PERIPROSTHETIC JOINT INFECTIONS: TO PREVENT, CURE OR CONTROL

BORG LEIJTENS

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Prevent if you can, cure if you must,
control what persists

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CHAPTER 1

INTRODUCTION, GENERAL BACKGROUND AND OUTLINE OF THIS THESIS

1

INTRODUCTION AND GENERAL BACKGROUND

Joint replacement surgery by total hip and total knee arthroplasty (THA and TKA) are among the most successful interventions in today's health care. Both operations are highly successful and cost-effective interventions for alleviating pain and disability associated with advanced joint disease [1–3]. Thanks to this success, THA and TKA are frequently performed procedures with a total of 29,937 and 26,030 in 2017 in the Netherlands, respectively [4]. These numbers are expected to increase with 125% in the coming 10 years [5]. Despite the great results, complications do occur, frustrating the positive outcome of an elective surgical procedure. One of these complications is the highly feared periprosthetic joint infection (PJI). A PJI is a deep infection at the prosthesis site. Bacteria easily adhere to the surface of the prosthesis and cause a fulminant infection with pus formation in acute PJIs and loosening of the prosthesis in chronic PJI [6]. This can result in severe pain, functional deficits, prolonged hospitalization, poor quality of life and even death [7]. Although PJI is an uncommon complication (1-3%), it is currently the leading cause of failure for primary and revision THA and TKA [8,9]. With increasing life expectancy, a growing healthcare burden due to osteoarthritis, and a predicted large rise in the numbers of primary TKA and THA being performed, the annual number of patients diagnosed with a new PJI may rise up to 2,100 by 2030 in the Netherlands [10].

PJIs commonly require further surgical interventions, which are associated with an increased risk of re-infection [11], prosthetic complications, subsequent revisions, repeated hospitalizations, and high costs [12]. Healthcare costs for treatment of an early PJI in the US are 25,000 USD on average, increasing to an average of 80,000 USD for a chronic PJI [13,14]. The higher costs of late versus early infections are explained by the fact that these infections are harder to treat and generally require more surgical procedures.

In order to assess the effectiveness of interventions in our healthcare system, a value-based health care framework has been defined by Porter et al [15]. In this framework the full cycle of care is valued in contrast to assessing solely one outcome of an intervention. This framework consists of a three-tiered outcome hierarchy in which the patient is followed through the entire process of care. Tier 1 covers the *health status achieved or retained*, tier 2 covers *the process of recovery* and tier 3 covers *the sustainability of health*. Considering Porter's framework for the intervention Total Joint Arthroplasty (TJA), PJI

influences all three tiers tremendously by decreasing patient's mobility and increasing the mortality rate (tier 1), influencing the process of recovery (e.g. readmission and reoperation) (tier 2) and decreasing the sustainability of heath (e.g. late implant revision surgery). The increasing number of patients affected by PJI, forces us to address this issue from a public health perspective. Appropriate prevention, recognition and management are critical to preserve or restore adequate function and reduce excess morbidity and burden to society. International Consensus Meeting (ICM) were held in 2013 and 2018 to identify the best practice for prevention, diagnosis and treatment of PJI [16, 17]. Despite extensive research, the best practice in PJI remains subject of debate. In daily practice as an orthopedic surgeon, one encounters several questions about optimal treatment *to prevent, cure or control* PJI. The general goal of this thesis is to provide the orthopedic community insights and specific practice guidelines in the prevention, treatment and control of a periprosthetic joint infection.

Defining and diagnosing PJI

Before going into detail about prevention and treatment of PJI, it is important to clarify the definition of PJI and explain how PJI is diagnosed. In general, a PJI is defined as an infection involving a joint prosthesis and adjacent tissue after total joint arthroplastic surgery (TJA) [18]. However, diagnosing a PJI has been subject of debate in the past few decades. A number of organizations have established diagnostic criteria in order to diagnose a PJI, as are summarized in table 1 [17,19]. In this thesis, the Musculoskeletal Infection Society (MSIS) criteria are applied. These are: PJI confirmed by the presence of a fistula from the prosthesis and/or ≥2 tissue cultures demonstrating growth of an identical pathogen and/or presence of ≥4 supporting criteria (see table 1) [18].

TABLE 1. Diagnostic criteria for PJI according to 4 organizations

Diagnostic criterium	IDSA; 2013	MSIS; 2011	ICM; 2018	PIF; 2018
Proving diagnosis*				
Pus at prosthesis site	x			x
Fistula from prosthesis	x	x	x	x
≥2 positive deep tissue cultures with the same micro-organism	x	x	x	x
≥1 positive deep tissue culture with a virulent micro-organism	x			
Leucocyte count > 2000/µl or > 70% granulocytes in synovial fluid				x
Acute inflammation at histopathology				x
Supporting diagnosis**				
preoperative				
raised CRP concentration		x	x 2 points	
ESR > 30 mm/h			x 1 point	
synovial fluid positive for α defensin			x 3 points	
CRP concentration > 6.9 mg/l in synovial fluid			x 1 point	
Leucocyte count > 3000/µl in synovial fluid		x	x 3 points	
80% granulocyte in synovial fluid			x 2 points	
perioperative				
pus at prosthesis site		x	x 3 points	
≥1 positive deep tissue culture with a micro-organism	x	x	x 2 points	
Acute inflammation at histopathology	x	x	x 3 points	

IDSA = Infectious Diseases Society of America, MSIS = Muscoloskeletal Infection Society, ICM = International Consensus Meeting on Muscoloskeletal Infection (Philadelphia, 2018); PIF = PRO-IMPLANT Foundation.
**presence of 1 or more of the proving criteria confirms PJI according to all 4 organizations*
*** MSIS: presence of four or more supporting criteria confirms PJI. ICM: a preoperative score ≥6 confirms PJI, 2-5 points supports the diagnosis of PJI, 0-1 rejects the diagnosis of PJI. A Perioperative sore of ≥6 points confirms PJI, 4-5 points supports the diagnosis of PJI, 0-3 rejects the diagnosis of PJI*

It is important to emphasize the difference between PJI and surgical site infection (SSI), a term mainly used in general surgical literature. SSI is defined according to the Infectious Centers for Disease Control guidelines with the presence of: (1) purulent incisional drainage, (2) positive culture of aseptically obtained fluid or tissue from the superficial wound, (3) local signs and symptoms of pain or tenderness, swelling, and erythema after

the incision is opened by the surgeon (unless culture negative), or (4) diagnosis of SSI by the attending surgeon or physician based on their experience and expert opinion [20]. Therefore, it may be possible to have an SSI without having a confirmed PJI.

In PJI, bacteria adhere to surface of the prosthesis. This is important because bacteria are capable of biofilm formation on the prosthesis, protecting them from the hosts immune system and antibiotics. The process of biofilm formation starts within 24 hours [6,21]. Further organization of this biofilm takes place in the next few days/weeks. In this biofilm persister bacteria form. These 'persisters' are metabolically inactive bacteria which are difficult to treat with antibiotics since many antibiotics are effective by interfering the metabolic process in bacteria [22]. Because biofilm formation starts immediately after bacterial adherence on the prosthesis, it is important to differentiate between acute (symptoms ≤3 weeks) and chronic PJI (symptoms > 3 weeks). Patients with an acute PJI present with acute wound problems (rubor, dolor, calor, wound leakage), fever and persistent raised CRP-levels. When the biofilm has not been fully developed in acute PJI, it is likely that successful treatment of PJI will be achieved with retention of the prosthesis because bacteria can be physically rinsed out and reached by antibiotics. To address the problem of persisting bacteria in prosthetic biofilms, which cannot be rinsed off by lavage nor be penetrated by antibiotics, cases of chronic PJI are usually treated with removal of the prosthesis (including biofilm and persister bacteria). A new prosthesis is then placed during the same or in a second stage surgery.

OUTLINE OF THIS THESIS

This thesis is structured by subdividing the research projects in three parts:

- Prevention of PJI
- Curative treatment of PJI
- Palliative treatment of PJI

Each part contains chapter(s) in which different research papers are presented. For each chapter of this thesis, research questions have been formulated in this introduction.

PART 1 - PREVENTION OF PJI - PREVENTION IS BETTER THAN TREATMENT

The emergence of bacterial overgrowth and a PJI appears to be a complex problem depending on multiple interacting factors in- and outside the host. To analyze the risk of developing a PJI this complex problem needs to be reduced to individual modifiable factors. Several factors influencing the risk of SSI have been clarified in previous research [23]. These factors include modifiable and unmodifiable patient characteristics, pre-operative care, peri-operative care, type of surgical intervention, and post-operative care. Figure 1 illustrates that an SSI emerges when a certain threshold level has been reached due to an interplay of negatively and positively influencing factors.

Although it is plausible that factors influencing the incidence of SSI also influence the chance of PJI, the impact of several factors in TJA is unknown [24]. We have learned that, in the presence of a foreign body (e.g. joint arthroplasty), it requires only 50-100 bacteria to cause an infection compared to 10,000-100,000 bacteria in absence of a foreign body [25]. By identifying risk factors that can be modulated, we can mitigate the risk for developing PJI. In this part of the thesis we focus on the identification of modifiable risk factors in TJA. In each chapter one of the possible factors is discussed.

Patients' temperature

Perioperative hypothermia

As pictured in figure 1, a patient's immune system is one of the factors in the battle against infections. The patient's body temperature plays an important role in the immune system. During surgery, body temperature can decline significantly and hypothermia can occur. Hypothermia is defined as a body temperature of <36.0˚C and negatively influences the immune system [26]. In general surgery, hypothermia has been shown to increase the incidence of postoperative infections [27]. The incidence of hypothermia in patients undergoing THA and TKA is unknown. Also, the relation of hypothermia to the incidence of PJI has not been addressed in previous research. In **chapter 2** of this thesis**,** perioperative hypothermia during THA and TKA is studied. We performed a cohort study of prospectively collected data in which we investigated the incidence of

hypothermia and its relation to the incidence of PJI in Canisius Wilhelmina Hospital, Nijmegen (CWZ). For this chapter we formulated the following research questions: What is the incidence of intraoperative hypothermia during THA and TKA surgery? Is there a correlation between the incidence of hypothermia during surgery and the incidence of PJI after TKA and THA?

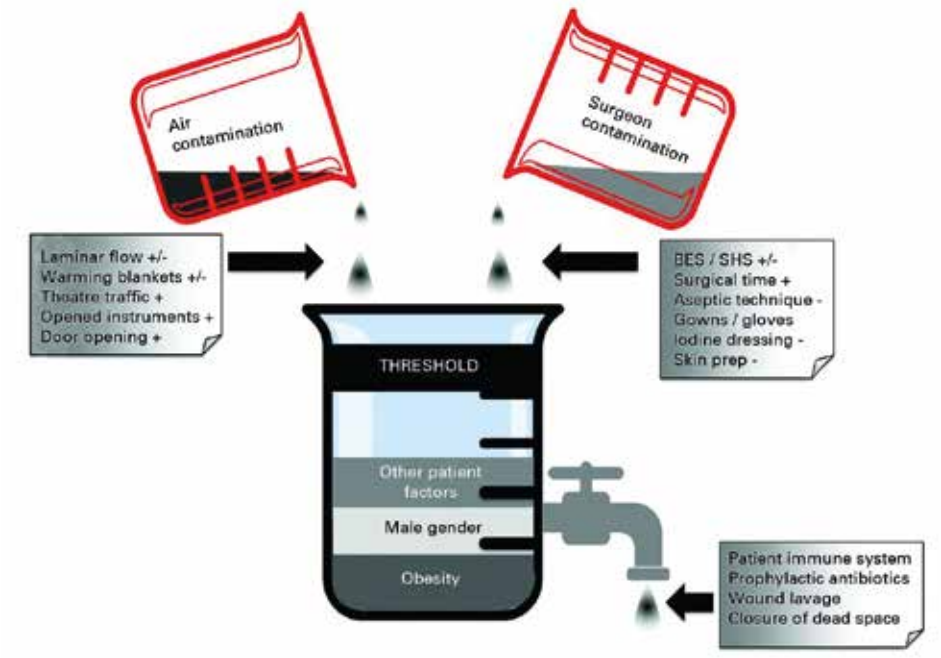

FIGURE 1. Model illustrating known factors influencing the development of SSI [23]. Patient factors that cannot be influenced decide the water level at the start of surgery. Air- and surgeon contamination both raise the water level. These can be influenced by several illustrated factors. The water tap illustrates influenceable factors to lower the water level.

BES=Body Exhaust Suits, SHS=Surgical Helmet System, +=increases risk of PJI, -=decreases risk of PJI, +/-= can both increase and decrease risk of PJI. (this figure is copied from an article in The Bone & Joint Journal, 2016. doi:10.1302/0301-620X.98B3.36775, written by Tayton et al. The impact of patient and surgical factors on the rate of infection after primary total knee arthroplasty. Permission for using this figure has been requested)

Thermoreflective blanket

In 2012 the use of a thermal reflective blanket was introduced in CWZ to prevent patients from cooling down during surgery. Before implementation of this measure to reduce hypothermia in TJA, we decided to investigate the effect of this intervention. In **Chapter 3** the effect of the use of an intra-operative thermoreflective blanket in patients undergoing primary THA or TKA is studied with a non-blinded randomized controlled trial after approval by the Institutional Review Board. A total of 58 patients were randomized, 29 received a thermal reflective blanket, 29 did not. Outcome measures were body temperature, thermal comfort and shivering. The main question to be answered was: Does the use of a thermo-reflective blanket influence the incidence of hypothermia during total hip and knee arthroplasty?

Perioperative hypothermia, follow-up

The research presented in **chapter 4** is a continuation of the above-mentioned study on incidence of hypothermia. An increased awareness of perioperative hypothermia could possibly result in changed behavior of medical staff and therefore reduce the incidence of hypothermia. As awareness of hypothermia seemed to increase in CWZ, we decided to perform a follow-up study on hypothermia. Also, we hypothesized that a high number of patients was needed to investigate the correlation between hypothermia and PJI incidence. In our follow-up study, 2600 patients were included versus 688 in the previous research. The two research questions for this chapter were: Does perioperative hypothermia correlate with the incidence of PJI after placing a THA and TKA? Does the incidence of hypothermia during surgery for total hip and knee arthroplasty change over time?

Anticoagulants

Bridging of anticoagulant therapy during TJA

There are many known preoperative risk factors for PJI. Patient (host) risk factors include male gender, previous surgery at surgical site, uncontrolled diabetes mellitus, malnutrition, morbid obesity, active liver or renal disease, smoking, excessive alcohol consumption, intravenous drug abuse, active infection elsewhere, inflammatory arthropathy, and severe immunodeficiency [23,24]. Also, prolonged wound leakage and hematoma formation have

been suggested to be risk factors for the development of a PJI [28,29]. After performing a matched case-control study in CWZ, in which 25 cases of PJI were compared to 50 controls with an uncomplicated postoperative course after TJA, a suspected correlation between postoperative wound leakage and PJI was confirmed [30]. Therefore, we questioned how to diminish the amount of postoperative wound leakage. A literature search revealed several factors that could influence the duration and amount of post-operative wound leakage [28,31]. One of these factors is the use of high dose (therapeutic) anticoagulants. In **chapter 5** we focus on bridging of anticoagulant therapy during TJA. Up to 10% of the patients planned to undergo elective PJA, use long-term anticoagulants to prevent thromboembolic events. In order to prevent massive intra-operative blood loss, the use of long-term anticoagulants need to be stopped before the operation. In 2012 the American College of Chest Physicians (ACCP) released a clinical practice guideline to address the management of patients who receive long-term anticoagulation and require elective surgery [32]. These guidelines include 'bridging' and are mainly focused on prevention of thromboembolic complications when oral anticoagulants (OAC) are stopped. The term bridging refers to the use of a high dose of low molecular weight heparins (LMWH) while stopping OAC. However, these measures to prevent thromboembolic events could put patients at risk for postoperative bleeding complications (e.g. anemia, prolonged immobilization due to hematoma, prolonged wound leakage). Implementing these guidelines, we noticed an increase in bleeding complications after TJA compared to patient not receiving bridging. In order to quantify this observation, we retrospectively analyzed patients selected to bridge OAC with a high dose of low molecular weight heparins (LMWH) around TJA surgery in CWZ. The question we will try answer is: What is the incidence of bleeding complications in patients undergoing THA or TKA in which bridging of anticoagulant therapy is indicated?

The role of anesthesia in PJI

General versus spinal anesthesia

Despite the increasing awareness of certain patient characteristics that influence the risk of PJI, the role of procedure related factors, such as the type of anesthesia, remains to be elucidated. The notion that anesthesia may influence the immune response has been

suggested as early as 1903 [33]. However, anesthetic techniques have changed dramatically and the clinical relevance and the precise role of anesthesia in the pathogenesis of postoperative infections remains unclear [33,34]. In recent literature, there are several studies suggesting spinal anesthesia reduces the risk for SSI when compared to general anesthesia in THA and TKA [35,36]. However, other studies suggest no significant effect on the incidence of SSI [37]. Furthermore, no prospective observational studies with well-defined definitions of PJI have been performed. Therefore, we investigated this possible correlation between general anesthesia and PJI following THA or TKA in a large prospective cohort study in Rijnstate Hospital, Arnhem. This study is described in **chapter 6**, answering the following research: Is there a correlation between type of anesthesia and the onset of a PJI after TJA?

PART 2 - CURATIVE TREATMENT OF PJI – PREVENT IF YOU CAN, CURE IF YOU MUST

Despite the extensive efforts to prevent PJI, it is still a leading cause of failure for primary and revision THA and TKA. In order to optimize the treatment of PJI, several guidelines have been developed in the past few decades [16,38–40]. As mentioned above, one must distinguish between acute and chronic PJI. An acute PJI can be an early postoperative infection (<3 weeks), a late hematogenous infections (with symptoms of a PJI ≤3 weeks) or PJI due to continuum of a local infection (with symptoms of a PJI ≤3 weeks). These infections typically present with an acute onset of pain, local inflammation, fever and raised CRP levels. International guidelines recommend to treat an acute PJI with Debridement, Antibiotics and Implant Retention (DAIR), reporting success rates of 72-91% [41–43]. On the contrary, chronic PJI commonly present with persistent pain, loosening of the prosthesis and/or fistula formation. In these cases, bacteria have had the chance to create a mature biofilm on the prosthesis which cannot be physically removed by lavage surgery nor be penetrated by antibiotics. Consequently, a chronic PJI is hard to treat with retention of the prosthesis. Therefore, chronic PJI are typically treated with one- or two stage revision of the prosthesis with success rates of 90-94% [11,44]. After the surgical procedure(s), patients are treated with long term antibiotics (6-12 weeks). Type, timing and amount of both surgical and antibiotic treatment is dependent on a patient's

general condition, local surgical conditions, causative bacteria, time after index surgery and socioeconomic conditions. Guidelines for treatment remain subject to debate in international consensus meetings. We investigated several steps in the curative treatment of PJI in Radboud University Medical Centre.

Intraoperative choices

Retention of bone cement

As in the treatment of any disease, specific choices have to be made in surgical treatment options for PJI. In cases of one- or two stage revision surgery, the surgeon has to decide which part of the implant is removed and revised and which part is left in situ. During removal of a cemented THA, the cement can be entirely removed or (partly) kept in situ. Removal of cement is time consuming and can cause excessive blood loss, bone loss, and femoral fractures [45]. However, as a foreign body, the cement mantle could be a hospitable surface for bacteria to grow due to possible biofilm formation on cement [46]. The preservation of the cement mantle in the femoral canal is well documented in current literature for aseptic revision surgery, but has not been investigated for septic revisions. In the research presented in **chapter 7,** the following research question will be answered: Does a two-stage revision of THA with the retention of bone cement for chronic PJI, result in acceptable success rates?

Antibiotics in bone chips

As described above, during the removal of a prosthesis, excessive bone loss can be created or encountered. In two stage revision, this bone loss can be reconstructed with impaction bone grafting (IBG) using allograft bone chips from a donor patient. This technique has been developed in Radboud University Medical Centre and is being widely used all over the world [47]. Because of the possibility of disease transmission and a possible immune response to allograft implantation, these bone chips are sterilized and demineralized [48]. These avascular bone chips are dead tissue and could therefore be more susceptible to infection [49]. To reduce this risk, local application of antibiotics in bone chips has been introduced [50]. Bone allografts might be a better carrier for antibiotics than cement and it is possible to mix large amounts of antibiotics through bone grafts resulting in high levels

of local tissue concentration without systemic effects such as nephrotoxicity. This has led to studies reporting promising results [49–51]. However, unnecessary use of antibiotics should be avoided considering the increase of antibiotic resistant bacteria. Furthermore, antibiotics could weaken the bone chips and interfere with ingrowth of the allograft bone chips. Follow up periods are relatively short in these studies, considering this is a patient group with a history of loosening of the prosthesis due to chronic PJI. In Radboud University Medical Centre, bone chips used for IBG are not routinely impregnated with antibiotics. This provides us the opportunity to answer the following research question; What is the re-infection rate in two-stage revisions of a THA for PJI with donor bone chips without additional antibiotics of the allograft?

For the research presented in **chapter 8** we investigated all patients treated with a two-stage revision for PJI with IBG without antibiotic impregnation between 1990 and 2009 in Radboud University Medical Centre.

Antibiotic treatment

Clindamycin and Rifampin

Staphylococcus spp. infections account for more than 50% of the periprosthetic joint infections [52]. Current guidelines recommend treatment of PJI caused by *Staphylococcus spp*. with rifampin combined with quinolones after surgery [39,40]. Since bacterial resistance against antibiotics is a growing global problem, the search for alternative combination therapy is paramount. In contrast to the current guidelines, some PJIs are treated with the combination of rifampin and clindamycin In Radboud University Medical Centre. However, the safety and effectiveness of this combination has not been described in literature. In order to evaluate the safety and effectiveness of these treatment regimen, we formulated the following research question: Is an oral rifampin-clindamycin combination therapy for 3 months after surgical treatment safe and effective in patients with a proven PJI of THA or TKA with a sensitive microorganism? In **chapter 9**, the study to answer this question is described based on retrospective data-analysis among patients treated between 2004 and 2010.

PART 3 - PALLIATIVE TREATMENT OF PJI - PREVENT IF YOU CAN, CURE IF YOU MUST, CONTROL WHAT PERSISTS

Antibiotic Suppressive Therapy (AST)

Many innovations in the prevention, diagnosis, and treatment of patients with periprosthetic joint infections have been seen. However, the incidence of this problem is increasing in conjunction with an increased number of arthroplasty procedures and the development of a number of drug-resistant organisms. Additionally, there is a shift in patient demographics and a rising prevalence of comorbid conditions, such as obesity and diabetes, which will continue to negatively affect patients undergoing arthroplastic surgery. Due to the rise of drug-resistant organisms and fragile patients, an increasing amount of PJI cannot be cured because patients are unlikely to survive extensive surgery and the required high dose of antibiotic treatment. In this patient group, suppression of the infection may be a reasonable alternative. This type of treatment is frequently used worldwide, despite the fact that little is known about the safety and effectiveness of this treatment. In Radboud University Medical Centre, patients on AST are closely monitored by the orthopedic surgeon, the infection specialist and the microbiologist. In a retrospective cohort study, presented in **chapter 10**, we investigated the safety and effectiveness of chronic AST in patients with a presumed incurable PJI of THA. Research question: Is the use of suppressive antibiotic therapy safe and effective in patients with chronic PJI after THA in which surgical intervention is contraindicated? Goal of this study is to provide orthopedic surgeons, infection specialists and microbiologists statistical information to predict the outcome when AST is considered.

General aim of this thesis

Performing arthroplasty, many questions rise to reduce the chance of PJI and increase the chance of successful treatment of PJI. The aim of this thesis is to provide the orthopedic community specific practical recommendations in the prevention, treatment and control of PJI by answering the above described research questions that rose during daily practice. In chapter 2-10 the research performed to answer the above research questions are presented in detail. In chapter 11 every chapter will be summarized and research questions will be answered. Implications for daily practice and recommendations for feature research *to prevent, cure or control* will be discussed.

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PREVENT IF YOU CAN

PART I:

PREVENTION OF PJI

CHAPTER 2

HIGH INCIDENCE OF POSTOPERATIVE HYPOTHERMIA IN TOTAL KNEE AND TOTAL HIP ARTHROPLASTY, A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Hypothermia, a body temperature of <36˚C, has been shown to increase cardiac mortality, the incidence of postoperative infections, and the length of hospitalization following general surgery. However, studies assessing the incidence of hypothermia during primary total hip and total knee arthroplasty (THA and TKA) have not previously been published. In this prospective observational study, incidence of hypothermia was measured among 672 patients (415 underwent THA and 257 TKA). The incidence of hypothermia for THA and TKA was 26.3 and 28.0%, respectively. In conclusion, over a quarter of patients in this study is exposed to hypothermia. This study highlights the requirement for interventions to prevent peri-operative hypothermia.

INTRODUCTION

Inadvertent hypothermia is an important complication of major surgery. Even mild perioperative hypothermia can cause a variety of adverse effects [1], such as morbid myocardial events [2], increased risk of surgical peri-prosthetic infections, increased duration of hospitalization [3-5], intra-operative blood loss [6-7] and prolonged postanesthetic recovery [8]. These effects can be considerable as a 1.9 °C decrease in core temperature triples the relative risk of surgical peri-prosthetic infection and increases the duration of hospitalization by 20% [3-5]. The World Health Organization guideline for safe surgery recommends perioperative normothermia and national guidelines in the Netherlands make the orthopedic surgeon responsible for maintenance of normothermia during arthroplastic surgery [9-10]. These recommendations are based on study results in major general surgery with a high absolute risk of complications such as abdominal surgery. At the time of writing, there is no published literature on the incidence of (mild) hypothermia during total knee or total hip arthroplasty (TKA or THA). The main objective of this prospective observational study is to assess the incidence of hypothermia in patients undergoing elective unilateral primary total hip or total knee arthroplasty for osteoarthritis. We compared total hip versus total knee arthroplasty in perioperative body temperature and incidence of peri-prosthetic joint infections (PJI). We assessed whether the incidence of PJI was related to the incidence of hypothermia.

MATERIALS AND METHODS

All patients undergoing primary elective unilateral total knee or total hip arthroplasty for osteoarthritis were included from August 2009 till November 2010 in Canisius Wilhelmina Hospital in Nijmegen, The Netherlands. We excluded patients who used any kind of corticosteroids or other immunosuppressive drugs, patients who recently had a fever and patients with a preoperative temperature above 38°C, at admittance. Mild hypothermia will refer to core temperatures between 34 and 36 °C [11]. During surgery patients were warmed with a forced air warming device (Bair-Hugger©) as long as the operation lasted. The use of a Bair Hugger© during surgery has been proven to be effective

in increasing peri-operative body temperature for total knee or total hip surgery [11;12]. The Bair-hugger© was placed to cover the patient's chest and arms and set on maximum temperature, adjusted to comfort of the patient. No other warming devices or warmed fluids were used during surgery. Before and after surgery patients were covered with two double folded half cotton blankets. The operating room temperature was kept constant, between 18 and 21˚C. All TKA patients were operated on using a tourniquet. General or spinal anesthesia was used in all patients depending on favor and risk factors of the patient. Reported operation time is the time between first incision and skin sutured closing of the wound.

The core temperature of the patient was measured at the tympanic membrane (Genius™ 2) immediately after peri-prosthetic closure. Age, gender, type of arthroplastic surgery, type of anesthesia, operation time and postoperative temperature were recorded. A prosthesis was classified as infected based on the PREZIES criteria [13]. In these criteria an infection is classified as a "deep" infection if there is:

- pain, local swelling, redness or warmth AND (within a year after surgery) pus coming from the depth of the wound or from drain
- OR spontaneous opening of the wound or reopened by surgeon
- OR abscess or other signs of infection at observation, reopening, histopathological or radiologic research.

Those patients were re-operated (including peri-prosthetic debridement and rinsing, leaving antibiotic containing beads) and subsequently treated with long-term antibiotics. During operation, peri-prosthetic cultures were taken to adjust antibiotic treatment to narrow-spectrum antibiotics when possible.

This study was approved by the local medical ethical committee.

Statistical analysis

Statistical analysis was carried out using SPSS© version 19.0. Baseline characteristics of the two groups (THA versus TKA) were compared using a chi square test and the independent samples t-test. The difference in incidence of hypothermia and peri-prosthetic infections between THA and TKA was tested using a chi square test. The difference between mean core temperature in the two groups (THA versus TKA) was tested with an independent

sample t-test. The influence of type of anesthesia and operation time on the difference in mean core temperature in both groups was analyzed with linear regression analysis. The difference in incidence of peri-prosthetic infections between hypo- and normothermic patients was tested with a chi square test.

Results with a p-value of less than 0.05 were considered to be statistically significant.

RESULTS

During the study period 688 patients underwent TKA or THA. 16 patients were subsequently excluded as they did not fit within the study inclusion criteria (figure 1). Table 1 shows the baseline characteristics of the 672 patients in our study population, 257 underwent TKA and 415 underwent THA. There was no significant difference in gender and mean age between the two groups (table 1). Type of anesthesia and mean operation time differed significantly between the two groups. In the TKA group 71% received spinal anesthesia versus 78.5% in the THA group. Mean operation time was 7 minutes longer in TKA than in THA group, 54 vs. 47 minutes respectively.

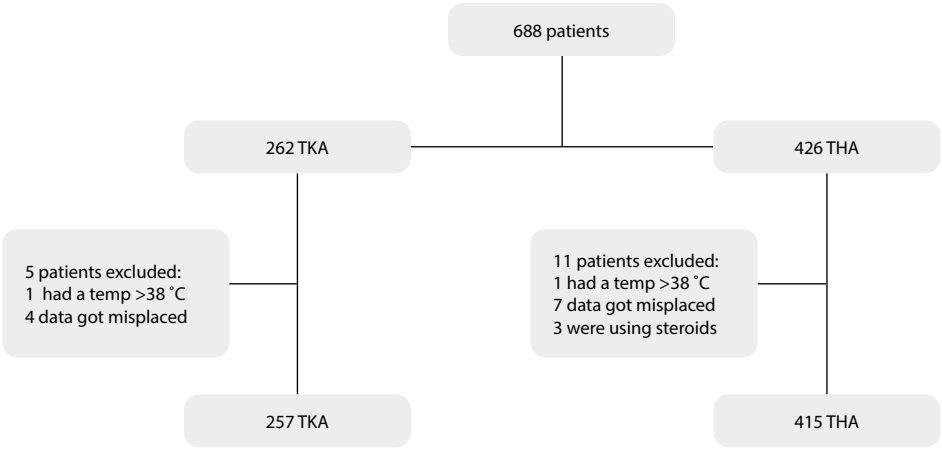

FIGURE 1. In- and exclusion

TABLE 1. Baseline characteristics. S= spinal anaesthesia, G= general anaesthesia

n = 672	TKA n= 257 (38%)	THA n=415 (62%)	p-value
Gender M : F (%)	99 : 158 (38.5% : 61.5%)	148 : 267 (35.7% : 64.3%)	0.455
Mean Age (years)	68.1	69.6	0.051
Type of Anaesthesia S : G*	183 : 74 (71% : 29 %)	326 : 89 (78.5% : 21.5%)	0.045
Mean Operation time (min)	54	47	0.000

The most important outcome was an overall incidence of 26.9% for hypothermia (core temperature below 36 °C). The incidence of hypothermia in the TKA group was 28.0 % versus 26.3% in the THA group. This difference was not statistically significant (P=0.62) (table 2).

Incidence of PJI was 1.0% in our total patient population. This incidence is comparable to other research (0-3%) (14). Seven patients in the THA group had a peri-prosthetic infection (1.7%) versus none in the TKA group, p=0.025 (table 2). Interestingly, four of those infections were among the 109 hypothermic patients (3.7%), versus three infections among the 306 normothermic patients (1.0%). This gives us a relative risk ratio of 3.7 (not significant p=0.061). All of these seven patients still have their total hip prosthesis in situ after one year of follow up.

Table 2. Mean postoperative body temperature and incidence of hypothermia and infections

n = 672	Total (n=672)	TKA (n=257)	THA (n=415)	p-value
% < 36 °C	181 (26.9 %)	72 (28.0 %)	109 (26.3 %)	0.619
Mean temp	36.25 °C	36.19 °C	36.29 °C	0.019
Infections	7 (1.0%)	0	7 (1.7%)	0.025
			4<36˚C	
			3≥36˚C	0.061

Mean core temperature directly after arthroplastic surgery was 36.25 °C (SD=0.53) (table 2). In the TKA and the THA group the mean temperature was 36.19 °C (SD=0.52) vs. 36.29 °C (SD=0.54) respectively. Despite this small difference of 0.1 °C, this was statistically significant (P=0.019). A linear regression analysis shows that this slight difference is still significant after correction for type of anesthesia and operation time (P=0.004). This analysis showed a linear negative relationship between operation time and temperature as well, p =0.010.

DISCUSSION

Our objective was to evaluate if hypothermia is a problem in major arthroplastic surgery. We found an incidence of 26.9% in primary total knee or hip arthroplasty, which seems disturbingly high. Over a quarter of our patients was exposed to hypothermia. We could state that this is concerning, considering the potential increased risk of complications, found in prior studies performed in general surgical procedures [1]. We found a 3.7 relative risk ratio of PJI for hypothermic patients in the total hip arthroplasty group. This indicates there may be a correlation between hypothermia and risk of PJI, although this study did not demonstrate statistical significance. Further research on the effect of hypothermia in patients undergoing total joint arthroplasty is needed. In this research, one should correct for difference in operative time. Since we found a negative linear relationship between body temperature and operative time. Especially in a relatively old population prevention of hypothermia seems very important since older people may be prone to worse outcomes if they experience a complication.

Apart from the above-mentioned complications, hypothermia was proven to increase incidence of subjective (thermal) discomfort, shivering and opioid use in patients undergoing total knee arthroplasty [15]. These proven negative effects of hypothermia form sufficient arguments to continue our search for effective warming methods, in Canisius Wilhelmina Hospital. Apparently, the peri-operative use of a Bair-hugger© alone is not sufficient to prevent hypothermia in every orthopedic patient.

Previously published recommendations in a systematic review include the following [16-17]:

- Use forced air warming in every surgery high risk for hypothermia
- Start forced air warming preoperative if temperature is below 36 ˚C.
- Measure temperature before and every 30 minutes after induction of anesthesia.
- Adjust settings of forced air warming device to maintain temperature above 36.5 ˚C.
- Maintain ambient temperature above 21 ˚C while patient is exposed (consider using equipment to cool the surgical team).
- Warm iv fluids and blood products to 37˚C.
- Continue forced air warming in recovery.

Introduction of the above points are recommendable worldwide, but more research on its effectiveness should be done. The National Institute for Health and Clinical Excellence (NICE) in the UK in 2008 [17] described that compliance remains poor In the USA despite guidelines [11]. It has been suggested that there are a number of factors contributing to this: a misguided belief that forced-air warming can increase the rates of infection, surgeons' complaints of discomfort, inconsistent monitoring, and a simple lack of appreciation of the causes and consequences of inadvertent peri-operative hypothermia.

Total hip versus total knee arthroplasty

The incidence of hypothermia was higher in the TKA group when compared to the THA group (28.0% and 26.3%) and mean core temperature was 36.2 ˚C in the TKA group versus 36.3˚C in the THA group. After correction for operation time and type of anesthesia this difference in mean core temperature was still significant. We used a tourniquet in all TKA surgeries and previous research suggested that the use of a tourniquet could explain the lower postoperative core temperature by redistribution of cold blood trough the body after deflation [18-19]. Also, there is a larger naked skin surface exposed to relatively cold air in the operation room, possibly causing a decline in body temperature.

We found a significantly higher infection percentage in the THA group compared to the TKA group (1.7% versus 0%), although mean core temperature was 0.1 degree higher during THA than during TKA. Of course there are other factors associated with a higher infection rate. These risk factors include mainly patient related factors like diabetes, renal

failure, nutrition status and surgical factors like blood transfusions and blood loss [20]. We did not compare these risk factors in our different groups.

Why does hypothermia cause complications?

Hypothermia is caused by the anesthetic induced impairment of thermoregulatory control and exposure to a cool operating room, internal redistribution of heat within the body, reduction in heat production from metabolism, inspiration of dry and cool anesthetic gases, and infusion of room temperature intravenous fluids [5].

Peri-operative hypothermia stimulates and amplifies adrenergic responses with the release of noradrenalin, which results in peripheral vasoconstriction and hypertension and increases the chances of myocardial ischemia [2]. Studies have shown that intra-operative hypothermia, accompanied by vasoconstriction, constitutes an independent factor that slows peri-prosthetic healing and increases the incidence of surgical wound infections and prolonged duration of hospitalization [3-4]. Hypothermia can alter physiologic coagulation mechanisms by affecting platelet function and modifying enzymatic reactions. Decreased platelet activity produces an increase in bleeding, greater intra-operative blood loss and allogenic blood requirement [6-7].

Study limitations

In the Canisius Wilhelmina Hospital the use of a Bair hugger© is protocol because of its proven effectiveness in increasing body temperature for total knee or total hip surgery [11-12,18]. Of course, this system is not available in every hospital setting. So, the incidence of hypothermia we found could be higher in other hospitals.

In this study we did not include bilateral procedures. Considering the fact that a longer operation time has a negative effect on postoperative body temperature, we suspect an even higher incidence of hypothermia in bilateral procedures.

Although we found a significant difference between TKA and THA in mean core temperature, it is a very small difference. Further research needs to be done to explain this difference. Postoperative core temperature could be compared in total knee arthroplasty with or without the use of a tourniquet. Previous research shows there is no significant difference in total blood loss, transfusion rate or other relevant outcomes comparing groups with or without the use of a tourniquet [18].

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CHAPTER 3

RANDOMIZED TRIAL PROVIDES EVIDENCE THAT ADDING THERMAL REFLECTIVE BLANKET DOES NOT PREVENT HYPOTHERMIA IN PRIMARY UNILATERAL TOTAL HIP OR KNEE

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ABSTRACT

Hypothermia in patients undergoing major clean surgery results in higher incidence of perioperative complications. Aim of this study was to evaluate whether the additional use of a thermal reflective blanket can prevent hypothermia in patients undergoing primary unilateral total hip or knee replacement surgery. A total of 58 patients were randomized, 29 received a thermal reflective blanket, 29 did not. Outcome measures were core temperature, thermal comfort and shivering. The mean of the lowest core temperature was below 36 degrees in both groups (35.9+/- 0.4°C vs. 35.8 +/- 0.4°C), thermal comfort and shivering were not significantly different between the groups. In conclusion, a thermal reflective blanket did not prevent hypothermia in this group of patients.

INTRODUCTION

Postoperative hypothermia is a common and serious complication in patients undergoing major surgery. Several prospective randomized trials [1-4] have quantified the consequences of hypothermia on postoperative complications in clean surgery. A hypothermia of only 1.9°C core temperature triples the wound infection risk, and mild hypothermia causes coagulopathy and can lead to increases in blood loss and augments allogenic transfusion requirements. Perioperative mild hypothermia prolongs the duration in the post-anesthesia care unit and patients experience more thermal discomfort [1,4]. Even hospitalization duration prolongs significantly due to hypothermia [1,2,5]. Normothermia is important to prevent these adverse effects.

Hypothermia occurs due to the anesthetic induced impairment of thermoregulatory control and exposure to a cool operating room environment [1,4]. To avoid a drop in body temperature as a result of the surgical procedure several measures can be taken, including the use of a thermal reflective blanket (thermoflect© blanket). This thermoflect© blanket is made of material that reflects a patient's endogenous radiant heat to prevent cooling of the patient during the surgical procedure. The blanket is lightweight, comfortable, durable and relatively cheap [4]. The thermoflect© blanket has been on the market for years. Several systematic reviews indicate that a thermoreflective blanket is widely used all over the world [6,7].

Hypothermia is a major issue in patients undergoing total joint replacement [1,2,4,8,9], and the incidence can be as high as 26.8% [10]. We preformed this prospective randomized controlled study to evaluate if hypothermia can be overcome by using a thermal reflective blanket. We therefore randomized patients undergoing THA and TKA to either the thermoflect© group or a control group. During surgery we used a Bair Hugger© in both groups because of its documented effectiveness [11-15]. Primary outcome parameters were hypothermia qualified as either a decreased perioperative core temperature (<36 °C) or a low subjective thermal comfort quantified using a visual analogue scale (VAS) score or a high shivering scale.

MATERIALS AND METHOD

Sample

The sample size was based on a pilot study. In this small observational study with ten patients -six patients were in the thermoflect© group and four patients in the control group- the temperature difference between the two groups was 0.57° C (SD 0.48). The mean postoperative temperature in the intervention group was 36.39° C, and the mean temperature in the control group was 35.82° C. The sample size calculation (with 80% power, alpha 0.05%, one sided test for additional value of thermal reflective blanket) indicated the need for twelve patients in each group to achieve statistical significance. We anticipated that we needed a study population of at least 30 to allow for potential missing data.

Patients

For this randomized single-blinded study, patients were randomly assigned by envelope randomization in either the thermoflect© or the control group. Patients with diagnosed osteoarthritis who were eligible for primary total knee or total hip replacement were included. Excluded patients were those using any kind of corticosteroids or other immunosuppressive drugs, and patients who recently had a fever.

Study protocol

Hypothermia was defined as a core temperature below 36 °C, this cut off point is based on the American Society of PeriAnesthesia Nurses (ASPAN) clinical practice guideline and the national guideline of infection prevention 16-18. All patients were brought to the operating room covered with two cotton blankets. No active warming method was used before surgery. Temperature in the operating room was kept between the 18 and 21°C. During surgery every patient in both groups was warmed with a Bair Hugger© from incision until closure of the wound. It was attached to the body with tape at the level of the umbilicus, covering the upper abdomen, anterior chest, upper extremities, head and neck. A high setting (43 °C) was used on the Bair Hugger© forced-air device. Warmed fluids were not used during surgery. The type of anesthesia, BMI and ASA classification were recorded (table 1).

TABLE 1. Baseline characteristics

	Thermoflect group (n=29)	Control group (n=29)	P-values
Mean age	68.14 (SD 9.55)	71.34 (SD 7.68)	0.164
Mean BMI	28.40 (SD 4.42)	28.36 (SD 4.05)	0.977
Gender:			
Male	12	8	
Female	17	21	0.269
Type of surgery:			
TKP	12	11	
THP	17	18	0.788
ASA classification:			
1	8	2	
2	18	25	
3	3	2	0.085
Type of anesthesia:			
General	11	7	
Spinal	18	22	0.256

In the thermoflect© group we used the thermo-reflective blanket from transport to the operating room until return on the ward. The control group did not receive the thermoflect© blanket at any time. Patients who had a core temperature below 36°C at the post-anesthesia care unit (PACU) were warmed with an electric heater above the patient until the core temperature was above 36°C.

Core temperature was measured at the tympanic membrane (Genius™ 2) as follows: 1) hospitalization on the ward, 2) before transport to operating room, 3) in operating room, 4) in operating room after surgery, 5) in PACU upon arrival, 6) in PACU at departure, 7) on return to the ward. The lowest recorded temperature at any time was used for analysis, since hypothermia at any time is considered relevant.

We evaluated thermal comfort with the visual-analogue scale on which 0 mm denoted intense cold, 50 mm denoted thermal comfort and 100 mm denoted intense warmth. The pain sensation was evaluated with a similar visual-analogue scale which 0 mm denoted no

pain and 100 mm intense pain. These scores were evaluated on the ward before and after surgery. The intensity of shivering was evaluated on the ward before and after surgery on a scale on which 0 denoted no shivering, 1 denoted intermittent shivering, 2 denoted continuous shivering and 3 denoted continuous intense shivering 2.
The local medical ethical committee approved the study, and all patients signed an informed consent.

Statistical analysis

Analysis was carried out using the statistical package SPSS version 18.0. To compare the characteristics of both groups an independent T-Test was used for age. For statistical analysis for gender, type of surgery, ASA classification, BMI and type of anesthesia the Pearson Chi-square test was utilized.

The lowest temperature measured at one of the seven measure moments was used for statistical analysis and was compared with the preoperative body temperature. The differences between the means of the lowest measured temperatures in both groups were tested with an independent sample T-test. For the analysis of the VAS scores for pain and thermal comfort for each group, sort of operation and gender we used mixed model analysis. All the results with a P value of less than 0.05 were considered to be significant and results with a higher P value where considered as not significant.

RESULTS

Patients

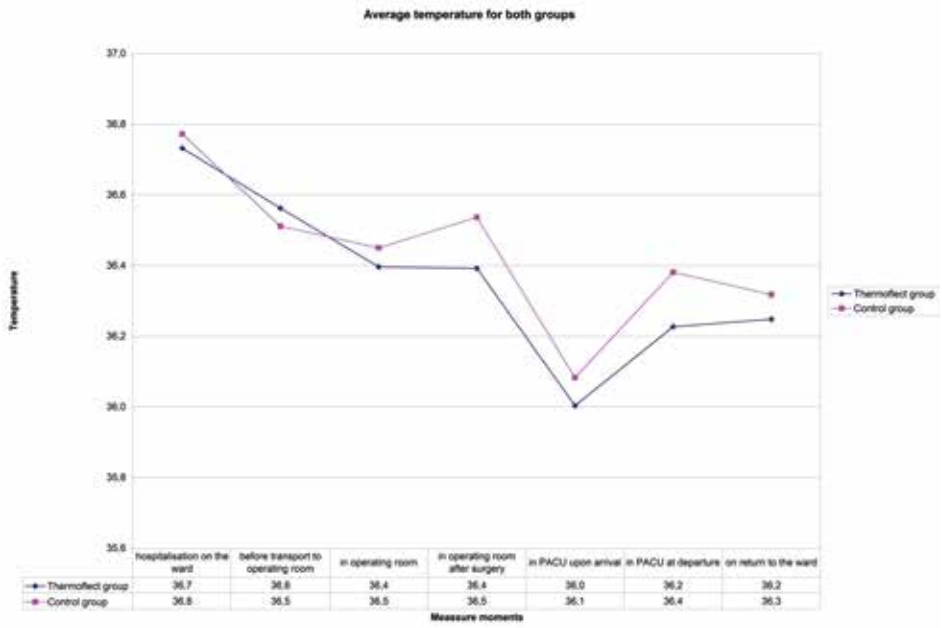
Patients were enrolled in the study from 1 December 2009 through 29 March 2010. Fifty-eight patients were recruited for the study. Twenty-nine patients were assigned to each group. All Fifty-eight patients were analyzed for this study. Patient characteristics are listed in table 1. There were no significant differences between both groups.

Core temperature

Table 2 lists outcome parameters for this study. The mean of the lowest core temperatures measured for the control group versus thermoflect© group did not differ statistically significant (35.9+/- 0.4°C vs. 35.8 +/- 0.4°C, P=0.172). The mean of the lowest core temperature was not dependent on gender (P=0.847). The incidence of hypothermia (<36°C) for the thermoflect© group and the control group was respectively 18 of 29 patients and 15 of 29 patients (p=0.462). The overall incidence of hypothermia was 33 of 58 patients. The mean lowest temperature for the patients in both groups was measured in the PACU post-surgery (See Figure 1). The mean lowest core temperature for patients undergoing a TKA was slightly lower than for patients undergoing THA (35.7 +/- 0.3°C vs. 35.9 +/- 0.4°C, P=0.06) (Table 2).

Table 2. Mean lowest core temperature, thermal comfort, shivering and VAS pain score

	Mean lowest core temp. (degrees Celsius)	**Thermal comfort VAS score** [0-100mm] On the ward before surgery	**Thermal comfort VAS score** [0-100mm] On the ward after surgery	**Shivering** 0 = no shivering 1 = intermittent shivering 2 = continuous shivering 3 = continuous intense shivering	**VAS pain score** [0-100mm] On the ward before surgery	**VAS pain score** [0-100mm] On the ward after surgery
Thermoflect group (N=29)	35.8	30	30	4 patients (scale 1)	30	24
Control group (N=29)	35.9	36	27	4 patients (scale 1 and 3)	25	25
THA group (N=35)	35.9	33	25	1 patient (scale 1)	26	24
TKA group (N=23)	35.7	35	33	7 patients (scale 1 and 3)	29	25



	hospitalisation on the ward	before transport to operating room	in operating room	in operating room after surgery	in PACU upon arrival	in PACU at departure	on return to the ward
Thermoflect group	36.7	36.8	36.4	36.4	36.0	36.2	36.2
Control group	36.8	36.5	36.5	36.5	36.1	36.4	36.3

FIGURE 1. Temperature course of the seven measure moments for both groups

VAS scores

There was no statistically significant difference in mean VAS thermal comfort score after surgery between the thermoflect© group and the control group (P=0.787). Also, for type of surgery (THA versus TKA) there was no statistically difference in mean VAS thermal comfort score (P=0.263). There was no correlation between a core temperature below 36°C, and a low VAS thermal comfort score. There were four patients who experienced shivering in each group. This number was considered too small for statistical analysis.

The mean VAS pain score after surgery (Table 2) was not significantly different between the thermoflect© group and the control group (P=0.782), or for the THA group versus the TKA group (p=0.936).

DISCUSSION

The Bair Hugger© and the thermoflect© blanket combined did not prevent hypothermia in patients undergoing total knee or total hip joint replacement surgery in this study. The mean lowest core temperature measured was still below 36°C in both groups. This is below the advised core temperature as implemented by the Dutch National Government guideline [16] and by the ASPAN guideline for prevention of postoperative wound infections [18]. The incidence of hypothermia is 33 per 58 patients. This study confirms, that hypothermia is a major issue in patients undergoing joint replacement surgery [10]. The thermoflect© blanket has no effect on mean lowest core temperature, incidence of hypothermia, thermal comfort or pain sensation after surgery in this study. Although hospitals around the world use the thermoflect© blanket, we have not found other published studies that support the use of a heat reflective blanket.

Several studies compared a forced air warming device (eg. Bair Hugger©) with a reflecting blanket [7,12,13,15,19] but none of them combined the use of these two warming devices. Research indicates that the influence of a Bair Hugger© is larger than the influence of the thermoflect© blanket, since the latter only uses the patients endogenous radiant heat to preventing cooling. We did not want to withhold patients from the Bair Hugger© because of its known effectiveness. Adding the thermoflect© blanket seemed a reasonable option, since it can be used in combination with a Bair Hugger©, particularly during transport from the ward to the operating room and back. However, we found that adding a thermoflect© blanket did not prevent hypothermia, and that despite the use of a Bair Hugger© during surgery, the mean lowest temperature occurred immediately postoperative in the PACU.

There was a trend toward a lower core temperature for patients undergoing total knee arthroplasty. It seems that patients undergoing TKA are more at risk for hypothermia than patients undergoing a THA. The use of a tourniquet during a TKA procedure might be an explanation, because relatively cold blood from the lower extremity spreads towards the rest of the body after deflation [12] .

In contrast to findings by other authors [1,2,17], we found no correlation between VAS thermal comfort, shivering and core temperature. Because even a mild hypothermia may result in adverse effects, we do not feel that shivering is reliable for signaling hypothermia. There appears to be a distinct incidence of shivering in normothermic patients [1]. This indicates that the core temperature needs to measured!

This study has several limitations. Although operating room temperature was between 18 and 20°C we did not correct for this confounder. Correction is hard because temperature can vary during the operation as well, due to the used of bone cement for instance.

A second confounder could be the use of an electric warmer on the PACU. Postoperative heating of a patient with an electrical warmer is common practice in our hospital, we felt it is unethical to withhold patients from this treatment.

Additional research to prevent hypothermia in patients undergoing total hip or total knee arthroplasty is needed. New interventions can be aimed at procedure or patient specific risks of hypothermia. Recent literature has shown that obesity results in a higher incidence of PJI after primary THA [20,21]. This might be caused by an increased risk of hypothermia in this group [18]. Additional research can focus on obese THA patients. However, when subgroups of patients need to be assessed, sample sizes have to increase, which affect the feasibility of the studies. A possible procedure specific intervention to prevent hypothermia could be the commencement of active warming preoperatively. This has been shown to be effective in other clean surgeries, and we suspect it can also be effective in THA an TKA surgery. In additional research we recommend the use of the data collection tool derived from the ASPAN guideline [18].

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CHAPTER 4

THE INCIDENCE OF MILD HYPOTHERMIA AFTER TOTAL KNEE OR HIP ARTHROPLASTY: A STUDY OF 2600 PATIENTS

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ABSTRACT

Hypothermia is associated with a higher risk of perioperative complications and occurs frequently after total joint arthroplasty (TJA). The incidence of hypothermia following total joint arthroplasty was assessed with its risk factors and its correlation with PJI.

Correlation of hypothermia with age, gender, BMI, type of arthroplasty surgery, type of anesthesia, operation time, blood loss, date of surgery and PJI was evaluated in 2600 patients.

Female gender and spinal anesthesia increased the risk for hypothermia whereas an increased BMI and surgery duration correlated with a decreased risk of hypothermia. The incidence of hypothermia decreased over time without a correlation with PJI.

INTRODUCTION

Perioperative hypothermia can be an inadvertent effect of major arthroplasty surgery, and may result in possibly avoidable complications. In a previous study we found that the incidence of hypothermia (a core temperature below 36 °C directly after surgery) was high, 26.7% [1]. There is scarce literature on the effects of hypothermia after total knee or hip replacement. Other authors have described the negative effect of hypothermia after other types of major surgery, like abdominal surgery. They found that even mild perioperative hypothermia can increase the incidence of post-operative complications (increased mortality, sepsis, stroke, surgical site infection) [2]. These effects can be considerable, a decrease of 1.9 °C in core temperature triples the relative risk of surgical site infection (SSI) and increases the duration of hospitalization by 20% [3]. Taking protective measures to prevent the negative cascade caused by hypothermia may be particularly important in patients undergoing elective total joint arthroplasty (TJA) because patients are typically older and at risk for similar complications and infection. Periprosthetic joint infection (PJI) after primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) has considerable medical consequences and a mortality rate as high as 2.5% [4].

Despite the consequences, hypothermia remains an underrated and unresolved issue. The World Health Organization 2009 guideline (among other national and international guidelines) advise perioperative normothermia to prevent unintended complications but offer no specific guidance to achieve that goal [5]. Since then, several studies have attempted to establish effective methods to maintain normothermia in patients undergoing surgery in different surgical fields. A recent Cochrane review showed that most technical methods for preventing hypothermia are ineffective, only forced air warming seems effective in increasing the patients core temperature after surgery [6].

We felt that the incidence of hypothermia in our previous study was unacceptably high and decided to do a follow-up study. We hoped to reduce the incidence of hypothermia, not by technical measures, but by raised awareness of hypothermia among the medical and nursing staff on the orthopedic ward and in the operating room (OR). In this current prospective observational cohort study, we describe the long-term results, using the incidence of hypothermia as a primary outcome. We evaluated the correlation of hypothermia with both its risk factors and with PJI.

METHODS

The study was approved by the institutional review board of (IRB) Canisius Wilhelmina Hospital. We included all consecutive patients in our hospital undergoing elective primary unilateral total knee or total hip arthroplasty for osteoarthritis from January 2011 till December 2014. We excluded patients undergoing bilateral surgery or revision surgery. Mild hypothermia is defined as a core temperature between 35 and 36 °C, severe hypothermia as a core temperature below 35°C. The core temperature was measured at the tympanic membrane (Genius™ 2) in the operation room directly after wound closure. Correlation with age, BMI, gender, type of arthroplasty surgery, type of anesthesia, operation time, blood loss, date of surgery was evaluated.

All patients were treated using the same measures to prevent hypothermia. The warming protocol was not changed during the study period. The use of a forced-air warming system (Bair-hugger©) was already implemented in our hospital, and no other warming system proved to be superior in preventing hypothermia in previous studies [7-10]. Our algorithm included the following measures:

- Use forced air warming (Bair hugger) placed over the patient's chest and arms as long as the operation took, irrespective of core temperature. The Bair hugger was set on maximum temperature (42°C) and adjusted for comfort of the patient
- No other warming devices were used
- Core temperature was measured before and directly after surgery in the OR
- Maintain ambient temperature between 18 and 21 °C
- Before and after surgery patients were covered with two double folded half cotton blankets.

We informed all medical and nursing professionals on the orthopedic ward and in the OR of the temperature measurement program. In another previous study we found that the largest decrease in body temperature occurred preoperatively on the orthopedic ward and during transport from the ward to the OR [10]. Therefore, we introduced routine measurement of preoperative core temperature and started pre-warming with an electric above-patient warmer if indicated (i.e. if body temperature was below 36 °C).

Operating technique was not changed during these years. All TKA patients were operated on using a tourniquet. All TKA's were cemented, all THA's were uncemented. General or spinal anesthesia was used in all patients depending on the patient´s personal favor and possible risk factors as assessed by an anesthesiologist. Reported operation time is the time between skin incision and closure of the operation wound.

Patients were diagnosed to have a PJI based on MSIS major and minor criteria [11]. In case of an early infection, as defined in the IDSA guidelines [4], debridement with implant retention was performed and six cultures were obtained. Until cultures were definitive, patients were treated with intravenous antibiotics (Cefazolin). If cultures proved positive antibiotic therapy was adjusted accordingly and administered for a total of 12 weeks. If this treatment was not sufficient, a one- or two stage revision of the prosthetic joint was performed.

Statistical analyses

Statistical analyses were carried out using the statistical package SPSS© version 23.0. Baseline characteristics of the patients with a THA or TKA were compared using the chi square and the Mann-Whitney U-test since the Kolmogorov-Smirnov test showed that age, BMI and surgery duration were not normally distributed. The difference between mean core temperature in the hypothermia versus the normothermia group was tested with an independent sample t-test. Difference in incidence of mild hypothermia and PJI between THA and TKA was tested with chi square test. The influence of type of anesthesia, operation time, age, gender, BMI and more recent surgery date on the difference in mean core temperature in both groups was analyzed with linear regression analysis. Results with a p-value of less than 0.05 were considered to be statistically significant.

This study was approved by the local medical ethical committee.

RESULTS

During the study period, a total of 2729 consecutive patients underwent TKA or THA. Subsequently, 129 patients were excluded because of missing temperature measurements. Table 1 shows the baseline characteristics of the 2600 patients in our study population,

1127 undergoing TKA and 1473 undergoing THA. There was no significant difference in type of anesthesia. However, there was a significant difference in gender, mean age, BMI and mean operation time between the two groups (table 1). 39.0% of the TKA patients were male versus 33.4% in the THA group. In the TKA group 74.9% received spinal anesthesia versus 77.5% in the THA group. Mean operation time was 13 minutes longer in the TKA group than in the THA group, 59 vs. 46 minutes respectively. Furthermore, the mean BMI was 29.9 in the TKA group and 27.4 in the THA group.

TABLE 1. Baseline characteristics. S= spinal anaesthesia, G= general anaesthesia

n = 2600	TKA n= 1127 (43,3%)	THA n= 1473 (56,7%)	p-value
Gender M : F (%)	440 : 687 (39% : 61%)	492 : 981 (33.4% : 66.6%)	0.003
Mean Age (years)	67.68	69.34	0.000
Type of Anaesthesia S : G	839 : 281 (74,9% : 25,1%)	1132 : 328 (77.5% : 22.5%)	0.120
Mean Operation time (min)	59,02	46,44	0.000
Mean Body Mass Index	29.97	27.46	0.000

Our primary outcome was an overall incidence of 11.7% of mild hypothermia. The incidence of mild hypothermia in the TKA group was 1.8% lower than in the THA group (10.7 vs. 12.5% respectively). This difference was not significant, p=0.172. We did not observe moderate or severe hypothermia. Mean core temperature directly after arthroplasty surgery was 36.5 °C in both groups (SD=0.51). There was no significant statistical difference between THA or TKA (p=0.521). A chi-square test showed a significant difference between the incidences of hypothermia between the years 2011 and 2012 (p=0.000), 2012 and 2013(p=0.042), but not between the years 2013 and 2014. A linear regression analysis shows a negative linear relationship between gender and core temperature (p=0.000) and type of anesthesia and core temperature(p=0.033). A positive linear relationship was shown between core temperature and BMI (p=0.000), female gender (p=0.000) and the date of surgery (p=0.000). Both patient age (p=0.062) and blood loss were not related with core temperature (p=0.221). Please refer to table 2 and 3 for more details.

TABLE 2. Mean postoperative body temperature and incidence of hypothermia and infections

n = 2600	Total (n=2600)	TKA (n=1127)	THA (n=1473)	p-value
% < 36 °C	305 (11.7 %)	121 (10.7 %)	184 (12.5 %)	0.168
Mean temp	36,5 °C	36.5 °C	36.5 °C	0.990
% Infections	46 (1.8%)	17 (1.5%)	29 (2.0%)	0.378

TABLE 3. Multivariate linear regression analysis model of the relation between gender, type of anesthesia, BMI, duration of surgery, date of surgery, age, arthroplasty type (hip or knee) and postoperative core temperature

n=2600	B	95% CI	P-value
Gender	–0.103	–0.148 to –0.059	0.000
Type of Anesthesia	–0.054	–0.105 to –0.004	0.035
Body Mass Index	0.008	0.004–0.013	0.000
Duration of surgery	0.001	0.000–0.003	0.110
Date of surgery	1.975E-9	0.000–0.000	0.000
Age	–0.002	–0.004 to 0.000	0.062
Arthroplasty of type	–0.018	–0.065 to 0.029	0.452

B=regression coefficient; 95% CI=95% confidence interval

Forty-six patients (1.8%) were diagnosed with PJI. In the TKA group the incidence of PJI was 1.5% PJI, in the THA group the incidence was 1.9%. This difference was non-significant (p=0.378). The incidence of PJI was 1.0% in hypothermic patients versus 1.9% in normothermic patients. This yields a non-significant (p=0.27) relative risk ratio of 0.52. In the THA group, in the normothermic subgroup the incidence of PJI was 2.2%, the incidence of PJI in the hypothermic subgroup was 0%. This difference was significant, p=0.041. After TKA, the incidence of PJI was 1.4% in the normothermic subgroup and 2.5% in the hypothermic subgroup. This difference was not significant (p=0.354).

DISCUSSION

This study indicates that the incidence of inadvertent hypothermia can be reduced. We found that the incidence of mild hypothermia decreased over the study period, with a ceiling effect after two years. We suspect that increased awareness among the staff on the ward and the OR combined with pre-operative heating may be an explanation for the decline in the incidence of hypothermia. We found an overall incidence of 11.7% in primary total knee or hip arthroplasty. This is much lower than the incidence we found in our previous 2013 study, which was 26.7%.

A higher BMI is positively correlated with a higher post-operative core temperature. Females appear to be at greater risk of developing hypothermia after TJA. Spinal anesthesia seems negatively correlated with post-operative body temperature. A previous study did not find significant differences between spinal or general anesthesia, but this could be due to the relative smaller sample sizes in those studies compared to this study [12]. Spinal anesthesia is believed to lead to hypothermia because of a decreased shivering- and vasoconstriction threshold and vasodilatation in the lower extremities [12]. Our data indicate that spinal anesthesia may result in greater decrease in body temperature than general anesthesia, but show no difference in mean post-operative core temperature after TKA or THA.

Mild hypothermia was not associated with a higher incidence of PJI. This is contradictory to the findings in other fields of surgery [2,13]. The difference might be explained by the severity of hypothermia. Perhaps only severe hypothermia leads to an increased risk of infection. Another possible explanation is that in patients with a high risk of PJI more attention is given to the prevention of hypothermia. A third possibility is that other factors are more important in the development of a PJI. A higher BMI is correlated to a higher core temperature but also leads to a higher chance of a PJI [14]. The international consensus group on PJI has identified certain host (or patient) factors for PJI, which include male gender, previous surgery, uncontrolled diabetes mellitus, malnutrition, morbid obesity, active liver or renal disease, smoking or excessive alcohol consumption, intravenous drug abuse, recent hospitalization, active infection, inflammatory arthropathy and severe immunodeficiency [11]. However, it could very well be that we have established a false-negative result. The latter might be due to the low

incidence of PJI in general. Even though we present a relatively large cohort of patients for a single-center study, our study is underpowered to identify a significant difference of <0.05.

Previous studies have tried to establish effective methods to prevent inadvertent hypothermia. These methods mainly consisted of equipment to either warm the patient actively or to passively keep the patient warm during surgery with intensified temperature monitoring. Large scale results show that only forced-air warming seems effective in preventing inadvertent hypothermia and that the use of thermal insulation methods are not effective in maintaining normothermia [6,7,9]. Combined strategies, including preoperative commencement of warming devices, are more effective then isolated measures in vulnerable groups (higher age or longer duration of surgery) [8]. One study showed that an underbody warming system could reduce the incidence of hypothermia in laparoscopic gastrointestinal surgery [15]. The latter might be useful as an additional method to warm patients during TJA, but to date no studies have been published on its use in orthopedic surgery. It remains doubtful if it has additional value, since arthroplasty procedures require less operating time then most laparoscopic procedures.

We conclude that creating awareness among the medical and nursing staff can result in a lower incidence of hypothermia in patients undergoing TKA or THA. This could be an important tool in the reduction of post-operative adverse events. Further studies assessing larger cohorts of patients are required to establish a correlation between hypothermia and PJI.

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CHAPTER 5

HIGH COMPLICATION RATE AFTER TOTAL KNEE AND HIP REPLACEMENT DUE TO PERIOPERATIVE BRIDGING OF ANTICOAGULANT THERAPY ACCORDING TO THE 2012 ACCP GUIDELINE

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ABSTRACT

An increasing number of patients receiving total joint replacement require bridging of long-term anticoagulants. Guidelines, aimed at preventing complications, focus on thrombo-embolic events but not on bleeding complications. In this retrospective observational study, bleeding- and thromboembolic (TE) complications were evaluated in patients requiring perioperative heparin bridging of antithrombotic therapy during primary unilateral total hip or knee arthroplasty (THA and TKA).

Between January 2011 and June 2012, we identified all patients receiving low molecular weight heparin (LMWH) bridging during THA or TKA, according to the 2012 ACCP guideline. Bleeding and TE complications, interventions and patient related outcome measurements (PROMs) were used for evaluation.

Among 972 patients there were 13 patients requiring bridging. 12 patients (92%) experienced bleeding complications. An intervention was required in nine patients (69%). Seven patients received blood transfusion (54%). Nine patients (69%) developed a hematoma and two patients (15%) a periprosthetic joint infection. A total of five patients were re-admitted to hospital (39%) and the length of stay increased in all patients. No TE complications were observed in any of these patients.

This study shows an alarmingly high complication rate in patients receiving LMWH bridging during elective TKA or THA surgery. All complications seem to be caused by, or secondary to bleeding. Patients need to be consulted about the risk of bleeding complications, and the risk of bleeding needs to be balanced over the risk of TE complications.

INTRODUCTION

In order to reduce the risk of perioperative bleeding, long-term anticoagulation therapy has to be interrupted in patients requiring major surgery. In high-risk patients bridging is advised; long-term anticoagulation are replaced by therapeutic dose of short acting agents like unfractionated or low-molecular-weight heparin (LMWH). Bridging aims to reduce the risk of venues thromboembolic events (VTE) but also increases the risk of bleeding complications [1].

The opinions on the optimal treatment protocol of these high-risk patients undergoing lower limb arthroplasty cause considerable debate between orthopedic surgeons and other physicians [2,3]. Cardiologists and internists argue that higher doses of anticoagulant lower the risk of thromboembolic (TE) complications, while orthopedic surgeons emphasize the fact that these agents raise the risk of complications such as increased blood loss, prolonged wound drainage or deep infection [4,5]. No evidence based scientific studies have been carried out regarding the best practice for perioperative bridging of anticoagulants during total joint arthroplasty (TJA) [6]. There are numerous medical papers on the issue of venous TE prevention, but there is a lack of reports on bleeding complications.

In 2012 the American College of Chest Physicians (ACCP) released a clinical practice guideline to address the management of patients who receive long-term anticoagulation and require elective surgery [7]. Orthopedic surgeons, keen to avoid potential litigation following TE complications, which comprise 2% of all National Health Service (NHS) claims in the past ten years [8], feel obliged to follow these guidelines [4]. The question is if these guideline really prevents patients from complications. Well intended guidelines may, paradoxically, do more harm to patients [3].

We hypothesized bleeding complication rate is high in patients requiring periprocedural bridging of anticoagulants during total hip THA and TKA. Therefore, we performed a retrospective analysis of prospective collected data focusing on major and minor bleeding complications in this group.

PATIENTS AND METHODS

Through a computer-aided search of hospital records, all patients who received a primary unilateral THA or TKA between January 2011 and June 2012 in Canisius Wilhelmina hospital were identified. Only patients receiving the high dose bridging regimen anticoagulation were included. Both their medical records and the complication register were reviewed to collect prospectively obtained data within 42 days after surgery. Baseline characteristics and indication for long-term anticoagulants were assessed. Complications and interventions were used as primary and secondary outcome measurements, respectively. Interventions were defined as blood transfusion, re-operation, additional hospital admission, and increase in length of stay. Hematoma formation was defined as a hematoma that caused prolonged blood leakage and/or delayed immobilization (≥ 2 days). Definitions of major surgical bleeding as described by the International Society on Thrombosis and Haemostasis are [9]:

I. Fatal bleedings.
II. Bleeding that is symptomatic and occurs in a critical area or organ.
III. Extrasurgical site bleeding causing a fall in hemoglobin level of 1.24 mmol/L (=20 g/L) or more or leading to transfusion of two or more units of blood or red cells.
IV. Surgical site bleeding that requires a second intervention or a hemarthrosis of sufficient size to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection.
V. Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least 1.24 mmol/L (=20 g/L), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells.

Additionally, patient related outcome measurements (PROMs) were used to assess the health status of these patients, one year after surgery. All included patients were asked to fill in the following questionnaires: the pain visual analogue scale (VAS), the European Quality of life score in 5 dimensions EQ-5D (+ VAS), the Oxford Hip- and Knee score (OHS/OKS) and the Hip- and knee disability and Osteoarthritis Outcome Score (HOOS/KOOS).

Bridging protocol According to the 9th ACCP 2012 guideline patients with a high thromboembolic risk need to be bridged. In high risk patients the need to prevent TE will dominate management irrespective of bleeding risk. High risk patients are patients with:

- Any mitral valve prosthesis, an older aortic valve prosthesis (caged-ball or tilting disc), or a mechanical heart valve and a recent stroke (<6 months) or transient ischemic attack (TIA)
- Or atrial fibrillation and: CHADS2 score 5-6, recent (within 3 months) stroke or TIA, or rheumatic valvular heart disease. CHADS2= congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack; VKA = vitamin K antagonist
- Or recent (within 3 months) venous thromboembolic event (VTE), recurrent VTE, severe thrombophilia

Patients were treated with a standardized periprocedural antithrombotic therapy [6]:

- Stop treatment with VKA 3-7 days preoperatively and start therapeutic LMWH
- Stop LMWH 24 hours preoperatively
- Restart heparin 12-24 hours postoperatively (if no bleeding)
- Restart VKA 2-3 days after surgery (if no bleeding)
- Stop heparin when INR (International Normalized Ratio) of coagulation time is in therapeutic range

The long-term anticoagulation, a vitamin K antagonist (VKA), was replaced by the short acting LMWH enoxaparin (Clexane®, Sanofi-Aventis, Gouda, the Netherlands). Therapeutic enoxaparin was dosed depending on patients' weight varying from 40mg to 100mg twice daily [10]. All included patients were at high risk of TE complication and therefore bridged with high dose LMWH.

Postoperatively, therapeutic dose of enoxaparin (as mentioned in table 2) was started the next day at 7.00 am.

Surgery THA was performed via a posterolateral approach, using uncemented technique. Wounds were closed over a suction drain, deep to the fascia lata. Cemented TKA, either

cruciate retaining or posterior stabilized, was performed via a medial parapatellar approach under tourniquet control and wounds were closed over a suction drain. Drains were removed and patients were mobilized on the first day after surgery.

RESULTS

Between January 2011 and May 2012, 972 patients received a primary THA or TKA. In this group, 13 patients (1.3%) were on long-term anticoagulation therapy (VKA) and had an indication for perioperative bridging with therapeutic dose of LMWH, according to the guideline. Patient and treatment characteristics, including exact indication for, and type of long-term anticoagulation, preoperative INR, operation time, timing of restart of LMWH and VKA and other possible anticoagulative medicine are summarized in Table 1.

Major surgical bleeding (according to the definitions of International Society on Thrombosis and Haemostasis [9]) occurred in 12 of these patients (92%) (table 2). In 12 patients, a fall in hemoglobin level of at least 1.24 mmol/L was observed. Due to prolonged surgical site bleeding, nine patients (69.2%) developed a hematoma (Figure 1) leading to prolonged immobilization for ≥ two days compared to 10.2% in our general population. Two patients (15.4%) subsequently developed a prosthetic joint infection versus 1.0% in the total group.

Because of bleeding complications, an intervention was required in nine patients (69.2%). Seven patients received blood transfusion (54%). A total of five patients were re-admitted to hospital (38.5%); two because of prosthetic joint infection, three because of excessive wound leakage. Patients with prosthetic joint infection required typical surgical debridement and additional intravenous antibiotic therapy. Median length of stay was 11 days (7-52). Mean length of stay was 14.2 days vs. 5.3 days for the total group of 972 patients. No TE event was observed in any of these patients.

FIGURE 1. Example of hematoma formation and wound leakage

PROMS

The postoperative results at 1 year are relatively good, despite the occurrence of complications (Table 3). All THA patients had a VAS score of 0 both at rest and at movement. The TKA patients did not score as well as the THA, with a mean VAS score at rest of 1.9 (range 0-8) and a VAS score at movement of 4.2 (range 0-10). The ED-Q5 was also better in the THA group than in the TKA group (0.86 vs. 0.67). Joint specific PROMs were also slightly better in the THA group than in the TKA group (HOOS/KOOS 17 vs. 15.6 and OHS/OKS 45.8 vs. 32.4). Only one patient (with a TKA) indicated that she would not undergo surgery again.

TABLE 1. Patient and treatment characteristics

	Sex	Age (years)	Indication for anticoagulation and bridging	Type of VKA	pre-op INR	Operation time (min)	Start of LMWH (hours after operation)	Other possible Anticoagulative drug	Restart VKA (days after operation)	Enoxaparin 100 mg/ml s.c. (ml)
THA 1	M	69	MHV	Acenoc	1.2	53	21.5	-	2	1.0 bd
THA 2	M	79	AF (CHADS 5)	Acenoc	1.2	41	21	prednison 5 mg	17	0.8 bd
THA 3	M	75	AF (CHADS 4)	Acenoc	1.2	48	14.5	-	2	0.4 bd
THA 4	M	83	TE + thrombus in apex	Acenoc	1.4	44	22	diclofenac 3x50 mg	28	0.8 bd
THA 5	M	81	MHV	Fenproc	1.4	40	22	-	28	0.8 bd
THA 6	M	77	MHV	Fenproc	1.2	46	17	-	28	0.8 bd
THA 7	F	81	TE	Acenoc	1.2	26	22		28	0.8 bd
THA 8	F	74	AF (CHADS 6)	Acenoc	1.3	37	21.5	asa 80 mg	28	0.6 bd
TKA 1	F	52	TE	Acenoc	1.0	65	21	-	28	1.0 bd
TKA 2	F	58	TE	Acenoc	1.1	58	17	-	2	0.4 bd
TKA 3	F	79	AF (CHADS 6)	Acenoc	1.2	60	19	-	28	0.8 bd
TKA 4	M	63	MHV	Acenoc	1.2	61	13.5	-	28	0.8 bd
TKA 5	F	79	MHV	Acenoc	1.1	51	18	-	28	0.8 bd
Median (range)		77 (52-83)			1.2 (1.0-1.4)	48 (26-65)	21 (13.5-22)		28 (2-28)	0.8 bd (0.4-1.0 bd)

*VKA; vitamin K antagonist, INR; International normalized ratio of coagulation, LMWH; Low Molecular Weight Heparin, THA; total hip arthroplasty, TKA; total knee arthroplasty, MHV; Mechanical Heart Valve, AF; Atrial Fibrillation, CHADS 2; congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack; TE; Thromoembolic Event, asa; acetylsalicylic acid, bd; twice daily. *total blood loss; peroperative + postoperative blood loss in drain*

TABLE 2. Results

			complications			Interventions				
THA/TKA	**Total postoperative blood loss* (ml)**	**Hb fall (mmol/L)**	**hematoma**	**infection**	**TE event**	**Blood transfusion**	**re-operation**	**re-hospitalization**	**length of stay (days)**	**major bleedling type†**
THA 1	720	4.7	+	+	-		+	+	4 + 6	IV
THA 2	350	0.3	+		-				7	IV
THA 3	300	2.1	+		-				11	IV
THA 4	980	2.5			-	+			12	V
THA 5	625	3.4			-	+			22	V
THA 6	400	3.4	+		-	+			11	V
THA 7	330	1.4			-				9	IV
THA 8	300	3.7	+		-	+		+	8 + 3	IV; V
TKA 1	750	4.3	+		-	+		+	5 + 3	IV; V
TKA 2	600	2.4			-				7	
TKA 3	600	3.7	+		-	+			13	V
TKA 4	200	3.3	+	+	-	+	+ (3x)	+	9 + 7 + 36	IV; V
TKA 5	300	2.1	+		-			+	6 + 6	IV
Total			9/13	2/13		7/13	2/13	5/13	185	12/13
%			69	15		54	15	39		92%
Median (range)	400 (200-980)	3.3 (0.3-4.7)							11 (7-52)	

TE = tromboembolic, BT= blood transfusion, TKA = total knee arthroplasty, THA = total hip arthroplasty, bd= twice daily.
** total postoperative blood loss consisted of blood drained during operation and content of drain pot at drain removal on day 1 after surgery*
† definitions and type of major bleeding as defined by International Society on Thrombosis and Haemostasis

TABLE 3. Patient recorded outcome measures

	VAS in rest	VAS movement	EQ-5D	EQ-VAS	HOOS/ KOOS	OHS/OKS	Re-operation
THA 1	0	0	0.69	50	17	44	Yes
THA 2	0	0	0.86	75	17	47	Yes
THA 3	0	0	0.83	50	17	46	Yes
THA 4	0	0	1.00	80	16	46	Yes
THA 5	0	0	1.00	80	16	48	Yes
THA 6	0	0	1.00	75	18	47	Yes
THA 7	0	0	0.51	75	17	42	Yes
THA 8	0	0	1.00	80	18	46	Yes
TKA 1	0	1	0.83	80	20	46	Yes
TKA 2	8	10	0.31	50	4	4	No
TKA 3	0	0	0.80	70	18	39	Yes
TKA 4	1.5	5	0.71	80	18	36	Yes
TKA 5	0	5	0.71	80	18	37	Yes
mean	0.7	1.6	0.8	71.2	16.5	40.6	93.0

VAS = visual analogue scale, EQ-5D = European quality of life - 5 dimensions, HOOS = hip disability and osteoarthritis outcome score, KOOS = knee disability and osteoarthritis outcome score, OHS = oxford hip score, OKS = oxford knee score, TKA = total knee arthroplasty, THA = total hip arthroplasty

DISCUSSION

This study shows an alarmingly high complication rate in patients receiving bridging with LMWH during elective TKA or THA surgery. All reported complications were caused by, or secondary to bleeding. Major bleeding occurred in 12 of these patients (92%). Length of stay was increased in 13 patients (100%), 5 patients (38.5%) were readmitted, and 2 patients developed a prosthetic joint infection (15.4%).

There is one previous study that demonstrates a direct correlation between administration of excessive anticoagulation and the development of periprosthetic infection [5]. This study compared comorbidities, medications, intraoperative, and postoperative factors in 78 cases who underwent revision for septic failure to 156 controls. A multicenter study (17.714 patients) describes that improved compliance to Surgical

Care Improvement Project Measures (including aggressive and early anticoagulation) leads to higher bleeding- and infection rates after major joint replacement surgery [11,12]. Infection rate was 1.60% in hospital with high compliance to TE prophylaxis versus 0.93% in hospitals with lower compliance ($p < 0.001$).

No TE complication occurred in our patient group. The question rises whether a less compulsory LMWH dose regimen would be sufficient as well. Historically, the incidence of developing a fatal pulmonary embolism after joint replacement surgery was as high as 3% [13], but using contemporary techniques it is now less than 0.5%. It seems that studies on which the guideline was based [3,14,15] used a rehabilitation protocol in which the patients were admitted for 8-12 days. This suggests a slow, restricted mobilization protocol. Prolonged bed rest is known to have a profound effect on the development of postoperative TE complications. Newer opioid sparing protocols allow faster rehabilitation and only 2-4 days hospital admittance. It is therefore debatable if the studies on which the guidelines have been based, reflect the actual possibility of developing a TE event [3]. In a recent fast track study of 1977 unselected patients who did not use prolonged LMWH the incidence of death was 0.15%, the incidence of clinical DVT was 0.56% and the incidence of pulmonary embolism was 0.30% [16,17]. This is why orthopedic surgeons worldwide have questioned the need for prolonged LMWH.

Furthermore, guidelines are based on thromboembolism risk estimates in patients outside of the peri-operative setting. These estimates are based on patients who were either not receiving anticoagulation or receiving sub-optimal therapy (e.g. aspirin)[18]. Indeed, the recent update of the ACCP guidelines gives orthopedic surgeons more latitude in their choice and management of VTE prophylaxis [19]. Possibly, our bridging protocol was too strict (mean time of restarting therapeutic enoxaparin was 21 hours after surgery). The new guidelines prescribe: In patients who are receiving bridging anticoagulation with therapeutic-dose subcutaneous LMWH and are undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48 to 72 h after surgery instead of resuming LMWH within 24 h after surgery [7].

In general surgery, anticoagulant-treated patients receiving perioperative heparin bridging appear to be at similar risk of thromboembolic event compared to non-bridged patients [1]. Literature discussing VTE prophylaxis in total joint replacement questions the

need for routine thromboprophylaxis, although they do not specifically address the high-risk chronically anticoagulated patient [4,20].

Interestingly, there are data that suggest perioperative continuation of long-term anticoagulation as a safe alternative [21]. However, the use of spinal anesthetic techniques are contraindicated in these patients.

We reported PROMS after one year to give an impression on how bleeding complications could influence long term postoperative results. Despite the occurrence of complications, the results are better than we expected. The results of the TKA group are not quite as good, and one (of five) patient with a TKA has a very poor result. Paradoxically, this patient did not have a major bleeding complication at surgical site in the first 42 days after surgery.

Study limitations

One of the weaknesses of this study is the small patient group. Only a small percentage of all patients receiving a total joint replacement, has an indication for bridging. However, we found such a high complication rate in this small group, that the orthopedic society should be alarmed. Another weakness is the retrospective non-controlled observational design. An issue with retrospective data is that it can have information bias, and can underestimate the prevalence of complications. However, the use of consecutive patients eliminates some potential bias, and eligible patients formed a specific and homogenous study group. Also, it seems unlikely that this potential bias would significantly alter the outcome of this study since the rate of complications is already so high. In our view conducting a prospective study in the same subject seems unethical, for exposing patients to such a high risk of bleeding induced complications. The issue is more what kind of VTE prophylaxis these patients really need, without exposing them to a high complication risk. The non-controlled study design makes it impossible to compare the treatment protocol to other protocols. We choose not to compare our patients to patients in our general population because baseline characteristic and risk profiles for bleeding and TE complications are totally different.

There is an urgent need for randomized studies to access which protocols will balance the risk of TE complications versus the risk of bleeding complications. The industry

that supported previous high dose, long duration LMWH trials may not initiate nor sponsor more restricted trials for obvious reasons. Newer trials need to be initiated by the orthopedic community.

The percentage of patients needing bridging is still relatively low, less than 1.5%. However, there is a relative rise of octogenarians receiving a THA or TKA. In addition, a 40% rise in the absolute numbers of THA and TKA patients is expected by 2026 [22]. This trend will result in a higher number of chronically anticoagulated patients needing periprocedural bridging [23]. This could lead to a high number of patients with postoperative complications and huge costs.

In conclusion, the risk of bleeding complications using bridging anticoagulation therapy during or after TJA seems to be alarmingly high, and needs to be balanced over the risk of thromboembolism.

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CHAPTER 6

GENERAL ANESTHESIA MIGHT BE ASSOCIATED WITH EARLY PERIPROSTHETIC JOINT INFECTION: AN OBSERVATIONAL STUDY OF 3909 ARTHROPLASTIES

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ABSTRACT

Background and purpose: Periprosthetic joint infection (PJI) remains a devastating complication following total knee or total hip arthroplasty (TKA/THA). Nowadays, many studies focus on preventive strategies regarding PJI, however, the potential role of anesthesia in the development of PJI remains unclear.

Methods: All consecutive patients undergoing elective primary unilateral TKA or THA from January 2014 through December 2017 were included. Exclusion criteria included femoral fractures as the indication for surgery and previously performed osteosynthesis or hardware removal on the affected joint. Age, BMI, ASA classification, gender, type of arthroplasty surgery, type of anesthesia, duration of surgery, smoking status and intra-operative hypothermia were recorded. Propensity score matched univariable logistic regression analysis was used to control for allocation bias.

Results: 3909 procedures consisting of 2111 (54%) THA and 1798 (46%) TKA were available for analysis. 1630 (41.7%) arthroplasties were performed under general anesthesia and 2279 (58.3%) under spinal anesthesia. 28 (1.7%) early PJI were observed in the general anesthesia group and 19 (0.8%) in the spinal anesthesia group. The multivariable logistic regression model demonstrated an odds ratio for PJI of 1.95 (95% CI 1.02 - 3.73) after general anesthesia (n = 1630) relative to the propensity score matched patients (n = 1630) who received spinal anesthesia.

Conclusion: These results suggest a potential association between general anesthesia and early PJI. Future research using large-scale data is required to further elucidate this clinically relevant association.

INTRODUCTION

Periprosthetic joint infection (PJI) remains one of the most devastating complications following total knee or hip arthroplasty (TKA/THA). PJI is responsible for up to 25% of failed TKA and 15% of failed THA [1,2]. The number of THA and TKA performed yearly is projected to increase to as much as 4 million by 2030 in the United States alone [3]. This increasing number of arthroplasty procedures will eventually lead to an increased number of surgical site infections (SSI) and subsequent PJI. The latter has led researchers to establish evidence-based methods for the prevention of PJI. Prevention of infection can only be achieved through a comprehensive understanding of the pathophysiology and predisposing risk factors. Regarding PJI, several patient-related risk factors have already been identified which can assist the attending surgeon estimate the potential risk of infection in patients at risk for PJI [4]. Despite the increasing awareness of certain patient characteristics that influences the risk of PJI, the role of procedure related factors, such as the type of anesthesia, remains to be elucidated [5]. Remarkably, the notion that anesthesia may influence the immune response has been suggested as early as 1903 [6]. In the late 70s and 80s several reviews identified the ability of anesthetic agents to influence a wide variety of specific and non-specific host defenses [6]. However, to date the clinical relevance and the exact role of anesthesia in the pathogenesis of postoperative infections remains unclear [6,7]. Several studies have suggested spinal anesthesia to reduce the risk for SSI when compared to general anesthesia in THA and TKA [8–11], however, other studies found no clear difference between both types of anesthesia and their influence on risk of PJI [12–19]. Still, a recent systematic review suggested that regional anesthesia seems to decrease the risk of SSI when compared to general anesthesia [20]. Despite several clues pointing to general anesthesia predisposing to infection, no studies assessing the role of anesthesia during THA and TKA with well-defined definitions of PJI have been performed.

Therefore, the aim of this study was to investigate the relationship between type of anesthesia (i.e. spinal or general) and PJI following THA or TKA in a large-scale observational cohort study.

MATERIAL AND METHODS

All consecutive patients undergoing elective primary unilateral TKA or THA for osteoarthritis in a single general teaching hospital from January 2014 through December 2017 were retrieved from the hospital's prospective database. Subsequent exclusion criteria were proximal femoral fracture or acetabular fracture as the indication for primary surgery and concomitant or previous hardware removal on the affected joint. Data were recorded regarding the patient's age, ASA classification, BMI, gender, smoking behavior, type of arthroplasty surgery, type of anesthesia, surgery duration, intra-operative hypothermia, and length of stay. The local institutional review board approved this study (study number: 2018-1276).

Over the course of the study period a similar surgical technique was used, and no changes to the surgical protocol were implemented. Patients received prophylactic administration of 2 grams of cefazolin 15 to 60 minutes prior to skin incision or tourniquet inflation, followed by three administrations of 1 gram after surgery with an 8-hour interval. All THA were performed by, or under direct supervision of, one of 7 hip surgeons. Accordingly, all TKA were performed by one of 4 knee surgeons. Several residents or trainees participated in most surgeries. All TKA patients underwent surgery while using a tourniquet which was inflated 15 to 60 minutes after infusion of the prophylactic cefazolin and deflated after applying a pressure bandage over the affected knee. Only patients with primary implant models and no revision models were included. All TKAs were cemented and performed using a medial parapatellar arthrotomy. THA was performed using a posterolateral approach. Both cemented and uncemented THA were performed with a patient age cut-off point below 75 years for uncemented THA. The bone cement (Palacos® R+G; Heraeus) used in both TKA and THA contained 0.75 grams of gentamicin per 61.2 grams of powder. The decision to apply either general- or spinal anesthesia during total joint arthroplasty (TJA) was at the discretion of one of the senior anesthesiologists and based on the patients' personal preference. Patients were extensively informed on both general- and spinal anesthesia, after which they could indicate their preference. To correct for potential allocation bias introduced through this selection procedure, propensity score-based matching of cases was performed (please refer to statistical methods for further information).

Surgical duration was defined as the time between skin incision and closure. The core temperature was measured at the tympanic membrane (Genius™ 2; Medtronic) in the operation room directly after wound closure.

Prior to discharge patients were closely monitored for signs of potential post-operative infection. Following discharge, all patients were subjected to protocolized surveillance of infection in the outpatient clinic for at least 3 months after surgery. In case of prolonged wound drainage (>10 days), suspected (superficial) SSI or superficial wound breakdown, surgical Debridement, with Antibiotics and Implant Retention (DAIR) was performed. During DAIR, six periprosthetic tissue biopsies were routinely obtained and subsequently cultured. Superficial SSI was defined according to the Infectious Centers of Disease Control (CDC) guidelines with the presence of: (1) purulent incisional drainage, (2) positive culture of aseptically obtained fluid or tissue from the superficial wound, (3) local signs and symptoms of pain or tenderness, swelling, and erythema after the incision is opened by the surgeon (unless culture negative), or (4) diagnosis of SSI by the attending surgeon or physician based on their experience and expert opinion [21].

Until final cultures results were obtained up to ten days after DAIR, patients were treated with intravenous antibiotics (flucloxacillin, 6g/day via continuous intravenous infusion).

PJI was diagnosed according to the major Musculoskeletal Infection Society (MSIS) criteria by means of 2 or more tissue cultures demonstrating growth of an identical pathogen [22]. If PJI was diagnosed, antibiotic therapy was adjusted accordingly in consultation with the attending microbiologist.

The primary outcome of this study was the incidence of PJI within 3 months of surgery.

Statistical methods

Multiple imputation by chained equations procedures were used for missing values to increase precision and to avoid bias [23]. We generated 25 independent imputed datasets, as current guidance recommends that one imputation should be performed per percent of incomplete observations [24]. Smoking behavior and hypothermia had 4.1% and 24.2% missing values, respectively, whereas other variables had less than 0.1% missing values (Table 1).

TABLE 1. Distribution of patient characteristics and missing data among the general anesthesia and spinal anesthesia groups

	Spinal anesthesia (n = 2279)	Missing data (%)	General anesthesia (n = 1630)	Missing data (%)	Cumulative missing data (%)
Age (mean (SD))	69.82 (9.48)	0 (0%)	67.27 (10.10)	0 (0%)	0 (0%)
Male gender (n (%))	789 (34.6%)	0 (0%)	597 (36.6%)	0 (0%)	0 (0%)
BMI (mean (SD))	28.71 (4.70)	0 (0%)	29.7 (5.17)	2 (0.1%)	2 (0.0%)
ASA 1 (n (%))	348 (15.3%)	0 (0%)	221 (13.6%)	1 (0.1%)	1 (0.0%)
ASA 2 (n (%))	1614 (70.8%)	0 (0%)	1049 (64.4%)	1 (0.1%)	1 (0.0%)
ASA 3 (n (%))	306 (13.4%)	0 (0%)	344 (21.1%)	1 (0.1%)	1 (0.0%)
ASA 4 (n (%))	11 (0.5%)	0 (0%)	15 (0.9%)	1 (0.1%)	1 (0.0%)
Active smoker (n (%))	231 (10.6)	101 (4.4%)	223 (14.2)	61 (3.7%)	162 (4.1%)
TKA (n (%))	1082 (47.5%)	0 (0%)	716 (43.9%)	0 (0%)	0 (0%)
2014 (n (%))	674 (29.6)	0 (0%)	286 (17.5)	0 (0%)	0 (0%)
2015 (n (%))	591 (25.9)	0 (0%)	391 (24.0)	0 (0%)	0 (0%)
2016 (n (%))	488 (21.4)	0 (0%)	518 (31.8)	0 (0%)	0 (0%)
2017 (n (%))	526 (23.1)	0 (0%)	435 (26.7)	0 (0%)	0 (0%)
Surgery duration	59.30 (15.92)	0 (0%)	61.69 (16.44)	0 (0%)	0 (0%)
Hypothermia	87 (5.6%)	724 (31.8%)	54 (3.8%)	223 (13.7%)	947 (24.2%)
PJI (n (%))	19 (0.8%)	0 (0%)	28 (1.7%)	0 (0%)	0 (0%)

Percentages are displayed as valid (calculated through discarding missing data) percentages. BMI: Body Mass Index, TKA: Total Knee Arthroplasty, PJI: Periprosthetic Joint Infection.

The difference in the risk for early PJI between cases that received spinal- and those that received general anesthesia might be biased by confounding. A particularly important type of confounding in this case is "confounding by indication," which occurs when the clinical indication for selecting a particular intervention also affects the outcome. For example, patients with more severe comorbidities (e.g. CVD) are more likely to receive general anesthesia, but they are also more likely to develop early PJI. Another type of confounding is "confounding by association", which occurs when both exposure (i.e. type of anesthesia) and outcome (i.e. early PJI) are associated with a third variable. For example, BMI is associated both with type of anesthesia and with increasing risk of early PJI. In order to adjust for potential confounding baseline characteristics, we matched patients based on their propensity scores [25]. The propensity score was defined

as the probability of receiving general anesthesia during TJA dependent on a case's recorded baseline characteristics. Propensity scores were estimated independently for each imputed dataset, using a logistic regression model with type of anesthesia as the dependent variable in relation to the following baseline characteristics: age, gender, BMI, ASA-classification, smoking status, type of arthroplasty surgery, and year of surgery. The selection of which variables to include in our analyses in order to minimize bias was done using directed acyclic graphs based on the approaches described by Shrier and Pearl [26,27]. A 1:1 optimal matching algorithm was applied without replacement to match exposed and non-exposed cases on their corresponding propensity scores within a caliper of 0.2 standard deviation of the logit of the propensity score [28]. A 1:1 matching on propensity score was used as it has been shown that it tends to minimize bias compared to many-to-one matching on propensity score [29]. The balance between both groups after matching was checked graphically and descriptively. A standardized difference of less than 10% indicates an appropriate balance [28]. Standardized differences (difference in means divided by the pooled standard deviation) of the baseline characteristics for a randomly selected matched dataset are provided in Table 2.

On each of the 25 imputed and propensity score matched datasets, a univariable logistic regression analysis with PJI within 3 months after surgery as the dependent variable and type of anesthesia as independent variable was performed. The resulting estimates were pooled using Rubin's rule [25]. Statistical analyses were performed using R 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

TABLE 2. Distribution of number and corresponding proportions or means and corresponding standard deviation of patient characteristics and comorbidities among the general anesthesia and spinal anesthesia groups before and after matching based on propensity scores for a randomly selected imputation set

	Before matching			After matching		
	Spinal anesthesia (n = 2279)	General anesthesia (n = 1630)	Standardized difference	Spinal anesthesia (n = 1630)	General anesthesia (n = 1630)	Standardized difference
Age (mean (SD))	69.82 (9.48)	67.27 (10.10)	-0.2526	68.07 (9.68)	67.27 (10.10)	-0.0778
Male gender (n (%)	789 (34.6%)	597 (36.6%)	0.0416	607 (37.2)	597 (36.6)	0.0000
BMI (mean (SD))	28.71 (4.70)	29.7 (5.17)	0.1278	29.14 (4.85)	29.37 (5.17)	0.0514
ASA 1 (n (%)	348 (15.3%)	221 (13.6%)	-0.0481	236 (14.5)	221 (13.6)	-0.0287
ASA 2 (n (%)	1614 (70.8%)	1049 (64.4%)	-0.1349	1105 (67.8)	1049 (64.4)	-0.0641
ASA 3 (n (%)	306 (13.4%)	344 (21.1%)	0.1881	279 (17.1)	344 (21.1)	0.0917
ASA 4 (n (%)	11 (0.5%)	15 (0.9%)	0.0458	10 (0.6)	15 (0.9)	0.0321
Active smoker (n (%)	231 (10.6)	223 (14.2)	0.1084	201 (12.3)	232 (14.2)	0.0541
TKA (n (%)	1082 (47.5%)	716 (43.9%)	-0.0715	735 (45.1)	716 (43.9)	-0.0148
2014 (n (%)	674 (29.6)	286 (17.5)	-0.3161	298 (18.3)	286 (17.5)	-0.0242
2015 (n (%)	591 (25.9)	391 (24.0)	-0.0455	425 (26.1)	391 (24.0)	-0.0560
2016 (n (%)	488 (21.4)	518 (31.8)	0.2226	465 (28.5)	518 (31.8)	0.0711
2017 (n (%)	526 (23.1)	435 (26.7)	0.0815	442 (27.1)	435 (26.7)	0.0000

BMI: Body Mass Index, TKA: Total Knee Arthroplasty.

RESULTS

Between January 2014 and December 2017, 4026 primary unilateral total hip and knee arthroplasties were performed. 58 THAs and 59 TKAs were excluded due to previous or concomitant hardware removal, leaving 3909 joints consisting of 2111 (54%) hips and 1798 (46%) knees available for analysis.

Among all eligible patients, 1630 (41.7%) arthroplasties were performed under general anesthesia and 2279 (58.3%) arthroplasties were performed under spinal anesthesia. Apart from the DAIR procedures, a total of 17 cases underwent revision surgery within 3 months of primary TJA (Table 3). None of these cases were eventually diagnosed with early PJI.

TABLE 3. Number of patients requiring revision surgery within 3 months of index surgery

	n	Frequency
Recurrent dislocation	7	41.2%
Periprosthetic fracture	8	47.1%
Spinout of insert	1	5.9%
Femoral stem subsidence	1	5.9%
Total	17	100%

n: number of cases.

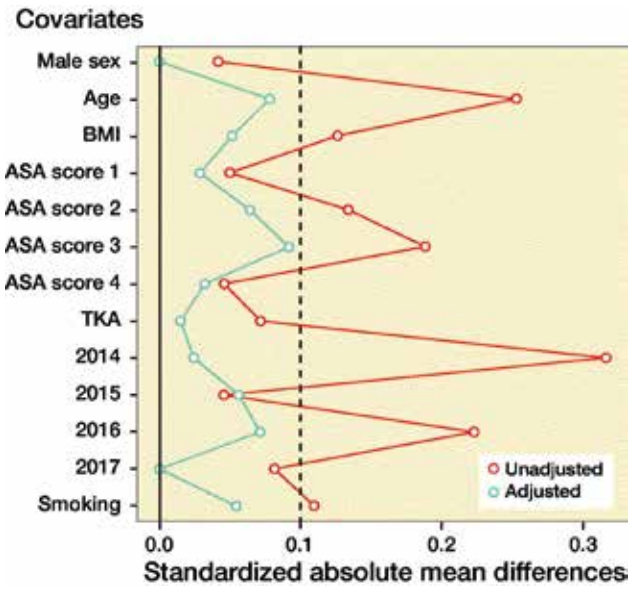

FIGURE 1. covariate balance before (unadjusted) and after (adjusted) propensity score matching. Standardized differences less than 10% (dashed line) indicate an appropriate balance (Austin 2010)

In total, 47 early PJIs were diagnosed through 2 or more positive intra-operative tissue cultures, obtained during DAIR, demonstrating an identical pathogen. Twenty-eight (1.7%) PJIs occurred in the general anesthesia group and 19 (0.8%) in the spinal anesthesia group.

The covariate balance before and after propensity-score based matching is displayed in figure 1 and table 2. In the 1630 patients who received general anesthesia 28 (1.7%) PJIs occurred, while in the 1630 matched participants who received spinal anesthesia, 13-15 (0.8-0.9%) PJIs occurred, depending on imputation set.

The odds ratio for early PJI was estimated to be 1.95 (95%CI 1.02 - 3.73; p = 0.04) for patients who received general anesthesia compared to matched patients who received spinal anesthesia.

Although no longer statistically significant, subsequent subgroup analysis addressing THA and TKA separately showed similar odds ratios (THA: 2.14 (95%CI 0.99 - 4.62; p = 0.05) & TKA: 2.04 (95%CI 0.53 - 7.9); p = 0.30).

DISCUSSION

Over the past decade, several studies have suggested that spinal anesthesia decreases the risk for SSI after TJA when compared to general anesthesia [8–11]. However, this remains subject to debate since many conflicting results have been reported and there is a paucity of high quality studies utilizing objective criteria for SSI [12–19]. The distinction between (superficial) SSI and early PJI in orthopedic surgery is far from straightforward yet clinically very relevant. In 1999, the Centers for Disease Control (CDC) formulated definitions for superficial-, deep incisional- and organ/space SSI [30]. However, there are no procedures or tests to reliably allow differentiation between these subtypes of SSI [31]. Furthermore, diagnostic criteria for superficial SSI such as tenderness, redness, localized swelling and local heat are subject to interobserver variability [32]. Therefore, previous studies addressing the effect of anesthesia on SSI, yield less reliable results compared to this study utilizing objectified PJI as the primary outcome measure.

The IDSA guidelines dictate a vigorous surgical treatment for (suspected) SSI following TJA including surgical debridement and rinsing of the implant [33]. In previous

studies these guidelines were not applied and as such the diagnosis of actual early PJI was not reliably established.

To the best of our knowledge this is the first study utilizing the IDSA guidelines where an association between the type of anesthesia and the incidence of objectified early PJI (utilizing the major MSIS criteria through the availability of at least six periprosthetic tissue cultures in every case with suspected infection) is shown. Our results indicate an increased risk of early PJI following TJA under general anesthesia, illustrated by an odds ratio of 1.95 (95% 1.02 – 3.73). Although no longer statistically significant, subgroup analysis for the type of arthroplasty (THA or TKA) demonstrated similar confidence intervals which indicate these results are robust and do not seem to depend on type of arthroplasty.

So far, the mechanism by which general anesthesia might increase, or spinal anesthesia might reduce the incidence of infection is not fully understood. However, increased tissue oxygenation (through reduced postoperative pain and the direct vasodilatory effect of spinal anesthesia) has been suggested as a potential mechanism in the past [34–39]. Next to these beneficial effects on tissue oxygenation, neuraxial anesthesia is also associated with reduced blood loss, a reduced requirement of blood transfusions and a reduced incidence of hyperglycemia. All these factors are known for their immunosuppressive effects [40,41].

Besides the suggestion of protective effects of spinal anesthesia several aesthetic agents which are commonly used in general anesthesia, may significantly inhibit leukocyte chemotactic migration, phagocytosis, lymphocyte function, inflammation or even directly support bacterial growth in case of contamination [6,7,42–44]. Furthermore, studies comparing general and spinal anesthesia showed that in spinal anesthesia these immunosuppressive effects were minimal [45].

On the other hand, one could speculate on a potential negative effect of spinal anesthesia on the incidence of early PJI induced by intra-operative hypothermia, which has been associated with an increased incidence of SSIs in other surgical specialties and is more prevalent during spinal anesthesia [46–48]. However, despite the latter, spinal anesthesia was still associated with a reduced risk of early PJI.

Limitations

First, due to the observational nature of the study, confounding (by indication) cannot be precluded. To control for this potential confounder, we matched patients based on propensity scores. Although matching of patients was successfully performed based on a subset of baseline characteristics, differences could theoretically still exist in unmeasured covariates (e.g. diabetes mellitus, rheumatoid arthritis and anticoagulant usage in this study) resulting in residual confounding. Anticoagulant therapy, for example, is generally considered as a contra-indication for the application of spinal anesthesia. This may have caused allocation of anticoagulant users to the general anesthesia group. However, since protocols for perioperative interruption of anticoagulant use (with or without bridging) are readily available and mandatory regarding elective TJA in our clinic, anticoagulant therapy is unlikely to cause allocation of patients towards the general anesthesia group. Furthermore, both diabetes and rheumatoid arthritis do not influence the choice for either spinal or general anesthesia in our hospital.

Another limitation is the fact that our data are sourced from one hospital only. Therefore, the major question remains whether our data and drawn conclusions will prove to be reproducible in in studies on, for example, national joint registries. However, on the other hand this last limitation warranted that a complete follow-up could be guaranteed and that no PJIs could have been missed.

In conclusion, this is the first study to suggest a potential association between general anesthesia and an increased risk of early PJI. This clinically relevant finding should encourage the set-up of future research using (multi-center) randomized large-scale data and national joint registry studies.

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CURE IF YOU MUST

PART II:

CURATIVE TREATMENT OF PJI

CHAPTER 7

TWO-STAGE REVISION OF INFECTED HIP REPLACEMENT WITH RETENTION OF THE FEMORAL CEMENT MANTLE

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ABSTRACT

This retrospective analysis evaluates ten patients with a late infection of a cemented total hip artroplasty (THA) treated with two-stage revision with retention of the original well-fixed femoral cement mantle.

Clinical, laboratory, and radiological outcomes were evaluated. The average age at the first stage revision procedure was 61.5 years (range 38-80). The mean follow-up period was 26 months (range 5 to 54).

Successful eradication of the primary microorganism was achieved in 2 patients. These patients had negative cultures at second stage and did not show any signs of infection during follow up.

The other 8 patients were considered as failures. In 3 patients, the femoral cement mantle was removed after the first stage due to recurrent infection in the Girdlestone situation. In 2 patients, cultures showed the same micro-organism at first and second stage, treated with 3 months of antibiotics after second stage. Two patients showed negative cultures at second stage but recurrent infection afterwards. This was treated with debridement and implant retention (DAIR) and 3 months of antibiotics. One patient was treated with suppressive antibiotics for persistent prosthetic joint infection after the second stage, despite DAIR and therapeutic antibiotic treatment.

In conclusion, results of two-stage revision with retention of femoral cement mantle are disappointing in treatment of infected THA in this study. Based on these results, we would not recommend the routine use of cement-within-cement revision PJI treatment until surgical techniques are optimized and treatment outcomes improve.

INTRODUCTION

Periprosthetic joint infection (PJI) is the third most common reason for revision of total hip arthoplasty (THA) and accounts for about 15% of all revisions [1]. The golden standard of treatment for a chronic periprosthetic infection of a cemented THA is a two-stage revision procedure [2]. In the first stage, all components including the cement at the acetabular and femoral side are removed. After a successful antibiotic treatment, a total hip prosthesis can be reinserted in the second stage [3]. However, complete removal of the femoral cement mantle is technically difficult, time-consuming and can cause excessive blood loss, bone loss, and femoral fractures [4-6]. Cement-within-cement revision on the femoral side (CWC) is successfully performed in aseptic revision of THA to overcome these problems [7], but data on this technique in septic revisions are limited. For CWC revision, an intact and well-fixed cement mantle is required. Accepted indications for CWC revision are: a broken original stem but intact cement mantle, removal of a well-fixed cemented stem to improve exposure for an acetabular revision or treatment of instability where stem revision is performed to alter offset or anteversion [8].

In the past, there has been debate whether it is possible to preserve the femoral cement in infected femoral hip replacements [9]. As a foreign substance the cement mantle can serve as a suitable environment for bacteria to grow [10, 11]. Despite the debate we found only one published article on the preservation of femoral cement in infected total hip revision. Morley et al. presented 15 patients who had undergone a two-stage revision for infected total hip replacement where the femoral cement mantle at the first stage procedure was left in situ. A successful eradication of infection was achieved in 14 of the 15 patients [12].

In this retrospective cohort study, we present 10 patients with an infected THA who were considered suitable for a two-stage CWC revision at the time of the first stage. In the first stage all prosthetic material was removed except for the femoral cement mantle. After the infection was successfully treated a second stage procedure was performed.

PATIENTS AND METHODS

Between May 2009 and March 2013, 333 revisions procedures of hip prosthesis were performed at our institution. All operation reports were reviewed and patients with an infected THA in whom the femoral cement mantle had been preserved during the first surgical procedure were included with the intention to reinsert the stem within this mantle in the second stage procedure. The group of patients included 6 men and 4 women with a mean age of 61.5 years (range 38-80) at the time of the first stage procedure. All individual characteristics are summarized in Table 1.

Diagnosis

Preoperative diagnosis of infection was based on medical history, clinical signs of infection and C-reactive protein (CRP) (>10 mg/l). In some cases, In-111-labeled non-specific human immunoglobulin G scintigraphy, technetium-99m-labeled methylene diphosphonate scintigraphy, or positron emission tomography (PET-CT) were performed to support the diagnosis. Barrack staging was used to assess the femoral cement mantle interface on loosening from the bone [13]. Definite diagnosis of PJI was confirmed by growth of the same microorganism in ≥ 2 cultures of synovial fluid or periprosthetic tissue, while at least 6 specimens were obtained for culture during the first stage.

Management of PJI was based on the treatment algorithm by Zimmerli et al. [14] and the current IDSA Guidelines [2], performed by a multidisciplinary team consisting of an orthopedic surgeon, a microbiologist and an infectious diseases specialist. This team had a weekly meeting, however if needed adaptation of the treatment based on new findings was performed on a daily basis.

TABLE 1. Patient characteristics, comorbidity, and previous operations on effected side and primary reason for THA.

Subject	Age (years)	Sex	Side	BMI	ASA-classification	Comorbidity	Previous operations on affected side	Reason for THA
1	71	M	R	28.7	III	Terminal renal failure **Coronary artery bypass graft** Atrial Fibrillation		Coxathrosis
2	68	F	R	23.1	III	Hypertension, DM II, COPD Gold III, PCI of carotic artery, renal failure	Traumatic hip fracture treated with cannulated crews	Secondary coxathrosis
3	74	M	L	24.6	III	Hypertension, CVA, Kahler`s disease	Revision due to recurrent dislocations	Coxarthrosis
4	43	M	R	23.6	I	-	Dynamic Hip Screw for femoral neck fracture THA for non-union of femoral neck fracture	Secondary coxathrosis
5	65	F	R	26.3	I	-	Revision due to aseptic loosening	Coxathrosis
6	70	F	R	32.9	II	-		Coxarthrosis
7	53	M	R	23.4	II	Psoriasis	Revision of with bone impacting graft Fracture of ramus superior and inferior due to trauma Revision with impaction bone grafting due to acetabular fracture	Periprosthetic fracture of cement and cup due to trauma
8	53	M	R	29.4	II	DM II Hypothyroidism Hypertension	Percutaneous SI-fixation and acetabulum fracture due to trauma.	Secondary coxathrosis
9	38	M	L	21.7	II	Congenital hypdysplasia	Fracture of the femur and acetabulum, treated with THA.	Secondary coxathrosis
10	80	F	L	19.6	II	Paroxysmal atrial fibrillation Mental retardation	Cup-revision due to multiple dislocations Revision of femoral stem Revision of THA due to periprosthetic fracture, complicated with PJI	Coxarthrosis
Mean	62.4	M/F 7/4	R/L 8/3	25.2				

First stage surgical procedure

First stage surgery involved a posterolateral approach without trochanteric osteotomy. After at least 6 cultures were taken (capsular, synovial fluid and bone interface), 2 grams of cefazolin was admitted intravenously. The femoral component was removed directly after dislocation of the hip prosthesis. Next, the neck of the femur was cut for 3 mm to expose the cement bone interface. In all cases there was no interface between the femoral bone and the cement detectable. This was tested by probing a surgical knife between the bone and cement. The acetabular component and all acetabular cement were removed afterwards. Debridement was performed and pulse-lavage was used with at least 3 liters of NaCl 0.9% solution. After debridement and synovectomy, gentamycin loaded beads were left behind in 9 patients for 2 weeks, depending on the surgeon's preference.

Antibiotic treatment

After first stage surgical procedure, all patients were treated with intravenous antibiotics, consisting of a betalactam (clindamycin intravenous (600 mg 3 times daily) or flucloxacillin intravenous (1 gram 6 times daily). Antibiotics were switched after the isolation and susceptibility had been identified. Total duration of antibiotic treatment was at least 6 weeks. After an intended antibiotic-free interval of 1 month with normal blood markers (CRP, Leucocytes and Erythrocyte Sedimentation Rate) and absence of clinical signs of infection, the second stage was performed. If there were clinical and biological signs of infection despite well set antibiotic treatment, the femoral cement mantle was removed after the first stage.

Second stage surgical procedure

After a successful antibiotic treatment, the second stage surgical procedure was performed. Antibiotic prophylaxis (cefazolin 2 grams intravenously) was given preoperatively. The same incision was used to approach the hip. During surgery, again, fluid and tissue specimens were sent for microbiological assessment. If indicated, acetabular bone defects were reconstructed with impaction bone grafting (IBG) [15]. A polyethylene cup was inserted using Simplex® bone cement with 500mg erythromycin and 3.000.000 EH colistin (Stryker, Newbury, UK) [16,17], which was followed by CWC revision of the femoral

part [3]. Since patients were assumed to be infection-free at the time of second stage, no antibiotics were administered after second stage.

Follow-up

Clinical, laboratory and radiological evaluation was performed at the outpatient clinic at 6 weeks, 3 months, 6 months, and then yearly. If there was a recurrent infection, debridement with implant retention (DAIR) was performed. Follow-up was continued until March 2015.

Definitions

Cure: (a) no clinical, radiological or laboratory signs of infection with femoral cement mantle in situ at the latest follow-up, with a minimum of 1 year after re-implantation, (b) proven negative perioperative cultures in case of reoperation for other reasons than infection.

Failure: (a) femoral cement removal before the second stage because of persistent signs of infection or (b) persistence/recurrence of infection despite surgical and antibiotic treatment after reimplantation.

RESULTS

All patient characteristics, co-morbidities, and the orthopedic history are shown in Table 1. The mean follow-up period was 26.3 months (range 5 to 54). Eight patients with Barrack A, 1 patient with Barrack B and 1 with Barrack C of the femoral cement mantle were included (Table 1). The mean time between the primary THA and first stage surgery to remove the infected implant was 94 months (range 2-300). Mean time between first stage and second stage surgery was 4 months (range 1-8). Cultured organisms at first stage and second stage, antibiotic treatment and clinical outcome are summarized in Table 2. None of the patients died during the follow-up period.

TABLE 2. Micro-organisms cultured from specimens taken at the time of first and second stage revision, study, treatment, and last follow-up times included progress and outcome

Subject	Barrack stage	Infecting organism cultured at the time of first stage	Antibiotic treatment	Organism cultured at the time of second stage revision.	Time from primary procedure to first stage. (Mths)	Time from first stage to second stage/ girdlestone. (Mths)	Time from first stage to last follow-up appointment. (Mths)	Progress	Outcome
1	A	*S. epidermidis*	Clindamycin + rifampicin for 3 months	No organism was cultured	3	8	23	No signs of infection after 2nd stage	Success
2	A	*E. faecalis*	Amoxicillin + ceftriaxone for 6 weeks	No organism was cultured	46	6	8	No signs of infection after 2nd stage	Success
3	A	*Streptococcus mitis*	Clindamycin for 6 weeks	No organism was cultured	120	3	28	Recurrent PJI†, successfully treated with DAIR* and 3 months of antibiotics (multiple organisms were cultured at DAIR*)	Failure
4	B	*S. epidermidis*	Clindamycin for 6 weeks	Staphylococcus epidermidis	8	3	28	Staphylococcus epidermidis cultured during first and second stage. Successfully treated with 3 months of antibiotics	Failure
5	A	*Coagulase-negative Staphylococcus*	Metronidazole and teicoplanin for 3 months	Coagulase-negative Staphylococcus	180	4	54	Coagulase-negative Staphylococcus cultured during first and second stage. Successfully treated with 3 months of antibiotics	Failure
6	A	*No organism was cultured*	No antibiotic treatment	No organism was cultured	6	1	20	Recurrent PJI, successfully treated with DAIR* and 3 months of antibiotics	Failure
7	A	*S. epidermidis*	Clindamycin/ vancomycin + rifampicin for 3 months	No organism was cultured	264	4	27	Recurrent PJI, Staphylococcus aureus was cultured at DAIR*. Suppressive doxycycline is needed to control PJI.	Failure
8	A	*Coagulase-negative Staphylococcus*	Clindamycin/ co-trimoxazol + rifampicin for 3 months	No organisme was cultured	12	4	48	Femoral cement was removed after first stage, due to recurrent infection.	Failure
9	A	*Pseudomonas and E. cloacae*	Teicoplanin/linezolid + rifampin until cement removal	Coagulase-negative Staphylococcus	2	8 Girdlestone	21	Due to recurrent infection, femoral cement was removed after first stage and a permanent Girdlestone situation was chosen	Failure
10	C	*S. aureus*	Clindamycin until cement removal	Girdlestone	300	4 Girdlestone	5	Due to recurrent infection, femoral cement was removed after first stage and a permanent Girdlestone situation was chosen	Failure
Mean					94.1	4	26.3		

*Debridement and Implant Retention † Prosthetic Joint Infection

Success

Two of the 10 patients were considered to be successfully treated. In subjects 1 and 2 primary micro-organisms, cultured at first stage were successfully treated with 3 months and 6 weeks of antibiotics, respectively. Second stage cultures were negative and there were no signs of infection during the follow-up period after reimplantation.

Failures

In subject 3 the primary organism cultured at the time of the first stage was successfully treated with 6 weeks of antibiotics. Cultures taken at second stage were negative. However, a PJI occurred in the first weeks after second stage. Therefore, debridement was performed with maintenance of prosthesis. Different organisms (*Corynebacterium jeikeium, Dermabacter hominis, Proteus mirabilis, Pseudomonas aeruginosa* and *Staphylococcus aureus*) were cultured. After 3 months of antibiotic treatment (levofloxacin + rifampin) there were no clinical or laboratory signs of infection. In subjects 4 and 5 the same microorganism was cultured during the first and second stage. Additional antibiotic treatment was needed after second stage surgery. These patients were successfully treated with 3 months of teicoplanin and rifampin (subject 4) and 1.5 month of teicoplanin and rifampin, followed by 1.5 month of linezolid and rifampin (subject 5).

One patient (Subject 6) had no positive microbiology at the time of first stage revision, nor at the time of second stage revision. Therefore, second stage surgery was performed after 1 month without clinical or laboratory signs of infection. The diagnosis of infection was made clinically. During the first stage surgical procedure a large collection of turbid fluid was rinsed out of the hip. After second stage the patient showed recurrent signs of infection. One week after second stage, incision and debridement was performed and cultures showed multiple organisms (*Escherichia coli, Enterobacter faecalis, Enterobacter cloacae* and *Coagulase-negative Staphylococcus*). This patient was successfully treated with 2 months of teicoplanin and rifampin, followed by 1 month of linezolid and rifampin. In subject 7, *Staphylococcus epidermidis* was cultured at first stage. No micro-organisms were cultured at the time of second stage. This patient developed a PJI during the second week after second stage. *S. aureus* was cultured at DAIR. Despite repeated DAIR and antibiotic treatment this patient is still treated with a suppressive antibiotic regimen (doxyciclin 100mg once daily), at latest follow-up (after 27 months). In subjects 8 the

femoral cement mantle was removed after the first stage due to persistent infection and second stage was performed 4 months later. In patients 9 and 10, the femoral cement mantle was removed due to persistent signs of infection, 8 and 4 months after the first stage procedure respectively. Multiple organisms were cultured in both subjects after removal of the femoral cement mantle. PJI persisted despite DAIR and antibiotic treatment. Therefore, the second stage procedure was not performed and a permanent Girdlestone situation was chosen.

DISCUSSION

In this study, a successful eradication of infection was achieved in 2 out of 10 patients with a PJI of the hip. Compared to recent studies, where the femoral cement mantle has been removed in a two-stage revision procedure for infected THA, we found a low success rate. All these studies show success rates over 90% [18-23].

Compared to the study published by Morely et al., presenting 15 cases of CWC revision, our study had a lower success rate; 2 out of 10 (20%) versus 14 out of 15 patients (93.3%). Seven out of 8 failures in our study had a remarkable list of co-morbidities/ previous hip operations (table 1). Morely et al. excluded Barrack C, where we included 1 Barrack C classified patient. Despite radiological Barrack C classification, cement mantle was judged to be firmly attached to the femur during first stage surgery and therefore left in situ. Retrospectively this case was likely to fail considering radiological classification. Furthermore, reaming up the cement in the femoral canal was not standardized in our first stage surgery. Morely et al. reamed the femoral cement mantle with a high-speed drill to remove membrane and debris and the intention of liberating further antibiotics from the existing mantle. Morely et al. also left a cement cylinder of antibiotics or gentamycin beads in the femur and a cement ball of antibiotics in the acetabulum, in order to create adequate local antibiotic levels. We used gentamycin beads in 9 out of 10 patients. Finally, contrary to our study, patients received post-operative antibiotics until the extended microbiological results were available. These differences in intra- and postoperative treatment could partly explain the difference in success rate.

The small number of patients in this study makes it difficult to draw significant conclusions. However, our results in managing an infected THA with CWC revision have been disappointing. The high re-infection rate indicates more research is needed before orthopedic surgeons are encouraged to routinely perform CWC revisions in infected total hip replacements. The old cement mantle should be considered a possible cause of re-infection. More research is needed to compare surgical techniques and to determine which patients are appropriate for cement-within-cement revision.

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CHAPTER 8

ANTIBIOTIC MIXING THROUGH IMPACTED BONE GRAFTS DOES NOT SEEM INDICATED IN TWO-STAGE CEMENTED HIP REVISIONS FOR SEPTIC LOOSENING

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ABSTRACT

Impaction bone grafts (IBG) in two-stage revision of Total Hip Arthroplasty (THA) for prosthetic Joint infection (PJI) might be more susceptible to re-infection. Therefore, antibiotic mixing through these donor bone grafts is often used. However, outcomes have not been compared with IBG without antibiotics and no long-term results are available. Therefore, we evaluated long-term infection-free outcome after the use of IBG without antibiotic supplement in two-stage revision for PJI. Patients were divided into positive (group 1, n=8) and negative (group 2, n=28) cultures at re-implantation and followed up to 18 years after re-implantation. Five of 36 patients died from non-orthopedic causes (median 37, range 24-149 months). Five patients had a re-operation not related to infection (median 39, range 7-140 months). These were censored in the Kaplan-Meier estimator at the last outpatient evaluation. We found an overall re-infection rate of 2.8% within 2 years, which matches comparative studies in which antibiotic impregnated bone grafts were used. In group 1, there was one re-infection after 44 months. In group 2, all 3 infections occurred within 5 years with an estimated infection free percentage at 10 years of 87% (95% CI 66;96). Follow-up should be extended beyond 2 years and randomized clinical trials are needed for good comparison with IBG with antibiotic impregnation.

INTRODUCTION

Two stage revision for prosthetic Joint infection (PJI) after Total Hip Arthroplasty (THA) can be demanding due to extensive bone loss. Reconstruction with impaction bone grafting (IBG) is an excellent option and favorable results have been reported [1-3]. Unfortunately, these avascular bone allografts might be more susceptible for infection [4, 5]. To prevent this complication, local application of antibiotics has been suggested [4,5]. Bone allograft might be a better carrier for antibiotics than cement [6, 7] and since one decade it is possible to mix large amounts of antibiotics through bone grafts resulting in high levels of local tissue concentration without nephrotoxicity. This has led to studies reporting infection recurrence of 0.0, 3.3 and 8.1% (n=12, n=30 and n=37, respectively) in two and one stage revision surgery using antibiotic impregnated allograft bone with a follow-up of 14-96 months [4, 5, 8]. However, unnecessary use of antibiotics should be avoided and there are reasons to doubt these studies before implementing the use of antibiotic mixing through bone grafts in standard care: Most importantly, the results were not compared with revisions using bone grafts without impregnated antibiotics. Also, the conventional 2-year follow-up period often used to report the success of eradication seems too short; Asymptomatic infection may still be present with persistence of bacteria in biofilms or as intracellular small-colony variants [9, 10]. In such cases, persistent infection may become symptomatic ≥ 2 years after treatment [11]. Goal of this study was to evaluate the long-term outcome of IBG without antibiotic supplement in 36 patients who underwent two-stage revision for PJI after THA. Follow-up was extended up to 18 years to present reliable long-term outcome data using Kaplan-Meier analysis.

PATIENTS AND METHODS

This historical prospective study was approved by our institutional review board. We included all patients who underwent a two-stage revision for PJI after THA between January 1990 and January 2009 with IBG of acetabulum and/or femur without mixing antibiotics in the allograft. Exclusion criteria were: hemiarthroplasty (n=7); prostheses for treatment of malignant tumors (n=8); no perioperative proof of infection (n=8);

early postoperative death due to non-orthopedic causes (n=2) and recurrent dislocation followed by open reposition 11 days after re-implantation (n=1). In total, 36 patients were included.

Baseline characteristics

Median age at re-implantation was 61 years old (range 28-85), 44% of the patients were male and median BMI was 25 (range 17-40). Risk factors for PJI were: rheumatoid arthritis (11%), prednisolone use (17%), Diabetes Mellitus (8%) and obesity (8%), previous hip operation before primary total hip arthroplasty (THA) (56%) and ten THA had previously been revised (28%). Eleven patients (31%) were referred from another hospital. There were 24 (67%) cemented THA versus 12 (33%) uncemented. Preoperatively, diagnosis of PJI was based on medical history, clinical signs of infection, C-reactive protein (CRP) and radiological signs of loosening of prostheses. In some cases, an In-111-labeled non-specific human immunoglobulin G scintigraphy and/or a technetium99m-labeled methylene diphosphonate scintigraphy were performed to support the diagnosis [12]. If preoperative signs of infection were indistinct, perioperative fresh frozen sections were performed to validate the diagnosis of an infection. PJI was confirmed by the following criteria: (a) purulence of synovial fluid or at the implant site, (b) presence of a sinus tract or (c) growth of the same micro-organism (MO) in ≥ 2 cultures of synovial fluid or periprosthetic tissue. Specimen were collected according to recommendations for chronic PJI [13, 14]. All implants and cement were removed in combination with a thorough debridement. Antimicrobial surgical prophylaxis (2 grams of cefazolin intravenously) was administered after cultures were taken. Gentamicin beads were inserted based on surgeons' preferences. Postoperatively, empiric antimicrobial treatment was started intravenously using flucloxacillin 1 gram 4 hourly or clindamycin 600mg 8 hourly, or other antibiotics were started based on pre-operative culture results. Antimicrobial treatment was adjusted based on the results from the perioperative cultures. Antimicrobial treatment was continued postoperatively for at least six weeks and was prolonged if necessary, based on clinical signs of infection and CRP level. The second stage was carried out in absence of clinical signs of infection and when CRP levels were normalized. Cancellous chips of 0.6-1 cm^3 were prepared from irradiated fresh frozen femoral heads and impacted into the acetabulum and femur as described [15, 16]. A cemented prosthesis was inserted in all cases using Simplex® bone cement with 500mg erythromycin and 3.000.000EH

colistin (Stryker, Newbury, UK). Patients who had positive cultures at re-implantation received antibiotics for a minimum of another six weeks. All patients started mobilization containing toe-touch weight-bearing with two crutches for six weeks, followed by six weeks of partial weight bearing. Patients were clinically and radiographically evaluated at the outpatient clinic at six weeks, three months, six months, and then yearly until failure of treatment or death. At re-implantation, a Waldemar Link® (Waldemar Link GmbH & Co. KG, Hamburg, Germany) modular stem prostheses was implanted in 2 cases. In all other cases an Exeter® (Stryker, Newbury, UK) cemented stem was used. In 13 patients the Contemporary® cup (Stryker, Newbury, UK) was used, in 10 patients the Muller® cup (Zimmer, Winterthur, Switzerland) and in seven patients the Exeter® cup (Stryker, Newbury, UK). Less frequently, the Charnley® (Elite) or the Full Profile cup (Depuy, Warsaw, UK) were implanted, both in three patients.

Kaplan-Meier survivorship analyzes were performed for the whole group of 36 patients and for the subgroup of patients with negative cultures (n=28) for the following endpoints: Persistence/recurrence of infection and re-infection. Persistence/recurrence was defined as proven infection at a new surgical event with the same micro-organism (MO) as found at first stage (removal procedure). Re-infection was defined as a new infection with a different MO. The infection-free period was defined as no clinical, radiological or laboratory signs of infection at the latest follow-up, with a minimum of two years after re-implantation or until a new operation for another indication than infection. The subgroup of patients with negative cultures at re-implantation was separately analyzed since results in this group are not biased by systemic antibiotic treatment after reimplantation.

RESULTS

Characteristics of the PJI and treatment are shown in table 1. Median follow up of all non-censored patients was 118 months (range 44-211). Long interim periods between prosthesis removal and re-implantation were observed, mainly due to removal of cement residues or additional debridement surgery because of persistent infection (Table 1). In some cases, diagnostic arthrotomies were performed to rule out persistent infection.

TABLE 1. Diagnosis and treatment *S. haemolytic group G, S. sanguines, †In one case, re-implantation occurred 3 weeks after removal of the prostheses

	Median (range) / n (%)		
	Total (n=36)	**Positive (n=8)**	**Negative (n=28)**
Signs and symptoms			
Early (≤ 3 months)	2 (6)	0 (0)	2(7)
Delayed (3-24 months)	11 (30)	4 (50)	7 (25)
Late (≥ 24 months)	23 (64)	4 (50)	19 (68)
Time until infection, months	55 (1-255)	37 (6-211)	56 (1-255)
Presentation, clinical			
Pain	32 (89)	7 (88)	25 (89)
≥1 clinical sign of inflammation	9 (25)	2 (25)	7 (25)
Migration/ Osteolysis/ Radiolucency	22 (61)	6 (75)	16 (57)
Elevated CRP threshold / total	19/23 (83)	6 / 6 (100)	13 / 17 (76)
Cultures at first stage			
Polymicrobial	12 (33)	3 (38)	9 (32)
Staphylococcus Aureus	2 (6)	1 (13)	1 (4)
Coagulase Negative Staphylococcus	10 (28)	2 (25)	8 (29)
Propioni	6 (15)	1 (13)	5 (18)
Streptococcus species*	2 (6)	0 (0)	2 (7)
Listeria monocytogenes	1 (3)	1 (13)	0 (0)
Enterobacter cloaca	1 (3)	0 (0)	1 (4)
Pseudomonas aeruginosa	1 (3)	0 (0)	1 (4)
Granulicatella Adiacens	1 (3)	0 (0)	1 (4)
First stage, minutes	145 (45-280)	145 (75-235)	145 (45-280)
Interim period, months	3.5 (0†-31)	2 (1-9)	5 (0†-31)
Second stage			
Surgical time, minutes	190 (105-310)	203 (115-310)	183 (105-265)
Impaction bone grafting			
Acetabular	16 (44)	6 (75)	10 (36)
Femoral and Acetabular	20 (56)	2 (25)	18 (64)

Postoperative Events

Table 2 presents all postoperative events and infections. No patient was lost to follow-up. In all 36 cases, five patients died from non-orthopedic causes between 24-149 months after re-implantation. Case 1 to 5 had a re-operation not related to infection between 7-140 months. Recurrences/re-infections Four patients (11%) developed a PJI after re-implantation after a median time of 38 months (after 1, 32, 44 and 56) (Case A-D). These patients are described in detail below. Case A was one of the 8 patients (13%) with positive cultures at re-implantation (group 1). Case C, B and D were among the 28 patients in group 2 (negative cultures at re-implantation). A Kaplan Meier curve was created for the patients in the whole group (36 patients) and for group 2 (n=28), since the latter group was not biased by postoperative antibiotics (figure 1 and 2, respectively). The infection-free percentage after 10 years is 86.8% (95% CI: 68.2-94.9) in the entire group (36 patients) and 87.5% (95% CI 65.7-95.8) in group 2.

TABLE 2. Postoperative events. ORIF= Open Reposition Internal Fixation

Case	Months	Indication	Event	Micro-organism	Cultures
1	39	Persistence of pain	Femoral head exchange	Negative	5
2	140	Aseptic loosening	One-stage	Negative	6
3	7	Periprosthetic fracture	ORIF	Negative	6
4	9	Recurrent dislocations	Femoral revision	Negative	2
5	73	Recurrent dislocations	Femoral head exchange	Negative	2
A	44	Infection	Girdlestone	Different	3
B	1	Infection	Debridement	Different	2
C	56	Infection	Debridement	Different	5
D	32	Infection	Two stage revision	Identical	2

In case A, a two-stage revision was performed 1.5 years after primary THA. *S. epidermidis* (resistant to flucloxacillin) was cultured at the time of removal for which teicoplanin iv and subsequently clindamycin orally was administered for a total of 3 months. At re-implantation after 3 months, cultures showed *S. epidermidis* with a different antibiogram

(susceptible to flucloxacillin, resistant for clindamycin). Antimicrobial treatment consisted of teicoplanin iv for two weeks and flucloxacillin orally for 4 weeks. Unfortunately, 3.5 years later the patient experienced fever and sudden pain in the hip. The prosthesis was removed and intraoperative cultures again showed *S. epidermidis* but with a substantial different antibiogram (based on a difference in susceptibility for ≥2 antibiotic classes) as compared to the bacteria isolated at removal and at re-implantation. A permanent Girdlestone situation was created. This was considered to be a re-infection.

Case B underwent a 2-stage procedure for PJI 6 years after primary implantation. Cultures at removal showed *coagulase-negative S. epidermidis*. Two diagnostic arthrotomies at 4 and 16 months after removal of the hip showed S. epidermidis and Propionibacterium species, respectively. Antibiotic treatment was administered until 1 day before reimplantation (2 months teicoplanin and 1-month linezolid after first arthrotomy and clindamycin for 6 weeks after the second arthrotomy). Cultures at re-implantation were negative. Three weeks after re-implantation the patient developed a PJI. Debridement, Antibiotics and Implant Retention (DAIR) was performed and *Enterobacter cloacae* was cultured. This was successfully treated with ciprofloxacin 500 mg tid for 3 months. This was considered to be a re-infection.

Case C developed a sinus tract and fever almost 9 years after an aseptic revision. The patient was initially treated with (DAIR) at which an *S. epidermidis* was cultured, treated with clindamycin and rifampin for 3 months. However, one year later the infection recurred and the prosthesis was removed. Intraoperative cultures showed *coagulase-negative Staphylococcus*. The patient was treated with a gentamicin containing cement spacer and clindamycin 600 mg tid was administered for 6 weeks. Re-implantation was performed 2 months after removal and all intraoperative cultures were negative. Five years after re-implantation, symptoms of chronic PJI reoccurred. Debridement showed a PJI with *Streptococcus anginosus*. Afterwards, the patient was successfully treated with clindamycin and rifampicin for three months. This case was also considered to be a re-infection.

Case D experienced an hematogenous *S. oralis* infection 5 years after primary THA. DAIR and four months of antimicrobial treatment with penicillin and clindamycin treatment was unsuccessful and the prosthesis was removed. Before reimplantation, the patient underwent three additional surgerical procedures, one to remove remaining cement and two diagnostic arthrotomies. Cultures collected during the first two operations showed *S. epidermidis* with identical susceptibility patterns. After extensive antimicrobial treatment, cultures collected during the last arthrotomy were negative. A successful reimplantation was performed two years after the removal, with negative intraoperative cultures. However, an infection became apparent 32 months after reimplantation. A two-stage revision was performed. Intraoperative specimen again showed *S. epidermidis*. Since antimicrobial susceptibility was identical to the previously isolated *S. epidermidis* isolated, this case considered to be a recurrence of PJI.

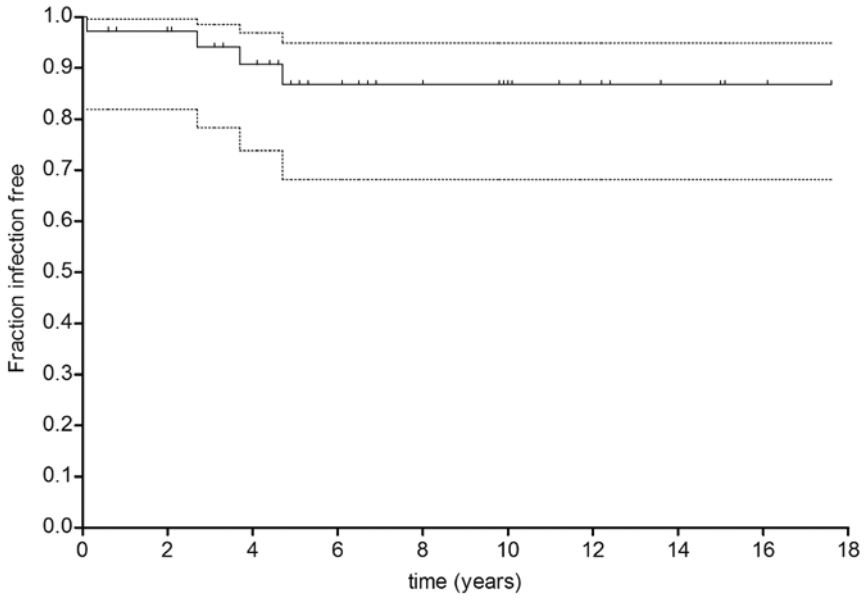

FIGURE 1. Kaplan Meier survival curve of THA in the whole group (36 patients)

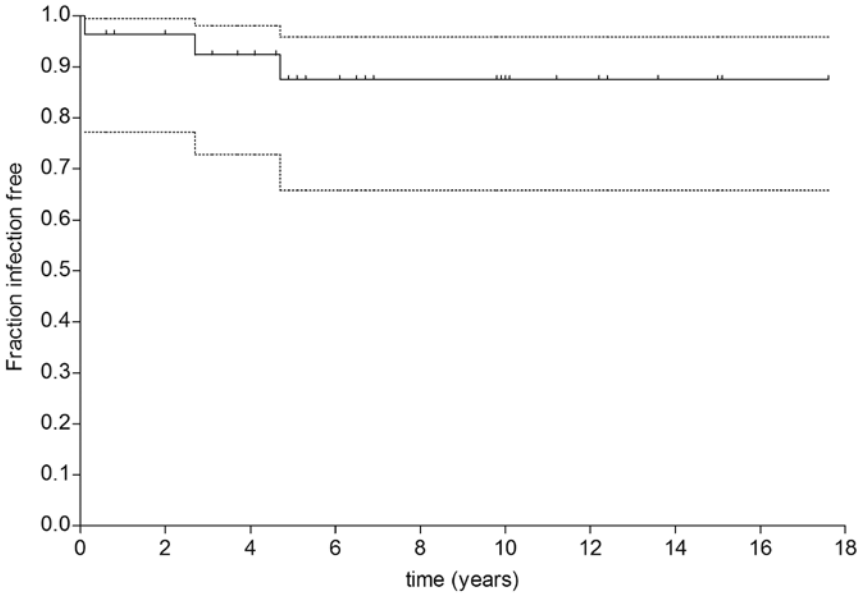

FIGURE 2. Kaplan Meier survival curve of THA in group 2 (28 patients with negative cultures at reimplantation)

TABLE 3. Literature on infection rate after two stage revision with IBG (Impaction Bone Grafting)

Author	Year of publication	N	IBG + antibiotics	Systemic antibiotics after re-implantation	Mean Follow-up (range), years	Infection rate
Michalack et al. [5]	2006	12	Yes	Yes (6 weeks)	3.9 (1.2-6.5)	0.0%
Butarro et al. [21]	2005	30	Yes	Yes	2.7 (2.0-5.0)	3.3%
English et al. [2]	2002	53	In 9 patients	Yes (mean 79 days)	4.4 (2.0-10.2)	7.5%
Ammon et al. [1]	2004	57	No	No	4.5 (2.0-10.5)	14.0%
Berry et al. [17]	1991	18	No	Yes	4.2 (2.0-8.1)	11.0%
Alexeeff et al. [18]	1996	11	No	Yes (3 months)	4.0 (2.0-6.0)	0.0%
Nusem et al. [19]	2006	18	No	Yes (48 hours)	9.0 (5.0-14.0)	1.0%
Hsieh et al. [3]	2005	24	No	Yes (one week iv)	4.2 (2.0-7.0)	0.0%
Current study	2014	36	No	Yes (if indicated)	9.8 (3.7-17.6)	11.0%
Subgroup		28	No	No	9.3 (3.7-17.6)	11.0%

DISCUSSION

In this study population of 36 patients, there was a low occurrence of infection within 2 years after two stage revision (1/36 = 2.8%) compared to 0.0-14.0% in previous studies with n>10 [1-5, 17-19] (table 3). However, at a median follow up of 10 years the infection percentage was 11% (4/36) in our group. In 3 of the 4 patients, an infection was diagnosed > 2 years after re-implantation (cases A, C and D). Only one infection, an early postoperative infection with *E. cloacae* (case B), occurred within 2 years which is the usual time of follow up to establish infectious complications after prosthesis surgery. In one patient infection with *S. Anginosus* occurred 56 months after reimplantation which was in keeping with a hematogenous infection (case C). Of interest, in the 2 other patients (case A and D) infection with *S. epidermidis* was diagnosed 32 months and 44 months after reimplantation. One of these infections was caused by the same micro-organism, while the other infection was caused by the same micro-orgamism with a different antibiogram, suggesting development of bacterial resistance. These findings suggest that the time of follow up should be extended beyond the 2 years to determine postoperative infectious complications. A long-term follow-up study (10-15 years) in 92 two stage revisions for PJI supports this statement with 6 infections occurring between two and ten years after revision [20]. To avoid bias due to systemic antibiotics we separately evaluated patients with negative cultures at re-implantation (and therefore not receiving systemic antibiotics). In this patient group (n=28), infection rate was 11.0% with a mean follow op of 9.3 months. The Kaplan-Meier estimated infection-free percentage at 10 years was 87.5% (95% CI 65.7-95.8). Two of the eight studies describing reinfection rates after two stage revisions for PJI with allografts (with n>10), used antibiotic supplemented bone grafts (table 3). Michalak et al in 2006, observed a 0.0% infection rate after a mean follow-up of 47 (14-78) months (n=12) [5]. Buttaro et al in 2005, found an infection rate of 3.3% after a mean follow-up of 32.4 months (24 to 60) (n=30) [4, 21]. We found one study describing one stage revisions for PJI using antibiotic impregnated allografts [8]. This study presented an 8.0% infection percentage after a mean follow-up of 4.4 years (2.0-8.0). Although these infection rates seem relatively low, all patients received oral or intravenous antibiotics after re-implantation, thereby masking the effect of the antibiotics in the bone graft. Table 3 summarizes the results of all eight studies we found on this topic with n>10.

Study limitations

We have recognized a few limitations in our study. First, there were 8 patients with positive cultures at re-implantation. The antibiotic treatment following these cultures makes it impossible to compare with two stage revisions with IBG with antibiotics. Therefore, we excluded those 8 patients for comparison. Second, in one case, the same MO was found at a new surgical event, 32 months after removal procedure. Multiple cultures at re-implantation had shown no infection. This could have been caused by preoperative antibiotics, which decrease culture sensitivity [22]. A third limitation is that definition of recurrent/persistent infection was based on matching antibiograms because molecular genotyping was not available.

Considerations

Bacterial resistance to antibiotics is increasing and aimless use of antibiotics should be avoided [23]. Therefore, the effect of antibiotic impregnation of bone grafts should be evaluated, before implementation as standardized practice. Vancomycin in particular, generally used for impregnation of bone grafts, serves as last resort for treatment of periprosthetic infections in many cases. So far, there is no proven decrease in infection rate in patients receiving antibiotic containing IBG compared with patients receiving IBG without antibiotics. Especially in two stage revisions, the use of antibiotic supplemented allograft seems contradictory because at re-implantation the infection has been treated and eradicated. Also, antibiotics in bone grafts may have a short delivery period which may lead to less than the minimally required local concentration levels in time, which results in emergence of bacterial resistance to antibiotics [24]. Finally, the effect of antibiotic impregnation on bone ingrowth of the donor bone graft in the host should be investigated. In future randomized controlled trials it is essential to differentiate between positive and negative cultures at re-implantation in order to evaluate the role of antibiotic-supplemented bone graft, because the antibacterial effect of the bone graft will be masked by intravenous/oral antibiotics.

Conclusion

Infection rates after two stage revision with IBG without antibiotics seem comparable to two stage revisions with IBG containing antibiotics, in the first two years of follow-up. However, it's preferable to extend the follow-up period beyond the conventional two years for definition of cure. Randomized controlled trials are needed to prove the benefits of mixing antibiotics through bone grafts.

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CHAPTER 9

CLINDAMYCIN-RIFAMPIN COMBINATION THERAPY FOR STAPHYLOCOCCAL PERIPROSTHETIC JOINT INFECTIONS

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ABSTRACT

Background: Staphylococcal species account for more than 50% of periprosthetic joint infections (PJI) and antimicrobial therapy with rifampin-based combination regimens after surgical treatment has been shown effective. The present study evaluates the safety and efficacy of clindamycin in combination with rifampin for the management of staphylococcal PJI.

Methods: In this retrospective cohort study, patients were included who received clindamycin-rifampin combination therapy to treat a periprosthetic hip or knee infection by *Staphylococcus aureus* or *coagulase-negative staphylococci*. Patients were treated according to a standardized treatment algorithm and followed for a median of 54 months.
Of the 36 patients with periprosthetic staphylococcal infections, 31 had an infection of the hip, and five had an infection of the knee. Eighteen patients underwent debridement and retention of the implant (DAIR) for an early infection, the other eighteen patients underwent revision of loose components in presumed aseptic loosening with unexpected positive cultures.

Results: In this study, we report a success rate of 86%, with five recurrent/persistent PJI in 36 treated patients. Cure rate was 78% (14/18) in the DAIR patients and 94% (17/18) in the revision group. Five patients (14%) discontinued clindamycin-rifampin due to side effects. Of the 31 patients completing the clindamycin-rifampin regimen 29 patients (94%) were cured.

Conclusion: Combined therapy with clindamycin and rifampin is a safe, well tolerated and effective regimen for the treatment of staphylococcal periprosthetic infection.

BACKGROUND

Periprosthetic joint infections (PJI) cause significant morbidity and a considerable claim on the health care resource utilization. Implant-associated infections are typically caused by microorganisms that adhere to the device surface and produce microbial biofilms. Staphylococci account for more than 50% of the periprosthetic joint infections [1]. The treatment is challenging, as the organisms in the biofilm are protected from antimicrobial agents and host responses, and have greater resistance to antimicrobial killing [2, 3]. Rifampin-based combination therapy regimens have been shown effective to eradicate staphylococcal biofilms and cure PJI [4] . In the widely-used algorithm proposed by Zimmerli et al. [3] and the IDSA (Infectious Disease Society of America) guidelines [5], rifampin is combined with quinolones and cure rates of 70-100% have been reported. Although other agents, e.g., betalactams, glycopeptides, minocycline, cotrimoxazole, linezolid, daptomycin, or fusidic acid have been investigated in combination with rifampin, their efficacy is in general inferior or data are anecdotal [4-7]. Clindamycin has been well established as antistaphylococcal therapy, but very few clinical data are available about its use in combination with rifampin for PJI. Therefore, clindamycin has not yet been recommended as an alternative to combine with rifampin to treat PJI in the IDSA guidelines [5]. Clindamycin has been shown to be effective in treatment of osteomyelitis [8], has excellent bioavailability, high levels of penetration into synovial fluid and bone [9-10], inhibits biofilm formation and bacterial adherence and is well tolerated [11-12]. In vitro, clindamycin prevents the emergence of rifampin resistance, and the combination displayed synergetic or additive bactericidal activity, as well as favorable cure rates in animal models [13-18]. To date, only 2 case series have reported on the efficacy of an oral clindamycin-rifampin combination therapy regimen for staphylococcal PJI in adults, with a success rate of 70% in 7 cases and 100% in 6 cases [6, 19].

In the present study, we evaluated the efficacy and safety of a clindamycin-rifampin combination therapy regimen for the management of PJI caused by Staphylococcus species.

METHODS

For this retrospective cohort study, patients who received complete treatment for PJI of the hip (118) or knee (36) in our hospital between January 2004 and June 2010 were eligible. Inclusion criteria were PJI due to *S. aureus* or *coagulase-negative staphylococci* (CoNS). The isolated staphylococci had to be susceptible in vitro to both clindamycin and rifampin which was determined by automated susceptibility testing using the BD Phoenix™ (BD Diagnostics, Sparks, MD, USA).

Diagnosis

PJI was diagnosed according to the MSIS criteria (MusculoSkeletal Infection Society) [20]; Presence of 1-2 major criteria and/or three minor criteria. Major criteria are: 1) two positive periprosthetic cultures with phenotypically identical organisms 2) A sinus tract communicating with the joint. Minor Criteria are: 1) Elevated serum C-reactive protein AND erythrocyte sedimentation rate 2) Elevated synovial fluid white blood cell count OR ++change on leukocyte esterase test strip 3) Elevated synovial fluid polymorphonuclear neutrophil percentage 4) Positive histological analysis of periprosthetic tissue 5) A single positive culture. In case of postoperative events, newly isolated microorganisms were typed by standard molecular techniques if necessary.

Management

Management of PJI was based on the treatment algorithm by Zimmerli et al. [3] and the IDSA Guidelines [5], performed by a multidisciplinary team consisting of an orthopedic surgeon, a microbiologist and an infectious diseases specialist.

Debridement

DAIR was applied for (a) early postoperative or acute hematogenous infection, with (b) duration of symptoms < 3 weeks, (c) a stable implant and (d) if soft tissue was in good condition. The wound was re-opened, deep cultures were taken, debridement was performed and pulse lavage was used with at least 3 liters of NaCl 0.9% solution. Gentamicin beads were inserted based on the surgeon's decision and removed after 2 weeks. No change of mobile parts was performed during surgery.

Revision

Patients included after revision procedure underwent a revision of (a part of) the prosthesis for presumed aseptic loosening in the absence of positive MSIS criteria preoperatively. In these included cases, two or more perioperative taken cultures showed bacterial growth and retrospectively proved a prosthetic joint infection according to the MSIS criteria. At the revision, debridement was performed and pulse-lavage was used with at least three liters of NaCl 0.9% solution. In case of purulence at the implant site, complete revision was performed. Otherwise, only loose parts of the implant were revised and stable parts were let in situ. So retrospectively, these patients underwent a one-stage revision of all loose parts of the implant for septic loosening. If indicated, bone defects were reconstructed with impaction bone grafting [21]. A cemented prosthesis was inserted using Simplex® bone cement with 500mg erythromycin and 3.000.000EH colistin (Stryker, Newbury, UK) [22-23].

Antimicrobial treatment

Surgical prophylaxis (cefazolin 2 grams intravenously) was administered after deep tissue cultures were taken. After surgery, initial intravenous therapy was continued for two weeks with a betalactam antibiotic, clindamycin or teicoplanin, based on previous cultures if present. Antibiotics were switched to oral within two weeks. Oral antibiotic regimen consisted of clindamycin (600 milligrams three times daily) and rifampin (450 milligrams twice daily) for a minimum of 3 months, once the isolate had been identified and found susceptible to both drugs.

Follow-up

Patients were clinically and radiographically evaluated at the outpatient clinic at six weeks, three months, six months, and then yearly. Follow-up was continued until April 2015 with a median of 54 months (range 1-120).

Definitions

Cure: (a) no clinical, radiological or laboratory signs of infection at the latest follow-up, with a minimum of two years after re-implantation, (b) proven negative perioperative cultures in case of reoperation for other reasons than infection or (c) positive cultures yielding a different microorganism after an uneventful follow-up of at least 2 years. Failure

(persistence/recurrence of infection): (a) persistent or recurrent signs of infection in the first two years after debridement or one-stage revision, regardless the microorganism in newly obtained cultures or (b) isolation of the same microorganism as found at the initial treatment at any reoperation on the affected side during follow-up.

Statistical analysis

GraphPad Prism© version 11.0 was used for creation of the Kaplan-Meier curves. Data were analyzed according to the intention-to-treat principle. No p-values were calculated since goal of this study was to evaluate the outcome of this antibiotic treatment protocol and not to compare the outcome of DAIR versus one-stage revision.

RESULTS

Between January 2004 and June 2010, 154 patients received treatment for PJI of the hip (118 patients) or knee (36 patients). PJI of the hip was treated with DAIR (38 patients), one-stage revision (31), two-stage revision (33) or prosthesis removal without prosthesis replacement (16). Patients with total knee arthroplasty infection were treated with DAIR (18 patients), one-stage revision (2), two-stage revision (13), arthrodesis (1) or amputation (2). Of the 89 patients treated with DAIR or one-stage revision, 51 patients had a staphylococcal PJI. Fifteen of those patients were excluded due to the following reasons: potential rifampin drug interaction (1); possibility of iMLSb phenotype resistance (1) [24]; clindamycin (5) or rifampin (5) resistance (in 9 out of these 10 patients, the microorganism was resistant to quinolones as well). Three patients were excluded based on protocol violation.

A total of 36 patients (23%) were treated with the clindamycin-rifampin combination therapy after DAIR (18 patients) or revision (18 patients). Demographic characteristics of all patients are shown in Table 1. Duration of symptoms before surgery was < 3 weeks in all cases in the debridement group. There were six patients with an acute hematogenous PJI in the DAIR group. Duration of symptoms was > 3 weeks in all patients in the revision group (4-79 weeks). Characteristics of all PJI are presented in Table 2.

TABLE 1. Patients characteristics.

	Debridement and retention n (%)	Revision n (%)
Number of patients	18	18
Age, years; median (range)	71 (39 – 89)	58 (30 – 87)
BMI[a], kg/m^2; median (range)	26 (20 – 32)	25 (19 – 35)
Gender, male	12	13
Prosthesis site		
Hip	13	18
Knee	5	0
Indication for prosthesis		
Primary arthrosis	5	3
Secondary arthrosis		
Childhood hip disease	1	4
Post traumatic	3	2
Osteonecrosis	1	1
Rheumatoid arthritis	1	0
Hemophilia	1	0
Revision arthroplasty	5	6
Unknown	0	2
Femoral neck fracture	1	0
Risk factors for PJI[b] / comorbidity		
Previous hip/knee surgery before primary THA/TKA	10	10
Immune suppression	1	2
Previous PJI	1	2
Diabetes Mellitus	2	2
Obesity (BMI[a] >30kg/m^2)	1	3
ASA[c] score; median (range)	2 (1 – 3)	2 (1 – 3)

[a]BMI, Body Mass Index; [b]PJI, Periprosthetic Joint Infection; [c]ASA, American Society of Anesthesiologists; THA, total hip arthroplasty; TKA, total knee arthroplasty

TABLE 2. Characteristics of periprosthetic infection

	Debridement and retention n	Revision n
Number of patients	18	18
Manifestation of infection		
Early (≤ 3 months)	12	3
Delayed (3-24 months)	2	2
Late (≥ 24 months)	4	13
Age of implant, weeks; median (range)	7 (1 – 442)	263 (29 - 862)
Referred from another hospital	0	9
Perioperative cultures		
Methicillin-susceptible *Staphylococcus aureus*	11	2
Methicillin-resistant *Staphylococcus aureus*	1	0
Co*agulase-negative staphylococci*	5	14
Polymicrobial	1	2
Number of positive cultures per patient; median (range)	3 (1 – 7)	6 (2 – 9)

Surgical treatment

In the debridement group, gentamicin beads were inserted in ten cases (56%) and removed at a second debridement. Median duration of surgery was 35 minutes (range, 18-94). In the revision group, complete revisions were performed in six cases and partial revisions in 12 cases (eight acetabular and four femoral), with a median duration of surgery of 171 minutes (90-290). In 15 patients (83%), bone defects were reconstructed with impaction bone grafting (table 3).

Antimicrobial treatment

Surgical prophylaxis (cefazolin 2 grams intravenously) was administered in all patients. Table 3 summarizes the antibiotic regimen in our patient group. The minimum duration of oral clindamycin-rifampin treatment was 70 days in the debridement group and 66 days in the revision group, both after initial intravenous therapy.

TABLE 3. Characteristics of surgical and antimicrobial therapy

	Debridement and retention n=18	Revision n=18	Total n= 36
	n	n	n
Surgery			
Duration of surgery, minutes; median (range)	34 (18-94)	1 71 (90-290)	91 (18-290)
Gentamicin beads used	9 (53)	-	
Bone impaction grafting	-	15 (83)	
Complete / partial revision	-	6 (33) / 12 (67)	
Antimicrobial therapy			
Prior intravenous antibiotics	12	9	21
Duration of iv therapy, days; median (range)	11 (2 - 56)	12 (2 - 15)	11 (2-56)
Duration of iv + oral antibiotic therapy, days; med (range)	101 (31 – 239)	92 (80 – 139)	98 (31-239)
< 90 days	3	2	5
Hip PJI, median (range)	98 (31-146)	92 (80-139)	95 (31-146)
Knee PJI, median (range)	182 (117-239)	-	
Rifampin dose reduction (300 mg twice daily)	3	3	6
Clindamycin-rifampin discontinuation	3	2	5
Due to:			
Comorbidities	2	1	3
Side effects			
Allergy/Rash	2	1	3
Nausea	2	1	3
Diarrhea	0	2	2
Treatment outcomes			
Failures	4	1	5
Successfully treated	14 (78%)	17 (94%)	31 (86%)
Patients completed clinda-rifamp regimen	15	16	31
Successfully treated	14 (93%)	15 (94%)	29 (94%)

Side effects and treatment discontinuation

Five of the 36 patients (14%) discontinued clindamycin due to side effects after 3-41 days (table 3). In the debridement group, one patient switched to levofloxacin because of fatigue and loss of appetite, one patient to flucloxacillin because of rash and one patient to ciprofloxacin due to an allergic reaction to clindamycin. In the revision group, one patient switched to teicoplanin and one patient to ciprofloxacin, both because of diarrhea, without demonstration of Clostridium difficile toxin. The latter patient experienced the same severity of diarrhea on ciprofloxacin as on clindamycin, but was able to complete antibiotic treatment. All five patients continued with rifampin treatment.

Dose reduction of rifampin (to 300 mg bid) was applied in six patients (17%), due to side effects (three patients) and co morbidities (three patients) (Table 3). All of these patients were treated successfully.

Treatment Outcome

As shown in table 3, 86% of the patients (31 out of 36 patients) were treated successfully. The Kaplan-Meier survival curve of time to treatment failure is shown in Figure 1. In patients completing the clindamycin-rifampin regimen, cure rate was even higher; 29 out of 31 patients (94%). Three patients died due to non-orthopedic causes without any signs of infection after 36-84 months of follow-up. Four patients underwent a re-operation of the affected side. In two of these patients' cultures at reoperation were negative. One patient experienced a periprosthetic fracture 4.5 years after one-stage revision for *S. aureus* infection. At re-operation two different strains of *CoNS* were isolated, both susceptible to clindamycin and rifampin. In another case, late prosthetic infection occurred at 54 months after complete clinical cure of PJI with *S. epidermidis*. A Girdlestone procedure was performed with collection of 12 cultures from 4 different areas. Again *S. epidermidis* was cultured that was now clindamycin and rifampin resistant. The stored isolates of the initial infection and the infection after 54 months were unrelated as established by fingerprinting using Raman spectroscopy, SpectraCell RA® method (River Diagnostics, Madison, WI) [25].

Characteristics of treatment failures are shown in table 4. In three of the five failures clindamycin was switched to an alternative antibiotic due to side effects; all after DAIR.

The two other failures had a recurrent PJI despite a complete clindamycin-rifampin treatment; one in the DAIR group, the other in the revision group.

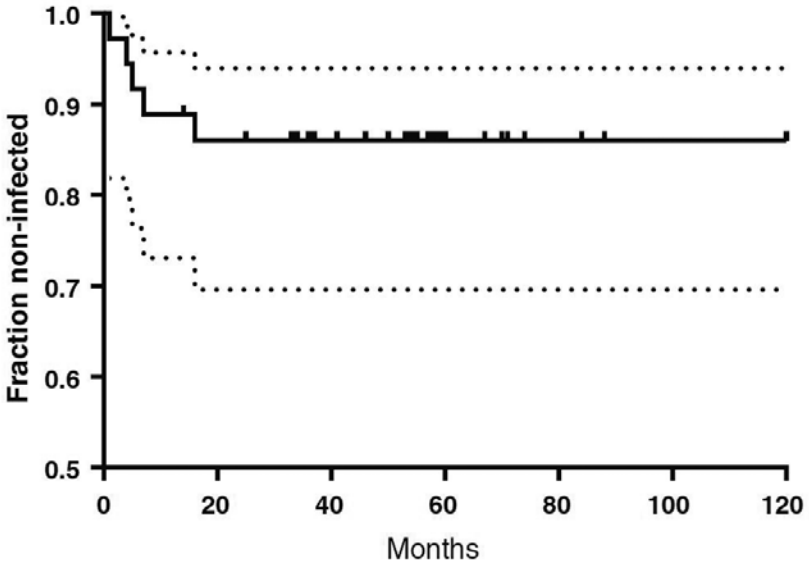

FIGURE 1. Probability of cure. Kaplan-Meier survival curves of the total group of 36 patients.

Tick marks indicate patients censored due to loss of follow-up or infection-unrelated events. Dotted lines indicate confidence intervals.

TABLE 4. Failures

Case	Surgical treatment	Time from primary prosthesis to PJI (months)	Cultures	Antibiotic treatment	Time to recurrence of infection after ceasing AB$^{\infty}$ (days)	Regimen	Cultures at reoperation
1	DAIR*	49	S. aureus	Clinda*/ rifampin 89 days	16	Suppressive clindamycin	-
2	DAIR	101	CoNS + S. mitis	Clinda / rifampin 41 days Levoflox † / rifampin 86 days	28	Suppressive doxyclin	-
3	DAIR	1.5	S. aureus	Clinda / rifampin 19 days Fluclox ‡ / rifampin 6 days	0 (infection persisted)	Girdestone	Negative
4	DAIR	11	S. aureus	Clinda / rifampin 12 days Ciproxin § / rifampin 83 days	320	two stage revision	S. aureus
5	Revision	48	S. capitis	Clinda / rifampin 92 days	0	Girdlestone	S. capitis

*PJI, prosthetic joint infection, AB, antibiotics, DAIR, debridement and implant retention, CoNS, coagulase negative Staphylococci, *Clindamycin, † Levofloxacin, ‡ Flucloxacillin, § Ciprofloxacin*

DISCUSSION

In the present report, we describe 36 patients with culture-confirmed staphylococcal PJI treated with the combination of clindamycin and rifampin, leading to a probability of cured infection of 86% after > 4 years of follow-up and 94% in patients able to complete clindamycin-rifampin therapy. These results are comparable to those reported in previous research combining rifampin with different antibiotics. Zimmerli et al. describe a 100% success rate after debridement and ciprofloxacin-rifampin combination therapy with a median follow-up of 35 months in 18 patients of whom 12 completed the treatment regimen [26]. In these 18 patients, rifampin dose was reduced in four patients (22%) and two patients (11%) discontinued rifampin or ciprofloxacin. Among these six drop outs there were two failures. Another retrospective cohort study presents a 77% infection-free survival after 24 months in 43 methicillin resistant staphylococcal PJI treated with

rifampin and fucidic acid after DAIR [27]. A large multicenter cohort study presents a 55% success rate in 328 PJI treated with rifampin plus any other antibiotic after DAIR [28].

The side effects of clindamycin-rifampin combination therapy were limited in our study. Treatment was discontinued in 5/36 (14%) patients, due to side effects. This adverse event rate is similar to that reported for other regimens, such as 14% (diarrhea) during rifampin-levofloxacin and 16% (nephrotoxity and diarrhea) during levofloxacin alone [29]. In the study where rifampin and fucidic acid were combined, 3 patients (7%) experienced side effects.

Our treatment protocol slightly deviated from the original algorithm published by Zimmerli et al [3]. First, not all patients were treated with 2 weeks of intravenous antibiotics initially. However, due to its excellent bioavailability, clindamycin seems appropriate for early oral therapy resulting in reduction of hospital stay and costs. Second, some patients with PJIs of the knee were treated for a limited period of time (17-34 weeks), whereas guidelines recommend antibiotic treatment for 6 months in case of periprosthetic knee infection [3]. The evidence supporting a long duration of treatment is limited [30], and 3 months of treatment may be sufficient similar to periprosthetic hip infection [31,32]. Third, the optimal dose of rifampin is unknown, and results from other studies suggest that rifampin 600 mg/24h is as effective as 900 mg/24h [6, 33]. Therefore, in 6 patients, rifampin dose reduction to 600 mg/24h was administered due to side effects, drug interaction or co-morbidity. All were treated successfully. This dose reduction regimen is supported by recently published data on rifampin dosage and frequency in PJI [33].

This study has several limitations. First, patients were not randomized to receive clindamycin-rifampin or a comparator regimen. However, the high success rate suggests that the present regimen may be as effective as quinolone-rifampin combination therapy, warranting a prospective, randomized controlled trial. A second limitation is the limited number of patients in the present study cohort. Also, we regret the heterogeneity of the cohort; In the DAIR group, gentamicin beads were inserted based on the surgeon's decision and removed after 2 weeks. In the revision group, complete revisions were performed in six cases and partial revisions in 12 cases. Furthermore, 15 of the 18 cases had a significant bone defect which was reconstructed with impaction bone grafting.

While performing this study, two articles on the pharmacokinetics of the clindamycin-rifampin combination regimen were published [34-35]. Bernard et al and Cruris et al reported a dramatic reduction of clindamycin serum concentration in patients receiving clindamycin with rifampin compared to patients receiving clindamycin without rifampin. This reduction could be explained by the induction of cytochrome P450 by rifampin. Clindamycin is metabolized through CYP3A4, a member of the cytochrome P450 system. Despite their low numbers of patients these studies found a significant decline of serum concentration levels of clindamycin, below therapeutic range. However, Bernard et al report an 82% success rate in 11 patients receiving clindamycin with rifampin for a staphylococcal osteo-articular infection. Cruris et al report a 100% success rate in 7 patients receiving clindamycin with rifampin. Zeller et al analyzed 24 patients receiving continuous iv clindamycin therapy combined with rifampin. Serum clindamycin concentrations declined after rifampin administration but not below therapeutic concentration [12]. Specific success rate of this group is not documented.

We emphasize that pharmacokinetics and optimal serum concentration levels of this combination regimen needs to be investigated. Another recently published article describes the termination of a prospective study due a dramatic decline in fusidic acid plasma concentration when used in combination with rifampin [36]. The likely explanation for this decline would again be the induction of CYP3A4 by rifampin.

The strengths of the present study are the inclusion of culture-proven PJI of the hip and knee only, excluding other implanted devices. In addition, we report high success rates in partial one-stage revisions in preoperatively considered aseptic loosening which turned out to be septic. This indicates that this antibiotic combination therapy is capable of eradicating a PJI without removal of all devices. Furthermore, during the entire study period, a standardized multidisciplinary approach according to international treatment algorithms was used.

Conclusion

Clindamycin-rifampin combination therapy results in a high success rate in the treatment staphylococcal PJI. The present findings warrant a randomized controlled trial to assess whether this combination regimen is a welcome addition to our arsenal against staphylococcal PJI.

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CONTROL WHAT PERSISTS

PART III:

PALLIATIVE TREATMENT OF PJI

CHAPTER 10

CLINICAL OUTCOME OF ANTIBIOTIC SUPPRESSIVE THERAPY IN PATIENTS WITH A PROSTHETIC JOINT INFECTION AFTER HIP REPLACEMENT

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ABSTRACT

Introduction: In Specific cases, curative treatment of a prosthetic joint infection (PJI) cannot be accomplished due to the increased risk of major complications after prosthetic joint revision surgery. In these patients, antibiotic suppressive therapy (AST) is often used to control the infection.

Aim: To describe the clinical outcome of patients with a PJI after hip replacement treated with AST.

Methods: Patients in which AST for PJI was started between 2006 and 2013, were retrospectively included. Follow-up was continued until October 2018. AST has been defined as treatment with oral antibiotic therapy intended to suppress PJI. Treatment was considered successful in patients without reoperation for PJI or death related to PJI during follow-up.

Results: Twenty-three patients were included. The most commonly used antibiotics were doxycycline (n=14) and cotrimoxazole (n=6). The mean duration of AST was 38 months (1–151 months). AST was considered successful in 13 patients (56.5%) after a median follow-up of 33 months. AST was least successful in PJI caused by *S. aureus* with 80% failures versus 33% in PJI caused by other microorganisms and in patients who had an antibiotic-free period before the start of AST with 83% failures. Two patients ended AST due to side effects.

Conclusion: AST can be an alternative treatment in selected patients with a PJI after hip replacement. However, there is a persisting and considerable amount of failures, particularly in PJI caused by *S. aureus* and in patient with an antibiotic-free period before the start of AST.

INTRODUCTION

Total hip Arthroplasty (THA) is a very successful surgical procedure improving patients' quality of life by providing pain relief and restoring function. However, a prosthetic joint infection (PJI) is a devastating complication occurring in 1-3% of patients after primary THA and 10-12% after revision procedures [1]. PJIs can be classified as early, delayed and late according to the time of symptom development after the index surgery [1-3]. Guidelines recommend to treat an early or hematogenous PJI with debridement, antibiotics and implant retention (DAIR). In general, a delayed or late infection is managed with either a one- or two-stage revision procedure combined with antibiotic treatment [4]. However, there are patients in which surgical strategies are contraindicated. This may be due to comorbidities, surgical conditions (e.g. poor bone stock) or patients' refusal to undergo surgical therapy. For these patients, antibiotic suppressive therapy (AST) may be an alternative treatment option. The aim of this suppressive treatment is to control clinical manifestations of the infection rather than cure the infection [5].

Previous studies regarding AST in PJI are few. We have found a total of eight studies reporting clinical outcome of PJI patients treated with AST between 1988 and 2017 [6-13]. These studies included 13-92 patients treated with a variety of suppressive antibiotics, reporting success rates varying from 23% to 86% with a mean follow-up of 2-5 years. These studies on AST give us variable data on AST in mostly inhomogeneous groups with PJI of hip, knee, shoulder and elbow joints, different type, dosage and duration of antibiotic therapy with relatively short follow-up [6-13].

The aim of this study is to describe the clinical outcome of patients with a PJI after hip arthroplasty who received AST. Factors influencing their clinical outcome are investigated. In our hospital, AST is mainly applied after hip arthroplasty. In order to research a homogeneous group, only patients receiving AST after hip arthroplasty are included.

MATERIALS AND METHODS

Study design and population

This retrospective cohort study was performed at the Radboud University Medical Centre in Nijmegen, the Netherlands. All patients with a PJI were discussed in a weekly multidisciplinary meeting with an orthopedic surgeon, an infection disease specialist and a microbiologist. All patients with a PJI in which treatment with AST was started between January 1, 2006 and December 31, 2013 were included. Follow-up was completed until October 31, 2018. PJI was diagnosed according to the MSIS criteria by means of 2 or more tissue cultures demonstrating growth of an identical pathogen or ≥1 cultured virulent micro-organism [14]. We also aimed to analyze the difference in success rate between patients treated with AST after DAIR, two-stage revision or PJI diagnosed after diagnostic puncture. The following data were collected from the patient files: general patient characteristics (age, gender, BMI, ASA classification, type of hip prosthesis, comorbidities), number of revision surgeries of the affected joint, time of onset of PJI, symptoms of PJI, causative microorganism, type, dosage and duration of AST and clinical and radiological outcome. We also collected laboratory results at the start of AST, i.e. C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and leucocyte count.

Antibiotic suppressive therapy

AST was defined as an oral antibiotic therapy without an end date, started with the intention to control the infection where curative treatment seems unachievable. The type and dosage were based on in vitro susceptibility of the cultured pathogens. Laboratory monitoring for potential toxicity and adverse events was performed.

Outcomes

AST was considered to be successful in cases with retention of the prosthesis without clinical relapse of infection at final follow-up. In cases in which follow up had ended due to the death of the patient unrelated to (the treatment of) PJI, AST was considered successful. Failure was defined as death related to PJI or new surgical intervention at prosthesis side due to persistent or recurrent infection.

Follow-up

Patients were seen at the outpatient clinic by the orthopedic surgeon or the infection specialist, every three months in the first year. The interval increased to yearly if there were no symptoms of PJI or adverse events due to antibiotics. Endpoints were (unrelated) death, re-intervention at prosthesis side due to infection or latest follow-up at outpatient clinic if no event occurred.

Statistical Analysis

The statistical analysis was performed with IBM SPSS statistics, version 22.0 (IBM Corp., Armonk, N.Y., USA). To describe overall survival without an event, a Kaplan-Meier survival analysis was performed according to an intention-to-treat principle. To assess the association of risk factors, known from previous studies [8-13], with clinical outcome, a univariate logistic regression analysis was performed. In case off missing values these data were deleted from our analysis. P-values < .05 were considered to be statistically significant.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local ethics committee has waived approval for this study.

RESULTS

A total of 23 patients (16 female) with a mean age of 70 years (range, 40-88 years) at start of their AST were included. Patient characteristics and medical history are shown in Table 1. The majority of the patients (66.7%) had a PJI after previous revision surgery of the hip. The mean number of previous surgical procedures on the affected side was five operations (range 1-9). Indications for AST were surgical complexity with poor bone stock and severe soft tissue injury (29%), patients wish not to be re-operated (13%), poor general medical condition (21%). 9 patients (38%) had a combination of reasons (surgical complexity, poor general medical condition and/or patients wish not to be re-operated).

TABLE 1. characteristics of 23 patients with PJI treated with antibiotic suppressive therapy suppressive

Characteristics	Number of patients
Gender	
Female, n (%)	16 (69.6)
Age at start AST, years, mean (range)	70 (40-88)
BMI, kg/m^2, mean (range)	26.6 (16.8-44.8)
BMI group, n (%)	
<20	4 (17.4)
20-25	6 (26.1)
25-30	7 (30.4)
30-35	5 (21.7)
>35	1 (4.3)
ASA score, n (%)	
1	3 (13.0)
2	12 (52.2)
3	8 (34.7)
Co-morbidity	
Cardiovascular	9 (39.1)
Rheumatoid arthritis	1 (4.3)
Diabetes mellitus type 2	2 (8.7)
Malignancy <5 years	3 (13.0)
Prosthetic joint, n (%)	
Total hip arthroplasty	21 (91.3)
Hemi arthroplasty	2 (8.7)
Arthroplasty, n (%)	
Primary implant	4 (17.4)
Revised implant	19 (82.6)
Type/onset of PJI, n (%)	
Early (<3 months)	7 (30.4)
Delayed (3-24 months)	8 (34.7)
Late (>24 months)	8 (34.7)
Previous PJI, n (%)	9 (39.1)

DAIR	
Yes	13 (56.5)
1 x DAIR	8
2 x DAIR	3
3 x DAIR	1
4 x DAIR	1
Physical examination at time of PJI symptoms, n (%)	
Fever	5 (21.7)
Sinus tract	5 (21.7)
Laboratory examination at time of PJI symptoms, n (%)	
Elevated CRP (>10 mg/l)	19 (82.6)
Elevated total leukocyte count (>11.0 x10^9/l)	5 (21.7)
Radiological examination at time of PJI symptoms, n (%)	
Loosening of the cup	2 (8.7)
Radiolucency of the cup	2 (8.7)
Protrusion of hemi arthroplasty with radiolucency stem	2 (8.7)
Broken osteosynthesis material	1 (4.3)

AST = antibiotic therapy, BMI = body mass index, ASA = American Society of Anesthesiologists DAIR = Debridement, Antibiotics and Implant Retention

Surgical therapy

Twenty (87.5%) patients underwent surgery before the start of AST; 13 of these patients underwent DAIR of whom 5 patients were treated with gentamycin polymethylmethacrylate beads. During all DAIR operations, modular implant parts were exchanged and rinsing was performed with 3 liters of betadine-saline solution and 3 liters of normal saline. 7 patients underwent partial or total revision for suspected aseptic loosening or periprosthetic fracture with unexpected positive intraoperative cultures. The 3 (12.5%) patients without surgery underwent a sterile puncture of the hip under suspicion of a chronic PJI. Cultures proved a PJI in these patients who were in a poor medical condition, not suitable for operative treatment. The isolated microorganisms are stated in Table 2.

TABLE 2. Identified microorganisms and agents, dosages and duration of the used antibiotic suppressive therapy

Case	Microorganism(s)	Type and dosage of AST	Time on AST (m)	Comments/adverse effects	Outcome
1	EC, CoNS	Cotrimoxazole 480 mg q.d	87	No doxycycline because usage of methotrexate	success
2	CoNS	Doxycycline 100 mg q.d	33		failure
3	Clostridium perfringens	Doxycycline 100 mg q.d Rifampin 300 mg b.i.d	67	Lower dosage because of nausea and dry mouth	success
4	CoNS, GBS	Cotrimoxazole 480 mg b.i.d Amoxicillin 500 mg t.i.d	19		failure
5	SA, PA	Doxycycline 100 mg q.d	62		success
6	SA	Doxycycline 100 mg q.d	36		failure
7	CA	Cotrimoxazole 480 mg q.d	7	Discontinuation because of possible toxicity (pleural effusion)	success
8	CoNS	Doxycycline 100 mg q.d	33		success
9	CoNS	Cotrimoxazole 960 mg q.d (3 months) followed by doxycycline 100 mg q.d	16	Switch to doxycycline because of nausea	failure
10	CoNS	Doxycycline 100 mg q.d	20	Lower dosage because of nausea	success
11	CoNS	Doxycycline 100 mg q.d	15		failure
12	SA	Ciprofloxacin 500 mg b.i.d	8		failure
13	SA, CoNS	Doxycycline 100 mg q.d	6		failure
14	SA, CoNS	Doxycycline 200 mg q.d	28		failure
15	CoNS, corynebacterium	Doxycycline 100 mg q.d	3	Discontinuation because of thrombocytopenia in patient with TAR syndrome*	success
16	CoNS	Doxycycline 100 mg q.d	69		success
17	Proteus Mirabilis, EF, corynebacterium	Amoxicillin-clavulanate 625 mg t.i.d.	1		failure
18	CoNS	Doxycycline 200 mg q.d	5	Itching sensation but continued treatment	failure
19	Pseudomonas, CoNS	Doxycycline 200 mg q.d Ciprofloxacin 750 mg b.i.d	5		success
20	CoNS, EF	Amoxicillin-clavulanate 625 mg t.i.d	20		success
21	CA	Cotrimoxazole 960 mg q.d	68		success
22	Gram+ rods	Doxycycline 100 mg q.d.	109		success
23	Serratia Marcescens	Cotrimoxazole 960 mg b.i.d	151		success

*EC = Enterobacter clocae, EF = Enterococcus faecalis, CA = Cutibacterium acnes, SA = Staphylococcus aureus, SE = Staphylococcus epidermidis, CoNS = coagulase-negative Staphylococci, GBS = group B Streptococci. q.d = once a day; b.i.d. = twice daily; t.i.d. = three times daily; q.i.d. = four times daily * TAR syndrome = Thrombocytopenia Absent Radius syndrome*

Antibiotic therapy

All 20 (87.0%) patients who underwent surgery before the start of AST, initially received intended curative antibiotic therapy for a mean duration of 13.4 weeks (range 0.71-29.9 weeks). In 16 of these patients a rifampin-based combination therapy was given after surgery, in the remaining 4 patients AST was started shortly after surgical intervention.

In 14 patients (60.9%), AST was started immediately after the initial treatment. In 6 patients (26.1%) AST was started when they had a clinical relapse of their symptoms after an antibiotic-free period ranging from 3-24 weeks (mean 16 weeks) after their initial treatment. In 3 patients (12.5%) AST was started after positive sterile puncture of the hip, without initial curative therapy. The mean duration of the AST in our patient group was 38 months (range 1-151 months). The type, dosage and duration of the AST are summarized in Table 2.

RESULTS OF AST

At time of final follow-up, AST was considered successful in 13 patients (56.5%) after a median follow-up of 33 months (range 1-151 months). Kaplan-Meier survival analysis estimates a mean symptom-free prosthesis retention period of 82 months (6.9 years) with a 95% confidence interval of 54-111 months. The Kaplan-Meier survival curve is shown in figure 1. 9 patients (39.1%) had no event during follow-up. Four patients (17.4%) died of causes unrelated to PJI. Two out of the 13 patients with a successful result ended AST during follow-up and retained their prosthesis without any sign of infection at final follow-up.

AST failed in 10 patients (43.5%). Seven patients (29.2%) had a relapse of infection with the same micro-organism and 3 patients (13.0%) developed a new infection with a different micro-organism. One of the failures underwent a new surgical intervention (DAIR) after 6 months of AST. In 8 of the failed AST patients a Girdlestone procedure was performed of whom one patient underwent a reimplantation after 3 months. One of the failures underwent a proximal femur resection.

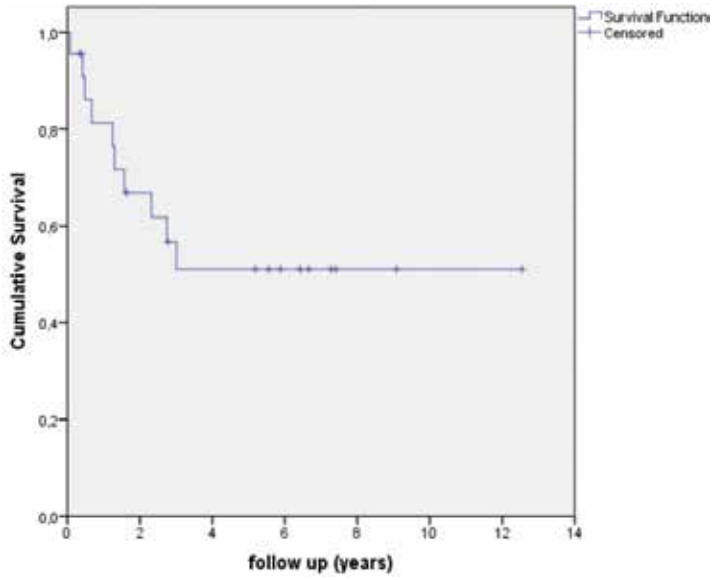

FIGURE 1. Kaplan-Meier curve showing survival/time without an event in the total group.

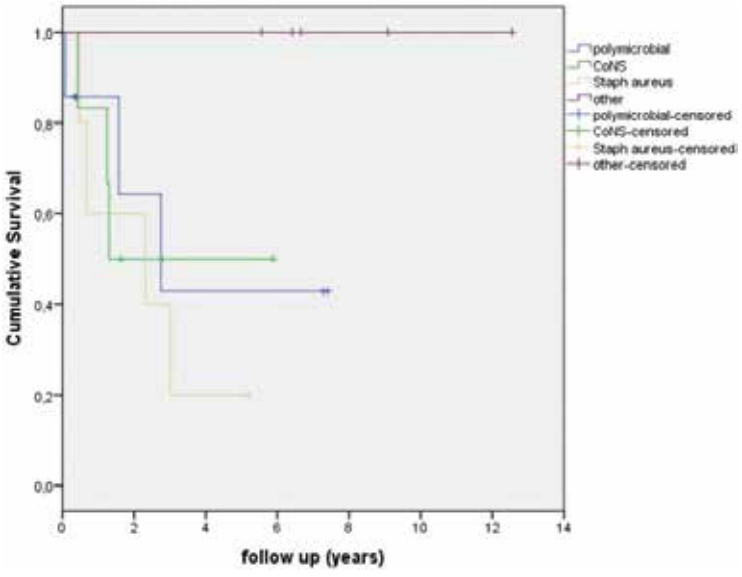

FIGURE 2. Kaplan-Meier curve showing survival/time without an event with different causative microorganisms

In this study 7 patients had a polymicrobial infection (30%), 6 patients had a *Coagulase Negative Staphylococci* (CoNS) infection (26%), 5 patients had a *S. aureus* infection (22%) and five infections were caused by other microorganisms (22%) (see Table 2). The Kaplan Meier survival curve in figure 2 shows the survival of different PJI infections. Figure 3 shows the Kaplan Meier survival curve of patients with a PJI with a *S. aureus* infection versus patients with PJI with a different microorganism. 4 out of 5 PJI caused by *S. aureus* failed (80.0%) versus 7 out of 19 failures (37.0%) in the patient group with an infection caused by other microorganisms. This difference however, was not significant (p=0.143). Figure 4 shows the Kaplan Meier survival curve of patients who had an antibiotic-free period before the start of AST versus patients receiving AST directly after intended curative treatment. In 5 out of the 6 patients (83.3%) with an antibiotic-free period, treatment failed, versus 4 out of 14 failures (28.6%) in patients receiving AST directly after surgery (p=0.045). In the three patients with an assumed low-grade infection in which AST was started after puncture, one failure was observed. Figure 5 shows the Kaplan Meier survival curve comparing patients who had a DAIR, one-stage revision or puncture before the start of AST. No significant difference was seen comparing these groups.

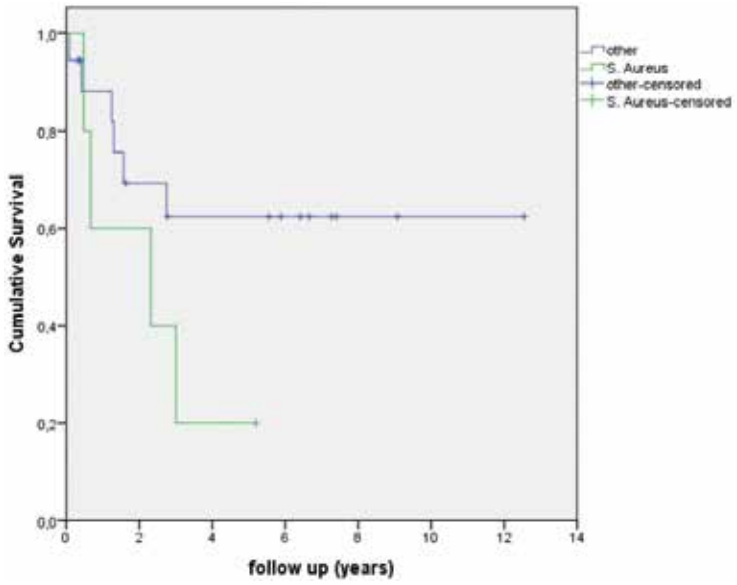

FIGURE 3. Kaplan-Meier curve showing survival/time without an event, *S. aureus* vs other causative microorganisms

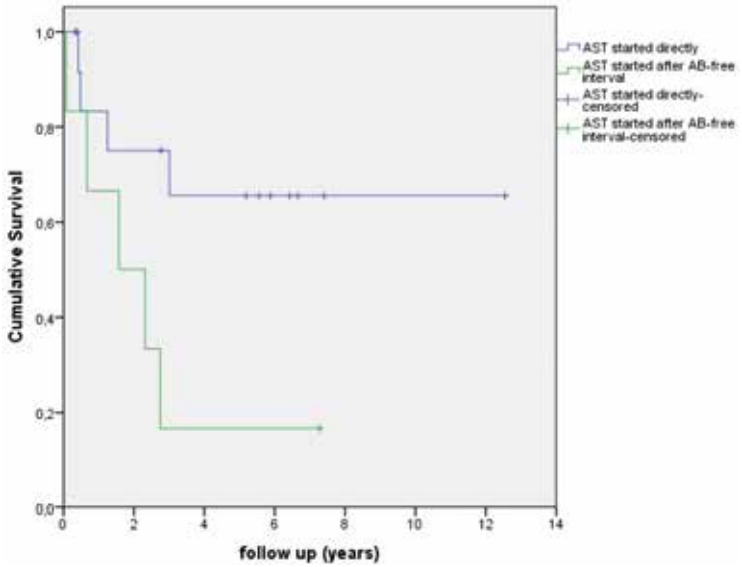

FIGURE 4. Kaplan-Meier curve showing survival/time without an event, AST started directly vs AST started after AB-free period

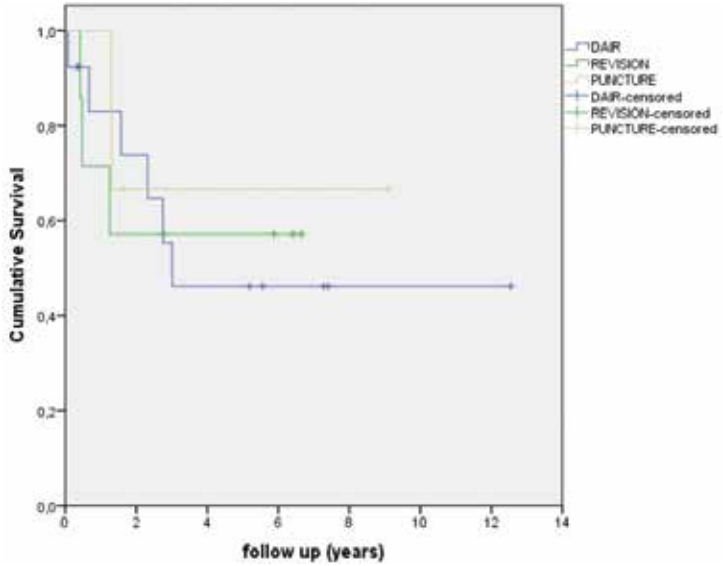

FIGURE 5. Kaplan-Meier curve showing survival/time without an event, DAIR vs Revision vs Puncture

DAIR = Debridement, Antibiotics and Implant Retention

TABLE 3. Univariate regression analysis

Variables	n	Failures (%)	Odds ratio for success (95% CI)	p-value [a]
Gender				
Male	7	3 (42.9%)		
Female	16	7 (43.8%)	1.04 (0.17-6.23)	0.968
Age				
<50	4	1 (25.0%)		
50-70	8	4 (50.0%)		
>70	11	5 (45.5%)		0.713
ASA score				
1	3	1 (33.3%)		
2	12	7 (58.3%)		
3	8	2 (25.0%)		0.331
Sinus tract				
Not present	19	9 (47.4%)		
Present	4	1 (25.0%)	2.70 (0.24-30.85.)	0.424
Microbiology				
CoNS	6	3 (50.0%)		
S. Aureus	5	4 (80.0%)		
Other	5	0 (0.00%)		
Polymicrobial	7	3 (42.9%)		0. 663
BMI				
<30	17	8 (47.1%)		
>30	6	2 (33.3%)	1.78 (0.25-12.45)	0.562
Arthroplasty				
Primary implant	4	1 (25.0%)		
Revised implant	19	9 (47.4%)	0.37 (0.03-4.23)	0.424
Type/onset of PJI				
Early	7	4 (57.1%)		
Delayed	8	3 (37.5%)		
Late	8	3 (37.5%)		0.687
CRP (3 missing values)				
<80	10	2 (20.0%)		
≥80	10	6 (60.0%)	6.00 (0.81-44.35)	0.079
Initial treatment				
DAIR	13	6 (46.2%)		
Revision	7	3 (42.9%)		
Puncture	3	1 (33.3%)		0.533
Duration of AST				
AST <6 months	4	2 (50.0%)		
AST ≥6 months	19	8 (42.1%)	1.375 (0.158-11.937)	0.773
AB free period				
Yes	6	5 (83.3)	0.080 (0.007-0.918)	0.042
None	14	4 (28.6)		
Puncture	3	1 (33.3%)		

RA = rheumatoid arthritis, DM = diabetes mellitus, PJI = prosthetic joint infection, ASA = American Society of Anesthesiologists, BMI = body mass index, [a] log rank test

Table 3 shows the results of the univariate logistic regression analysis for variables that could possibly be associated with an increased failure rate. None of the variables were significantly associated with an increased risk of failure except for an antibiotic-free period before the initiation of AST.

There were 4 patients in which follow up ended before 6 months of AST. Two of these patients had a clinical relapse of PJI and were marked as failures. One patient died of a cardiac cause unrelated to PJI treatment and the other patient stopped AST due to side effects but retained his prosthesis until final follow up. We separately analyzed patients receiving at least 6 months of AST showing a success rate of 63.2% (12 out of 19 patients).

Adverse events

Six patients (26.1%) experienced adverse events during AST. Four of these patients experienced gastrointestinal problems, a rash or itching but could continue suppressive treatment; in 2 of these patients the dosage was reduced, in another patient cotrimoxazole was switched to doxycycline and 1 patient experienced a temporary itching sensation without the need to change or stop the AST. The other 2 patients (8.7%) ended their therapy due to adverse events. 1 of them was suspected to have pleural effusion as an adverse event; further analysis however did not confirm this. The other patient had to end the suppressive therapy due to thrombocytopenia during the use of Doxycycline in combination with TAR syndrome (thrombocytopenia-absent radius syndrome).

DISCUSSION

AST is suggested to be an alternative treatment in selected patients with a PJI in which further surgical intervention is unattractive. The aim of this study was to describe the clinical outcome of patients treated with AST in PJI after hip arthroplasty.

We found a 56.5% success rate after a median follow-up of 33 months. Considering an estimated mean survival of 82 months (95% CI 54-111), AST appears to be a rational treatment option when curative treatment seems impossible. Success rate in previous studies vary from 23 to 86% [6-13]. Table 4 summarizes the results of previous studies reporting on AST [8-13]. The presented studies in Table 4 included a wide variety of PJI

including infections of total hip, knee, elbow and shoulder prosthesis. Both Siquira et al and Pradier et al found that infection involving the hip joint was associated with a better outcome compared to other PJIs [11, 13]. To be able to give a fair impression of what to expect from AST after hip surgery, solely PJI after hip arthroplasty were included.

TABLE 4. Previous studies on AST in PJI

Author	Year and Journal of publication	Number of patients	Mean follow-up (years)	Success rate (%)
Goulet et al [6]	1988, J. Arthroplasty	19	4.1	63.0
Tsukayama et al [7]	1991, J. Orthopedics	13	3.1	23.0
Segreti et al [8]	1998, Clin Inf Disease	18	4.1	83.0
Rao et al [9]	2003, CORR	36	4.4	86.2
Predki et al [10]	2014, Int J Inf Disease	38	2.0	60.0
Siqueira et al [11]	2015, J Bone Joint Surg Am.	92	5.8	68.5
Wouthuyzen [12]	2017, J Bone Joint Infect	21	1.8	67.0
Pradier et al [13]	2018, Infection	78	2.8	71.8

The study by Siqueira et al. was the first study comparing 92 patients treated with AST for PJI with a matched cohort of patients with PJI not receiving AST (ratio 3:1) [11]. They found a significant difference in five-year infection-free prosthetic survival rate of 68.5% in the AST group compared to 41.1% in the non-suppression group. Interestingly, they found a greater benefit from AST in patients with a S. *aureus* infection compared to patients with a S. *aureus* infection not treated with AST.

In other previously published literature, several variables associated with a lower chance of survival are described; S. *aureus* infection [8, 9, 10, 12], older age (>85 years), female gender, hypoalbuminemia, presence of a sinus tract [10], tumor prosthesis, higher level of inflammation blood values, rheumatoid arthritis [12], longer initial curative treatment and discontinuation of AST after 2 years [13]. We performed a univariate logistic regression analysis for all of these variables as described in Table 3. In accordance with other studies we found a higher failure rate among PJI caused by S. *aureus* (80% versus 37%). However,

this difference is not statistically significant. Consistent with the findings of Wouthuyzen et al [12], we found a higher failure rate among patients with higher inflammatory parameter; 60% of the patients with a CRP level ≥ 80ml/L failed, versus 20% of the patients with a CRP level < 80ml/L at the start of AST. In our study, this difference was not statistically significant (p=0.79). Interestingly, we did find one statistically significant variable in this study. We have included 6 patients who had an antibiotic-free period before AST was started. In these patients PJI relapsed after initial curative treatment. In 5 of these patients (83.3%) AST failed versus 4 out of 14 failures (28.6%) in patients receiving AST directly after initial curative treatment (p=0.045). Despite no multivariate regression analysis could be performed, this finding suggests that AST should only be started when followed directly after curative antibiotic treatment and that bacterial load reduction seems essential for AST to be successful. However, the lower success rate in this subgroup of patients could also be explained by the fact that these patients already have shown a relapse of PJI at the start of AST. The inclusion of these patients could possibly explain a lower success rate in our study compared to previous studies described in table 4 [8,9,11-13].

Strengths of this study

This is the first study on AST solely describing patients with a PJI after hip replacement. An intention-intention-to-treat analysis gives a fair impression of what to expect when considering AST in PJI treatment after hip arthroplasty. All patients had a microbiologically proven PJI, the microorganism was susceptible to oral antibiotic therapy, and the type of antibiotic therapy was based on in vitro susceptibility of the pathogen. Almost all of our patients used either doxycycline or cotrimoxazole.

The optimal regimen and duration of AST remains uncertain. We generally prescribed doxycycline 100 mg q.d. and cotrimoxazole 480-960 mg q.d. This is half of the recommended dosages of doxycycline 100 mg b.i.d. and cotrimoxazole 960 mg b.i.d., as described in the IDSA guidelines [4]. Especially in patients who are treated with AST because of their medical condition, a low dosage of antibiotics is favored because of the possible side effects. Only two patients (8.7%) had to end their antibiotic therapy due to adverse events. Rao et. al showed a similar percentage of 8% [9]. In the patient group presented by Segreti et al. 22% percent of the patients showed adverse events [8].

Study limitations

As in previously performed studies on AST, the retrospective design and low number of patients are the main limitations of our study. Because of the small sample size, a multivariate analysis with Cox-regression analysis could not be performed to assess variables associated with an increased risk of treatment failure. A third limitation of this study is the use of different initial treatment regimens.

CONCLUSION

AST may be the only treatment option in patients in which curative treatment with surgical intervention is contraindicated. In addition to previous literature, this study suggests the use of chronic suppressive antibiotics is safe with acceptable outcomes, considering the absence of alternative treatment strategies. When considering the start of AST, one should be aware of a possible decreased success rate among patients who had an antibiotic-free period before the start of AST, patients with high inflammatory parameters and S. *aureus* infections.

Due to the small sample size and inhomogeneous study group in the current and previous studies, we have not been able to identify definite risk factors for failure of AST. Therefore, recommendation on the use of AST in the current international guidelines remains based on the few available data and expert opinions. Ideally, a prospective randomized controlled trial with larger numbers is performed to assess the optimal regimen and safety of antibiotic suppressive treatment. However, this seems an unachievable goal given the exceptional inhomogeneous group of patients and lack of alternative treatment options. Therefore, we emphasize a systematic review of the currently available studies is necessary to facilitate the development of guidelines for routine practice.

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CHAPTER 11

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Periprosthetic Joint Infections – to prevent, cure or control

A periprosthetic Joint Infection (PJI) after total hip- or knee arthroplasty (THA or TKA) is a serious complication with a large impact on the quality of life for a patient and high costs for society. PJI after THA or TKA can cause pain, functional decline, low quality of life and even death [1]. The infection rate after the THA or TKA varies between 1 and 3% in the Netherlands [2,3]. Due to the high numbers of total joint replacements (24.709 THA and 29.520 TKA in 2017 in the Netherlands), PJI is often encountered, with an estimated incidence of approximately 1,300 per year in the Netherlands [4,5]. Treatment of PJI is expensive with average additional medical costs of 25,000 USD in case of early infections and 80,000 USD in case of late infections compared to an average of 12,000 USD for primary total joint replacements [6–8]. The higher costs of late versus early infections are explained by the fact that late infections are hard to cure and generally require more surgical procedures. Total direct and indirect costs of PJI after THA for the society are estimated to be 390,806 USD on average for a 65-year-old patient [9]. These estimated costs include surgical treatment, hospital admittance, antibiotic treatment, homecare, physiotherapy, and lost income due to the morbidity of PJI. Worldwide, the number of total joint replacements increases every year [10]. This leads to an increase in the absolute number of PJI. Additionally, a slight increase in incidence of PJI is seen, possibly explained by improved registration of PJI [11,12]. Prevention, early diagnostics and optimal treatment is paramount in patients undergoing elective surgical procedures and of course; *prevention is better than cure*. However, preventing bacteria from colonizing a prosthesis is easier said than done. A PJI is a complex problem in which many factors affect the onset and treatment. In order to win this battle and reduce the likelihood of a PJI, we have to reduce the problem to individual causal factors and focus on those factors that are modifiable.

In the first part of this thesis "Prevention of PJI" three different possible modifiable factors to reduce the chance of PJI, are studied; hypothermia, anticoagulants and type of anesthesia. This has led to recommendations for orthopedic practice at the outpatient

clinic, the orthopedic ward and the operation room. By the continuous battle against PJI, infection rates after TKA or THA are relatively low.

Despite all these efforts, complete eradication of infections has not been achieved. Therefore, once an infection does occur, optimal treatment is required. International congresses and consensus meetings have already led to internationally recognized guidelines for the treatment of PJI. However, there are still many unanswered questions about the optimal treatment of PJI. In part 2 of this thesis, "curative treatment", these questions are addressed by research on the effectiveness of various treatment options applied in clinical practice. And so, the slogan of this thesis is extended from *prevention is better than cure* to *prevent if you can, cure if you must.* This has led to practical recommendations in the operating room on the removal of cement, the use of antibiotics in bone chips and on the treatment of PJI with clindamycin and rifampicin.

The final part of this thesis addresses palliative treatment of PJI when cure seems unachievable. The ongoing research and improvements in PJI treatment have led to cure rates up to 90% [13]. However, this means there is still a considerable number of patients with persistent PJI despite extensive treatment. In case curative treatment of PJI seems unachievable, Antibiotic Suppressive Treatment (AST) may be an option, but the safety and effectiveness of this treatment is unknown [14]. Part 3 of this thesis is the result of a study into the effectiveness and safety of AST. For this part of the thesis our slogan was extended to *prevent if you can, cure if you must, control what persists.*

In the following section of this thesis, the most important research results and an answer to the research questions are summarized. This summary will end with implications and recommendations for clinical practice and future research.

PART 1 – PREVENTION - PREVENTION IS BETTER THAN CURE

Hypothermia

In existing literature, research has shown that intraoperative hypothermia (a body temperature <36.0 C°) during general surgery increases the likelihood of postoperative infection [15]. Also, hypothermia increases the risk of cardiac morbidity, the use of pain medication and length of stay in the hospital [16]. As both the incidence of hypothermia and the correlation with PJI have not been demonstrated in hip and knee arthroplasty, a data analysis described in **chapter 2** of this thesis, has been carried out in CWZ, with two main research questions: What is the incidence of intraoperative hypothermia during THA and TKA surgery? Is there a correlation between the incidence of hypothermia during surgery and the incidence of PJI after TKA and THA?

In a retrospective cohort study, the incidence of hypothermia among 672 patients undergoing THA (415) or TKA (257) between August 2009 and November 2010, was investigated. The incidence of hypothermia for THA and TKA was 26.3% and 28.0%, respectively. Risk factors were investigated. Increased age, spinal anesthesia and female gender were significantly correlated with an increased risk of hypothermia. Against our expectations, increased BMI and increased duration of surgery were correlated with a reduced risk of hypothermia. Among patients undergoing THA, a higher infection rate was found in hypothermic patients as compared to patients who were normothermic during surgery (3.7% vs 1.0 %). However, this difference was not statistically significant.

In conclusion, we found a disturbingly high incidence of hypothermia during THA and TKA with more than a quarter of the operated patients experiencing hypothermia and a higher incidence of PJI in this group. Although, this increased incidence did not reach statistical significance. Considering the known negative effects of hypothermia during other surgical interventions, we emphasize the importance of investigations on possible causes of hypothermia and measures to prevent hypothermia during THA and TKA. The finding that prolonged duration of surgery was associated with a reduced risk of hyperthermia, could be explained by the influence of perioperative warming with a forced air warming system. This theory indicates that we should start warming the

patients earlier. A recent meta-analysis on the effect of pre-operative warming of patients supports this statement reporting a relative risk of SSI of 0.60, 95% CI 0.42–0.87 in prewarmed patients before surgery [17].

Thermo-reflective Blanket

In order to prevent intraoperative hypothermia the use of an additional thermo-reflective blanket was introduced in CWZ, in 2010. However, the effect of this blanket during THA and TKA had never been investigated. Before introducing an intervention as standard treatment, the effect should be investigated. Therefore, a randomized trial on the use of a thermo-reflective blanket was initiated in 2010, described in **chapter 3** of this thesis. The main research question for this study was: Does the use of a thermo-reflective blanket affect the incidence of hypothermia during total hip and knee arthroplasty?

For the purpose of this study, 58 patients were randomized. 29 patients received an additional thermo-reflective blanket in addition to the standard hospital blanket. The other 29 patients only received the standard hospital blanket. Outcome parameters were intra- and postoperative body temperature, temperature comfort and the occurrence of shivering during the operation and after the operation in the recovery room. The average lowest measured body temperature was below 36°C in both groups and did not significantly differ (35.9 +/-0.4 °C with thermo-reflective blanket vs. 35.8 +/-0.4 °C without thermo-reflective blanket). In addition, temperature comfort and the occurrence of shivering on the operating or recovery room did not differ significantly. In conclusion, the thermo-reflective blanket is of no added value in TKA and THA and usage of this blanket in orthopedic surgery was discontinued in CWZ. This research was repeated in a feasibility trial among 224 patients in Washington, DC, in 2016 [18]. No significant difference was found in patients receiving both a thermo-reflective blanket and warmed cotton blanket versus a warmed cotton blanket alone.

Follow up of hypothermia

The high incidence of hypothermia (body temperature <36°C) during orthopedic surgery in 2009 and 2010, as described in Chapter 2, gave rise to a follow-up study which is described in **chapter 4** of this thesis. Standardized recording of perioperative body

temperature facilitated a retrospective data analysis with larger numbers. Analyzing a larger patient group could potentially show a significant difference in infection rate. Research questions for this study were:

Does intraoperative hypothermia correlate with the incidence of PJI after placing a THA and TKA?

Does the incidence of hypothermia during surgery for total hip and knee arthroplasty change over time?

We investigated all patients who underwent THA and TKA between 2011 and 2014. A total number of 2,600 patients were enrolled with a hypothermia incidence of 11.7%. This incidence is considerably lower than the incidence in the previous cohort in 2009-2010 (26.9%). Also, the average intraoperative body temperature increased by 0.6°C higher to 36.5 °C in patients operated between 2011-2014 compared to the patients enrolled in our previous study, operated in 2009-2010. A linear regression analysis confirmed a significant rise in average body temperature over time in this specific study group between 2011 and 2014. Against the expectations, we found a lower PJI incidence among hypothermic patients compared to normothermic patients; 1.0% versus 1.9%, respectively. However, this difference was not statistically significant.

An important question to ask is why the average body temperature has risen over the years and why the incidence of hypothermia has declined? One possible explanation could be that behavior of medical staff has changed because they are aware of the high incidence and negative effects of hypothermia. The use of proven interventions to warm up patients, such as the pre-and intraoperative use of a forced-air warming system and simple cotton blankets, may have increased over time [19]. Also, the "Hawthorne effect" could play a role in the change of behavior among medical staff. In the Hawthorne effect, the behavior of a studied population changes, just because they are being observed [20]. By intraoperative measurement of body temperature, medical staff is triggered to take timely measures to warm up patients if necessary. So, both the awareness of the high incidence of hypothermia and continuation of intraoperative measurement of body temperature is important. A final possible explanation of the change in average body temperature in the two study groups could be a statistical phenomenon called regression-to-the-mean. Regression-to-the-mean occurs when an extreme value, far from the actual mean,

is measured in a first study and the same parameter is measured a second time [21]. The average is very likely to 'regress to the mean' in the second measurement. However, this phenomenon is less likely to have occurred in these studies, considering the large study groups in both studies.

Bridging of anticoagulants

Clinical research on the orthopedic ward in CWZ drew our attention towards postoperative hematoma formation and wound leakage as a risk factor for PJI [22]. But is postoperative wound leakage a symptom or a risk factor for a PJI? A question that every orthopedic surgeon must have asked multiple times in his or her career. The answer to this is ambiguous as direct postoperative wound leakage seems to be a risk factor for PJI in the beginning and could be a symptom of PJI a few days after surgery. Wound leakage is defined as discharge of fluid from the surgical wound. During surgery, bleeding occurs in the operation area. This blood contributes to wound healing. When too much blood accumulates in the surgical wound, this blood finds the way of least resistance and wound leakage occurs. So, wound leakage in the initial postoperative period seems to be a sign of hematoma formation but not a symptom of PJI. However, since blood can be a great source of nutrition for bacteria, hematoma formation is a risk factor for PJI [23]. As soon as hemostasis is achieved, hematoma formation and hereby wound leakage will stop. Consequently, when wound leakage persists after hemostasis, it may be caused by an inflammatory process initiated by the presence of bacteria. In this case, persistent wound leakage seems to be a symptom of PJI rather than a risk factor [24,25].

Regardless of the answer to the above question it is important to decrease the risk of wound leakage and it seems reasonable to focus on the reduction of hematoma formation. In order to reduce hematoma formation intra- and postoperative hemostasis and coagulation should be optimized. Assuming optimal visible hemostasis during surgery, a study into the relationship of anticoagulant medication and the emergence of PJI, was initiated. This study is described in **chapter 5**.

An ever growing number of patients undergoing TJA uses oral anticoagulants (OAC) to prevent thrombo-embolic events [10]. Before TJA, these OAC should be stopped in order to prevent bleeding complications during and after surgery. In selected cases, "bridging" of the OAC is indicated due to a greater need to prevent thrombo-embolic events. In

these cases, the OAC is replaced with a high dose of short-acting anticoagulants (low molecular weight heparin; LMWH) before and shortly after surgery [26]. This therapeutic dose of LMWH is four to eight times higher than the standard prophylactic dose to prevent deep venous thrombosis after THA or TKA. In theory, this can increase the risk of significant blood loss, bleeding complications, hematoma formation and wound leakage and consequently increase the likelihood of a PJI. We therefore formulated the following research question: What is the incidence of bleeding complications and PJI in patients undergoing THA or TKA in which bridging of anticoagulant therapy is indicated?

A retrospective cohort study was initiated in which the complication rate within a bridging group was recorded and compared to a control group. Between January 2011 and June 2012, 972 patients underwent THA or TKA. In 13 patients, bridging of OAC was indicated, receiving a therapeutic dose of LMWH around THA or TKA, according to the international guidelines [26]. Bleeding and thromboembolic complications, as defined by the International Society on Thrombosis and Haemostasis (see chapter 5 of this thesis), were analyzed [27]. Bleeding complications occurred in 12 patients (92%) and an intervention was indicated in nine of them (69%); Seven patients received blood transfusions (54%) and in two patients (15%) an early PJI was diagnosed and treated surgically. Hematoma formation resulting in prolonged immobilization for ≥2 days, occurred in nine patients (69%). All patients had an increased length of stay in the hospital as compared to the control group. Median length of stay was 11 days (7–52). Mean length of stay was 14 versus 5 days for the control group ($p < 0.05$).

In conclusion, there was an alarmingly high complication rate in patients undergoing THA or TKA receiving bridging of OAC. All these complications were related to an increased bleeding tendency. These findings resulted in a change in the anticoagulant policy within this patient group in CWZ; therapeutic dose of LMWH is now initiated at least 24 hours after surgery, provided that the wound is dry. Switching back to OAC after surgery is initiated at least seven days after surgery.

In a recently published systematic review and meta-analysis, the recommendations are even more vigorous; they found a significantly increased bleeding risk in bridged patients versus non-bridged patients and no difference in thromboembolic events. Therefore, they

advise against bridging when oral anticoagulants are interrupted for invasive surgery [28]. A multicenter RCT with adequate patient selection is indicated in order to draw a final conclusion on which international guidelines can be formulated.

Anesthesia technique

During surgery for THA or TKA, there are generally two anesthesiologic options; spinal or general anesthesia. For the orthopedic result of the operation, there seems to be no clear preferred anesthetic technique. However, in orthopedic literature there is evidence that SSI occurs more frequently in general than in spinal anesthesia [29]. This raises the question whether this increased risk also applies to PJI. Research question for the presented research in **chapter 6** was: Is there a correlation between type of anesthesia and the onset of a PJI after TJA?

In order to answer this question a retrospective data analysis was initiated in Rijnstate hospital in Arnhem, studying the infection rate after THA and TKA for general versus spinal anesthesia. All patients who underwent a THA or TKA in the period 2014-2017, were enrolled. Age, BMI, gender, THA versus TKA, type of anesthesia, duration of operation, and length of operation were recorded.

A total of 3909 patients were included (2111 THA and 1798 TKA). 1630 (41.7%) patients were operated under general anesthesia versus 2279 (58.3%) under spinal anesthesia. Early PJI (≤ 3 months after surgery) was diagnosed in 47 cases; 28 (1.7%) In the group of general anesthesia versus 19 (0.8%) in the spinal anesthesia group. Binary logistic regression analysis showed that both general anesthesia and an increased BMI is significantly correlated with an increased risk of PJI. The explanation for the difference in PJI incidence for general versus spinal anesthesia is not fully understood. The increased tissue oxygenation and reduced blood loss after spinal anesthesia are plausible suggested explanations [30–33]. Also, certain anesthetic agents which are commonly used in general anesthesia, inhibit leukocyte chemotactic migration, phagocytosis, lymphocyte function, inflammation or even directly support bacterial growth in case of contamination [29,34–36].

To sum up, there seems to be a correlation between general anesthesia and an increased risk of PJI. We recommend that these findings are taken into account when

general or spinal anesthesia is considered. In most hospitals, this choice is made at the anesthesiologic outpatient clinic, after THA or TKA is indicated by the orthopedic surgeon. It is therefore important that the anesthesiologist is aware of this increased risk.

PART 2 – CURATIVE TREATMENT - PREVENT IF YOU CAN, CURE IF YOU MUST

Despite all efforts to prevent PJI, it remains a major concern, occurring in 1-3% of THA and TKA. Therefore, optimal treatment of PJI is paramount to be able to fight this devastating complication and keep our patients ambulant. Treatment of PJI depends on the time of onset and the etiology. In Radboud University Medical Centre, research is performed on the optimal treatment of patients with a PJI after TJA, both in surgical technical terms and in the antibiotic treatment. For the second part of this thesis, the effect of innovative surgical techniques (cement-within-cement revisions and the mixing of antibiotics by cement) and the treatment with innovative antibiotic combinations, is studied.

Cement-within-cement revision

PJI is usually classified as early (≤ 3 month after primary surgery) or a late infection (> 3 months after surgery) [37]. In case of a chronic (usually low virulent) infection, pain occurs around the joint because the infection causes loosening of the prosthesis. In general, there is no fulminant onset of complaints in such cases. It is very difficult to eradicate these infections because the causing microorganism has created a biofilm on the prosthesis [38]. The golden standard of treatment in these cases is a two stage revision in which all prosthetic components are removed in the first stage and, after a 6-12 weeks period of antibiotic treatment, a new prosthesis is placed [37]. In case of PJI of a cemented hip prothesis, complete removal of the cement mantle can be challenging since it is often firmly attached to the bone surface. Attempts to completely remove the cement can result in significant bone loss, complicating the second stage operation. Therefore, it raises the question if removal of bone cement is actually necessary. It has been suggested that biofilm formation mainly occurs on the prosthesis and is possibly prevented on the bone-

cement interface by antibiotic impregnation of bone cement at the index operation [39–41]. Consequently, solely removal of the prothesis and keeping the cement mantle in place could be sufficient to treat PJI. At the time of onset of this study, only one study was published on this subject; Morley et al found acceptable outcomes in case of two-stage revisions where the cement mantle was left in situ, with a success rate of 93.3% in 15 patients with an average follow-up of 82 months [42]. Since this procedure is performed in Radboud University Medical Centre as well, it is interesting to see the long-term results in our population and a retrospective cohort study was initiated. Research question for the described study in **chapter 7** was: Does a two-stage revision of THA with the retention of bone cement for chronic PJI, result in acceptable success rates?

For this retrospective analysis, operation reports of all total hip revision procedures, performed between May 2009 and March 2013, were reviewed (n=333). There were 10 patients with an infected THA in whom the femoral cement mantle had been preserved during the first surgical procedure with the intention to reinsert a new prosthesis within this mantle during the second stage procedure. Clinical, biochemical and radiological outcomes were evaluated with a mean follow-up of 26 months. Successful treatment of the infection was achieved in 2 patients only. In the other 8 patients, the same micro-organism was found during second stage surgery or PJI reoccurred within one year after reimplantation. According to these numbers, results of femoral cement retention in two stage revision for chronic PJI were disappointing. Considering the contradicting success rates found by Morley et al, we searched for differences in treatment regimen. One possible important difference is the fact that, in the Radboud University Medical Centre, the inside of the cement mantle was not routinely reamed with a highspeed drill. It is possible that Morley et al. removed the biofilm by reaming the cement during first stage operation. Another difference could be the inclusion of early PJI by the group of Morley et al. Theoretically, there could be a difference in bacterial contamination of the bone-cement interface in case of early versus chronic infections. Finally, the group of Morley used an antibiotic loaded cement spacer for the interval period between the two surgical procedures, as opposed to our study group.

In conclusion, this research does not support the retention of femoral bone cement as routine practice in two-stage revisions for chronic PJI. However, due to the small sample

size we cannot draw definite conclusions from this research. Furthermore, we emphasize that results could improve once selection criteria and surgical techniques are optimized. At the time of writing this thesis, there are no newly published articles on cement retention at two-stage revisions. Research on partial two-stage revisions for chronic PJI after THA generally support the retention of a well fixed part of the prosthesis [43–45]. However, patient selection is critical and numbers are low in these papers.

Antibiotics in bone chips

Bone loss during the removal of a prosthesis or cement at revision surgery for PJI can cause insufficient bone stock and frustrate the fixation of a new prosthesis. In Radboud University Medical Centre, an operative technique has been developed to overcome this lack of bone stock; Impaction Bone Grafting (IBG)[46]. With this technique bone chips are impacted in the acetabulum and/or femur. For revision surgery, these bone chips are usually allografts from a donor femoral head collected during primary THA of selected donors. In order to reduce the likelihood of a new infection, it is suggested in the literature to mix antibiotics through these bone chips [47]. Some articles have been published with promising results of antibiotics in donor bone chips [48,49]. However, it is unknown whether the antibiotics weaken the bone chips, mitigate bone incorporation in the host or even result in the onset of infections with multidrug resistant organisms. Due to the increasing number of antibiotic-resistant microorganisms, unnecessary use of antibiotics should be avoided. Results of IBG with additional antibiotics of the graft have never been compared to IBG without mixing with antibiotics. In Radboud University Medical Centre, plane cancellous bone grafts without antibiotics are routinely used. The institutional outcome registry with thorough follow-up facilitates a retrospective study on patients treated with IBG, as described in **chapter 8**. Research question: What is the reinfection rate in two-stage revisions for PJI after THA for PJI with donor bone chips without additional antibiotics of the graft?

A total of 36 patients were enrolled in this study, operated between 1990 and 2009. We found a re-infection rate of 2.8% within 2 years. When the follow-up is extended to 10 years, re-infection rate rises to 11.0%. This is comparable to infection rates after two-

stage revisions without the use of IBG reported in a pooled individual participant data analysis of 44 cohort studies; 13.8% after a median follow-up of 3.3 years [50]. At the time of publication of this article, there were two studies reporting on results of two-stage revisions with antibiotics impregnated bone chips. These studies had an average follow up of 2 to 4 years with re-infection rates of 0.0% (n = 12) and 3.3% (n = 30)[48,49]. It is likely that these infection rates increase with longer follow-up because low grade infections commonly become symptomatic after a longer period of follow-up.

In conclusion, we found fairly acceptable reinfection rates after two-stage revisions with IBG without additional local antibiotics. Since the positive effect of antibiotic impregnation of donor bone grafts has only demonstrated in vitro and because of the potentially increased emergence of resistant micro-organisms and possible diminished bone incorporation, we do not recommend using this as standard treatment. Research based on large volume registries could provide useful information on the reinfection rates and bone incorporation in both groups.

Systemic antibiotics

After surgical treatment of PJI, patients are usually treated with antibiotics for 3 months. The choice of antibiotics is dependent on cultured bacteria and their susceptibility. To prevent bacterial resistance and biofilm formation, a combination of 2 different antibiotics is advised [37,51]. Approximately 50% of the PJI is caused by *Staphylococcus* spp. [52]. In case of PJI with susceptible *Staphylococcus* spp., international guidelines advise an antibiotic regimen combining a quinolone with rifampicin [37]. This advice is based on a study with a small patient group with acceptable outcomes [53]. Although other combination regimens are used in routine practice, they are not included in the international guidelines, mainly due to the lack of (published) research. However, as bacterial resistance to our antibiotic arsenal is increasing, the search for alternative antibiotic regimes is paramount [54]. Patients in Radboud University Medical Centre are treated with one of these alternative treatment regimens; rifampin with clindamycin. However, the efficacy and safety of this regimen in PJI was never studied, before publication of the presented paper in **chapter 9**. Therefore, we decided to evaluate the clinical outcome of patients treated with the antibiotic combination of rifampicin and clindamycin in PJI caused by a *Staphylococcus*

spp. susceptible to both antibiotics. Research question: Is an oral rifampin-clindamycin combination therapy for 3 months after surgical treatment, safe and effective in patients with a proven PJI of THA or TKA with a sensitive microorganism?

Retrospectively, all patients treated with an oral clindamycin-rifampin combination therapy between January 2004 and June 2010, were enrolled (n=36). Patients were followed for 54 months on average. Half of the patients (18) had undergone debridement and implant retention for early PJI and the other half (18) had undergone one-stage revision of their prosthesis followed by this antibiotic regimen. The later 18 patients had unexpected positive cultures after a suspected aseptic revision and were therefore treated with a one-stage revision, as opposed to a two-stage revision, the golden standard in case of chronic PJI.

We found an overall re-infection rate of 14% (5/36). Successful treatment of PJI was achieved in 78% (14/18) in the DAIR group and 94% (17/18) in the one-stage revision group. In five patients (14%) clindamycin was switched to another antibiotic due to side effects. Re-infection occurred in 3 of these patients. In the 31 patients completing three months of oral clindamycin-rifampin, successful treatment was achieved in 94% (29/31). These outcomes are comparable to the outcomes in the study cited in international guidelines [37,53,55]. The optimal dosage and serum concentration of both clindamycin and rifampin is still unknown. As rifampin induces an enzyme that breaks down clindamycin, this needs further investigation [56,57].

To conclude, the oral combination therapy of clindamycin with rifampicin seems to be safe and effective in the treatment of PJI with susceptible *Staphylococcus* spp. Research on the optimal dosage and concentration of both rifampicin and clindamycin is indicated to prevent over- or underdosage.

PART 3 - PALLIATIVE TREATMENT - PREVENT IF YOU CAN, CURE IF YOU MUST, CONTROL WHAT PERSISTS

By applying standardized treatment methods, successful treatment of both early and chronic PJI can be achieved in the majority of the patients [50,58]. Unfortunately, however, there are patients with persistent PJI despite repetitive operations and antibiotic treatment. In some cases, surgical intervention is contraindicated due to comorbidities or surgical complexity. In these patients, antibiotic suppressive therapy (AST) may be indicated [14]. In order to control the infection and suppress clinical symptoms, these patients are treated with a relatively low dose of antibiotics, possibly for the rest of their lives. However, little is known about the effectiveness and safety of AST. Therefore, we have carried out a retrospective data analysis in patients treated with AST in Radboud University Medical Centre for **chapter 10** of this thesis. Research question: Is the use of suppressive antibiotic therapy safe and effective in patients with chronic PJI after THA in which surgical intervention is contraindicated?

A total of 24 patients in which AST for chronic infected THA was started between 2006 and 2013, were followed up until October 2018. AST was defined as a low dose of oral antibiotic treatment with the intention to suppress the infection lifelong. Choice of antibiotics was based on susceptibility of the cultured microorganism and the most commonly used antibiotics were doxycycline (n=15) and cotrimoxazole (n=6). AST was considered successful if the prosthesis was still in situ without symptoms of PJI at latest follow up or at the time of death. AST was successful in 13 patients (54.2%) with a mean follow up of 38 months. The probability of successful treatment was significantly decreased when AST was started after an antibiotic-free period. Within this subgroup there was a re-infection in 5 of the 6 patients. Also, PJI caused by *S. aureus* and CRP levels >80 were associated with a high failure rate of AST, however, not significant.

We concluded that a selected patient group can be treated with AST when curative treatment options are contraindicated. Particularly patients who had an antibiotic-free window before the start of AST, patients with a *S. Aureus* PJI and patients with high serum infection parameters are at risk for failure of AST. Since randomized controlled trials seem impossible due the lack of treatment alternatives and the inhomogeneous

group of patients, we encourage systematic outcome monitoring of these patients. International guidelines for routine practice must rely on the currently available literature as summarized in chapter 10 of this thesis.

CONCLUSIONS AND RECOMMENDATIONS OF THIS THESIS

As long as joint replacements are performed, we will face periprosthetic joint infections. The serious consequences of PJI for patients and the burden to society have been the main drivers for this thesis. Goal of this thesis is to provide knowledge and insights to mitigate the risk of PJI and increase the chances of successful treatment. PJI is a complex problem with many interacting factors influencing the occurrence and its successful treatment. Given the relatively low incidence of PJI, retrospective research is the preferred research method to identify these factors. Each study described in this thesis covers one these factors. This has led to the following conclusions and recommendations for routine (orthopedic) practice:

1. Perioperative hypothermia is a common problem faced during total hip and knee replacement surgery. This problem may be reduced by an increased awareness among medical staff and timely measurements of body temperature.
2. Perioperative hypothermia is not directly related to a higher PJI incidence.
3. A thermo-reflective blanket does not contribute to the prevention of hypothermia during THA or TKA.
4. Patients in whom bridging therapy of anticoagulant medications is indicated during THA and TKA, have an increased risk of postoperative bleeding complications.
5. In such cases LMWH should be re-started at least 24 hours after surgery and switch to OAC should be avoided until adequate hemostasis is assured.
6. When the choice is made between general and spinal anesthesia for TJA, it should be realized general anesthesia is associated with an increased risk of PJI.

7. Preservation techniques of the cement mantle in two-stage revisions of infected THA are currently insufficient. However, clinical advantages of this technique mandate further optimization of this technique.
8. The use of bone chips mixed with antibiotics does not reduce the incidence of PJI compared to bone chips without antibiotics in two-stage revisions for PJI in THA.
9. The combination of clindamycin and rifampicin is safe and effective in the treatment of PJI with susceptible *Staphylococcus* spp. The optimal dosage and concentration should be investigated.
10. Palliative treatment of PJI with suppressive antibiotics has an acceptable chance of success in a selected patient group when curative treatment is not feasible.

In addition to the above, this thesis forms a basis for a scientific career in which we will continue research in the prevention and optimal treatment of PJI.

To prevent, cure or control!

The battle continues...

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CHAPTER 12

NEDERLANDSE SAMENVATTING EN ALGEMENE DISCUSSIE

NEDERLANDSE SAMENVATTING EN ALGEMENE DISCUSSIE

Geïnfecteerde gewrichtsprotheses – voorkomen, genezen of beheersen

Een geïnfecteerde gewrichtsprothese of -in het Engels- een Periprosthetic Joint Infection (PJI) na het plaatsen van een totale heup- of knieprothese (THP of TKP) is een ernstige complicatie met een grote impact op de kwaliteit van leven voor een patiënt en hoge kosten voor de maatschappij. Een geïnfecteerde THP of TKP kan leiden tot veel pijn, functionele achteruitgang, lage kwaliteit van leven en zelfs tot de dood [1]. Het infectiepercentage na het plaatsen van een prothese varieert in Nederland tussen de 1 en 3% [2,3]. Vanwege de hoge aantallen geplaatste totale knie en heupprotheses (24.709 en 29.520 in 2017, respectievelijk in Nederland) is een PJI van een THP of TKP een veelvoorkomend probleem met een geschatte incidentie van 1.300 per jaar [4,5]. De behandeling van een PJI is kostbaar met gemiddelde medische kosten van 25.000 USD in geval van vroege infecties en 80.000 USD het in het geval van late infecties [6–8]. De hogere kosten van late versus vroege PJI worden verklaard door het feit dat deze infecties moeilijker te behandelen zijn en daarbij vaak meerdere chirurgische ingrepen nodig zijn. De totale directe en indirecte kosten voor de samenleving van een PJI na een THP worden geschat op gemiddeld 390.806 USD voor een 65-jarige patiënt [9]. Deze geschatte kosten omvatten chirurgische behandeling, ziekenhuis opname, antibioticabehandeling, thuiszorg, fysiotherapie en verloren inkomen als gevolg van de morbiditeit van PJI. Wereldwijd stijgt het aantal geplaatste gewrichtsprotheses elk jaar [10]. Dit leidt tot een toename van het absolute aantal PJI. Overigens wordt een lichte toename van de incidentie van PJI mogelijk verklaard door een verbeterde registratie van protheseinfecties [11,12]. Preventie, vroege diagnostiek en optimale behandeling is uitermate belangrijk om patiënten die een electieve operatie ondergaan op de been te krijgen en te houden. Daarbij is natuurlijk het al oude adagium *Preventie is beter dan genezen* onomstotelijk van toepassing. Het voorkomen dat een bacterie een prothese koloniseert is echter gemakkelijker gezegd dan gedaan. Een PJI is een complex probleem waarbij vele factoren van invloed zijn op het ontstaan en dus ook op de behandeling. Om de kans op een PJI te verkleinen moeten we het probleem reduceren tot specifieke oorzakelijke factoren en focussen op die factoren die beïnvloedbaar zijn.

In het eerste deel van dit proefschrift "preventie van PJI" worden drie beïnvloedbare factoren om de kans op een PJI te verkleinen, onderzocht; hypothermie, antistolling en type anesthesie. Dit heeft geleid tot aanbevelingen voor de orthopedische praktijkvoering op de polikliniek, de afdeling en de operatiekamers. Door continu bezig te zijn met preventie van PJI ligt het infectiepercentage na een TKP of THP in Nederland relatief laag.

Helaas blijkt volledig voorkomen van infecties vooralsnog een utopie. Indien een PJI toch ontstaat, is derhalve optimale behandeling van PJI minstens zo belangrijk. Internationale congressen en consensus bijeenkomsten hebben reeds geleid tot internationaal erkende richtlijnen voor de behandeling van PJI in algemene zin. Er zijn echter nog vele specifieke vraagstukken over de optimale behandeling van PJI. Deel 2 "curatieve behandeling" van dit proefschrift is dan ook tot stand gekomen door klinisch onderzoek waarin enkele van deze vraagstukken worden behandeld. En zo wordt het adagium van dit proefschrift uitgebreid van *preventie is beter dan genezen* naar; *voorkom wat je kunt voorkomen en genees wat je niet voorkwam.* Onderzoek naar de effectiviteit van verschillende behandelingsmogelijkheden die in praktijk worden toegepast, wordt in deel 2 van dit proefschrift behandeld. Dit heeft geleid tot praktische aanbevelingen in de operatiekamer over het verwijderen van cement, het gebruik van antibiotica in botchips en over de behandeling met specifieke antibiotica.

In het laatste deel van dit proefschrift, "palliatieve behandeling", is de effectiviteit en veiligheid van suppressieve antibiotische behandeling onderzocht. De behandeling van een PJI is in de meeste gevallen succesvol. Aanhoudend onderzoek en verbeteringen in de behandeling van PJI hebben geleid tot genezingspercentages van 90% [13]. Helaas betekent dit dat er nog steeds een aanzienlijk aantal patiënten niet zal genezen van PJI. In deze gevallen zou een suppressieve antibiotische behandeling (Antibiotic Suppressive Treatment; AST) een optie zijn om de infectie onder controle te houden [14]. Voor deze patiënten zal het adagium uitgebreid moeten worden: *PJI*; *voorkom wat voorkomen kan worden, genees wat je niet voorkwam en beheers wat niet geneest!*

In deze Nederlandse samenvatting leest u de belangrijkste bevindingen per onderzoek en een antwoord op de onderzoeksvragen gesteld in hoofdstuk 1. De samenvatting wordt afgesloten met implicaties en aanbevelingen voor de (orthopedische) praktijk en voor onderzoek in de toekomst.

DEEL 1 – PREVENTIE – PREVENTIE IS BETER DAN GENEZEN

Hypothermie

In de bestaande literatuur heeft onderzoek uitgewezen dat onderkoeling of hypothermie (een lichaamstemperatuur <36,0 °C) tijdens een operatie de kans op een postoperatieve wondinfectie verhoogd [15]. Een te lage lichaamstemperatuur geeft een verhoogde kans op cardiale morbiditeit, patiënten hebben meer pijnmedicatie nodig en patiënten verblijven langer in het ziekenhuis [16]. Omdat zowel de incidentie van hypothermie als de correlatie met PJI niet aangetoond zijn bij heup- en knie prothesiologie werd voor **hoofdstuk 2** van dit proefschrift een data-analyse uitgevoerd in het CWZ met de volgende onderzoeksvragen: Wat is de incidentie van intra-operatieve hypothermie tijdens een THP- of TKP-operatie? Is er een correlatie tussen de incidentie van peroperatieve hypothermie en de incidentie van PJI na TKP en THP?

In een retrospectieve cohortstudie werd de incidentie van hypothermie in 672 patiënten die een THP of TKP ondergingen (415 THP en 257 TKP) tussen augustus 2009 en november 2010 onderzocht. De incidentie van hypothermie voor THP en TKP was 26.3% en 28.0%, respectievelijk. Tevens werden risicofactoren voor hypothermie onderzocht. Hogere leeftijd, spinale anesthesie en het vrouwelijk geslacht verhogen de kans op hypothermie. Tegen de verwachtingen in was een hoger BMI en een langere operatieduur gecorreleerd met een lagere kans op hypothermie. Onder de patiënten die een THP-operatie ondergingen, werd een hoger infectiepercentage gezien bij patiënten die tijdens de operatie hypotherm waren vergeleken met patiënten die normotherm waren (3.7% vs. 1.0%). Dit verschil was echter niet significant.

In conclusie vonden we een verontrustend hoge incidentie voor hypothermie tijdens THP en TKP-plaatsing met meer dan een kwart van de geopereerde patiënten blootgesteld aan hypothermie. Hoewel een significante correlatie met PJI niet werd aangetoond, werd wel degelijk een trend gezien van een hoger infectiepercentage onder patiënten die tijdens de operatie hypotherm waren. Gezien deze bevindingen en de bekende negatieve effecten van hypothermie, is het belangrijk onderzoek te blijven doen naar mogelijke oorzaken van hypothermie en naar mogelijkheden om hypothermie te voorkomen

tijdens het plaatsen van een THP of TKP. De bevinding dat langdurige operaties gepaard gaan met een verminderd risico op hypothermie, zou kunnen worden verklaard door de invloed van perioperatieve opwarming met een luchtverwarmingssysteem. Deze theorie impliceert dat we eerder moeten beginnen met het opwarmen van de patiënten. Een recente meta-analyse over het effect van preoperatieve opwarming van patiënten ondersteunt deze theorie met een relatief risico op SSI van 0,60 (95% BI 0,42–0,87) bij voorverwarmde patiënten voor de operatie [17].

Thermo-reflectief deken

Om peroperatieve hypothermie te voorkomen werd het gebruik van een additioneel thermo-reflectief deken tijdens operaties in 2010 ingevoerd in het CWZ. Het effect van dit deken bij THP en TKP werd echter nooit onderzocht. Alvorens een interventie als standaardbehandeling in te voeren, dient het effect onderzocht te worden. Derhalve hebben we een onderzoek opgezet naar het effect van een thermo-reflectief deken tijdens het plaatsen van een THP of TKP, zoals beschreven in **hoofdstuk 3**. De belangrijkste onderzoeksvraag voor dit onderzoek was: Beïnvloedt het gebruik van een thermisch reflecterend deken de incidentie van hypothermie tijdens totale heup-en knie prothesiologie?

Ten behoeve van dit onderzoek randomiseerden we 58 patiënten. 29 patiënten kregen een additioneel thermo-reflectief deken naast het standaard ziekenhuisdeken, 29 patiënten kregen alleen het standaard ziekenhuisdeken. Uitkomstparameters waren per- en postoperatieve lichaamstemperatuur, temperatuurcomfort en koude rillingen tijdens de operatie en na de operatie op de verkoeverkamer. De gemiddelde laagst gemeten lichaamstemperatuur was onder de 36 graden in beide groepen en niet significant verschillend (35.9 +/- 0.4°C met deken vs. 35.8 +/- 0.4°C zonder deken). Er was tevens geen significant verschil in comfort en het voorkomen van koude rillingen op de operatie- of verkoeverkamer. Concluderend zagen we geen toegevoegde waarde van het thermo-reflectief deken en werd het gebruik hiervan binnen de orthopedische chirurgie in het CWZ afgeschaft. Dit onderzoek werd herhaald in een haalbaarheidsstudie onder 224 patiënten in Washington DC, in 2016 [18]. Er werd geen significant verschil gevonden in

patiënten die zowel een thermoreflecterend deken als een opgewarmde katoenen deken kregen versus patienten die alleen een opgewarmde katoenen deken kregen.

Follow up van hypothermie

De hoge incidentie van hypothermie in 2009 en 2010, gaf aanleiding een follow up onderzoek te doen, beschreven in **hoofdstuk 4**. Het protocollair vastleggen van peroperatieve lichaamstemperatuur maakt het daarbij mogelijk een retrospectieve data-analyse te doen met grotere aantallen. Door een grotere patiëntengroep te analyseren zou mogelijk een significant verschil aangetoond kunnen worden in infectiepercentage.

De onderzoeksvragen voor dit onderzoek luidden: Correleert intra-operatieve hypothermie met de incidentie van PJI na het plaatsen van een THP en TKP? Verandert de incidentie van hypothermie tijdens THP- of TKP-plaatsing over de tijd?

We onderzochten alle patiënten die een THP of TKP-operatie ondergingen tussen 2011 en 2014. In totaal werden 2.600 patiënten geïncludeerd en vonden we een incidentie van 11,7% van hypothermie. Deze incidentie is aanzienlijk lager dan de incidentie in het vorig cohort in 2009-2010 (26,9%). De gemiddelde lichaamstemperatuur tijdens de operatie was tevens 0,6 °C hoger in deze studie, namelijk 36,5 °C versus 35,9 °C in 2009-2010. Een lineaire regressieanalyse bevestigde dat de gemiddelde lichaamstemperatuur met de tijd toenam tussen 2011 en 2014. Tegen de verwachtingen in vonden we een hogere PJI-incidentie onder de normotherme patiënten vergeleken met de hypotherme patiënten; 1,9% versus 1,0%, respectievelijk. Dit verschil was echter niet significant.

De vraag is natuurlijk waarom de gemiddelde lichaamstemperatuur in de loop der jaren is gestegen en de incidentie van hypothermie is gedaald? Een mogelijke verklaring is dat door het voorgaande onderzoek een toegenomen bewustwording van hypothermie op de afdeling, de voorbereidingsruimte en de operatiekamers bestond, waardoor er tijdig maatregelen werden getroffen om hypothermie te bestrijden. Bewezen interventies zoals het pre- en peroperatief gebruik van een deken met verwarmde lucht, zoals de Bairhugger©, en verwarmde katoenen dekens kunnen hierbij worden ingezet [19]. Daarnaast kan er sprake zijn van het zogenoemde Hawthorne effect [20]. Hierbij wordt het gedrag van een onderzoeksgroep beïnvloedt door het onderzoek zelf. Met andere woorden; medisch personeel gaat anders handelen omdat de lichaamstemperatuur gemeten wordt.

Dus zowel het bewustzijn van een hoge kans op hypothermie tijdens deze operaties als het continueren van meten van de lichaamstemperatuur tijdens deze operaties is belangrijk. Een laatste mogelijke verklaring voor de verandering van gemiddelde lichaamstemperatuur in deze studiegroepen is het statistisch fenomeen regression-to-the-mean. Dit treedt op wanneer er een extreme waarde worden gemeten van een bepaalde parameter in een eerste onderzoek die afwijkt van het eigenlijke gemiddelde [21]. Wanneer dan een vervolgonderzoek wordt gedaan, is het waarschijnlijk dat de gemiddelde waarde dichter bij het gemiddelde ligt. Het lijkt echter onwaarschijnlijk dat dit fenomeen heeft opgetreden in deze studies gezien de grote studiegroepen in beide onderzoeken.

Bridging van anticoagulantia

Klinisch onderzoek op de orthopedische afdeling in het CWZ trok onze aandacht naar postoperatieve hematoomvorming en wondlekkage als risicofactor voor PJI [22]. Maar is postoperatieve wondlekkage een symptoom of een risicofactor voor PJI? Een vraag die elke orthopedisch chirurg (in opleiding) meerdere malen in zijn of haar carrière moet hebben gesteld. Het antwoord hierop is tweeledig, omdat wondlekkage direct na de operatie een risicofactor voor PJI lijkt en een paar dagen later een symptoom van PJI kan zijn. Wondlekkage wordt gedefinieerd als vloeistof dat zich uit de chirurgische wond ontlast. Tijdens de operatie, ontstaat bloeding in het operatiegebied. Dit bloed draagt bij aan de wondgenezing. Wanneer te veel bloed ophoopt in de chirurgische wond, vindt dit bloed de weg van de minste weerstand en ontstaat wondlekkage. Deze wondlekkage is in de eerste uren na de operatie dus een teken van hematoomvorming maar geen symptoom van PJI. Bloed is echter wel een goede voedingsbodem voor bacteriën en derhalve is hematoomvorming een risicofactor voor PJI [23]. Zodra hemostase is bereikt, stopt hematoomvorming en daarmee tevens de lekkage van bloed. Wanneer wondlekkage toch aanhoudt na hemostase, wordt dit waarschijnlijk veroorzaakt door een ontstekingsproces, geïnitieerd door de aanwezigheid van bacteriën. In dit geval lijkt aanhoudende wondlekkage een symptoom van PJI te zijn in plaats van een risicofactor [24,25].

Ongeacht het antwoord op de bovenstaande vraag lijkt het zinvol om het risico op hematoomvorming en wondlekkage te verminderen. Om hematoomvorming te verminderen, moeten intra-en postoperatieve hemostase en stolling worden

geoptimaliseerd. Uitgaande van optimale hemostase tijdens chirurgie, werd een studie opgezet naar de relatie van antistollingsmiddelen en het ontstaan van PJI.

Een groeiend aantal patiënten die een gewrichtsvervanging ondergaat, gebruikt Orale AntiCoagulantia (OAC) om thrombo-embolische complicaties te voorkomen[10]. Vóór de operatie, moeten deze OAC worden gestopt om bloedverlies tijdens en na de operatie te voorkomen. In specifieke gevallen, is "bridging" van deze AOC geïndiceerd vanwege een hoge kans op thrombo-embolische complicaties; de OAC worden vervangen voor een hoge dosis kortwerkende anticoagulantia (laag moleculair gewicht heparine; LMWH) voor en kort na de operatie [26]. Deze therapeutische dosis LMWH is vier- tot achtmaal hoger dan de standaard profylactische dosis om trombose na een THP of TKP te voorkomen. In theorie kan dit het risico op significant bloedverlies, bloedingscomplicaties, hematoomvorming en wondlekkage verhogen en daarmee de kans op een PJI vergroten. We hebben daarom de volgende onderzoeksvraag geformuleerd voor **hoofdstuk 5** van dit proefschrift: Wat is de incidentie van bloedingscomplicaties en PJI bij patiënten die THA of TKA ondergaan waarbij bridging van de OAC is geïndiceerd?

Er werd een retrospectieve cohortstudie geïnitieerd waarbij het complicatiepercentage van patiënten bij wie bridging was geindiceerd werd vergeleken met het complicatiepercentage binnen een controlegroep. Tussen januari 2011 en juni 2012, ondergingen 972 patiënten een THP of TKP. Bij 13 patiënten was bridging van OAC geïndiceerd, waarbij een therapeutische dosis LMWH rondom THA of TKA werd toegediend volgens de internationale richtlijnen [26]. Bloedings- en trombo-embolische complicaties, zoals gedefinieerd door de International Society on Thrombosis and Haemostasis (zie hoofdstuk 5 van dit proefschrift), werden geanalyseerd [23]. Bloedingscomplicaties traden op bij 12 patiënten (92%) en bij 9 patiënten was een interventie nodig (69%); zeven patiënten kregen een bloedtransfusie (54%) en bij twee patiënten (15%) werd een vroege PJI gediagnosticeerd en behandeld. Hematoomvorming met langdurige immobilisatie gedurende ≥ 2 dagen tot gevolg, trad op bij 9 patiënten (69%). Alle patiënten hadden een langere verblijfsduur in het ziekenhuis dan de controlegroep. De mediane ziekenhuisopname duurde 11 dagen (7-52) en was gemiddeld 14 dagen, versus 5 dagen voor de controlegroep ($p < 0,05$).

Concluderend was sprake van een alarmerend hoog complicatiepercentage bij patiënten die THP of TKP-operatie ondergingen waarbij OAC "gebridged" werd. Al deze complicaties waren gerelateerd aan een verhoogde bloedingsneiging. Deze bevindingen resulteerden in een verandering in het antistollingsbeleid binnen deze patiëntengroep in het CWZ; de therapeutische dosis LMWH wordt nu ten minste 24 uur na de operatie pas opgestart, op voorwaarde dat de wond droog is. Daarnaast wordt er tot minimaal 7 dagen na de operatie gewacht met het terug overschakelen naar OAC. In een recent gepubliseerde systematisch review en meta-analyse zijn de aanbevelingen zelfs nog voortvarender; Zij vonden een significant toegenomen bloedingsrisico en geen verschil in thromboembolische events in bridging versus geen bridging. Het bridgen raaden zij derhalve af wanneer orale anticoagulantia onderbroken worden voor invasieve chirurgie [28]. Een multicenter RCT met adequate patientenselectie is geindiceerd om een definitieve conclusie te kunnen trekken waarop internationale richtlijnen kunnen worden geformuleerd.

Anesthesietechniek

Om het plaatsen van een totale heup of knieprothese mogelijk te maken bestaan er in het algemeen twee anesthesiologische opties; spinale of algehele anesthesie. Doorgaans is er orthopedisch gezien geen duidelijke voorkeurstechniek te benoemen. In de literatuur zijn er echter aanwijzingen dat een oppervlakkige infectie (SSI) vaker voorkomt bij algehele dan bij spinale anesthesie [29]. Voor **hoofdstuk 6** van dit proefschrift stelden we de vraag of dit toegenomen risico tevens geldt voor PJI: Is er een correlatie tussen type anesthesie en het ontstaan van een PJI na het plaatsen van een THP of TKP?

Om deze vraag te beantwoorden werd in het Rijnstate ziekenhuis in Arnhem een retrospectieve data-analyse uitgevoerd naar de infectiepercentages na het plaatsen van een THP of TKP bij algehele versus spinale anesthesie. Hierbij werd specifiek gekeken naar vroege infecties (≤ 3 maanden na primaire TKP of THP plaatsing).

Alle patiënten die een THP of een TKP ondergingen tussen januari 2014 en december 2017 werden geïncludeerd. Leeftijd, BMI, geslacht, TKP versus THP, type anesthesie, duur van operatie, en lengte van operatie werden geanalyseerd.

Er werden 3.909 patiënten geïncludeerd, 2.111 THP en 1.798 TKP. Hiervan werden 1.630 (41,7%) patiënten geopereerd onder algehele anesthesie versus 2.279 (58,3%) onder spinale anesthesie. Er werden 47 vroege PJI gezien, 28 (1,7%) in de groep van algehele anesthesie versus 19 (0,8%) in de spinale anesthesie groep. Binaire logistische regressieanalyse liet zien dat zowel algehele anesthesie als een verhoogd BMI gecorreleerd is met een verhoogde kans op vroege PJI. Het is niet geheel duidelijk waardoor dit verschil in PJI incidentie verklaard wordt.Toegenomen weefseloxygenatie en verminderd bloedverlies na spinale anesthesie zijn mogelijke verklaringen [30–33]. Daarnaast remmen enkele anesthetica, die vaak worden gebruikt voor algehele anesthesie, de chemotactische migratie van leukocyten, fagocytose, lymfocyten functie en kunnen deze anesthetica zelfs direct bacteriële groei ondersteunen in geval van besmetting [29,34–36].

In conclusie lijkt de kans op een PJI bij een operatie onder algehele anesthesie hoger dan bij een operatie onder spinale anesthesie. We adviseren deze bevindingen in acht te nemen wanneer er kan worden gekozen tussen algehele of spinale anesthesie. In de meeste ziekenhuizen wordt deze keuze gemaakt door de anesthesioloog, nadat de indicatie in gesteld door de orthopedisch chirurg. Het is daarom belangrijk dat ook de anesthesist zich bewust is van dit verhoogde risico.

DEEL 2 - CURATIEVE BEHANDELING – VOORKOM WAT JE KUNT VOORKOMEN, GENEES WAT JE NIET VOORKWAM

Ondanks de preventieve maatregelen treedt een PJI nog regelmatig op (1-3% van de geplaatste protheses). Een optimale behandeling ter bestrijding van deze complicatie is essentieel om deze patiënten, die een electieve operatie ondergaan, op de been te gehouden. De behandeling van PJI is afhankelijk van het tijdstip van ontstaan en de etiologie. In het Radboud Universitair Medisch Centrum wordt onderzoek gedaan naar de juiste behandeling van patiënten met een PJI, zowel in operatie technisch opzicht als in de antibiotische behandeling. Voor het tweede deel van dit proefschrift, werd onderzoek gedaan naar het effect van vernieuwende operatietechnieken (cement-within-cement revisies en het mixen van antibiotica door cement) en de behandeling met vernieuwende antibiotica combinaties.

Cement-within-cement revisie

Een PJI wordt doorgaans geclassificeerd als een acute infectie (symptomen gedurende ≤ 3 weken) of een chronische infectie (symptomen gedurende > 3 weken) [37]. In het geval van een chronische (doorgaans laag virulente) infectie ontstaan er klachten rond het gewricht omdat de bacterie zorgt voor loslating van de prothese. Er is dan geen sprake van een fulminante ontsteking. Het is erg moeilijk om deze infectie te bestrijden omdat de bacterie een biofilm op de prothese heeft gevormd [38]. De gouden-standaard behandeling is dan om de prothese volledig te verwijderen en het plaatsen van een nieuwe prothese na een antibiotische behandeling van 6-12 weken [37]. In het geval van PJI van een gecementeerde heupprothese, is het volledige verwijderen van de cementmantel vaak moeilijk en tijdrovend omdat het vaak stevig gehecht is aan het botoppervlak. Pogingen om het cement volledig te verwijderen kan resulteren in significant botverlies wat de reimplantatie van een prothese bemoeilijkt. De vraag rijst dus of de verwijdering van botcement daadwerkelijk noodzakelijk is. Er wordt gesuggereerd dat biofilm vorming voornamelijk plaatsvindt op de prothese en mogelijk wordt voorkomen op de bot-cement interface door antibioticum impregnatie van botcement bij de primaire heupoperatie [39–41]. Derhalve volstaat het wellicht om alleen de prothese te verwijderen en de cement mantel te laten zitten. Bij aanvang van deze studie werd slechts één studie over dit onderwerp gepubliceerd; Morley et al vond acceptabele uitkomsten bij two-stage revisies waarbij de cement mantel in situ werd gelaten, met een genezingspercentage van 93,3% bij 15 patiënten met een gemiddelde follow-up van 82 maanden [42]. Aangezien deze procedure ook wordt uitgevoerd in het Radboud Universitair Medisch Centrum, is het interessant om de resultaten op de lange termijn in onze populatie te onderzoeken en werd een retrospectieve cohortstudie geïnitieerd voor **hoofdstuk 7** van dit proefschrift. De onderzoeksvraag luidde hierbij: Resulteert een two-stage revisie i.v.m. chronische PJI waarbij het cement in situ wordt gelaten, in acceptabele succespercentages?

Voor deze retrospectieve analyse werden alle operatieverslagen van THP revisie operaties, uitgevoerd tussen mei 2009 en maart 2013, geanalyseerd (n=333). Patiënten bij wie een goed gefixeerd femorale cementmantel in situ werd gelaten tijdens de eerste operatie van een two-stage revisie voor een late chronische infectie, werden geïncludeerd (n=10). Klinische, biochemische en radiologische uitkomsten werden geëvalueerd

met een gemiddelde follow-up van 26 maanden. Succesvol bestrijding van het micro-organisme werd slechts bereikt bij twee van de 10 patiënten. Bij de andere 8 patiënten werd hetzelfde micro-organisme gevonden tijdens reïmplantatie procedure of was er sprake van terugkerende infectie binnen 1 jaar na reïmplantatie. Natuurlijk zijn deze resultaten van two-stage revisies met behoud van de cementmantel voor chronische PJI zeer teleurstellend. Gezien de tegenstrijdige succespercentages gevonden door Morley et al, zochten we naar verschillen in behandelregime. Een mogelijk belangrijk verschil is het feit dat, in het Radboud Universitair Medisch Centrum, de binnenkant van de cement mantel niet routinematig werd "gereamed" met een High Speed boor. Het is mogelijk dat Morley et al. de biofilm heeft verwijderd door het cement te reamen tijdens de eerste operatie en daarmee de kans op succesvolle behandeling werd vergroot. Een ander verschil is mogelijk de inclusie van vroege PJI door de groep van Morley et al. Theoretisch kan er een verschil bestaan in bacteriële besmetting van de bot-cement-interface in het geval van acute versus chronische infecties. Ten slotte gebruikte de groep Morley een met antibiotica geimpregneerde cementspacer voor de intervalperiode tussen de twee chirurgische ingrepen, in tegenstelling tot onze studiegroep.

In conclusie, pleiten de resultaten van dit onderzoek tegen het routinematig behoud van het femoraal botcement in two-stage revisies voor chronische PJI. Vanwege de kleine onderzoeksgroep kunnen we echter geen definitieve conclusies trekken. Bovendien, benadrukken we dat de resultaten kunnen verbeteren zodra selectiecriteria en chirurgische technieken zijn geoptimaliseerd. Op het moment van schrijven van dit proefschrift zijn er geen nieuw gepubliceerde artikelen over cementretentie in two-stage revisies. Onderzoek naar gedeeltelijke two-stage revisies voor chronische PJI na THP ondersteunt over het algemeen retentie van een goed gefixeerd deel van de prothese [43–45]. Kritische selectie van patiënten is echter belangrijk en de aantallen zijn laag in deze artikelen.

Antibiotica in botchips

Het botverlies bij een revisie van een prothese i.v.m. een infectie kan ervoor zorgen dat er te weinig bot overblijft om een nieuwe prothese te kunnen fixeren. In het Radboud ziekenhuis is een operatietechniek ontwikkeld om het botverlies op te vangen; impaction bone grafting (IBG) [46]. Bij deze techniek worden er botchips gebruikt die worden geïmpacteerd in het acetabulum en/of het femur. Voor revisiechirurgie wordt voor deze

botchips gebruik gemaakt van allografts van een donor femurkop, die wordt verkregen tijdens een primaire THP-operatie van geselecteerde donoren. Om de kans op een nieuwe infectie te verkleinen wordt in de literatuur gesuggereerd om antibiotica door de donor botchips te mixen [47]. Er zijn enkele artikelen verschenen met veelbelovende uitkomsten van antibiotica in botchips [48,49]. Het is echter niet bekend of de antibiotica de botchips zwakker maken, zorgen voor een slechtere ingroei of zelfs de kans op een infectie met een multiresistent micro-organisme vergroten. Vanwege het toenemend aantal antibiotica-resistente micro-organismen, moet onnodig gebruik van antibiotica worden vermeden. De resultaten van IBG met antibiotica zijn nooit vergeleken met IBG waarbij er botchips worden gebruikt zonder antibiotica. Binnen het Radboud Universitair Medisch Centrum wordt gebruik gemaakt van botchips zonder antibiotica. De nauwkeurige follow-up van deze patiënten maakt het mogelijk een gedegen retrospectief onderzoek uit te voeren naar de resultaten binnen deze groep. Dit onderzoek is beschreven in **hoofdstuk 8**. Onderzoeksvraag: Wat is het re-infectiepercentage bij two-stage revisies voor PJI na een THP waarbij gebruik is gemaakt van IBG met donor botchips zonder lokale antibiotica in de graft?

Er werden 36 patiënten geïncludeerd in deze studie, geopereerd tussen 1990 en 2009. We vonden een re-infectie percentage van 2,8% binnen 2 jaar. Wanneer de follow-up wordt verlengd naar 10 jaar, zagen we een re-infectie percentage van 11,0%. Dit is vergelijkbaar met re-infectie percentages na two-stage revisies zonder het gebruik van IBG, gepubliceerd in een pooled individual participant data analysis van 44 cohort studies; 13,8% na een mediane follow-up van 3,3 jaar [50]. Op het moment van publicatie, waren er twee studies die de resultaten van two-stage revisies met antibiotica geïmpregneerde botchips beschrijven. Deze studies hadden een gemiddelde follow-up van 2 tot 4 jaar met re-infectie percentages van 0,0% (n = 12) en 3,3% (n = 30)[48,49]. Het is waarschijnlijk dat deze reinfectie percentages toenemen met een langere follow-up omdat lowgrade infecties doorgaans symptomatisch worden na een langere periode van follow-up.

In conclusie, vonden we een acceptabel re-infectie percentage na two-stage revisies met IBG zonder de toevoeging van lokale antibiotica. Gezien het feit dat het positieve effect van het mixen van antibiotica door donorbotchips niet aangetoond is en het potentiele gevaar van vroege loslating door verminderde botingroei, adviseren we dit niet

als standaard behandeling te gebruiken. Onderzoek gebaseerd op groot volume registers kan ingezet worden om meer duidelijkheid te krijgen over de succespercentages in beide groepen.

Systemische antibiotica

Na chirurgische behandeling van PJI worden patiënten (doorgaans 3 maanden) behandeld met antibiotica. De keuze van antibioticum is afhankelijk van de gekweekte micro-organismen en de gevoeligheid voor antibiotica. Om bacteriële resistentie en biofilmformatie te voorkomen, wordt een combinatie van 2 verschillende antibiotica geadviseerd [37,51]. Ongeveer 50% van de PJI wordt veroorzaakt door een *Stafylokokken* infectie [52]. Bij een dergelijke infectie wordt in de internationale richtlijn een antibiotisch regime geadviseerd waarbij een quinolone gecombineerd wordt met rifampicine indien de Stafylokok gevoelig is voor beide antibiotica [37]. Dit advies is gebaseerd op een studie met een kleine patiëntengroep met acceptabele uitkomsten [53]. Hoewel in praktijk andere combinatieschema's worden gebruikt, zijn deze niet opgenomen in internationale richtlijnen, mogelijk vanwege het ontbreken van (gepubliceerde) onderzoek. Omdat bacteriële resistentie tegen ons antibiotisch arsenaal toeneemt, is het zoeken naar alternatieve antibiotica regimes essentieel [54].

In het Radboud Universitair Medisch Centrum worden patiënten behandeld met een van deze alternatieve behandelingcombinaties; rifampine met clindamycine. Echter, de effectiviteit en veiligheid van dit regime bij de behandeling van PJI werd nooit geëvalueerd. Daarom hebben we, voor **hoofdstuk 9** van dit proefschrift, besloten om de klinische uitkomst te evalueren bij deze patiëntengroep met een PJI veroorzaakt door een *Staphylococcus* spp. die gevoelig is voor beide antibiotica. Onderzoeksvraag: Is orale rifampicine-clindamycine combinatie therapie voor 3 maanden na chirurgische behadeling effectief en veilig bij patiënten met een bewezen PJI met een gevoelig micro-organisme?

Retrospectief werden 36 patiënten geïncludeerd die zijn behandeld met een clindamycine-rifampicine combinatie therapie. Patiënten werden gemiddeld 54 maanden gevolgd. De helft van deze patiënten (n=18) onderging een DAIR behandeling gevolgd door dit antibiotisch regime, vanwege een vroege PJI. De andere helft (n=18) onderging een

one-stage revisie van de prothese gevolgd door dit antibiotisch regime. Bij deze laatste 18 patiënten was er preoperatief een verdenking op aseptische loslating maar bleek uit de peroperatief afgenomen kweken dat er sprake was van een chronische PJI met *Staphyloccocus* spp. Derhalve werden deze patiënten niet behandeld met een two-stage revisie, de gouden standaard voor chronische PJI.

We vonden een succespercentage van 86%, met vijf re-infecties. Genezing werd bereikt bij 78% (14/18) in de DAIR-groep en 94% (17/18) in de revisie groep. Vijf patiënten (14%) stopten met de clindamycine of rifampicine vanwege bijwerkingen. Van de 31 patiënten die wel door konden gaan met deze antibiotica vonden we een succespercentage van 94% (29/31). Deze uitkomsten zijn redelijk vergelijkbaar met de uitkomsten van het onderzoek dat in internationale richtlijnen wordt aangehaald [37,53,55]. De optimale dosering en serumconcentratie van zowel clindamycine als rifampicine is nog onbekend. Aangezien rifampicine een enzym activeert dat clindamycine versneld afbreekt, moet dit worden onderzocht [56,57].

In conclusie lijkt de orale combinatietherapie van clindamycine en rifampicine veilig en effectief in de behandeling van PJI met gevoelige *Staphyloccocus* spp. Onderzoek naar de optimale dosering en serumconcentratie van zowel rifampicine en clindamycine is nodig ter voorkoming van over- en onderdosering.

DEEL 3 – PALLIATIEVE BEHANDELING – VOORKOM WAT JE KUNT VOORKOMEN, GENEES WAT JE NIET VOORKWAM EN BEHEERS WAT JE NIET GENAS

Door toepassing van de gestandaardiseerde behandelmethoden kan zowel een vroege als late PJI in een meerderheid van de gevallen succesvol bestreden worden [50,58]. Helaas zijn echter niet alle patiënten met een PJI curatief te behandelen ondanks herhaaldelijk chirurgisch ingrijpen en langdurige antibiotische behandeling. Een operatie kan daarnaast te risicovol zijn vanwege co-morbiditeit van de patiënt of chirurgische complexiteit. Bij deze patiënten kan gekozen worden voor Antibiotisch Suppressieve Therapie (AST) [14]. Patiënten worden hierbij, in opzet levenslang, behandeld met een relatief lage dosering

antibiotica om de infectie te onderdrukken. Er is echter weinig bekend over de effectiviteit en veiligheid hiervan. Derhalve hebben we een retrospectieve data-analyse uitgevoerd naar de effectiviteit van deze behandeling in het Radboud Universitair Medisch Centrum, zoals beschreven in **hoofdstuk 10** van dit proefschrift. Onderzoeksvraag: Is het toepassen van AST effectief en veilig bij patiënten met een chronische PJI na een THP waarbij operatief ingrijpen gecontra-indiceerd is?

Een totaal van 24 patiënten met een geïnfecteerde heupprothese bij wie een behandeling met AST werd gestart in de periode 2006-2013, werd geïncludeerd met een follow-up tot 2018. AST wordt gedefinieerd als behandeling met een lage dosering orale antibiotica met de intentie om de infectie levenslang te onderdrukken. Het toegepaste antibioticum was gebaseerd op gevoeligheid van gekweekte micro-organismen en was bij het merendeel van de patiënten doxycycline (n=15) en cotrimoxazol (n=6). Een patiënt werd beschouwd als "succesvol behandeld" indien de prothese nog in situ is zonder symptomen van PJI bij laatste poliklinische controle of ten tijde van overlijden. AST bleek succesvol bij 13 patiënten (54,2%) met een gemiddelde follow-up van 38 maanden. Hierbij was de kans op succesvolle behandeling significant kleiner wanneer AST gestart werd na een antibioticavrije periode. Binnen deze subgroep was er sprake van een re-infectie bij 5 van de 6 patiënten. Tevens lijken een PJI door *S. Aureus* en CRP waarden >80, risicofactoren voor het falen van de behandeling. Deze correlaties waren echter niet significant.

We concludeerden dat een geselecteerde patiëntengroep veilig en effectief behandeld kan worden met AST indien er geen curatieve behandeling meer mogelijk lijkt. Er moet echter rekening worden gehouden met een niet te negeren aantal patiënten bij wie de prothese alsnog verwijderd dient te worden, met name in geval van een antibioticavrij interval voor de start van AST, in geval van *S. aureus* infectie en bij patiënten met hoge infectieparameters in het bloed. Middels dit onderzoek zijn we in staat om patiënten beter te informeren over de kans van slagen van een suppressieve behandeling wanneer men twijfelt of het risico van een revisieoperatie genomen moet worden. Aangezien een RCT naar AST onmogelijk lijkt vanwege het gebrek aan behandelingsalternatieven en de inhomogene groep patiënten, moedigen we systematische uitkomst monitoring van deze patiënten aan. Wellicht kan evaluatie van de momenteel beschikbare literatuur, zoals beschreven in hoofdstuk 10, een advies in internationale richtlijnen mogelijk maken.

CONCLUSIES EN AANBEVELINGEN

Zolang er gewrichtsprotheses worden geplaatst, zullen we te maken hebben met geïnfecteerde gewrichtsprotheses. De ernstige gevolgen van een PJI voor de patiënt en de gevolgen voor de maatschappij zijn de belangrijkste drijfveren geweest voor dit proefschrift. Doel van dit proefschrift is om kennis en inzichten te bieden om het risico op PJI te verminderen en de kans op een succesvolle behandeling te vergroten. PJI is een complex probleem met veel factoren die van invloed zijn op het optreden en de succesvolle behandeling. Gezien de relatief lage incidentie van PJI leent retrospectief onderzoek zich uitstekend om deze factoren te identificeren. Elk onderzoek, beschreven in dit proefschrift, behandelt een van deze factoren. Dit heeft geleid tot de volgende conclusies en aanbevelingen voor de (orthopedische) praktijk:

1. Peroperatieve hypothermie komt regelmatig voor tijdens de plaatsing van een THP of TKP. Dit probleem kan gereduceerd worden door bewustwording onder het medisch personeel en tijdig meten van de lichaamstemperatuur.
2. Peroperatieve hypothermie is niet direct geassocieerd met een hogere PJI incidentie.
3. Een thermo-reflectief deken draagt niet bij aan de preventie van hypothermie bij plaatsing van een THP of TKP.
4. Patiënten bij wie bridging van antistollingsmedicatie is geïndiceerd rondom het plaatsen van een TKP of THP, hebben een verhoogd risico op postoperatieve bloedingscomplicaties.
5. Herstarten van LMWH in het geval van bridging, dient minimaal 24 uur na de operatie te gebeuren en herstart van OAC moet vermeden worden tot men zeker is van adequate hemostase.
6. Wanneer de keuze wordt gemaakt tussen algehele of spinale anesthesie voor een TKP- of THP operatie, moet men zich realiseren dat algehele anesthesie gecorreleerd is met een verhoogde kans op het ontstaan van PJI.
7. Operatietechnieken met het behoud van de cementmantel bij two-stage revisies van een THP zijn momenteel insufficiënt en dienen geoptimaliseerd te worden.
8. Het toevoegen van antibiotica in botchips is niet bewezen beter dan botchips zonder antibiotica in het geval van two-stage revisies voor PJI bij THP.

9. De combinatie van clindamycine en rifampicine is veilig en effectief in de behandeling van PJI met gevoelige *Staphylococcus* spp. De optimale dosering en concentratie dient onderzocht te worden.
10. Palliatieve behandeling van een PJI met suppressieve antibiotica heeft bij een geselecteerde patiëntengroep, bij wie curatieve behandeling niet mogelijk is, een acceptabele kans van slagen.

Naast bovenstaande aanbevelingen vormt dit proefschrift een basis voor een wetenschappelijke carrière waarin we zullen doorgaan met onderzoek naar preventie en optimale behandeling van PJI.

Voorkomen, genezen en beheersen!

The battle continues…

REFERENTIES

Zie referenties hoofdstuk 11.

DATA MANAGEMENT
AND RESEARCH ETHICS

RIHS PORTFOLIO

LIST OF PUBLICATIONS
AND PRESENTATIONS

CURRICULUM VITAE

ACKNOWLEDGEMENT / DANKWOORD

DATA MANAGEMENT AND MEDICAL RESEARCH ETHICS

Data management

The primary and secondary data obtained during my PhD are centrally stored in digital files on the local server of the orthopedic research laboratory of Radboud University Medical Centre (on N: schijf). These data are accessible with a password by associated senior staff members involved in the research projects. Published data generated or analyzed in this thesis are part of published articles and its additional files are available from the associated corresponding authors on request.

In order to protect the privacy of patients, data are anonymized and personal data were removed from the files. The privacy of the participants in this study is warranted by use of encrypted and unique individual subject codes. This code correspondents with the code on the patient- and physicians' files. To ensure interpretability of the data, all filenames, primary and secondary data and scripts used to provide the final results are documented along with the data.

The data will be saved for 15 years after termination of the study (follow-up of the latest study ended October 31st, 2018). Using these patient data in future research is only possible when performed for health care improvement analyses. The datasets analyzed during these studies are available from the corresponding author on reasonable request.

Declaration of Helsinki

This thesis is based on the results of data analysis of patient files, which were conducted in accordance with the principles of the Declaration of Helsinki. The studies in this thesis have been conducted in order to analyze and improve provided clinical care. The studies described in Chapter 2, 4 and 5 are retrospective studies performed in Canisius Wilhelmina Hospital (CWZ). For these studies there was a protocol approved by the Local Ethical Committee of CWZ. Also, for the prospective study described in chapter 3, the study protocol was approved by the Local Ethical Committee of CWZ. The study described in chapter 6 was a retrospective study conducted in Rijnstate Hospital Arnhem (RHA). For this study there was a protocol approved by the Local Ethical Committee of RHA.

The studies described in chapter 7 and 8 were retrospective patient file studies performed in Radboud University Medical Centre. At the time of writing, retrospective data research to improve clinical daily practice, performed by involved medical staff, was approved by the Local Ethical Committee of Radboud University Medical Centre. The studies described in chapter 9 and 10 were retrospective patient file studies performed in Radboud University Medical Centre. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, has given approval to conduct these studies.

Institute for Health Sciences
Radboudumc

RADBOUD INSTITUTE FOR HEALTH SCIENCE PHD PORTFOLIO

Name PhD Cadidate: B. Leijtens
Department: Orthopedic Surgery
Graduate School: Radboud Institute for Health Sciences
PhD period: 01-08-2012 – 01-12-2019
Promotor(s): Prof. dr. M. de Kleuver
Prof. dr. B.W. Schreurs
Co-promotor(s): Dr. S. Koëter

	Year(s)	EC points
TRAINING ACTIVITIES		
Courses and Workshops		
Good Clinical Practice Course, Nijmegen	2012	0.8
Scientific Integrity course	2018	1
Statistics for PhD candidates by using SPSS	2013	0.75
Introduction day Radboudumc	2013	0.5
ROGOO educational program for orthopedic residents	2015-17	4
Followed courses for orthopedic training (AO trauma advanced, ATLS refresher course, Knee revision course, Stralingshygiëne voor medisch specialisten, complex primary knee prosthesis, Core principles in Total Hip arthroplasty, Knie prothesiologie cursus, Starterscursus voetchirurgie, OTC trauma course III, ALERT course Radboudumc, AO trauma principle of fracture management, FCCS training course, ATLS primary course)	2014-19	5

Symposia and congresses		
Visiting scientific congresses: NOV (6x), European Bone and Joint Infection society (EBJIS) (4x), NVOT (2x), Fortius (1x), NVA (5x), EHS (1x)	2012-19	5
Poster and Oral presentation: NOV 2012, EFORT 2014, EBJIS (3x), NVOT 2016	2012-19	2.5
Organizing symposia on Refugee healthcare in sint Maartenskliniek	2017	2
Organizing symposia on Sports related injuries in sint Maartenskliniek	2017	2
Other		
Research meetings Orthopedic department "Spiegeluur"	2014-19	1.5
Radboud Research Rounds	2019	1
Visiting weekly Seminars and lectures Rijnstate, St. Maartenskliniek and RadboudUMC (approx. 100)	2012-19	10
Co-organizing Sports Event for Orthopedic surgeons and Residents (2017-2018-2019)	2017-19	3
Lecturing / education / Supervision interships		
Student internship coaching (Approx 1-hour supervision per week)	2014-19	5
Journal clubs and clinical presentations in Rijnstate, Maartenskliniek and RadboudUMC (8x)	2014-19	8
Seminar advising medical student how to perform clinical research	2014	1
Seminar on advising the student choosing their specialty	2014	1
TOTAL		**60.25**

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2012 Annual meeting of the Dutch orthopedic Society, Utrecht: High incidence of hypothermia at primary hip and knee arthroplasty is not preventable by the use of thermo-reflective blankets

2014 EFORT, London; Clindamycin-rifampin combination therapy for staphylococcal periprosthetic joint infections

2014 European Bone and Joint Infection Society congress, Utrecht; Clindamycin-rifampin combination therapy for staphylococcal periprosthetic joint infections

2014 Pathology congress, the Dutch epidemiology congress; Combining CRP and Frozen Sections aids in diagnosing prosthetic hip infections.

2015 European Bone and Joint Infection Society congress, Lisbon;

- Two-Stage Revision of Infected Hip Replacement with Retention of The Femoral Cement Mantle
- A Bundle of Care to Reduce Surgical Site Infections in Total Hip Arthroplasty. A retrospective Cohort Study

2016 European Bone and Joint Infection Society congress, Oxford;

- Decreasing incidence of hypothermia in major arthroplastic surgery and its correlation with prosthetic joint infections

2016 NVOT Our Worst Case; De "subcapitale/suboptimale" humerusfractuur

2017 Organizing a Symposium in Sports related orthopaedics in sint Maartens clinic Nijmegen

CURRICULUM VITAE

Borg Leijtens was born in Beuningen (Gelderland) on the 29th of May in 1986. He grew up in Beuningen and attended High School at Stedelijk Gymnasium in Nijmegen. After graduating in 2004, he started Medical School at Radboud University in Nijmegen in the same year.

With lots of pleasure, Borg completed his medical school with international internships in India and Tanzania. During his own surgical procedure after an anterior cruciate ligament rupture in 2008, Borg decided to become an orthopedic surgeon. His surgeon, Dr. Hu, hired him for a short internship and as an assistant at the orthopedic operation room afterwards. His first job as a doctor was at the orthopedic department in CWZ, Nijmegen. The presented research on prosthetic joint infections was started at this department under supervision of co-promotor dr. S. Koëter, as a base for this thesis. In 2013, Borg started working on the orthopedic department in Radboud University Medical Centre followed by 6 months of research on the orthopedic research lab, under supervision of promotor prof. dr. B.W. Schreurs and promotor prof. dr. M. de Kleuver.

In 2014, Borg started his orthopedic residency at the department of general surgery at CWZ hospital, followed by the orthopedic departments of Radboud University Medical Centre, Sint Maartenskliniek in Nijmegen and Rijnstate Hospital in Arnhem. During this period Borg continued his research on prevention and treatment of PJI. The research projects have led to a variety of publications and presentations at national and international congresses and above all to skills and knowledge for a further scientific carrier.

Borg is engaged to Imke and they are happy to expect their first child in June 2020. In August 2020, they will move to Adelaide, Australia, where Borg will start an orthopedic fellowship for 1 year.

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