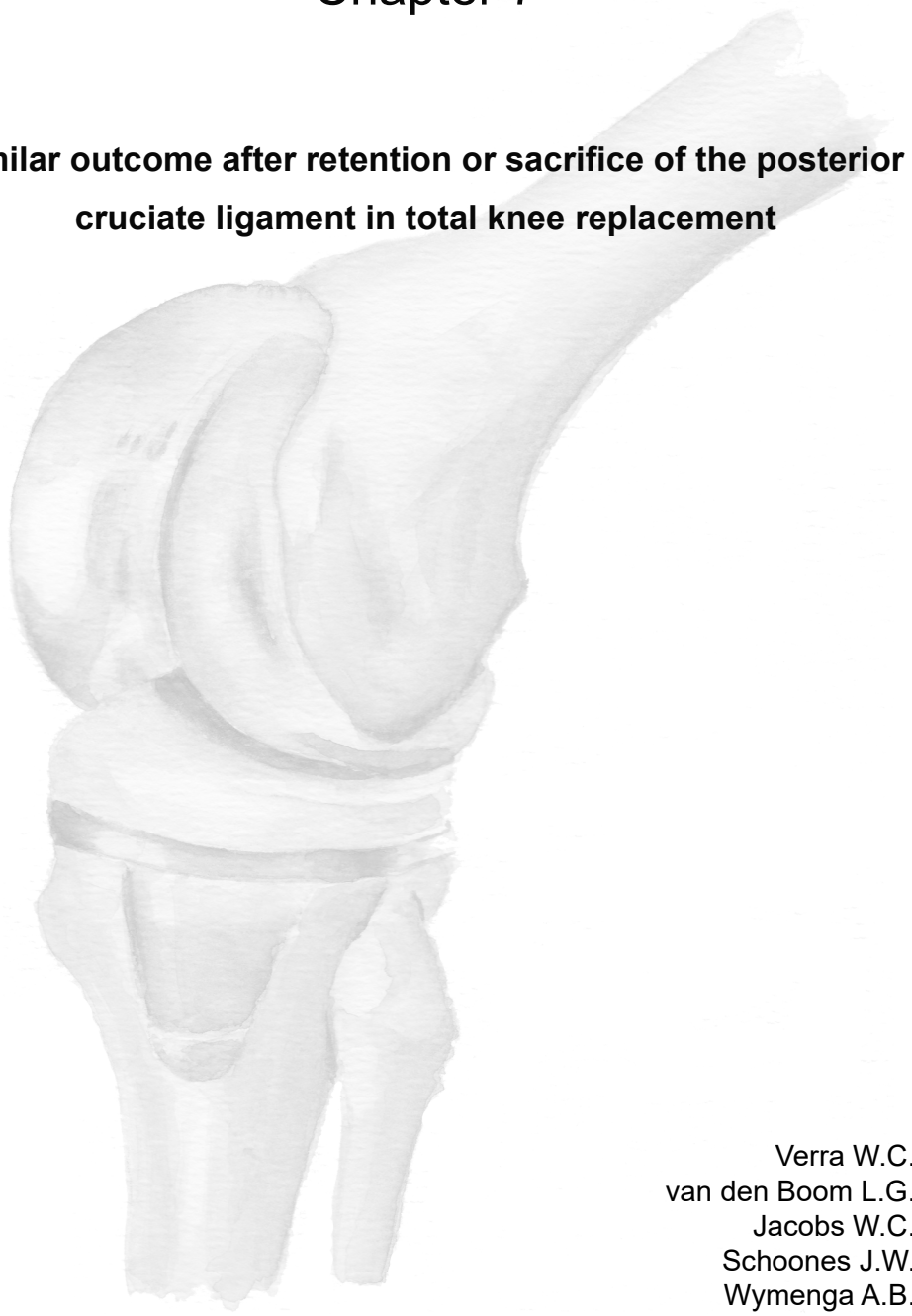
Patients with increased risk (because of co-morbidity)

Within 4 hours after surgery	More than 4 hours after surgery
Hb ≥ 5.5 mmol / l = 0 packed cell	Hb ≥ 6.0 mmol / l = 0 packed cell
5.0 - < 5.5 = 1 packed cell	5.5 - < 6.0 = 1 packed cell
4.5 - < 5.0 = 2 packed cells	5.0 - < 5.5 = 2 packed cells
< 4.5 = 3 packed cells	< 5.0 = 3 packed cells

In all cases these are transfusion guidelines, of which the clinical presentation of the patient is of greater importance to which transfusion policy is followed.

Chapter 7

Similar outcome after retention or sacrifice of the posterior cruciate ligament in total knee replacement



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Abstract

Background. To retain or to sacrifice the posterior cruciate ligament (PCL) in total knee replacement (TKR) remains a matter of discussion. This systematic review aims to find differences in functional and clinical outcome between PCL retention and sacrifice.

Methods. A systematic review and meta-analysis was conducted including all RCT's and quasi RCT's comparing PCL retention with PCL sacrifice in TKR with a minimum of 1 year follow-up. Primary outcome was range of motion. Secondary outcomes were knee pain and, preferably validated, clinical scoring systems (PROM's). Quality of evidence was graded using the GRADE-approach. All outcomes available for data-pooling were used for meta-analysis.

Results. Twenty studies (1.877 patients, 2.347 knees) were included. In meta-analysis the postoperative flexion angle had a mean difference of 2.1 degrees (95%-CI 0.23, 3.98 p=0.03) and the KSS functional score was 2.4 points higher (95%-CI 0.41; 4.30 p=0.02) in favor of PCL sacrifice. Analysis showed no further statistical difference with respect to other measured clinical outcomes like, WOMAC, KSS pain, clinical and overall score, HSS score, SF-12, radiolucencies, femoro-tibial angle, and tibial slope. The quality of the studies was highly variable with moderate to high risk of bias.

Interpretation. There are no clinically relevant differences between PCL retention and PCL sacrifice in TKR in terms of functional and clinical outcomes. Quality of the studies ranged from moderate to low. Based on the current evidence no recommendation can be made whether to retain-or to sacrifice the PCL.

Introduction

The debate whether to retain or to sacrifice the posterior cruciate ligament (PCL) during TKR surgery is ongoing. Arguments for PCL retention are maintenance of the natural movements of the knee while maintaining stability from extension to flexion.[1,2] Furthermore, the PCL is supposed to have different types of mechanoreceptors detecting joint position (proprioception) and joint motion (kinesthesia), thus the PCL might yield a better "sense" of the postoperative knee.[3,4] Retention of the PCL leads to the need of adequate balancing of the ligament. Inadequate balancing of the PCL (i.e. when the PCL is either too tight or too loose after placement of the TKR) leads to a deficient knee with pain, deteriorated range of motion and instability.[5,6] On the other hand, sacrificing the PCL could be helpful in balancing knees with deformities or contractures. Another advantage of sacrificing the PCL is preventing paradoxal femoral rollback as demonstrated by PCL retaining implants.[7] Femoro-tibial movement will then be dictated by the degree of congruency between the femur and the tibial insert.[8] Sacrificing the PCL leads to an increase in the flexion gap and to a lesser extent an increase in the extension gap.[2,9] A Cochrane systematic review in 2005 could not indicate what treatment option is best regarding functional, clinical and radiological outcome parameters.[10] An update of this review was published (in Cochrane) in 2013 still showing no relevant differences between both groups.[11]

Since the aforementioned literature search, several new reports of randomized controlled trials (RCT's) have been published that compare PCL retention with PCL sacrifice, necessitating an update of the current evidence. We aimed to find differences in functional, clinical and radiological outcome between PCL retaining and PCL sacrificing TKR within the current literature.

Methods

Literature search and study selection

We used the same study protocol as developed for our Cochrane systematic review and meta-analysis.[10,11] We conducted a sensitive search in order to retrieve all available literature. In consultation with an experienced librarian (JS) of the medical library of the Leiden University Medical Centre we searched the following databases:

Medline (via PubMed), the Cochrane Central Register of Controlled Trials, Embase, Web of Science, CINAHL, Academic Search Premier, Current Contents Connect, and Science Direct. All databases were searched up to May 19th 2014 using an adapted syntax for every single database (Appendix table A). No restrictions or limits were formulated. A final check that no relevant articles were missed was carried out by screening the references from the articles and by performing citation tracking on the articles that were included.

Articles were selected in two steps. In the first step only title and abstract were available. In the second step, articles which passed the first step were retrieved full text and again evaluated against the in-and exclusion criteria. These criteria were:

- The intervention evaluated in the trials had to be primary TKR comparing PCL retention with sacrifice.
- The indication for TKR had to be osteoarthritis.
- Minimal follow-up had to be twelve months.
- Studies had to be RCT's or quasi RCT's. Quasi RCT's are studies using for example date of birth, patient identification numbers or alternating sequences for randomization.

Two reviewers (WV, LB) independently selected the trials to be included in the review. Disagreements were resolved by consensus. When no consensus could be reached, a third reviewer (WJ) was available for the decisive vote.

Data collection

A pre-developed and tested data extraction form was used to extract data from the included studies. Items collected were study design features, population data, statistical analysis techniques, intervention characteristics and all reported outcome parameters, including results. The primary outcome was range of motion (ROM), including flexion and extension angle separately. Secondary outcomes were knee pain (Visual Analogue Scale, Knee Society clinical pain sub-score), validated clinical scoring instruments (such as Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Osteoarthritis Outcome Scale (KOOS), Oxford knee score), other clinical questionnaire-scores (such as the Knee Society Score

(KSS), Hospital for Special Surgery score (HSS), etc.), radiological implant migration (preferably using radiostereometric analysis (RSA)), complication rate, and other radiological outcomes (such as rollback, radiolucencies). All data were entered into Review Manager 5.2 (The Cochrane Collaboration, 2012).

The risk of bias (e.g. selection bias, performance bias, detection bias, attrition bias) was assessed for every study. The risk of selection bias was judged by assessing how the randomization sequence was generated and by assessing how the treatment allocation was concealed. Risk of performance-and detection bias was judged by evaluating the blinding methods of participants, personnel and observers, as described in the studies. Risk of attrition bias was assessed by judging the completeness of the data, including the follow-up rate. The possible judgements that could be made were low risk of bias, high risk of bias and unclear risk of bias.

The quality of the evidence was assessed using the GRADE approach.[12] In this method for grading quality, RCT's are considered as high quality evidence; however this can be downgraded to moderate, low, or very low quality for several reasons. These reasons are study limitations (e.g. high risk of bias), inconsistent results, indirectness of evidence, imprecision or publication bias. The Cochrane collaboration recommends using this approach to grade the quality of studies in systematic reviews.[13]

Analysis

Statistical analyses were conducted using Review Manager 5.2. Continuous data were entered as means and standard deviations, dichotomous outcomes as number of events. Standard deviations were used when available. If not provided, standard deviations were imputed from comparable studies or from original scores (i.e. confidence intervals). In the meta-analysis, if the studies (patients, interventions, outcomes) were regarded to be clinically homogeneous, heterogeneity was first assessed by visual inspection of the forest plots. Furthermore it was investigated with the I^2-statistic and, if significant ($p<0.05$ using the Q statistic), the source of heterogeneity was investigated by doing a sensitivity analysis and considering additional clinical reasons for potential clinical heterogeneity. In the absence of significant heterogeneity, and given sufficient included trials, results were combined

Table 7.1: Characteristics of the studies

Authors	Sample size			TKR type		Mean age		Female (%)		Outcome	Follow-up
	Patients	*Knees*	*OA (%)*	*CR*	*CS*	*CR*	*CS*	*CR*	*CS*		
Aglietti 2005	197	210	100	103	107	71	69.5	86	81	ROM, VAS pain, KSS and radiographic evaluation system, mechanical axis, radiolucencies	Up to 4y
Catani 2004	40	40	100	20	20	70 +/-6.0	71 +/-7.0	65	75	ROM, RSA, KSS, HSS	2y
Chaudhary 2008	100	100		51	49	69.2 +/-9.1	70.2 +/-8.4	53	45	ROM, RAND-36, WOMAC	2y
Clark 2001	128	128	97	59	69	71.8 +/-12.2	71.2 +/-13.6	n/a	n/a	ROM, KSS, SF-12, WOMAC	Up to 3y
de Andrade 2009	85	85	89.4	36	49	66.3 (41-78)		74		KSS (overall)	1.3y
Harato et al. 2008	192	222	100	111	111	68.3	66.0	34	34	KSS, WOMAC, SF-12, radiolucencies, kinematics	5.0-7.3y
Kim 2009	250	500	100	250	250	71.6 +/-6.0		96		ROM, KSS, HSS, WOMAC pain, radiological	2.3y
Maruyama 2004	20	40	100	20	20	74.3 (65-84)		60		ROM, KSS, joint line	Up to 2.6y
Matsumoto 2012	41	41	100	19	22	73.5 +/-1.3	74.4 +/-0.9	100	100	ROM, KSS, laxity	5y
Misra 2012	103	105	92	51	54	66.8	67.2	67	59	ROM, HSS, satisfaction score (1-10), radiological outcomes	4.8y
Roh 2012	86	86	100	42	44	69.8 +/-4.7	71.0 +/-4.9	95	93	ROM, tibiofemoral angle, KSS, HSS, WOMAC	Up to 3.1y

Seon 2011	95	95	100	48	47	68.2 +/-7.0	69.1 +/-6.7	91		ROM, HSS, WOMAC, tibiofemoral angle and kinematics	2y
Shoji 1994	28	56	54	28	28	60.2 (48-85)		71		ROM, HSS	Up to 4.5y
Straw 2003	*167*	*167*		*66*	*101*	*72.6*	72.6 (PS) 74.1 (resection)	*44*	*45*	ROM, KSS, pain score, stability knee	Up to 6.5y
Tanzer 2002	37	40	97	20	20	68.0	66.0	75	80	Flexion angle, KSS	2y
Thomsen 2013	36	72	97	36	36	67.2 (49-84)		58		ROM, knee pain, satisfaction score, ability to perform ADL, SF-36	1y
Wang 2004	185	224	91	128	96	54.5	55.0	80	80	ROM, KSS, tibiofemoral angle, radiolucencies, SF-12 functional score, ligament laxity	Up to 5.5y
Yagishita 2012	29	58	100	29	29	74.3 +/-7.2		86		ROM, KSS, pain score, radiolucencies	5y
Yansheng 2013	38	38	100	19	19	65.9	63.9	68	63	ROM, WOMAC, proprioception	Up to 1.4y
Yoshiya 2005	20	40	100	20	20	73.8 (62-84)		66		ROM, KSS, fluoroscopic motion analysis	Up to 4.4y

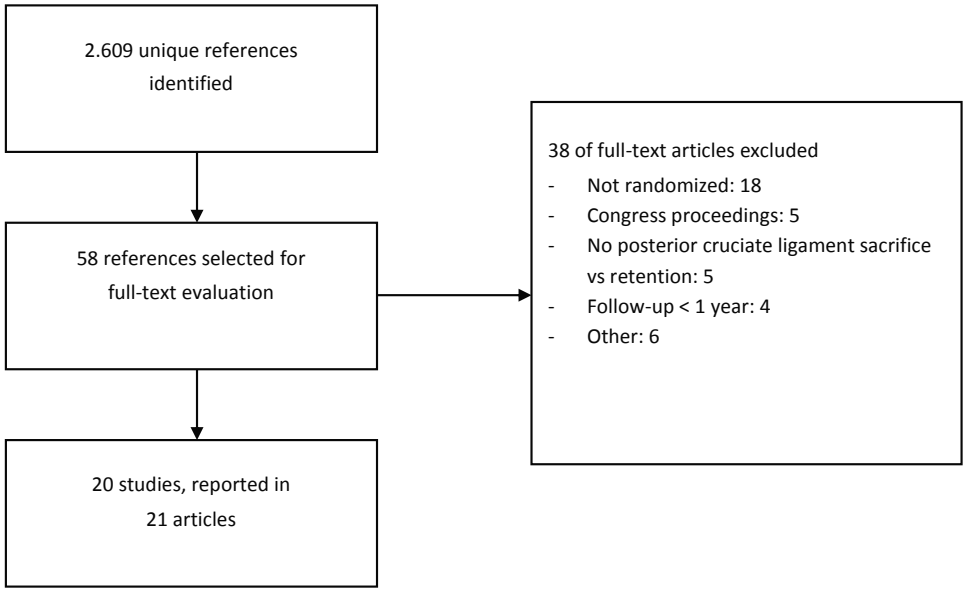
CR: (posterior) cruciate retaining, CS: cruciate sacrificing, ROM: range of motion, VAS: visual analogue scale, RSA: radiostereometric analysis, WOMAC: Western Ontario and McMasters Osteoarthritis Index, SF: short form, KSS: Knee Society Score, HSS: Hospital Special Surgery score, ADL: activities of daily living

using mean differences for continuous data, and relative risk for dichotomous data. A random effects model was used for all analyses.

Results

A total of 2.609 unique references were identified. A total of 58 articles were selected for further evaluation, resulting in twenty-one full-text papers used for analysis (Figure 7.1, PRISMA flowchart).[14-34]

Figure 7.1: Flow-chart study selection



The article of Victor et al. described a population that is also part of the study population of Harato et al.[19,30] Data from both articles were used only once. The article from de Andrade et al. was written in Portuguese and the article from Yansheng et al. was written in Chinese.[18,33] Data were extracted by professional translators. Characteristics of the studies are presented in table 7.1.

Study characteristics

The twenty studies included 1.877 patients and 2.347 knees. In seventeen studies the comparison between the two arms was PCL retention with a cruciate-retaining design versus PCL-sacrifice using a posterior stabilized design.[14-22,25,28,29,30-34] In three studies the same (cruciate-retaining) TKR design was used for both groups.[23,24,26] One study used all three treatments (i.e. cruciate retaining design with ligament retention and with ligament sacrifice and posterior stabilized design.[27]

All studies used a clinical rating scale, either well-validated (e.g. WOMAC) or less validated (e.g. Knee Society Score or Hospital for Special Surgery score) and reported range of motion or flexion measurements. The report of radiostereometric analyses (RSA) was scarce.

Risk of bias and quality of evidence

Twenty-five percent of the included studies were assessed as having 'low risk of bias'. Five studies (25%) described how the randomization sequence was generated.[16,19,23,24,29] The method of concealment of allocation was reported in six studies (30%).[16,19,20,22,25,29] Three studies used quasi-randomization; Aglietti et al. based treatment choice on odd/even patient identification numbers, Maruyama et al., used alternating sequences and Wang et al. used hospital admission moment to base treatment on.[14,21,31] Blinding of the outcome assessor was reported in ten studies.[14,16,18,20,22,23,25,27-29] Seon et al. explicitly reported that no blinding was applied.[25]

Studies reporting on the primary outcome of knee flexion were graded according to the GRADE approach. These studies were assessed, on average, as being of low quality. Quality was downgraded due to the high amount of studies with unclear risk of bias and the presence of studies rated with high risk of bias. Also studies reporting on the secondary outcomes were graded as being of average to low quality.

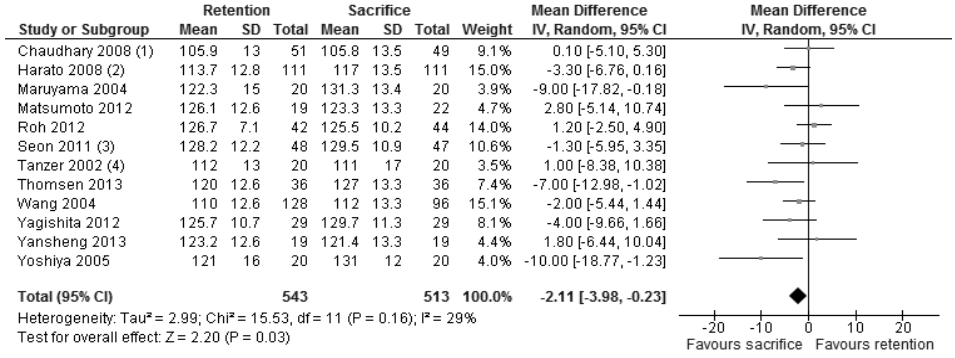
Meta-analysis

There is low quality of evidence from twelve studies (1.056 knees) that PCL sacrifice results in a better flexion angle, with a mean difference of 2.1 degrees (95%-CI 0.2; 4.0, p=0.03). This is a homogeneous result (I^2 =29%, p=0.16). Furthermore, there is

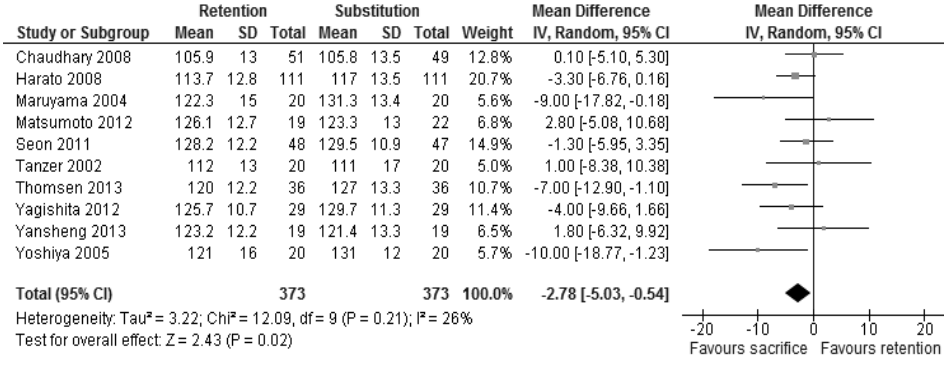
low quality of evidence from nine studies (1.530 knees) that PCL sacrifice results in a higher Knee Society Score functional score of 2.4 points (95%-CI 0.4; 4.3 p=0.02) (Figure 7.2). These are the only homogeneous and statistically significant differences between PCL retention and sacrifice. The WOMAC score was used in five studies; there was a 0.7 points difference between both groups (95%-CI -0.4; 1.8, p=0.19) in favor of PCL sacrifice. See Figure 7.2.

Figure 7.2: Forest plots. **A**. Knee flexion from all PCL sacrificing and retaining TKR's. **B**. Knee flexion from PCL retaining design vs. PS design. **C.** Knee Society Score functional score **D.** WOMAC score

A



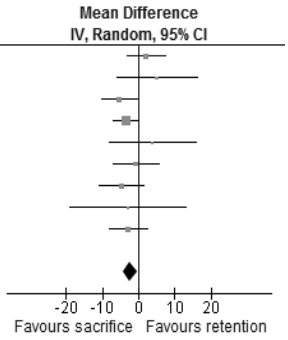
B



C

Study or Subgroup	Retention Mean	SD	Total	Sacrifice Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Aglietti 2005	84	19.7	103	82	19.6	107	13.4%	2.00 [-3.32, 7.32]
Catani 2004	81	17	20	76	19	20	3.0%	5.00 [-6.17, 16.17]
Harato 2008	69.6	19.7	111	74.9	18.7	111	14.8%	-5.30 [-10.35, -0.25]
Kim 2009 (1)	80.2	19.7	250	83.7	19.6	250	31.9%	-3.50 [-6.94, -0.06]
Matsumoto 2012	88.6	19.7	19	84.8	19.6	22	2.6%	3.80 [-8.26, 15.86]
Roh 2012	83.8	16.6	42	84.6	13.6	44	9.2%	-0.80 [-7.23, 5.63]
Straw 2003 (2)	69	19.7	66	73.7	19.6	101	10.2%	-4.70 [-10.80, 1.40]
Tanzer 2002	73	24	20	76	28	20	1.5%	-3.00 [-19.16, 13.16]
Wang 2004	84.2	20.8	128	87	19.6	96	13.4%	-2.80 [-8.13, 2.53]
Total (95% CI)			**759**			**771**	**100.0%**	**-2.36 [-4.30, -0.41]**

Heterogeneity: Tau² = 0.00; Chi² = 7.80, df = 8 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.37 (P = 0.02)

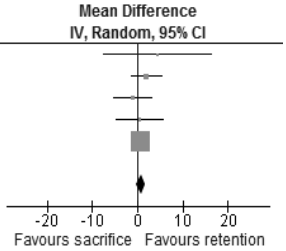


(1) Weighted average sd from reported sd's in studies
(2) Weighted average sd from reported sd's in studies

D

Study or Subgroup	Retention Mean	SD	Total	Sacrifice Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Clark 2001	22.8	35.4	59	18.5	32.9	69	0.8%	4.30 [-7.61, 16.21]
Harato 2008	10.4	13.4	111	8.5	12.3	111	10.0%	1.90 [-1.48, 5.28]
Roh 2012	15.9	8.6	42	17	10.7	44	6.8%	-1.10 [-5.19, 2.99]
Seon 2011	28.4	13.8	48	27.9	12.2	47	4.2%	0.50 [-4.74, 5.74]
Yansheng 2013 (1)	10	1.9	19	9.3	1.9	19	78.2%	0.70 [-0.51, 1.91]
Total (95% CI)			**279**			**290**	**100.0%**	**0.72 [-0.35, 1.79]**

Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 4 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)



No other validated scoring systems were available for meta-analysis. Meta-analyses on the outcomes: KSS pain, KSS clinical score, KSS overall score, HSS score, SF-12 mental, radio-lucent lines, femoro-tibial angle, and tibial slope showed no significant differences and were comparable in terms of statistical homogeneity.

Sub-analyzing outcomes of low quality studies comparing PCL retention with sacrifice using the same, PCL-retaining, TKR design in both groups, showed no significant differences. Comparing knee flexion in PCL retention with the PCL sacrificing PS design ten studies of moderate quality (746 knees) demonstrated a 2.8 degrees mean difference in favor of posterior stabilization (95%-CI 0.54; 5.03 p=0.02).

Complications were reported in twelve studies.[14-16,19-24,29,32,33] Reported complications ranged from anterior knee pain and femoral notching to deep infection. Table 7.2 lists the complications per study.

Table 7.2: Complications reported in the selected studies

Study	PCL retention	PCL sacrifice
Aglietti 2005	None	Septic loosening: 1
Catani 2004	Anterior knee pain: 1 Limited ROM: 1	Anterior knee pain: 2
Chaudhary 2008	Deep infection: 1	Limited ROM: 1
Harato 2008	Stiff knee (< 90^0 flexion): 7 Knee pain: 5 Infection: 1	Stiff knee: 1 Knee pain: 2 Infection: 3
Kim 2009	Femoral notching: 2 Superficial infection: 1	Femoral notching: 3 Superficial infection: 1
Maruyama 2004	None	None
Matsumoto 2012	None	Deep venous thrombosis: 1
Misra 2003	Stiff knee (< 30^0 flexion): 2 Infection: 1 Aseptic loosening: 2 Instability: 3	Stiff knee: 2 Aseptic loosening: 3 Dystrophy: 1 Instability: 3
Roh 2012	PCL laxity: 2 PCL tightness: 1	None
Thomsen 2013	Infection: 1	None
Yagishita 2012	None	Deep venous thrombosis: 1
Yansheng 2013	None	None

PCL = posterior cruciate ligament, ROM = range of motion

Discussion

In this study of the current literature comparing PCL retention with PCL sacrifice in TKR no clinical relevant differences were seen between the two TKR groups. Based on the data of the 1.877 patients (2.347 knees) in twenty RCT's, a statistical significant difference existed of 2.1 degrees of flexion and a difference of 2.4 points in

the Knee Society functional score, both in favor of the PCL sacrifice, which are not clinically relevant. Furthermore, the RCT's were graded having low to moderate quality of evidence. This study was performed according to the Cochrane guidelines a described in the Cochrane Handbook for Systematic Reviews.[13] An extensive report on this topic analyzing seventeen studies, was published by our group in 2013 within the Cochrane library of systematic reviews, the newly added studies did not add new evidence on this topic.[11]

The twenty selected studies are the best available evidence to date to evaluate the difference between PCL retention and PCL sacrifice in TKR. The assessment of the quality of the evidence showed that evidence was low to moderate. Incompleteness of reporting issues such as failure to quote randomization methods and blinding raises the likelihood of bias in the studies resulting in lower quality of evidence grades. However, an improving trend in reporting is seen, as the chronologically more recent publications were generally assessed as having a lower risk of bias.

Despite the fact that RCT's are qualified as providing the least biased evidence they are not suited for all outcomes. Survival analysis of the TKR cannot be easily investigated by RCT's, and in addition classic survival analyses can be biased by competing risks, which should be issued for valid outcome interpretation.[35,36] Observational, long-term follow-up cohort studies are valuable alternatives. Survivorship analyses of, relatively large cohorts, showed a ten-or fifteen year survival of 91% and 90% respectively in the PCL retaining group and 76% and 75% in the PCL sacrificing, posterior stabilized group.[37,38] However, other factors could influence these results such as differences in TKR design or materials between PCL retaining and stabilizing components.[39] A minimum data set for cohort studies has been advocated by the AQUILA consortium.[40] Furthermore, a topic under-discussed in the current RCT's on PCL retention versus sacrifice in TKR is the issue of secondary anterior-posterior instability due to secondary insufficiency of the PCL. Probably because no long term follow-up reports of RCT's are published, this issue has not been described.

This study has several strengths. We used a very sensitive search in eight relevant databases with no language limitations. We also checked references and used

citation tracking. Recently published meta-analyses found and included only between eight and twelve articles instead of twenty-one.[41-43] We excluded several RCT's because of follow-up less than a year.[4,44-46] Since our study was performed according to the Cochrane guidelines, an elaborate and systematic assessment of quality of evidence and risk of bias was performed. In the meta-analysis we analyzed the subgroups of PCL sacrifice using a PCL retaining design and PCL sacrifice using a posterior stabilized design versus PCL retention separately.

A limitation is the lack of high quality evidence in meta-analysis. Furthermore we could not present information on outcome measures like patient experience and satisfaction, gait analysis, micro-motion of the components (RSA) and kinematic outcomes measures such as antero-posterior stability and contact position. The importance of the predictive value of RSA and survival in TKR had been extensively analyzed.[47,48]

Future research in the field of PCL retention or sacrifice in TKR should consist of RCT's that have identical follow-up moments, that include long(er) term follow-up in their protocols and that add outcome measures such as patient experience and satisfaction, gait analysis, antero-posterior stability of the knee, and contact position. To study long-term TKR survival or complications large observational studies are needed focusing on PCL retention versus sacrifice. Furthermore reporting of future studies have to be more complete in describing study methods in order to reduce the likelihood of bias and should also mention important confounders for outcome like preoperative ROM measurements.

Conclusion

Based on this systematic review and meta-analysis of all currently available RCT's there are no clinically relevant differences between retention or sacrifice of the PCL in terms of clinical, functional or radiological outcome.

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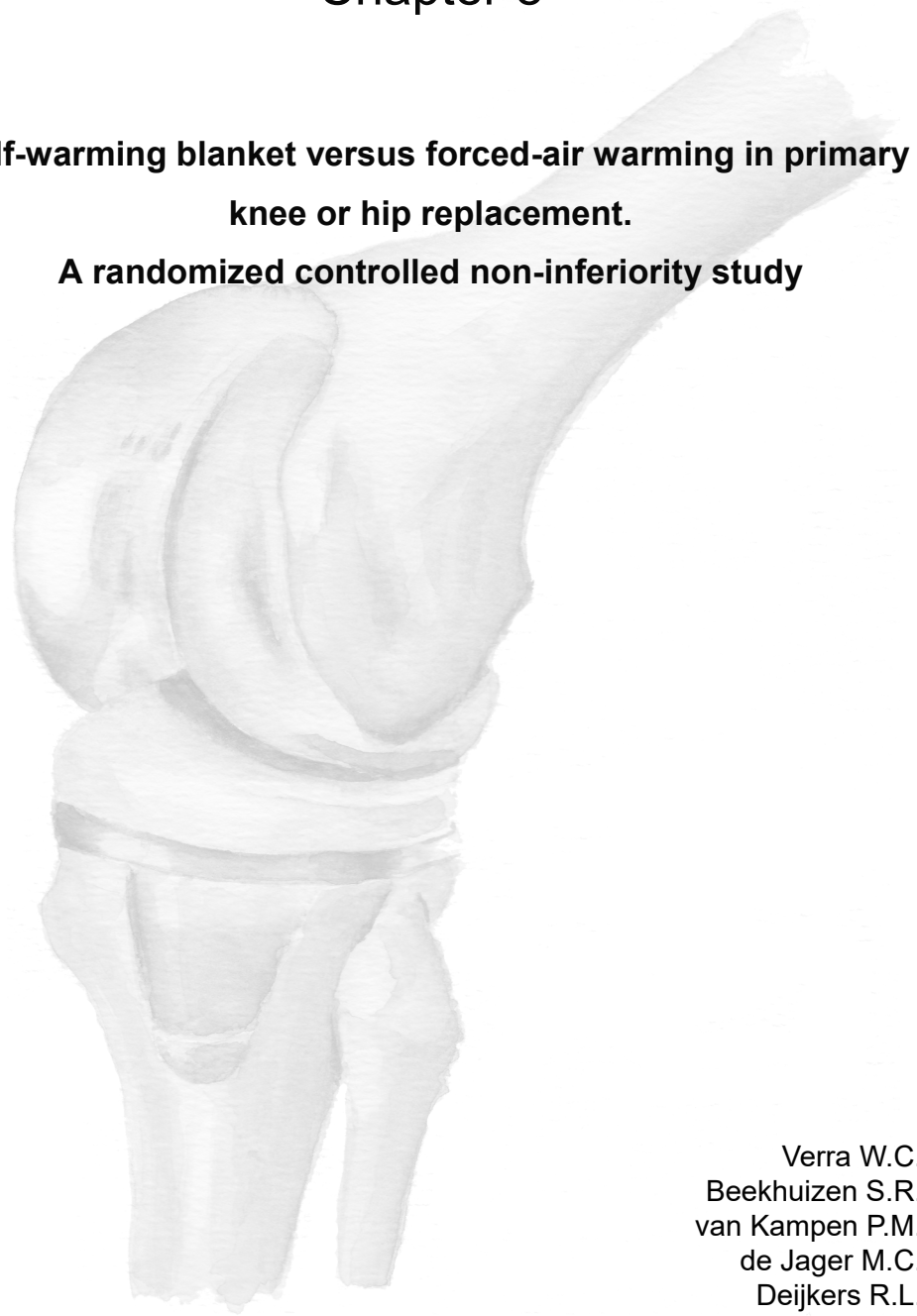
Appendix table A: Syntax used for Medline search

Search strategy syntax adopted for Medline (Pubmed)
("Arthroplasty, Replacement, Knee"[Mesh] OR "Knee Prosthesis"[Mesh] OR "knee replacement arthroplasty"[tw] OR "total knee arthroplasty"[tw] OR "total knee"[tw] OR tka[tw] OR "total knee replacement"[tw] OR "knee prosthesis"[tw] OR "knee implantation"[tw] OR "knee implant"[tw] OR "knee implants"[tw] OR "knee prosthesis"[tw] OR "knee joint replacement"[tw] OR "knee joint arthroplasty"[tw] OR tkr[tw] OR "Knee Replacement Arthroplasties"[tw] OR "Total Knee Replacements"[tw] OR "Knee Prostheses"[tw] OR "Knee endoprosthesis"[tw] OR "Knee endoprostheses"[tw] OR "Knee joint arthroplasty"[tw] OR "Knee joint arthroplasties"[tw] OR "knee joint prosthesis"[tw] OR "knee joint prostheses"[tw] OR "knee prosthetic"[tw] OR "Knee endoprosthetic"[tw] OR "knee joint prosthetic"[tw] OR "Knee joint endoprosthetic"[tw] OR "knee prosthetics"[tw] OR "Knee endoprosthetics"[tw] OR "knee joint prosthetics"[tw] OR "Knee joint endoprosthetics"[tw] OR "Knee replacement"[tw] OR "Knee replacements"[tw] OR "knee arthroplasty"[tw] OR "knee arthroplasties"[tw]) AND ("osteoarthritis"[Mesh] OR "arthritis"[Mesh] OR "posterior cruciate ligament"[Mesh] OR Osteoarthrosis[tw] OR Osteoarthroses[tw] OR Osteoarthritides[tw] OR Osteoarthritis[tw] OR Osteoartrosis[tw] OR Osteoartroses[tw] OR Osteoartritides[tw] OR Osteoartritis[tw] OR Degenerative Arthritis[tw] OR Degenerative Arthritides[tw] OR Degenerative Artritis[tw] OR Degenerative Artritides[tw] OR Arthrosis[tw] OR Arthroses[tw] OR Arthritides[tw] OR Arthritis[tw] OR arthritic[tw] OR RA[tw] OR rheumatoid[tw] OR rheumatic[tw] OR Artrosis[tw] OR Artroses[tw] OR Artritides[tw] OR Artritis[tw] OR Osteoarthrosis Deformans[tw] OR Osteoartrosis Deformans[tw] OR Posterior Cruciate Ligament[tw] OR Posterior Cruciate Ligaments[tw] OR Cruciate[tw] OR PCL[tw]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[Mesh] OR "random allocation"[Mesh] OR "double-blind method"[Mesh] OR "single-blind method"[Mesh] OR "placebos"[Mesh] OR random*[tw] OR ramdom*[tw] OR ramdon*[tw] OR randon*[tw] OR rct[tw] OR rct's[tw] OR rcts[tw] OR ((single[tw] OR double[tw] OR treble[tw] OR triple[tw]) AND (mask*[tw] OR blind*[tw])) OR placebo*[tw] OR random*[tw] OR compare*[ti] OR versus[ti] OR vs[ti])

Chapter 8

Self-warming blanket versus forced-air warming in primary knee or hip replacement. A randomized controlled non-inferiority study



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Abstract

Introduction. After primary total knee/hip replacement (TKR or THR respectively) a prosthetic joint infection could develop. Hypothermia could raise the risk of infection. Heating by forced-air can disrupt laminar airflow at the operation room (OR), potentially raising the risk of infection. We aimed to study non-inferiority of an active self-heating blanket (*BARRIER EasyWarm, BE*) compared to a forced-air blanket (*BairHugger, BH)* in preventing hypothermia.

Methods. A randomized controlled non-inferiority trial (N=86 patients) was performed comparing BE versus BH in elective primary TKR/THR patients. Primary outcome was lowest measured temperature during surgery. Secondary outcomes were patients' core temperature before, during and after surgery, thermal comfort visual analogue score (VAS) and complications during hospitalization.

Results. Lowest measured temperature was 35.9°C(±0.6) in BE and 36.1°C(±0.5) in BH group (p=0.05). No significant correlation was found with duration of surgery or temperature of the OR. No significant difference in core temperature was found before surgery (BE 36.8°C±0.4, BH 36.8°C ±0.5, p=0.49), after induction of anesthesia (BE 36.6°C±0.5, BH 36.7°C ±0.5, p=0.22) nor as a mean during surgery (BE 35.8°C±1.6, BH 36.0°C±1.3, p=0.68). BE patients were 'colder' at the recovery bay, 35.8°C(±0.6) compared to BH patients, 36.1°C(±0.5) (p=0.04). Mean VAS thermal comfort was 53.3(±15.7) in BE and 52.9(±12.3) in BH patients. No difference in complication rate was found.

Conclusion. In this study both warming blankets did not prevent perioperative hypothermia. Although a difference of 0.2^{o}C was found between both groups at the end of TKR/THR surgery, this is most probably not clinical relevant. Complication rate in both groups was the same.

Introduction

Most general anesthetics impair thermoregulatory responses resulting in mild hypothermia.[1] Mild hypothermia, defined as a body temperature between 34.0 and 36.0 degrees Celsius (^{o}C), during primary total knee or hip replacement surgery (TKR or THR respectively) is associated with adverse events.[2] Studies showed that mild hypothermia might result in more postoperative discomfort, prolonged length of hospital stay, higher risk of myocardial infarction and a higher risk of surgical site infection.[3-5] This is why warming of joint replacement patients has become routine practice. Several strategies can be used to warm patients during surgery; two commonly used techniques are active warming by forced-air devices or warming using self-warming blankets.[6,7]

Clean laminar airflow in operating rooms is considered to reduce the risk of infection in TKR or THR surgery.[8] This downward directed airflow has shown to be disrupted by forced-air warming devices when hot air moves upwards against this downward air current.[8,9] Furthermore, this upwards directed air current has could potentially induce prosthetic joint infection (PJI) by creating air currents with a downward directed flow on the operating field.[10]

In an effort to further reduce the risk of developing prosthetic joint infection we hypothesized that using a self-warming blanket would keep the core temperature of the patient at the end of surgery at the same level as the forced-air devices, but with the advantage that no air currents were present or disturbed. So we aimed to study the non-inferiority of the self-warming blanket compared to the, more frequently used, forced-air warming.

Methods

This prospective, randomized controlled, single-center non-inferiority trial was approved by the Medical Ethics Committee (METC ZWH, no.17-049). The trial was registered in the Dutch Trial Registry (NTR6495).

Participants

Inclusion took place between June and August 2017. All consecutive patients who were planned for primary TKR or THR surgery, older than 18 years of age and able to speak and understand the Dutch language were considered eligible and were asked to participate in the study. They were included after signing informed consent. Patients with severe peripheral arterial disease were excluded from the study. All surgeries were performed in one large general training hospital in the Netherlands.

Intervention

Participants were randomized to one of two treatment groups;

1. Forced-air warming using the Bair Hugger™ device (3M Co. St.Paul, MN, USA)
2. Self-warming blanket BARRIER EasyWarm™ (Mölnlycke Health Care AB, Götenborg, Sweden)

At the ward all participants received the self-warming blanket to pre-heat before going to the operating room (which is standard protocol of care at our institution). At the anesthesiology bay patients received the SpotOn™ (3M Co. St.Paul, MN, USA) thermometer.[11] This is a non-invasive device continuously measuring and recording core body temperature.[11] All data were directly saved into the electronic patient-care system. At the end of the surgery tympanic temperature was recorded as well. Patients in both groups were operated on according to the standard protocol for TKR or THR. In case of THR the patient was supine and the direct anterior approach was used in all cases. In case of TKR patients were also supine and the median incision, medial parapatellar approach was used in all cases. Both warming systems were applied on the upper part of the body of the patient in a way that most of the skin was covered by the blanket. Temperature of the operating room during all procedures was recorded continuously. Upon return of the patient at the postoperative recovery bay a visual analogue scale (VAS) regarding temperature comfort experience was recorded. The scale on this VAS ranged from extreme cold (0) to extreme hot (100).

Outcomes

Primary outcome was the lowest temperature measured during surgery.

Secondary outcomes measures were core temperature preoperatively at the holding, after induction of anesthesia, intraoperatively and postoperatively at the recovery ward. Also tympanic temperature at the end of surgery, the total number of measurements <36.0°C, thermal comfort VAS and complications during hospitalization were recorded.

Randomization

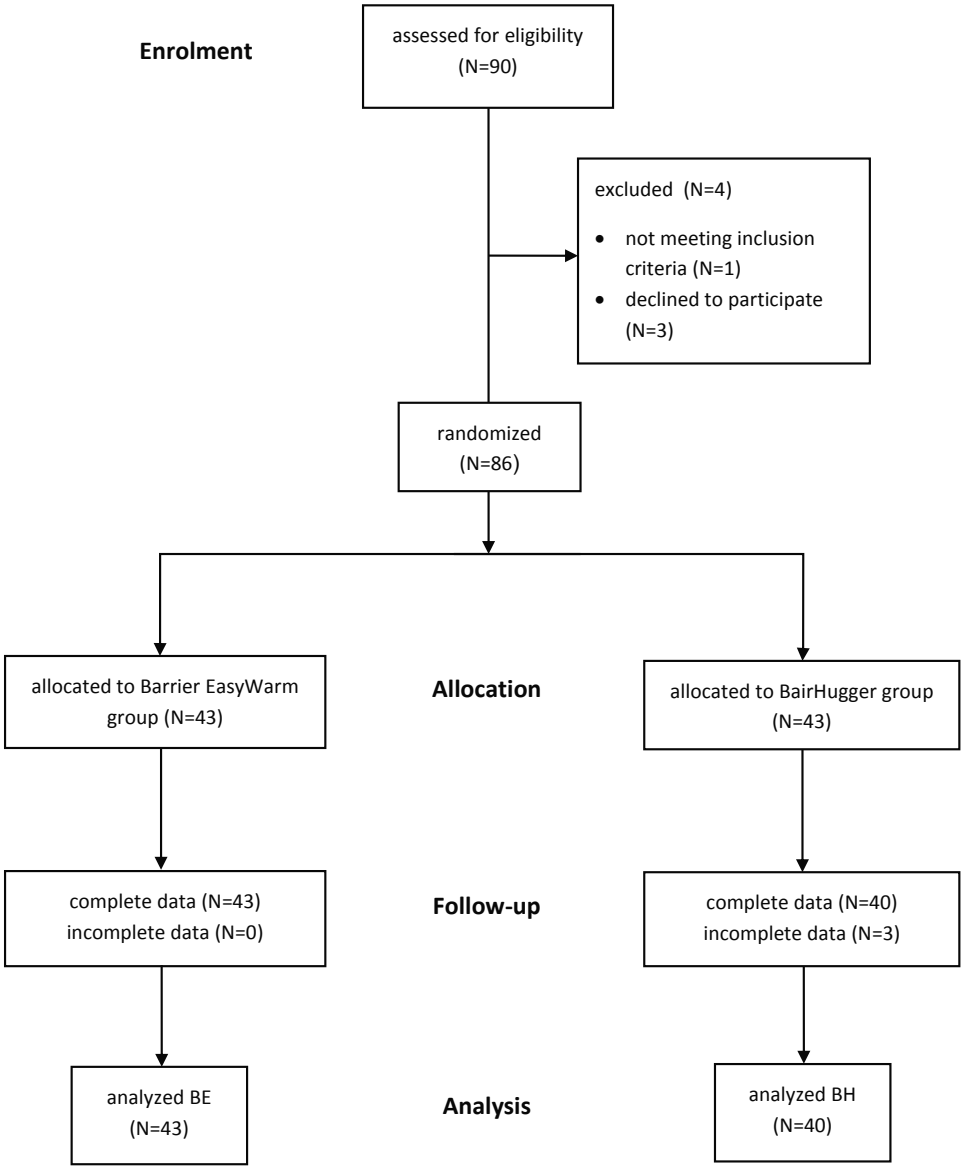
Allocation of treatment sequence was generated by a computer using Castor EDC data management software (Castor EDC, Amsterdam, the Netherlands). Variable block randomization was used with block sizes of 2, 3 or 4. Before entering the OR-center the bed of the patient was tagged with the allocated treatment. Blinding during surgery was not possible due to the obvious differences between the two warming systems. Investigators assessing outcomes were blinded for treatment allocation.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, version 24.0. (Armonk, NY: IBM Corp.) To calculate sample size, a power analysis for equivalence (unpaired test) was performed. Based on Brandt et al. (2010) lower and upper equivalence bounds were ±0.5°C, with a standard deviation of 0.6°C. To achieve a power of 90% to detect equivalence within the equivalence bounds of ±0.5°C, a total sample size of 40 patients per group (80 patients) was estimated, including loss of follow-up. The primary outcome was analyzed by a TOST (two-one sided test), a test of equivalence that is based on the classical t-test used to test the hypothesis of equality between two means, as well as an independent sample t-test.[12]

Demographic variables, secondary outcomes regarding to core temperatures and thermal comfort (VAS) were calculated with independent samples t-test. To determine correlations between the lowest mean preoperative core temperature and OR temperature or duration of surgery a logistic regression analysis was performed. Dichotomous variables were calculated by chi-squared test. Results are expressed in means ± standard deviation or 95% confidence intervals (95%-CI). Differences were considered statistically significant at $p<0.05$.

Figure 8.1: Flowchart of patient inclusion



Results

From 90 consecutive patients 86 were randomized to receive one of the two warming systems (Figure 8.1). All patients were treated according to allocation. Table 8.1 shows baseline characteristics per treatment group. Groups were comparable in terms of demographic and clinical characteristics.

Table 8.1: Baseline characteristics

	BARRIER EasyWarm (N=43)	**Bair Hugger** (N=42)
Age years (SD)	71.2 (10.1)	72.1 (10.9)
Gender (male/female)	15/28	15/27
Body Mass Index kg/m^2 (SD)	27.7 (3.8)	28.3 (4.5)
Diabetes Mellitus (type1/type2/none)	0/3/40	0/3/39
Cardiovascular diseases N (%)	26 (60)	11 (26)
Anesthesia		
General (N)	8	11
Spinal (N)	35	31
Procedure		
Total hip replacement (N)	27	23
Operated side (left/right)	13/14	7/16
Total knee replacement (N)	16	19
Operated side (left/right)	5/11	7/12
Tourniquet (yes/no)	5/11	5/18
Tourniquet time min(SD)	18.8 (17.8)	19.0 (12.4)
Duration of surgery min (SD)	69.9 (18.6)	65.8 (16.0)
Duration of anesthesia min (SD)	89.8 (21.8)	88.8 (18.7)
Blood loss (mL)	199 (253)	164 (228)
OR temperature start °C (SD)	18.6 (0.4)	18.6 (0.4)
OR temperature end °C (SD)	18.6 (0.4)	18.6 (0.4)

SD: Standard deviation

Table 8.2 shows outcome measures. For the primary outcome; the mean lowest measured core temperatures were respectively 35.9(±0.6)°C for the BARRIER EasyWarm (BE) group and 36.1(±0.5)°C for the Bair Hugger (BH) group.

A secondary non-inferiority test (TOST) showed non-inferiority of the BE in relation to the predetermined delta of 0.5°C. In relation to the zero-point (i.e. no difference between BE and BH) the BE is just inferior by 0.2°C.

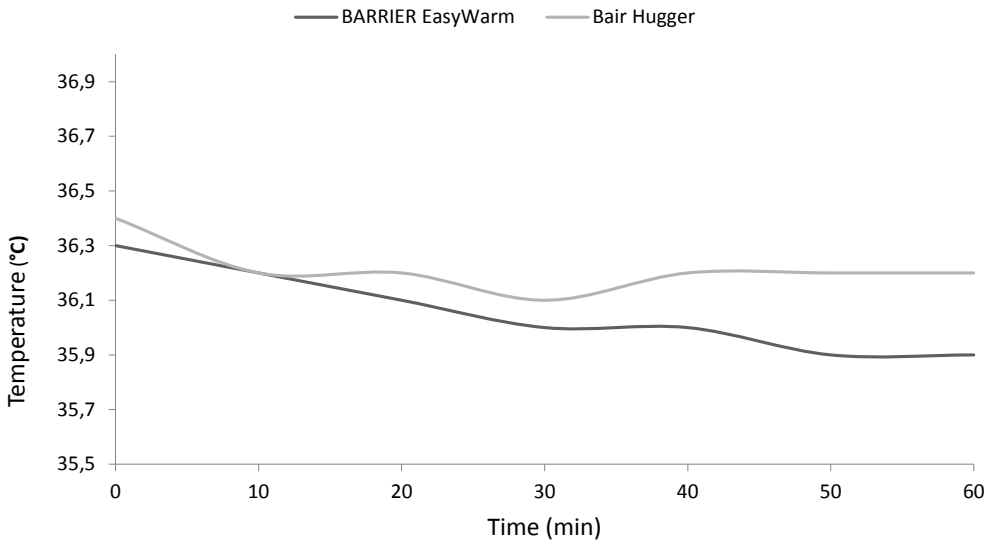
No correlation was shown between the mean lowest measured core temperature during surgery and the duration of surgery (p=0.12), nor with the temperature in the operation room (OR) at the start or end of the operation (p=0.11 and p=0.06 respectively). Mean core temperature before surgery did not differ significantly between the two groups (p=0.49), nor did mean core temperature after induction of anesthesia (p=0.22), at the start of surgery or mean core temperature during surgery (p=0.68). A significant difference (p=0.02) in core temperature was found at the end of surgery, 35.9°C ±0.6 for the BARRIER EasyWarm group and 36.2°C ±0.5 for the Bair Hugger group. After surgery, at the recovery bay, the BE group was 'colder' compared to the BH group, 35.8°C ±0.6 and 36.1°C ±0.5 respectively (p=0.04). Figure 8.2 shows mean core temperature during surgery.

Table 8.2: Outcome measures

	BARRIER EasyWarm (N=43)	**Bair Hugger** N=40)	p-value
Mean core temperature holding °C (SD)	36.8 (0.4)	36.8 (0.5)	0.49
Mean core temperature after induction of anesthesia °C (SD)	36.6 (0.5)	36.7 (0.5)	0.22
Core temperature start °C (SD)	36.3 (0.5)	36.4 (0.5)	0.56
Mean intraoperative core temperature °C (SD)	35.8 (1.6)	36.0 (1.3)	0.68
Mean lowest peroperative core temp °C (SD)	35.9 (0.6)	36.1 (0.5)	0.05
Core temperature end °C (SD)	35.9 (0.6)	36.2 (0.5)	0.02
Mean core temperature recovery °C (SD)	35.8 (0.6)	36.1 (0.5)	0.04
Measurements <36°C N (%)	26 (60)	15 (38)	0.24
Measurements <36°C (n)	2.6 ± 2.5	2.0 ± 2.7	0.32
Complication during hospitalization (yes/no)	2/41	2/41	1.0
Thermal comfort VAS mean (SD)	53.3 (15.7)	52.9 (12.3)	0.90

All temperatures are in ^{0}C. SD = standard deviation, VAS = visual analogue scale, rang from 0 (extreme cold) to 100 (extreme hot).

Figure 8.2: Mean perioperative core temperature



Measurements below 36.0°C were seen in both groups (BE: 26/43 (60%), BH: 15/40 (38%) p=0.24) and the number of measurements below 36.0°C was comparable; 2.6 ±2.5 for the BE group and 2.0 ±2.7 for the BH group (p=0.32). Tympanic temperature measurement showed a mean difference of approximately 0.1°C (range -1 – 1.1) compared to the SpotOn core thermometer. Evaluation of patients' experienced thermal comfort, using a Visual Analogue Scale (VAS), showed no differences between both groups (p=0.90). The mean VAS was 53.3 ±15.7 in the BE group and 52.9 ±12.3 in the BH group. The number of complications was equal between both groups. In each group two complications during hospital stay occurred. In the BE group one THR treatment was complicated by persistent wound leakage postoperatively. CRP (44) and BSE (31) were elevated. This resulted in surgical debridement and microbial cultures were taken two weeks after the primary surgery. Cultures showed growth of enterococcus faecalis and staphylococcus lugdunensis. The patient was treated with intravenous vancomycin and rifampicin and subsequent oral antibiotics (Augmentin/rifampicin) during three months. The second complication

in the BE group had a history of hemorrhagic stroke. Postoperative clinical signs of aphasia, which was a result of a cerebral infarction, was seen. Acetylsalicylic acid and dipyridamole were started for secondary prophylaxes.
In the BH group one THR patient had persistent wound leakage postoperatively. Lab results, showed elevated infection parameters (CRP44, BSE93), which gradually decreased during the postoperative period in several days. The patient was discharged without antibiotics or other intervention. Follow-up showed no infection. The other complication in the BH group had also THR. Several days after surgery, the patient was evaluated for tachypnea and hypotension. High infection parameters (CRP222, BSE56) and fever were present, the patient was diagnosed with a urinary bladder infection. Antibiotics were started. The patient improved clinically and was discharged to a temporary rehabilitation clinic.

Discussion

Both intraoperative patient warming methods failed to prevent hypothermia from occurring during the perioperative phase in our study. Measurements below 36.0^{o}C were seen in 60% of the patients in de BE group as well as in 38% in the BH group. The results show that the self-warming blanket (BE) is less effective compared to the forced air blanket (BH) at the end of surgery and postoperatively at the recovery bay. It is important to consider whether the differences between both systems are clinically relevant because apparently both methods failed to prevent hypothermia.
The complications, that occurred in both groups, might be related to hypothermia. Hypothermia affects the immune system. Decreased cell-mediated immunity and NK-cell activity, suppression of B lymphocytes and defective function of T lymphocytes is seen due to hypothermia.[13,14] There is also an association with suppressed phagocytic activity and reduced bacterial killing. It could be possible that hypothermia contributes to the immune alterations perioperatively and thereby increase the risk of postoperative complications.[13,14]
Comparing both groups, no differences in complications related to the surgery were seen during hospital stay. Hypothermia, which could be a result of temperature redistribution due to induction of anesthesia, fluid loss and reinfusion during surgery,

is difficult to manage with passive methods, making active warming necessary. High incidences of postoperative hypothermia are seen in THR and TKR.[5,15] Because hypothermia could result in several complications it should be managed properly.[2] There are different active warming methods, but for each of them their safety and efficacy should be questioned.

The Bair Hugger system has widely been used in studies on perioperative warming.[16] In contrast to the Bair-Hugger, the BARRIER EasyWarm system is quite new. A randomized study showed that the BE system was superior to passive thermal insulation.[17] However, another randomized study reported that a thermal reflective blanket was not able to prevent hypothermia during surgery.[16] This finding is consistent with our study. Fanelli et al. randomized 56 patients undergoing elective THR to be warmed either by a forced-air system or by a resistive heating blanket.[6] Primary outcome was temperature as measured by tympanic thermometer. No significant differences were found, mild hypothermia was found in both groups at the end of surgery.[6] A Cochrane systematic review and meta-analysis comparing forced-air with active resistive heating was unable to show differences in terms of thermal comfort and also in terms of postoperative blood loss.[16]

This study has several strengths and limitations. In this single-center randomized controlled non-inferiority trial we were able to randomize 86 of 90 consecutive TKR and THR patients without any loss to follow-up. Core temperature from all patients was measured in a uniform way. The reliability of tympanic temperature measurement is questioned with regard to accuracy compared to core temperature.[18] A relevant difference between both recording methods was not found. One factor that might compromise generalizability is that all THR patients were operated in a supine position via the direct anterior approach while the lateral decubitus position is still more frequently used in hip replacement surgery.

Another possible limitation of our study is that a considerable amount of patients dropped below a temperature of 36.0 ^{o}C. The inability to prevent hypothermia in the BE group could be the result of a deviating use of the blanket; the BE was not directly placed on the patient as instructed by the manufacturer; a cotton blanket was placed in between and could have limited the penetration of warmth towards the patient, the

warmth has to penetrate this cotton blanket before reaching patient's skin. Possibly prevention of hypothermia could have be better without placing this cotton blanket in between, as instructed by the manufacturer. The reason to use this interposing cotton blanket was prevention of burn lesions to the skin. To optimize the use of the BH, the operators' manual cites to use a cotton blanket on top of it, in our study the Bair Hugger was used without blanket. Another factor, applicable for both groups, is that the patient could not be fully covered by the BE nor the BH due to the sterile field, with a larger uncovered field during THR compared to TKR.

One of the potential advantages of the BE self-warming blanket is the possibility to use it continuously; before, during and after surgery, there is a constant active warming of the patient possible without interruption. The BH was turned on as soon as the sterile draping procedure was finished, the time during which the patient was moved from the bed to the operating table until finishing the sterile draping procedure of the surgical site no active warming was used for the patient.

An advantage for the surgical team of a self-warming blanket over a forced-air blanket is the comfort of the operating team during surgery. A forced-air device has continuous flow of warm air affecting the surrounding air, if it is close to the operating staff it could feel quite 'hot'. The warmth that a self-warming blanket generates remains close to the patient, possibly less affecting the surrounding air and thereby operating staffs' comfort. Another factor affecting the staff's comfort is the amount of noise in the OR; it goes without saying that a blanket is quiet while forced-air devices contribute to noise pollution in the OR.[16]

Conclusion

In this study both warming blankets did not prevent hypothermia from occurring in both the self-warming blanket group as well as in the forced-air blanket group. A statistical significant difference between both groups was found in core temperature at the end of TKR or THR surgery. Whether the difference of 0.2 ^{o}C is clinically relevant remains to be evaluated, it was nevertheless less than the hypothesized difference of 0.5 ^{o}C for our non-inferiority study. For that matter the self-warming

blanket was non-inferior to the forced-air blanket. But since many patients in both groups showed hypothermia, this should be addressed better.

At the end of surgery and at the recovery room the BE group had significant, although little, lower core temperatures, whether such a small difference is clinically relevant remains to be discussed.

We should ask ourselves the question if it is more important to keep the patient normothermic by using the BH with slightly better results, but with the risk of an infection due to interruption of the laminar flow and thereby affecting the sterile field. Perhaps it would be better to optimize the BE protocol, without interrupting the air flow and thereby reducing the risk of infection. However, hypothermia is also associated with infections. Both aspects, managing normothermia and avoiding interruption of laminar air flow, should be optimized to reduce the risk of infection and therefore further research is needed.

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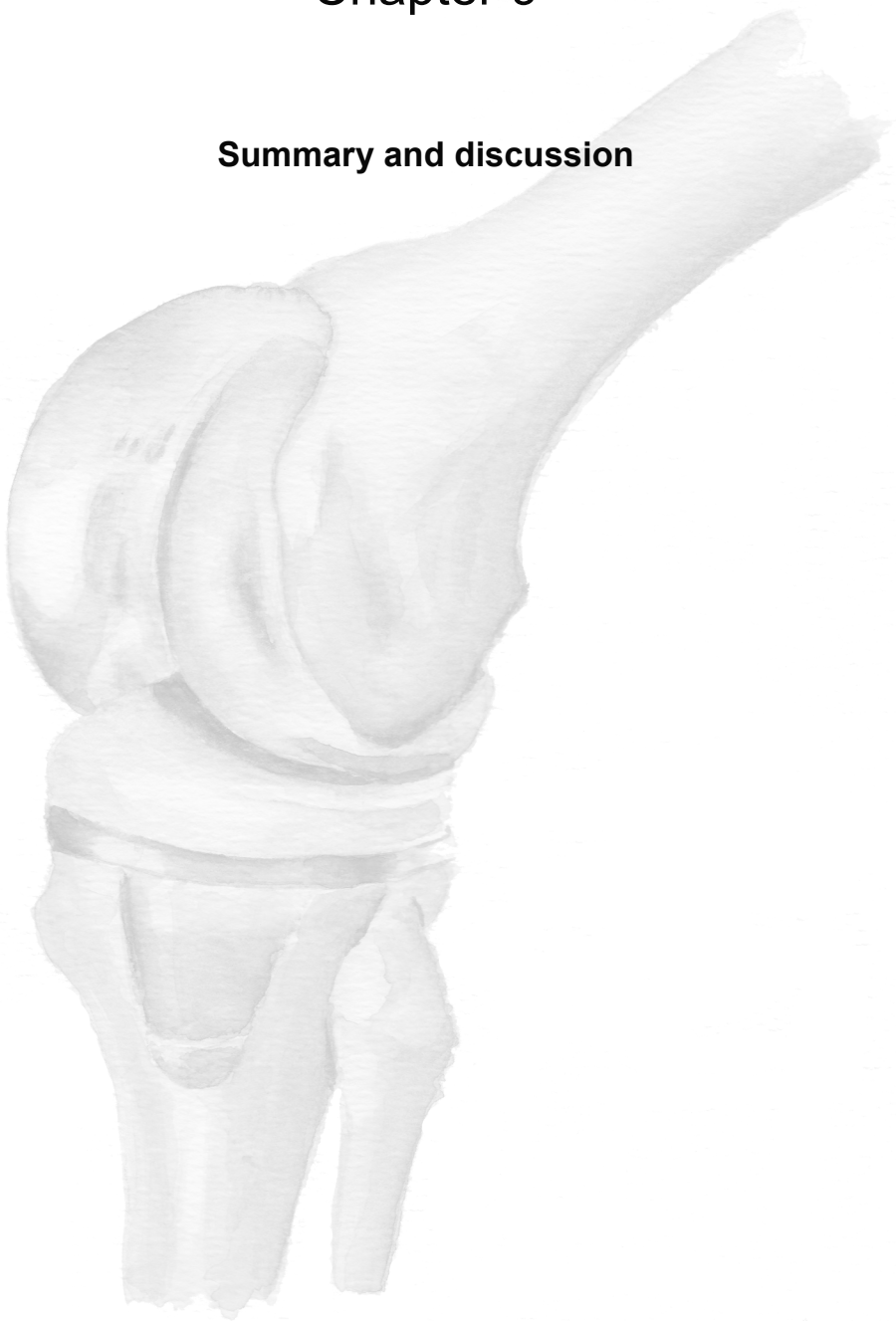
Chapter 9

Summary and discussion



The number of Total Knee Replacement (TKR) surgeries performed in the Netherlands per year is growing, from about 20.000 in 2010 to about 28.000 in 2016, an increase of 40% (www.lroi.nl). TKR is the end-stage treatment for symptomatic osteoarthritis (OA) of the knee. The performance of orthopedic implants is traditionally measured by a mean survival rate after a certain period of time. Since survival rates for TKR are quite good in general (i.e. mean survival after 10 years is about 90% for the endpoint "revision surgery"), other patient related outcome measures, such as patient satisfaction or quality of life, are becoming increasingly important.[1] In **chapter 2** long-term patient satisfaction and quality of life (where long term is considered ten years or more after primary surgery) are reported after total knee or hip replacement (THR). Interestingly, patients are less satisfied after TKR (up to 20-25%) than after THR. The latter might be related to the indication for surgery. Patients with little preoperative radiological osteoarthritis of the knee (Kellgren & Lawrence grade 1 or 2) perform in general less compared to patients with more severe radiological OA of the knee. Other factors, like pain sensitization are important to take in consideration too, when indicating for total joint replacement during the shared decision making process with the patient.

This thesis can be divided into two parts; in the first part we analyzed which patient receives a TKR and which patient does not, what is the timing and what is the outcome at patient level. In the second part we studied how to improve the TKR surgery as a procedure; what can be done (or not) to improve TKR treatment.

Part 1 – on patient selection

The indication, and thus patient selection, to perform TKR is a major driver for outcome and thus for differences in postoperative patient satisfaction. No clear guidelines exist for the indication of TKR, except the presence of "enough pain".[2] In order to get an idea when TKR is recommended in the Netherlands we performed a study asking all Dutch orthopedic surgeons whether they would perform TKR or not in three different cases (**chapter 3**). It seemed that radiological OA grade and old age were important factors to recommend TKR in daily clinical practice. For Dutch orthopedic surgeons, pain level as such (according to literature more important than

radiological OA grade), seemed not that important. In **chapter 4** Dutch orthopedic surgeons recommending TKR or THR are compared to their colleagues from several other countries. Using data from over 1.900 patients from nine different countries it was found that TKR was less frequently recommended by Dutch orthopedic surgeons. Furthermore Dutch patients had the highest preoperative (joint related) quality of life.

In **chapter 5** results from the Leiden 85+ study are reported on functional performance of the oldest old patients (i.e. 85 years and older) who had a TKR or THR in the past. The functional level and health status of the oldest old with total joint replacement was comparable with the oldest old patients without joint replacement surgery at twelve years of follow-up.

Osteoarthritis

The development of OA is a complex process, involving genomics, metabolomics and environmental risk factors invoking molecular changes- and structural changes of cartilage and subchondral bone, with subsequent destruction of the joint.[3] Molecular interactions between cartilage, subchondral bone and synovial membrane play an important role in the pathogenesis of OA.[3] Metalloproteases (MMP's) are believed to play an important role in cartilage degeneration (e.g. MMP-13).[4] Furthermore several pro-inflammatory cytokines (i.e. IL-1β) and cartilage regeneration factors such as tumor growth factor β (TGF- β), insulin-like growth factor (IGF-1) and bone morphogenic proteins (BMPs) are extensively studied for their role in the development of OA.[4,5] Also other cell types, like mast cells, are suggested to play a role in OA.[6] Another factor contributing to the development of knee OA is overweight, via not entirely clear mechanisms. Limb alignment is also a factor, where valgus alignment increases the odds of lateral progression of OA and varus alignment medial progression. The presence of intra-articular damage in the history of the knee, ranging from isolated meniscal tear to anterior cruciate ligament rupture to major intra-articular knee injuries, contributes to the odds of developing knee OA too.[7]

Resurfacing the knee joint with a TKR is the final step in the treatment of OA of the knee. First, conservative (i.e. non-operative) treatment (like stepped care treatment) should be used exhaustively.[8,9]

Disease modifying OA drugs (DMOADs)

Oral diacerein, an IL-1β inhibitor, showed significant improvement of symptoms in patients with knee or hip OA.[10] Also an agent like chondroitin sulphate has proved to have DMOAD potential. Several placebo controlled trials showed more radiographic joint space narrowing in placebo users compared to chondroitin sulphate users.[11,12] Tetracycline analogues, like doxycycline, inhibit some MMPs. A placebo controlled study showed less joint space narrowing in patients who received doxycycline versus placebo.[13] However it seems that the symptomatic benefit of doxycycline is minimal, while the small benefit in terms of reduction of joint space narrowing is of questionable clinical relevance and outweighed by safety issues.[14] Other agents, like (oral) bisphosphonates, calcitonin (i.e. second generation calcitonin peptides), strontium, cathepsin K inhibitors, and sprifermin are promising and are currently under investigation in different phases of trials.[15]

Clinical relevant OA

Patients' main complaint when seeking clinical help for knee OA is pain. Radiographic OA is only weakly associated with pain.[16] This suggests that other features, such as biochemical, cellular or structural changes, but also pain sensitization are important factors in pain perception.[17] Although the link between radiological OA and pain is weak, some authors show an association between pain and structural, subchondral bone changes.[18] Other studies, using contrast enhanced MRI, suggest an association between synovitis and pain.[19-21] The cause of synovitis is not fully understood.[17] A connection with nerve growth factor (NGF) has been proposed in the literature.[22] NGF is identified to mediate in inflammatory joint pain and NGF blocking agents showed pain reduction in patient with knee OA.[22] Research in this direction can add pain reducing agents to the traditional acetaminophen, NSAIDs and opioids currently in use in the treatment of OA.

Total knee replacement; expectations and satisfaction

Patient satisfaction after TKR is important since its goals is to improve quality of life.[23] In Sweden 17% of over 25.000 patients after primary TKR were dissatisfied or uncertain on their outcome after TKR. Comparable results were found by our group in two cohort studies.[24-26] This Swedish study showed also that satisfaction was related to the chronicity of the disease; those who suffered longer (e.g. in rheumatoid arthritis) were more satisfied after TKR than those who suffered from knee OA of more recent onset.[24] Also preoperative radiological OA was associated with postoperative satisfaction.[25,26] The largest risk factor for dissatisfaction are unmet preoperative expectations (Risk Ratio, RR, of 10.8), which is even higher compared to a RR of 1.9 for postoperative complications requiring re-admission to the hospital.[23] Furthermore satisfaction is most strongly associated with improvement of pain scores after TKR.[27] Other studies showed that, despite not all expectations are fulfilled, patients seem to be good to reasonably satisfied after TKR.[28,29]

Recently the ICHOM working group on hip and knee OA defined a 'Standard Set' of outcome measures intended for evaluating the treatment of hip and knee OA hereby facilitating international comparisons of treatment and benchmarking on outcome and patient values across health care systems.[30]

Implications for the future

An important part of research in the field of osteoarthritis the coming years will focus on the prevention of OA. The step by step revelation how OA develops and how pain originates from the joint or acts as a centrally modulated entity will be important. Postponing and possibly preventing TKR surgery by conservative treatment options is only feasible if the patient has good functional results with high quality of life. Therapeutic intervention should focus on a combination of pain relief and functional improvement. With the end-goal in future to stop disease progression. For that matter, selective targeting IL-1β drugs are currently one of the most promising OA treatment strategies but many other disease modifying and pain reducing agents are currently being investigated.

Focus should shift away from fixing radiological OA to treating and counseling patients. As part of the patient informed consent procedure on TKR surgery,

assessment of patients' expectations is important. If a mismatch between expectations of patient and orthopedic surgeon exists, TKR surgery should be postponed and expectations should be managed.

A more uniform approach in the treatment of knee OA will benefit not only research, education and economic analyses in knee OA patients between centers and between countries, but will mainly benefit patient perceived and expected outcome. Tools as the ICHOM Standard Set or the OECD (organization for economic collaboration and development, www.OECD.org) should be used.[30]

Overall, treatment of knee OA should be more holistic, which means taking the patient and not only the "knee" into account. The latter implies to take also lifestyle interventions, patient education, physical exercises, oral medication, intra-articular injections with steroid derivatives to TKR into account as possible treatment options.

Part 2 – on intra-operative issues

TKR is a rather successful treatment which is routinely performed by orthopedic surgeons worldwide. Several topics to improve TKR still remain under discussion. It has been suggested that topical application of a fibrin sealant (a locally applied hemostatic agent) could be beneficial in terms of reducing hemoglobin loss or the frequency of red blood cell transfusions. In **chapter 6** results of a large multi-center randomized controlled trial are reported. With current restrictive transfusion protocols, transfusion rates have diminished and are not as important an outcome as before. However it is suggested that after TKR surgery still 650-700 mL blood loss occurs. This volume of blood in the knee can impair postoperative function. In our study primary outcome was knee extension after TKR, this did not differ when fibrin sealant was applied during surgery. Also, when taking into account the use of vacuum drainage no difference in knee extension (or other functional outcomes) was identified.

An ongoing discussion in TKR is whether or not to sacrifice the posterior cruciate ligament (PCL). **Chapter 7** describes the results from a large systematic review and meta-analysis conducted within the Cochrane framework and published both in a journal and in the Cochrane library for systematic reviews. Because 2.347 knees were included in this analysis the identified mean difference in flexion angle, in favor

of PCL resection, of 2.1 degrees was statistically significant. This difference is clinically not relevant. So it can be concluded that no functional, clinical or radiological differences were found between TKR with or without PCL sacrifice.

After primary TKR or THR a prosthetic joint infection could develop. Hypothermia could raise the risk of infection. Heating the patient by forced-air can disrupt laminar airflow at the operation room (OR), potentially raising the risk of infection. In **chapter 8** we aimed to study the occurrence of hypothermia in patients who received active heating or forced-air heating. In this study both warming blankets did not prevent hypothermia during the surgery. Although a difference of 0.2 ^{o}C was found between both groups at the end of TKR/THR surgery, we consider this difference not clinically relevant. The complication rate in both groups was the same.

Surgical issues to consider

In TKR surgery several issues can be considered, all of them having (strong) advocates and opponents. One of these issues is implant design. Besides the issue of retention or sacrifice the posterior cruciate ligament (as discussed in **Chapter 7** of this thesis) another point of debate is the use of a fixed or mobile bearing for the tibial baseplate. Some authors report superior results of one of these bearings, however systematic reviews report no significant differences on a wide range of outcomes for either one of these bearings.[31-33]

A TKR can be placed either in a measured resection (i.e. bony referenced) or ligament balanced fashion. In both techniques the goal is to match flexion and extension gaps in order to produce a stable and mobile TKR, without resecting too much bone and without altering the joint line to a too great extent.[34,35] In a systematic review and meta-analysis comparing both techniques clinical outcomes were reported to be similar, ligament balanced TKR showed slightly more femoral component external rotation and joint line elevation than measured resected TKRs.[36]

TKR can be placed using computer navigation. During the past twenty years computer navigation has improved (less outliers in alignment or component positioning), became less expensive, faster, but has failed to show improvement in patient reported outcomes in terms of functionality or satisfaction.[37-39] It should be noted that, based on experiences in the past, a phased introduction of TKR and TKR

related techniques is important.[40] Radiostereometric analysis might aid in this process, since it detects within two years whether the implant has good implant-bone fixation, a proxy for late loosening if continuous migration is present.[41] In line with developments in computer assisted TKR, robotic-assisted TKR is developed. Several systems are on the market with names as Robodoc, Navio, iBlock, MAKO and PiGalileo. Results are promising, safety has improved greatly, yet the use of robotics is still expensive and its benefits have to be proven in studies.[42,43]

The development of three-dimensional printing technology has enabled the development of patient-specific cutting blocks. Studies show no improvement in clinical and functional outcomes when patient specific instrumentation is used.[44,45] The cutting block might be of use when extra-articular deformities are present, or when conventional placement is not possible (e.g. presence of osteosynthesis materials or an intramedullary tumor).[46]

The frequency of red blood cell transfusions after TKR has significantly been decreased recent years.[47] This is due to a more evidence based restrictive rationale on patient blood management. The use of tranexamic acid, intravenously, peri-operatively, significantly reduces blood loss. Because of the low price of tranexamic acid this intervention is highly cost-effective.[48,49] Evidence suggest that the either intravenous registration or the topical application of tranexamic acid in TKR surgery yield similar results.[50]

Using a pneumatic tourniquet and its timing of release during TKR surgery remains a topic of debate. A tourniquet is said to reduce blood loss, facilitate optimal cementation and yield better visualization of the surgical field. However, neuromuscular injuries can occur, as well as postoperative pain, delayed wound healing and increased thrombotic events.[51,52] Several systematic reviews on the timing of tourniquet release show reduced incidence of wound complications in early tourniquet release compared to late release, no other evident differences are seen.[52,53]

Peri-operative pain management traditionally consisted of oral medication (acetaminophen, NSAIDs and/or opioids) in combination with spinal and/or epidural anesthetics with adjuncts such as long acting peripheral nerve blocks. These

modalities have multiple side-effects delaying rehabilitation after TKR surgery.[54,55] Local infiltrative analgesia (LIA) during the TKR surgery is proved to be beneficial in both reducing pain and preventing the aforementioned side-effects.[56] Several 'cocktails' are described, all containing ropivacaine and epinephrine. The solution is injected during several moments of the surgery, within the posterior capsule, the anterior capsule and the subcutaneous layer.[55]

About two decades ago, first in the USA (Florida), later on in Denmark, the idea of fast track TKR started to spread across parts of the world.[57] The program consists of patient education, the peroperative use of local infiltrative anesthesia (LIA) instead of postoperative opioids, no drains, standardized physiotherapy and the use of a skilled and dedicated surgical and rehabilitation team. This ultimately can result in daycare surgery for TKR in selected patients.[57-59] A recent study from Denmark showed that 15% of unselected TKR and total hip replacement patients can be discharged at the day of surgery.[60] Although some studies report some a relapse of functional deficit once the patient is home in his or hers own social environment.

Analyzing and evaluating the outcome after TKR and all related issues can be done by clinical studies with respect to functional, clinical and/or radiological outcomes. On the other hand revision rates, infection rates, implant survival can be studied better using data from implant registries.[61,62] Including PROMS in registry data might yield better understanding of (patient) factors that contribute to pain relief, functional improvement and patient satisfaction.[63] There is some experience abroad.[64,65] It is worth mentioning that valuable correlations can be identified using registry data, however confounding should be considered when analyzing these kind of datasets.[66] An international working group published recommendations for choice of PROMS, survey logistics, timing, reporting missing values and analysis of data.[67]

Implications for the future

Some technical issues in TKR surgery could be left to the surgeons' preference; whether to sacrifice the posterior cruciate ligament or not, whether to use a fixed or mobile bearing implant and whether to use a measured resection or ligament balanced technique since the surgical technique itself is individualized not only to the

patient but also for a specific surgeon. Orthopedic surgeons should think about the use of a pneumatic tourniquet (preferably not to use a tourniquet) and if still used the timing of release is important. Tranexamic acid should routinely be used perioperatively as well as local infiltrative analgesia (LIA) during surgery if not contraindicated otherwise.

Patient specific instrumentation could have a place in the future when used for strict indications (e.g. extra-articular deformities, intramedullary tumors), but not for routine use. Robotic assisted TKR might have a place in the future of TKR.

Patients should remain within the hospital as long as appropriate. Outpatient TKR on selected on unselected patients should be further evaluated. Both in terms of safety aspects and potential economic benefits.

PROMs need to be recorded in the Dutch registry LROI in order to understand and interpret registry data, but mainly as a quality control tool to monitor performance of the surgical procedure, indication for surgery and outcome. Preferably these data should be benchmarked with colleagues in order to improve outcome for patients. The Dutch Orthopedic Association (NOV), using national registry data (LROI data), has developed a protocol on how to deal with outlier clinical practices (i.e. 1% highest revision rate practices) since 2017. Since TKR is only one small step in the clinical pathway of OA treatment of the lower extremity, which is indicated by data showing that within one year after TKR/THR surgery, about 20% of patients will have severe clinical symptoms of the contralateral knee or hip or ipsilateral hip and are in need for a total joint replacement.[68] Thus, a more holistic approach towards OA as a disease and not as a single joint problem is necessary. For that matter the orthopedic surgeon should have expertise on etiology and conservative treatment modalities in order to recommend optimal management, which can be both pharmacological as well as surgical or using physiotherapy. Only then shared decision making between patient and orthopedist (i.e. who is both surgeon as well as expert in conservative treatment options) is possible.

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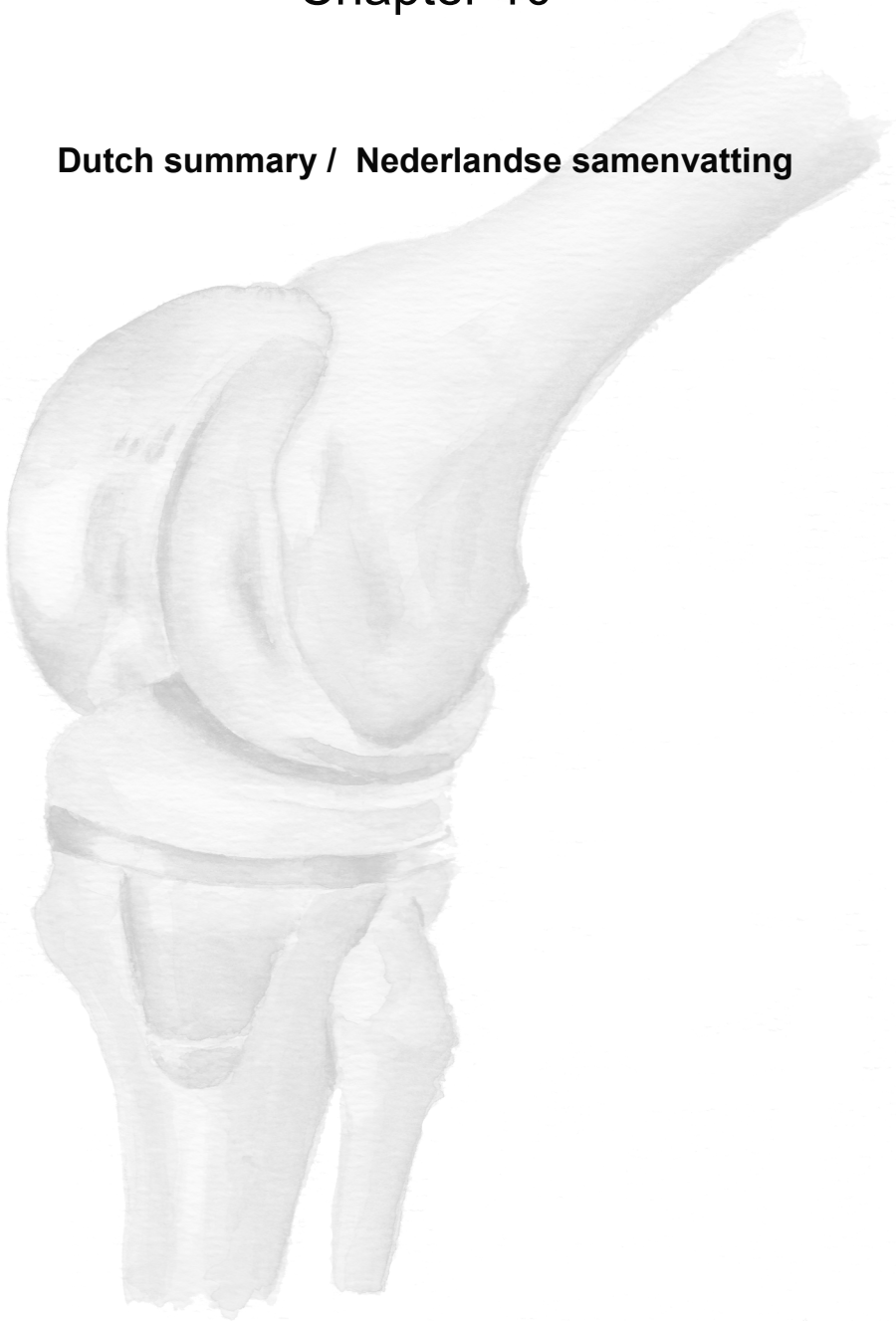
Chapter 10

Dutch summary / Nederlandse samenvatting



Nederlandse samenvatting

Het aantal Totale Knie Protheses (TKP's) dat per jaar wereldwijd geplaatst wordt groeit nog altijd. De TKP wordt gezien als het eindstadium in de behandeling van gonartrose; artrose van de knie. Van oudsher worden prestaties van orthopedische implantaten gemeten in overlevingsstatistieken. Het doel hiervan is om te zien hoe lang het duurt voordat de TKP gereviseerd moet worden. De overleving van TKP's is in het algemeen goed, daarom is er de laatste jaren steeds meer aandacht voor patiënt gerelateerde uitkomsten zoals patiënttevredenheid of kwaliteit van leven na de operatie. In **hoofdstuk 2** wordt een studie beschreven naar de patiënttevredenheid en de kwaliteit van leven lange tijd na een TKP of totale heup prothese (THP) operatie; dat wil zeggen meer dan tien jaar na deze operatie. Hieruit blijkt dat zowel patiënten na TKP als na THP zeer tevreden zijn en hoge kwaliteit van leven scores laten zien. Het lijkt er echter ook op dat de mensen na een heupprothese iets meer tevreden zijn dan na een knieprothese.
De indicatiestelling (het selecteren van de juiste patiënten voor de behandeling) voor het overgaan tot het plaatsen van een TKP is in het algemeen belangrijk, maar zou ook een rol hebben kunnen spelen bij het eerder genoemde verschil in tevredenheid. Op dit moment bestaan er geen harde richtlijnen wanneer een TKP te plaatsen. Om een idee te krijgen wanneer in de praktijk in Nederland een orthopedisch chirurg overgaat tot het plaatsen van een TKP werd een onderzoek gedaan onder alle Nederlandse orthopedisch chirurgen. Zij kregen drie casus beschrijvingen toegestuurd met de vraag of ze een TKP zouden plaatsen of niet. De casus waren helemaal identiek op één onderdeel na en de orthopedisch chirurgen kregen willekeurig één van de twee versies voor zich (**hoofdstuk 3**). Het lijkt erop dat in de praktijk de graad van radiologische artrose en het hebben van oudere leeftijd belangrijke factoren waren om over te gaan tot het aanbevelen van een TKP. De mate van pijn leek minder belangrijk bij het stellen van de indicatie, hoewel uit de literatuur voortkomt dat het hebben van voldoende pijn de belangrijkste indicatie zou moeten zijn. In **hoofdstuk 4** wordt vervolgens de indicatiestelling voor TKP vergeleken tussen Nederlandse orthopedisch chirurgen met die uit verschillende andere landen. Gebruikmakend van gegevens van meer dan 1.900 patiënten uit

negen landen lijkt het erop dat Nederlandse orthopedisch chirurgen het meest terughoudend zijn in het aanbevelen van een TKP. Uit ditzelfde onderzoek blijkt dat Nederlandse patiënten ten tijde van de indicatiestelling de hoogste kwaliteit van leven scores hadden.

In **hoofdstuk 5** worden uitkomsten van de Leiden 85+ studie besproken. Het gaat hier om uitkomsten op het gebied van functionele prestaties van de oudste ouderen, namelijk die van 85 jaar en ouder, met TKP of THP en die prestaties bij oudste ouderen zonder een dergelijke prothese. De oudste ouderen met prothese presteerden functioneel net zo goed als de oudste ouderen zonder prothese. Ook het gezondheidsniveau was vergelijkbaar tussen de twee groepen.

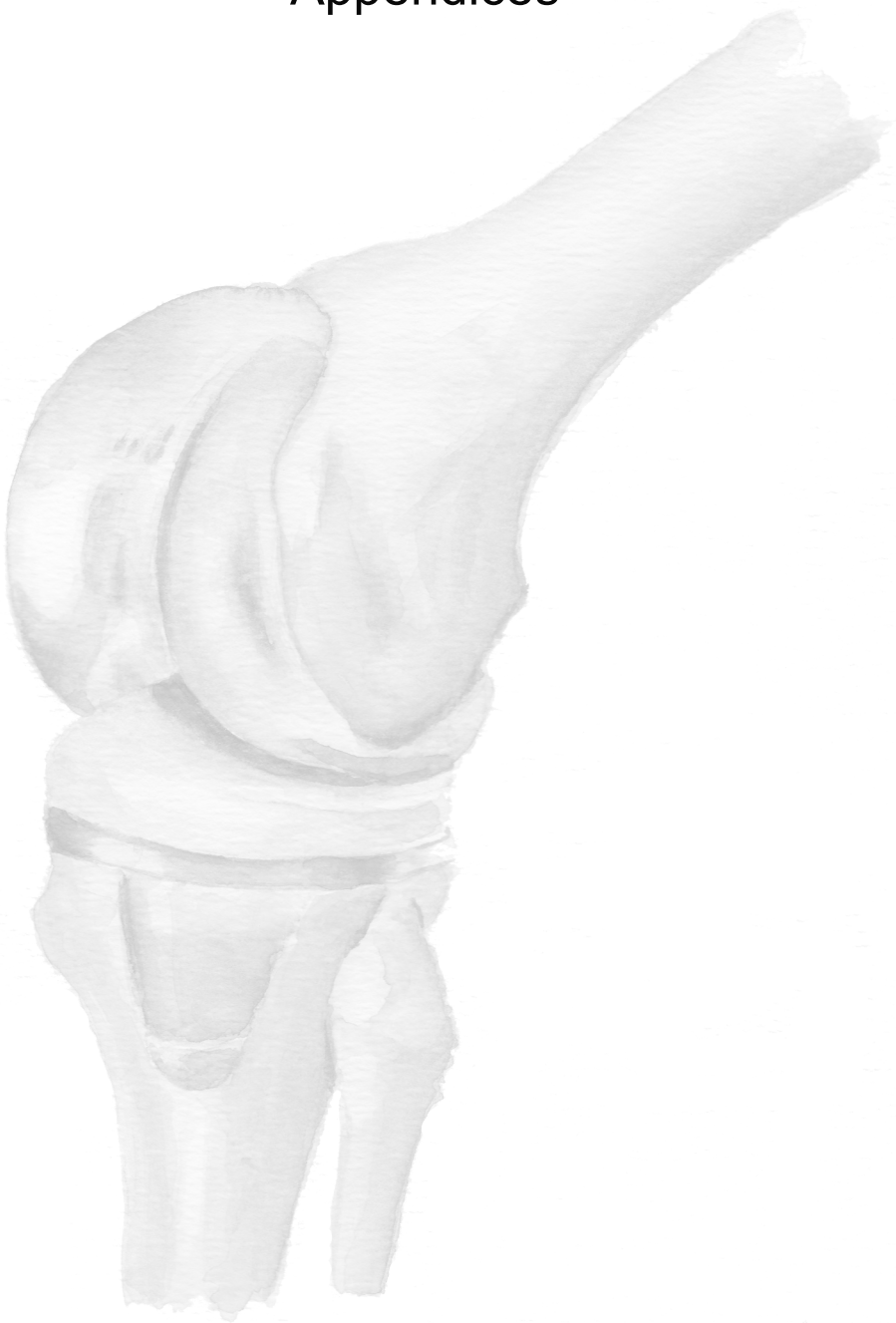
TKP wordt gezien als een succesvolle behandeling van gonartrose en wordt wereldwijd door vele orthopedisch chirurgen ingezet. Er blijven rondom de TKP behandeling een aantal zaken punt van discussie. Zo wordt er gesteld dat het aanbrengen van een fibrinelijm in de knie tijdens de operatie een gunstig effect zou hebben op het hemoglobine verlies of op het aantal bloedtransfusies rondom de operatie. In **hoofdstuk 6** worden de resultaten beschreven van een grote gerandomiseerde klinische studie in meerder ziekenhuizen naar het effect van een fibrinelijm bij TKP operaties. De huidige zorgpaden bij TKP zijn zeer terughoudend met het toedienen van bloedtransfusies en het routinematig controleren van hemoglobine gehalte in het bloed. Vandaar dat in de studie met fibrinelijm gekozen is voor een functionele uitkomstmaat, namelijk de extensie (‘het strekken’) van de knie. Uit eerder onderzoek weten we dat er na TKP operaties zo’n 650-700 mL bloedverlies is wat onder andere in de knie kan blijven en kan zorgen voor een extensiebeperking (strekbeperking) van de knie met als gevolg een mogelijk moeizamere revalidatie van de operatie. Er werd geen verschil gevonden in knie extensie tussen patiënten die met of zonder fibrinelijm geopereerd waren. Ook wanneer het gebruik van drains meegenomen werd in de analyse werd er geen verschil gevonden.

Een andere voortdurende discussie onder kniechirurgen is het al dan niet offeren van de achterste kruisband. **Hoofdstuk 7** rapporteert de resultaten van een systematische review en meta-analyse binnen het kader van Cochrane waarvan de

resultaten zowel als artikel in de Acta Orthopaedica zijn gepubliceerd als in de *Cochrane Library for Systematic Reviews*. Er konden 2.347 knieën geanalyseerd worden in de meta-analyse waardoor er uitkwam dat TKP's waarbij de achterste kruisband geofferd was 2.1 graden meer konden buigen. Dit was statistisch significant maar klinisch niet relevant. Uit dit onderzoek kan geconcludeerd worden dat er geen functionele, klinische of radiologische verschillen gevonden werden tussen TKP met of zonder opofferen van de achterste kruisband.

Na TKP of THP kan een prothese infectie ontstaan. Dit is één van de meest gevreesde complicaties van de behandeling en er wordt veel moeite gedaan om het risico op een infectie tot een minimum te beperken. Hypothermie (waarbij de temperatuur van patiënten tussen de 34 en 36 ^{o}C is) kan ontstaan tijdens de operatie en kan het risico op infectie doen toenemen. Hierom worden patiënten tijdens de operatie verwarmd. De meest gebruikte deken hiervoor maakt gebruikt van warme lucht. Deze warme lucht kan de luchtstroom op de operatiekamer dusdanig verstoren dat het risico op infectie van het operatiegebied weer toeneemt. In **hoofdstuk 8** beschrijven we een onderzoek waarbij we onderzocht hebben of de warme lucht deken en een deken die uit zichzelf warm is en daarbij de luchtstroom niet verstoord beiden in staat zijn om hypothermie te voorkomen. Met het idee dat wanneer de deken die de luchtstroom niet verstoord even effectief is als de ander dat deze wellicht de voorkeur zou moeten genieten. We vonden een verschil van 0.2 ^{o}C ten nadele van de deken die zelf verwarmd. Dit verschil beschouwen we als niet relevant. In beide groepen werden ook geen verschillen in complicaties gevonden.

Appendices



List of other publications

Myeloid sarcoma presenting as a recurrent, multifocal nerve root entrapment syndrome. **Verra WC**, Snijders TJ, Seute T, Han KS, Nieuwenhuis HK, Rutten GJ. *J Neurooncol 2009 91(1):59-62.*

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Curriculum vitae

Wiebe Verra was born on March 20th 1984 in Leiden, the Netherlands. After primary school he attended the gymnasium at the Visser 't Hooft Lyceum in Leiden. He became a medical doctor studying Medicine at Utrecht University in the city of Utrecht, the Netherlands. In 2010 he started working as senior house officer in the Sint Maartenskliniek in Nijmegen. In September 2010 he started working within the Leiden University Medical Center on the research described in this thesis. For about 1.5 years he was full-time researcher until in July 2012 he started his general surgery training at the Spaarne Ziekenhuis, Hoofddorp. In January 2014 he started his first year of training in orthopedic surgery at the Leiden University Medical Center (prof.dr. R.G.H.H. Nelissen). From January 2015 until July 2016 he was trained at the Medisch Centrum Haaglanden/Bronovo (currently Haaglanden Medisch Centrum) (dr. E.R.A. van Arkel). Then he was trained at the Haga Ziekenhuis (dr. R.L.M. Deijkers) and started in January 2018 to complete his training at the LUMC (prof.dr. P.D.S. Dijkstra) in the final part of 2018. In this final year he also attended a knee fellowship at Charité Universitätsklinikum Berlin (prof. dr. C. Perka). Wiebe lives in Amsterdam with his fiancée.