FOOT ANKLE TRAUMA SURGERY

Prevention of Surgical Site Infections and Patient Reported Outcome

Fay Sanders

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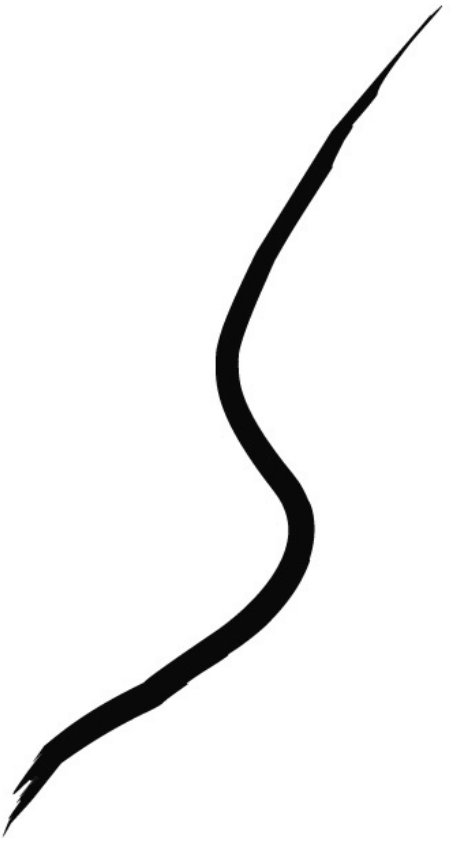

Foot ankle trauma surgery; prevention of surgical site infections and patient reported outcome

This PhD thesis was embedded within Amsterdam Movement Sciences research institute, at the Trauma Unit, Department of Surgery, Amsterdam UMC, University of Amsterdam, the Netherlands.

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FOOT ANKLE TRAUMA SURGERY

Prevention of Surgical Site Infections and Patient Reported Outcome

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TABLE OF CONTENTS

GENERAL INTRODUCTION

Foot/ankle surgery is probably not the first thing that comes to mind when you think of trauma surgery. A trauma surgeon, to the layman's eyes, is a doctor who heroically saves victims with the gravest injuries, either in the hospital or directly on-site. Perhaps this is due to the word 'trauma', of which all definitions include the word 'severe'. The Cambridge Dictionary defines trauma as *'severe emotional shock and pain caused by an extremely upsetting experience'*, or (the medical definition) *'severe injury, usually caused by a violent attack or an accident'*[1]. However, if we go a bit further back in history, the word is actually derived from the ancient Greek 'τραῦμα', which means damage or wound[2]. This word gets closer to defining the full range of patients that are treated by a trauma surgeon in the Netherlands (orthopedic trauma surgeon in the rest of the world), namely all patients with an injury, whether that injury is severe/resulting from multi-trauma, or more isolated damage like a broken foot or ankle.

Although the foot/ankle area seems small, it is nonetheless a vital part of your body. The foot and ankle consist of 30 bones, 34 joints, 107 ligaments, and 19 muscles, working together like a Swiss clock. Without the full function of our lower extremities, 'normal' day to day activities would be significantly impaired. Therefore it is of paramount importance to aim for the restoration of full function of the lower limb after an injury. Luckily, to a certain extent, the body was built to naturally regenerate, and doctors merely have a supporting role.

Part of the oath that we swear by upon receiving the title of doctor, is the sentence "first, do no harm" (primum non nocere)[3]. In a way, surgery itself might be considered harm, which is why it is so important to always outweigh the benefits and risks of a procedure and to involve the patient in this process. A big part of not doing harm, is to prevent unfavorable outcomes of surgical interventions, or complications. One of the most frequently seen complications of orthopedic lower extremity surgery is a surgical site infection (wound infection), with the highest incidences in trauma-related surgery[4]. In procedures of the foot/ankle area, the surgical site infection rate seems to be particularly high, compared to other parts of the body[5]. The aim of this thesis was to identify the incidence and risk factors for surgical site infection, to prevent surgical site infections and to evaluate the outcome of trauma-related foot/ankle surgery. Since restoration of functionality is one of the most important goals of trauma surgery, the focus lies on patient reported outcome measures.

THESIS OUTLINE

PART ONE

Incidence and Risk Factors of Surgical Site Infections

Orthopedic trauma procedures of the foot and ankle have a relatively high rate of surgical site infections[4,6]. This seems to be comparably high in both acute fracture surgery and in elective procedures, such as implant removal[5,7]. In **Chapter 1** we will investigate this rate in a literature review, focusing on the incidence of surgical site infections in syndesmotic screw removal, a common procedure in orthopedic trauma surgery. In addition to the incidence, the risk factors for developing a surgical site infection will be addressed. These risk factors can be divided in 1. patient-related factors, 2. injury-related factors, 3. procedure-related factors and 4. environmental risk factors.

The first three categories of risk factors contain variables that are consistently mentioned in studies investigating surgical site infections (e.g. gender, age, type of fracture, type of surgery, duration of surgery)[8,9]. This might be due to the fact that these factors are usually well documented in medical records, which makes it easier to collect them, also in retrospective studies. Another reason could be that these risk factors are relatively easy to explain and unifactorial (not consisting of multiple potentially causative factors). This makes that these variables are relatively easy to use in prediction models for infection. **Chapter 2** assesses the role of these unifactorial risk factors in calcaneal fracture surgery and aims to identify which factors are significant predictors for surgical site infections.

The last mentioned category, environmental risk factors, contains variables such as geographical region, socioeconomic status, and season[10,11]. These are all multifactorial risk factors, in which the element responsible for a possible correlation is not always clear. One of these risk factors, season of surgery, has been described to be of influence in orthopedic surgery where surgical site infections seemed to be particularly common in summer[12,13]. In **Chapter 3** we explore “seasonality” as a potential predictor of wound complications in trauma surgery of the foot, ankle and lower leg. Moreover, we try to analyze possible variables that could cause this effect.

PART TWO

Prophylactic Antibiotics to Prevent Surgical Site Infections

Since the implementation of prophylactic antibiotics in closed fracture surgery, infection rates have decreased[14,15]. First-generation cephalosporins (e.g., cefazolin) are the

recommended prophylactic antibiotics in orthopedic/trauma surgery because of their broad-spectrum effect on the most common pathogens, and relatively low costs[16]. However, the evidence to support the correct dose, duration and indication for prophylactic antibiotics remains limited. In order to prevent infections using prophylactic antibiotics, sufficient concentrations at the target site (location of surgery) are required. In **Chapter 4** we will assess the effect of: 1. variation in dose (1 or 2 g) of cefazolin, and 2. the location of the target site, on measured target site antibiotic concentrations during orthopedic lower extremity surgery.

To further explore the clinical meaning of different administered dosages of cefazolin, we will look at the difference in infection rate between patients receiving 1g and 2g of cefazolin in a retrospective cohort study **(Chapter 5)**. The WIFI trial previously investigated the effect of a single dose of 1g of cefazolin as prophylaxis in implant removal below the level of the knee[7]. Surprisingly, the infection rates in the WIFI trial were high but did not differ between intervention and placebo groups. Since both dosage and location of the target site (distal part of lower extremity) might have been an issue in this trial, the WIFI-2 trial was designed. In **Chapter 6** we will describe the protocol of the WIFI-2 trial, in which we will investigate the effect of 2g of cefazolin on the rate of surgical site infections in implant removal below the level of the knee. Moreover, in this trial we will measure target site concentrations of cefazolin and try to link these results to the clinical outcome.

PART THREE

Patient Reported Outcome in Foot/Ankle Surgery

Given the high rate of surgical site infections in foot/ankle surgery, it is always important to outweigh the benefits and risks of a procedure. Although in orthopedic trauma surgery the decision to operate is often not a choice but a necessity, this is not the case for all procedures. Implant removal for example is an elective procedure, meaning that it is "plannable" care and not always strictly necessary. For some implants however, routine removal is still common practice. In **Chapter 7** we describe the functional outcome after elective implant removal below the level of the knee. Using the secondary outcome measures of the WIFI trial (LEFS, EQ-5D) we assess whether there is a statistical difference, but also whether the minimal clinically import difference is exceeded, resulting in a clinically relevant improvement.

A specific type of implant, the syndesmotic screw (used in syndesmotic injuries) are commonly removed after 8-12 weeks because they are believed to limit range of motion and cause pain or break when left in place. Since more recent studies have indicated that a broken screw left in place might in fact not be cause for a worse functional outcome, the RODEO trial (**Chapter 8**) was initiated. In this multicenter randomized controlled trial we compare functional outcome 12 months after syndesmotic screw fixation between routine

removal (8-12 weeks) and on demand removal (upon patients request). In both chapter 7 and 8 we use validated questionnaires as patient reported outcome measures. Another form of patient reported outcome that is interesting for research purposes is claim analysis. In **Chapter 9** we investigate malpractice claims from a medical liability insurer that insures around 50% of non-academic hospitals in the Netherlands. We will analyze the incidence, characteristics and outcome of claims in orthopedic foot/ankle surgery. Since these claims were all patient reported, whether or not they were settled or declined, they are an interesting representation of patient's complaints and can offer valuable lessons by helping to identify opportunities to improve care.

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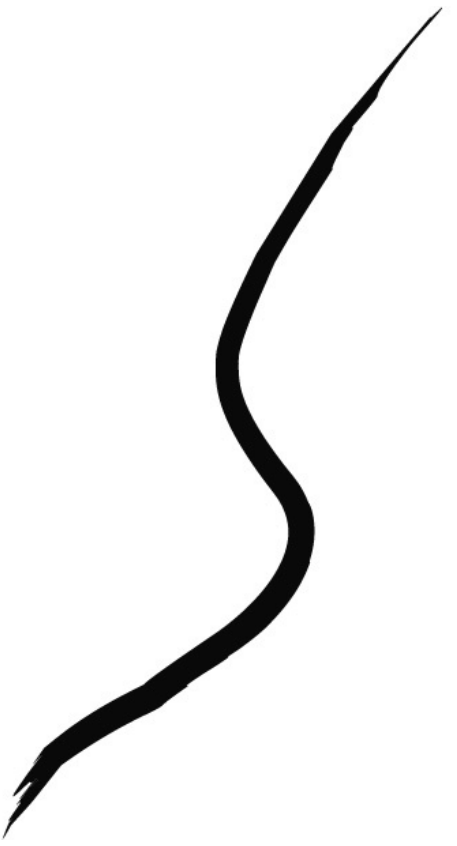
PART 1

INCIDENCE AND RISK FACTORS OF SURGICAL SITE INFECTIONS

CHAPTER



1

SURGICAL SITE INFECTIONS FOLLOWING ROUTINE SYNDESMOTIC SCREW REMOVAL; A SYSTEMATIC REVIEW

Sanders FRK, Birnie MFN, Penning D, Goslings JC, Schepers T

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ABSTRACT

INTRODUCTION

Distal tibiofibular syndesmotic injuries are a common problem in foot/ankle surgery, being present in approximately 15-20% of surgically treated ankle fractures or as an isolated injury. One of the most commonly used ways of fixation is the syndesmotic screw (SS), which is usually removed 8-12 weeks after placement. Besides the fact that it is not always easy to remove implants, surgical site infections (SSIs) occur in up to 20% following implant removal. Aim of this systematic review was to investigate the incidence of SSIs after routine removal of SSs.

METHODS

A systematic literature search was performed in the PubMed, Cochrane, and EMBASE databases for studies published online before April 30th 2019, using the key words and synonyms of “syndesmotic screw”, “ankle fractures” or “syndesmotic injury” and “implant removal”. Studies were eligible for inclusion when they described adult patients undergoing elective/scheduled removal of the SS. Primary outcome was SSI, secondary outcomes included predictors for infection and other complications.

RESULTS

After screening and selection, 15 articles remained for inclusion, of which the majority were retrospective cohort studies. The mean age of all included patients [N=936] was 39.9 years old and the majority was male (61.6%). The percentage of SSIs ranged from 0 to 9.2%, with a weighted mean of 4%, comprising both superficial and deep infections. The largest proportion of these infections were superficial (3%, 95% CI: 2-5), compared to 2% deep infections (95% CI: 1-4). Predictors for infection could not be identified, although some studies described a benefit from prophylactic antibiotics.

CONCLUSIONS

The SSI rate after SS removal found in this review is comparable to that of other foot/ankle procedures. Although prophylactic antibiotics may be able to reduce this rate, the individual indication of SS removal should be carefully considered.

INTRODUCTION

Current literature shows that syndesmotic injuries are commonly diagnosed in foot/ankle surgery with an incidence of 15-20% in surgically treated ankle fractures, which does not include isolated syndesmotic injury[1,2]. The need for fixation of syndesmotic injuries and the preferred method to be used are still subject to debate. Most studies conclude that if intraoperative stress testing following stable fixation of the fractures shows instability (diastasis) of the syndesmosis, indicating that the congruity of the ankle joint is at risk, surgical treatment is warranted[2–5]. However, there is still some questioning whether or not fixation ensures a better functional outcome, even in positive intraoperative stress tests[6]. In isolated syndesmotic injury (without accompanying fracture), diagnosing syndesmotic disruption may be even more difficult since intraoperative stress testing is not applicable. However, if diastasis is present at radiographic imaging, indicating unstable syndesmotic injury, studies agree that surgical fixation is indicated and that non-surgical management shows high complication rates[4].

The jury is still out on the optimal fixation method of syndesmotic injury, and questions continue to arise with the emergence of new techniques[4,7]. However, the most commonly used methods of fixation remains the syndesmotic screw (SS)[4,7,8]. With one or two positioning screws, placed through three or four cortices of the fibula and tibia, adequate alignment and congruity of the mortise is achieved. Since the distal syndesmosis is a dynamic joint, limiting the natural movement of this joint by placement of a SS is thought to impair full range of motion of the ankle[9]. Therefore, SSs are often routinely removed after 8-12 weeks, despite a lack of obvious improvement of range of motion or functional outcome[10–12].

Although implant removal in general is a frequently performed and relatively short procedure, it has proved not to be without risk[13]. Besides the fact that it is not always easy to remove implants[14], surgical site infections (SSIs) occur in up to 20% following implant removal[15–17]. This systematic review therefore aims to investigate the incidence of SSIs after routine removal of SSs.

METHODS

Search strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. It was registered in the PROSPERO International prospective register of systematic reviews under registration number CRD42019144807. A systematic literature search was performed in the PubMed, Cochrane, and EMBASE databases for studies published online before February 6th, 2020. The databases were searched using terms and synonyms of “syndesmotic screw”, “ankle fractures” or “syndesmotic injury” and “implant removal”.

Study Selection

Titles and abstracts were screened for relevance by two independent reviewers (FS and MB). Subsequently full-text articles were assessed by the same reviewers, based on the inclusion and exclusion criteria. Reference lists of all included papers and PubMed 'related articles' were screened manually to identify initially missed but relevant studies. Conflicts in screening were discussed by the two reviewers and if needed by a third (TS) until consensus on eligibility was reached.

Studies were eligible for inclusion when they described adult patients undergoing elective/scheduled removal of the SS. This was defined as removal on a pre-established point in time, at least 6 weeks after initial fixation of the syndesmosis. Single cohort studies and comparative studies were both included. If a study described both planned removal and on demand removal, it was only included if it was possible to extract data specifically for eligible patients. Studies including only patients undergoing implant removal because of complaints were excluded. Studies were excluded if SSIs or wound complications of implant removal were not described/mentioned, if the implant removal encompassed not only the SS but other material (plate or additional screws) as well or if they were animal/cadaver studies. Editorials, proceedings, conference abstracts and (systematic) reviews were also excluded, as well as articles without a full text in English, Dutch, German, French, Spanish or Italian.

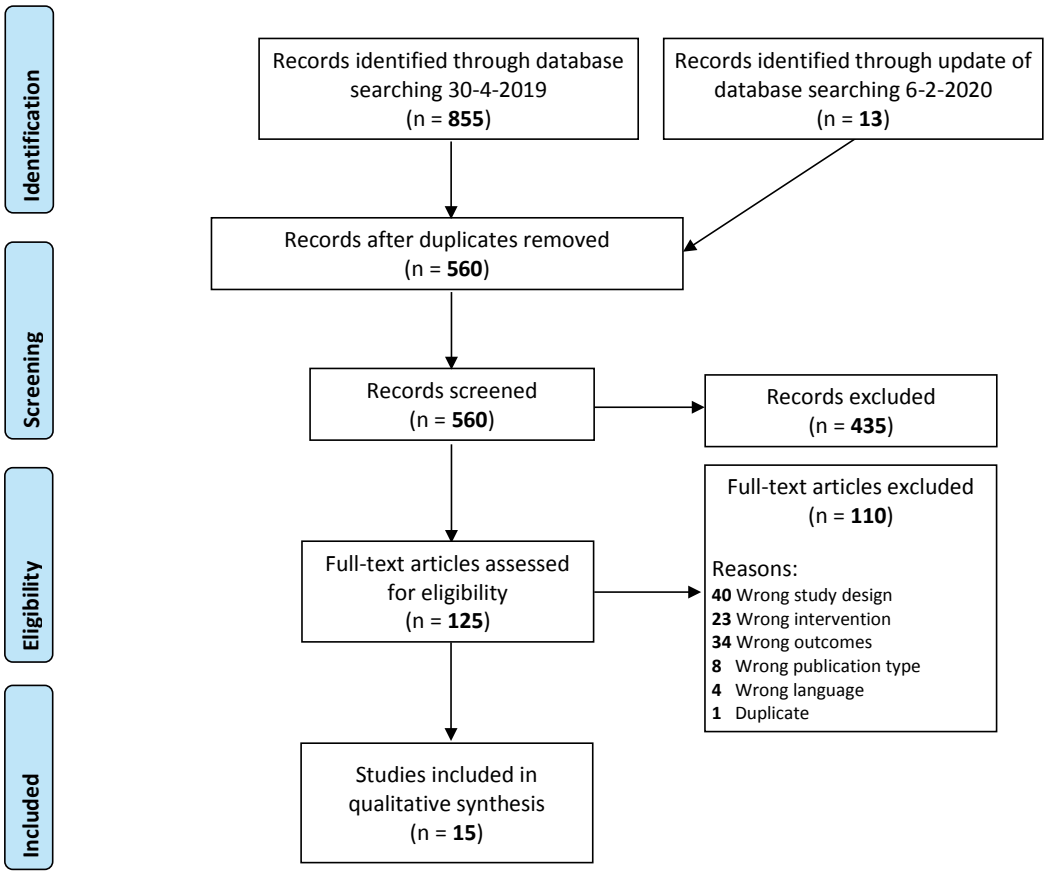
Data Extraction

Data was extracted using a customized extraction sheet (based on the a Cochrane template). One reviewer (FS) extracted the data and the other reviewer (MB) verified it. Multiple publications using the same study population were filtered out by juxtaposing author names and reviewing study inclusion periods, study designs and treatment combinations. In case of duplicate publications, all published information was combined to ensure comprehensiveness of data. Extracted were: characteristics of the studies, the study population, the intervention and the outcome of interest. Study characteristics included: author, year of publication, number of included patients, and study design. Population characteristics consisted of inclusion and exclusion criteria, age, gender, BMI, comorbidities and smoking habits of the participant, and whether or not they were allowed weight-bearing before screw removal. Characteristics of the intervention were: type and number of placed screw(s), timing of removal (in days after placement), prophylactic antibiotics, whether or not it was complete implant removal or isolated syndesmotic screw removal while additional material remained in place and what the weight-bearing protocol was after removal. The outcome of interest was SSI after syndesmotic screw removal (SSR), divided in superficial SSI and deep SSI. Additionally, other complications of SSR were extracted, as well as potential risk factors for SSI identified within the cohorts.

Statistical Analysis

Descriptive statistics were used to present data from the included studies. The primary outcome was presented as a weighted mean, using inverse variance. All statistical analyses were performed using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and RStudio (RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/).

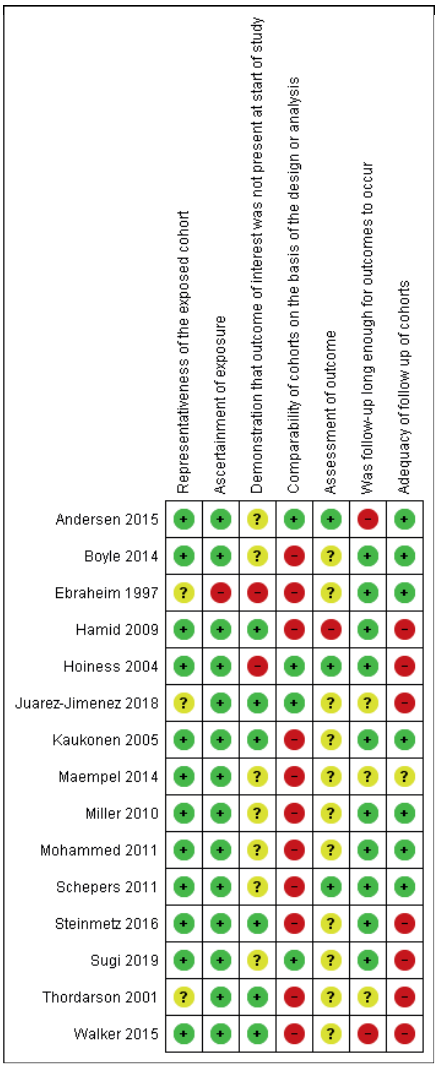
Figure 1. PRISMA flow diagram of inclusion



Risk of Bias Assessment

Studies were individually screened for quality and risk of bias using the Newcastle-Ottawa Scale (NOS), designed to assess the quality of nonrandomized cohort studies (Wells et al., 2013). Using a modified version of this scale with topic specific rating criteria, studies were judged on seven items within three domains; selection, comparability and outcome. Each item was scored as either good, poor or unclear, a "good" score resulting in one or two stars, with a maximum of eight stars. Quality screening was performed by one reviewer [FS] and subsequently checked by another reviewer [MB].

Figure 2 Risk of Bias Assessment



RESULTS

After screening and selection, 15 articles remained for inclusion, as shown in Figure 1[18–32]. The included studies consisted of 10 retrospective cohort studies[18,20–22,24–26,28,30,33]; 4 randomized controlled trials[19,23,27,29]; and 1 prospective cohort study[31].

Risk of bias

A summary of the quality assessment is shown in Figure 2. A minimal score on the NOS, suggesting good quality or low risk of bias, has not been established. However, the overall risk of bias in the included studies seemed high, with only 4 studies scoring 5 stars or more out of 8[18,20,27,29]. Especially the number of studies correcting for confounders was low, and the adequacy of follow-up was often lacking.

Baseline characteristics

Patient's baseline characteristics and surgical characteristics are shown in Table 1. The mean age of all included patients [N=936] was 39.9 years old and the majority was male [61.6%]. In 75.9% of patients, only 1 SS was placed and in 71.6% of cases the screw[s] were placed through 4 cortices. Out of the 10 studies who described their weight-bearing protocols, 8 allowed patients some form of weight-bearing before removal. After SSR, nearly all studies reported that immediate full weight-bearing was allowed, except for Sugi et al., where a small part of patients had a partial or non-weight bearing policy for 2 weeks after SSR[22]. The timing of SSR ranged from 6 weeks to 4 months, with an average of 12 weeks after syndesmotic screw placement.

Table 1 Study characteristics

Study			Population						Intervention				
Study	N in this review/in total in study	Des-ign	Patients	Age, years, mean (SD) [range] Sex, No (%) males	Smok-ing	BMI, mean (SD)	Rele-vant disease	Weight-bearing (before SSR)	type/nr of screw(s)	timing removal, mean (SD) [range]	proph. AB	Residual material	weight bearing (after SSR)
Andersen 2015	161/161	RC	All RR of SS 2007-2012	49.2 (17.6) [14-86] 85 (53%)	29 (18%)	26.6 (4.1)	ND	ND	1x 4cortical 4.5mm (N=149) 1x 4cortical 3.5mm (N=8) 1x 4cortical 4.0mm (N=2) 2x 4cortical 4.5mm (N=1) 2x 3cortical 3.5mm (N=1)	78.6 (13.6) [29-132] days	no	plate 115 (71%)	imm full
Boyle 2014*	24/72	RCT	SSR(N=26) vs retained SS (N=25) in age 16-65 with acute dist. fib# 2011-2012 (excl open #)	30.8 (12.8) 19 (71%)	9 (35%)	30.6 (4.6)	DM (N=0)	imm touch	1x 4cortical 4.0mm (N=24)	116 [81-177] days	yes (unspecified)	plate 100%	imm full
Ebraheim 1997	17/32	RC	Supra-syndesmotic fib# 1987-1995 (excluding maisonneuve #)	29 [16-49] 18 (78%)**	ND	ND	ND	ND	ND	9wks	ND	ND	ND
Hamid 2009	15/52	RC	Acute ORIF + SS comparing SSR (N=15), intact SS (N=27), broken SS (N=10) 2001-2005 (excl. BA and complications of fixation)	50 [21-69] 8 (53%)	ND	ND	ND	9.7wk (8-13)	1x 3cortical 3.5mm, N=8 1x 4cortical 3.5mm, N=2 2x 3cortical 3.5mm, N=5	13.1 [11-20] wks	ND	ND	imm full
Hoiness 2004	30/64	RCT	Retaining 2x tricortical SS(N=34) vs. routine removal 1x 4 cortical SS (N=30) in Si 1998-1999	41.8 (17.9) 17 (57%)	4 (13%)	27.1	DM (N=1)	imm. touch, full >SSR	1x 4cortical 4.5mm, N=30	9.5 wks (1.4)	ND	ND	imm full
Juarez-Jimenez 2018	207/207	RC	Sample of all SSR 2015-2016 (excluding patients with complication of fixation)	38.2 104 (50%)	61 (29%)	Over-weight: 40%	DM (N=18, 9%)	ND	1x (N=174) 2x (N=73)	73 days	60 (29%)	ND	ND
Kaukonen 2005	18/38	RCT	Comparing StS (N=18) vs. BA (N=20) in all ankle# + syndesmotic injury 1998-1999	45.6 [9-72] 9 (50%)	ND	ND	ND	0-4wk 50%, 4-6wk full	1x 4cortical 4.5mm (N=18)	*>8 wks*	ND	ND	ND

Maempel 2014	19/35	RC	Comparing TR/SS in all ankle# + syndesmotic injury 2008-2009 (excl. previous ankle pathology/procedures)	41 [18-88] ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Miller 2010	25/25	PC	All SS 2007-2008 (excluding open#, crush injury)	40 [17-78] 11 (44%)	ND	ND	ND	>6wk full	2x 4cortical (N=25)	*4 mos*	ND	ND	imm full
Mohammed 2011	12/12	RC	Weber C# +SS 2007-2008 (excluding open#, surgery >6wk after #)	35 [20-48] 6 (50%)	ND	ND	ND	0-6wk NWB, 6-8 PWB	1x 3cortical 3.5mm (N=11) 1x 4cortical (N=1)	8 wks	ND	ND	imm full
Schepers 2011	76/76	RC	All SS 2004-2010 (excluding BA and no SSR)	42.6 (17.6) 48 (63%)	ND	ND	ND	2wk NWB, 4wk WB cast	2x (N=17) 1x (N=59) 3cortical (N=60) 4cortical (N=16)	11.8 [5-182] wks	ND	ND	imm full
Steinmetz 2016	126/126	RC	All SS + ATFL repair 2004-2011 (excl. patients with confounding injuries, lost to FU or dead)	45 (15.7) 77 (61%)	ND	ND	ND	6-8wk NWB	1x 3cortical 3.5mm (N=87) 1x 4cortical 3.5mm (N=39)	*6-8 wks*	ND	ND	imm full
Sugi 2019	170/269	RC	All ankle# +SS within 5 years	31.3 137 (80.6%)	ND	ND	ND	12wk NWB	3cortical 3.5mm (N=5) 3cortical 4.5mm (N=6) 4cortical 3.5mm (N=36) 4cortical 4.5mm (N=123) 1x (N=41) 2x (N=128)	*12 wks*	1-7days oral AB after SSR (N=110): Cephalexin, Clindamucin, Levofloxacin, Trimethoprim/ sulfamethoxazole	ND	imm full (N=133) 2wk NWB (N=27) 2wk PWB (N=10)
Thordarson 2001	15/32	RCT	Comparing StS (N=15) vs BA (N=17) in PER ankle # with syndesmotic injury	24.2 25 (78.1%)***	ND	ND	ND	6wk NWB	1x 4cortical 4.5mm (N=15)	13.4 wks	ND	ND	ND
Walker 2015	21/36	RC	All Weber C 2012-2013	33.4 (13.7)*** † 23 (63.9%)***	ND	ND	ND	ND	1x (N=25) 2x (N=11) 4.5mm (N=33) 3cortical (N=18) 4cortical (N=18)***	Median IQR: 20 wks [16-22]	ND	ND	ND

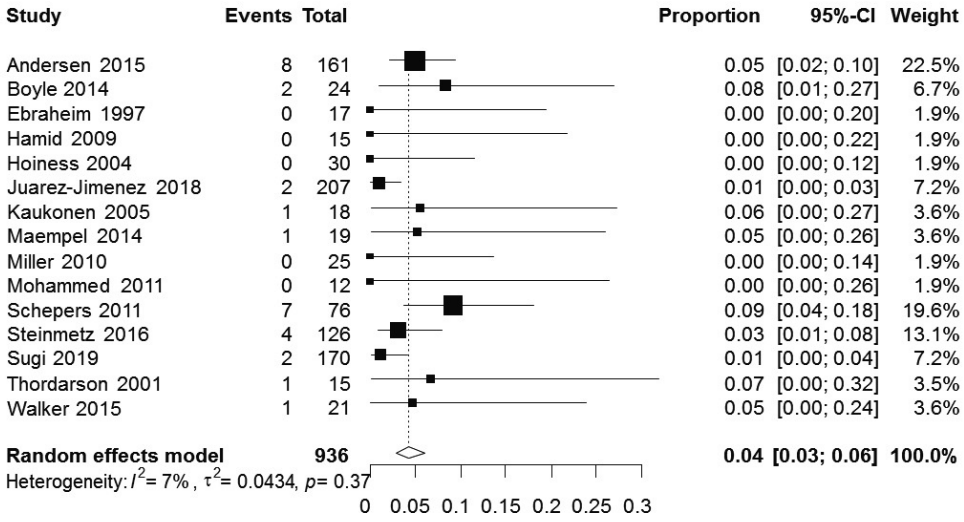
Abbreviations: Av: average, dist.: distal, BA: bio-absorbable screw, FU: follow-up, imm.: immediate, mos: months, ND: not described, NWB: non weight-bearing, PWB: partial weight-bearing, PC: prospective cohort, PER: pronation-exo-rotation, RC: retrospective cohort, RCT: randomized controlled trial, RR: routine removal, Si: syndesmotic injury, SS: Syndesmotic screw, SSR: syndesmotic screw removal, StS: stainless steel, TR: tightrope, wks: weeks, #: fracture

*baseline criteria of patients randomised for removal
**of 23 SS patients only
***of total population
†Estimation based on median and IQR (33 [24.75-42.5]) using methods of Wan et al.[70]

Complications

The percentage of SSIs ranged from 0 to 9.2%, with a weighted mean of 4%, including both superficial and deep infections (Table 2, Figure 3). The rate of superficial SSIs was 3% (95% CI: 2-5), compared to 2% deep infections (95% CI: 1-4). How the included articles defined SSI is shown in Table 2. Other SSR complications documented were recurrent diastasis, complex regional pain syndrome (CRPS), pain with another etiology and wound dehiscence (Table 2). Wound dehiscence was defined as a partial or total separation of previously approximated wound edges, due to a failure of proper wound healing, without clinical signs of infection, therefore not qualifying as a SSI according to the Centers for Disease Control and Prevention (CDC) criteria[34]. Breakage of the SS before removal and potential corresponding complications were not documented.

Figure 3 Incidence of Surgical Site Infections



Within studies with a minimum score of 5 stars on the quality assessment, the weighted mean proportion of SSIs was 6% (Figure 4). The proportion of superficial and deep SSIs in these studies was 4% (95% CI: 2-7) and 2% (95% CI: 1-5) respectively.

Figure 4 Incidence of Surgical Site Infections in high quality studies

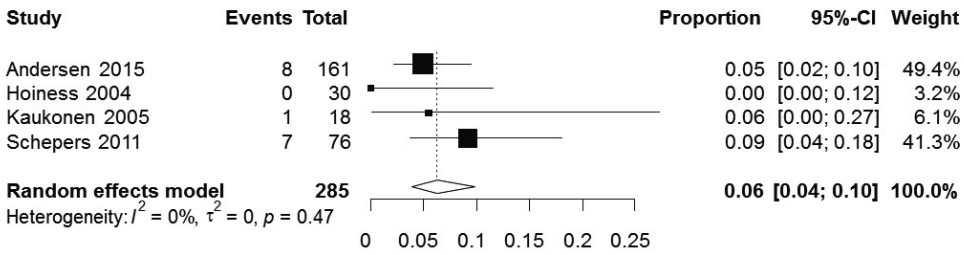


Table 2 Complications of Syndesmotic Screw Removal

Study	N*	Definition/description SSI**	SSI (%)*	Superficial Deep	Other compl.	Total compl.
Andersen 2015	161	ND, deep: hospitalization/revision	8 (5.0%)	5 (3.1%) 3 (1.9%)	RD (N=1) DVT (N=1) hypersens. Scar (N=1)	10 (6%)
Boyle 2014	24	ND, superficial: AB, deep: AB+ debridement+ IR	2 (8.3%)	1 (4.2%) 1 (4.2%)	0	2 (8.3%)
Ebraheim 1997	17	ND	1 (5.9%)	1 (5.9%)	RD (N=2)	3 (17.6%)
Hamid 2009	15	ND	0		0	0
Hoiness 2004	30	CDC criteria	0		ND	0
Juarez-Jimenez 2018	207	ND, 1: AB, purulent discharge/pain/fistula, 1: AB	2 (0.96%)	2(0.96%)	WD (N=2) RD (N=1)	5 (2.4%)
Kaukonen 2005	18	ND, purulent arthritis	1 (5.6%)	1 (5.6%)	0	1 (5.6%)
Maempel 2014	19	ND	1 (5.3%)	1 (5.3%)	WD (N=1) RD (N=1)	3 (15.8%)
Miller 2010	25	ND	0		ND	0
Mohammed 2011	12	ND	0		RD (N=1)	1 (8.3%)
Schepers 2011	76	CDC criteria, superficial: AB, deep: hospitalization/revision	7 (9.2%)	5 (6.6%) 2 (2.6%)	RD (N=5)	12 (15.8%)
Steinmetz 2016	126	ND, superficial: local wound care, deep: debridement+ AB+ local wound care	4 (3.2%)	1 (0.8%) 3 (2.4%)	CRPS (N=12) anterior impingement (N=2)	18 (14.3%)
Sugi 2019	170	CDC criteria, 1: AB, stitch abscess, 1: AB, incisional cellulitis	2 (1.2%)***	2 (1.2%)	0	2 (1.2%)
Thordarson 2001	15	ND, superficial: AB	1 (6.7%)	1 (6.7%)	0	1 (6.7%)
Walker 2015	21	ND, superficial: oral AB	1 (4.8%)	1 (4.8%)	lateral ankle pain (N=2) AVN tibial plafond (N=1)	4 (19%)

AB: antibiotics, AVN: avascular necrosis, CRPS: complex regional pain syndrome, DVT: deep venous thrombosis, IR: implant removal, ND: not described, RD: recurrent diastasis, RR: routine removal, SS: Syndesmotic screw, SSI: surgical site infection, WD: wound dehiscence

*No of patients with RR of SS

** The definition of SSI that included studies mentioned in the Methods section and/or description of how the individual SSIs were defined/treated

***1.2% of total, 3.3% of patients not receiving AB

Risk factors

Of the 10 studies which found infectious complications after SSR, 4 described the presence or the effect of known risk factors on the infection rate. Andersen et al. could not identify a significant relationship between infection and gender, age, time from primary surgery to screw removal, BMI, remaining hardware, ASA classification or smoking status[18]. Juárez-Jiménez et al. displayed the presence of several risk factors (Diabetes Mellitus, being underweight, obesity, smoking, prophylactic antibiotics, atopy, autoimmune disease, HIV) for each patient with a complication and found that of the two patients with an infection; one did not receive prophylactic antibiotics and one was obese[28]. Kaukonen et al. reported that the one patient with a deep SSI after SSR was a 50 year old female with no known chronic disease[29]. Sugi et al. provided a description of the two patients with an infection. The first was a 32 year old man, the second a 36 year old woman, both with no past medical history and a one-third tubular plate on the fibula left in place at screw removal. Both patients did not receive prophylactic antibiotics, whereas a majority of the patient in this study received empirical oral antibiotic coverage 1-7 days after SSR[22].

DISCUSSION

The amount of studies describing SSIs after SSR was limited. The overall SSI rate found in these studies was 4-6%, of which a small majority was comprised of superficial infections. Two studies identified lack of antibiotic prophylaxis as a potential risk factor for developing a SSI[22,28]. Other risk factors could not be identified.

Complications

The infection rates found in this review were relatively comparable to those found in previous literature on implant removal in general. In previous studies infection rates varied between 1.8% and 14.9% with higher rates in implant removal of the lower limb[13,14,35–38].The large range of SSI incidences in these studies could potentially be explained by underreported (superficial) SSIs in retrospective studies due to loss to follow-up (treated by a general practitioner or at another center), causing an underestimation of the true SSI rate[39]. This hypothesis is supported by the higher proportion of superficial SSIs found in a RCT by Backes et al.[38] when compared to the retrospective cohort studies[13,14,35–37]. Patients with superficial SSIs are more inclined to be treated by a general practitioner or at another (local) hospital. Moreover, they may be diagnosed less frequently given that the symptoms and criteria for a superficial SSI are less strictly documented than for a deep SSI. Since our review comprised mainly cohort studies, without SSI as a primary outcome measure, this underestimation of [superficial] SSIs might apply to our results as well. Regardless of this, the SSI rate after SSR was higher than expected, especially in the studies with a low risk of bias. The incidence was not just similar to that of implant removal but also to that of general foot/ankle surgery[40], even though SSR rarely lasts more than an hour and is considered a

"clean surgery" according to the CDC[34]. The reliability of the CDC wound classification in predicting development of SSIs has been questioned however[41].

Risk factors

Regarding risk factors for SSI in lower extremity surgery, previous literature has identified a few well-known patient related factors such as age, Diabetes Mellitus, ASA classification, smoking and BMI[41–46]. It seems likely that these patient related risk factors would also apply here, but unfortunately most studies included in this review did not investigate or correct for the influence of these characteristics. Therefore, no overall conclusions on patient related risk factors can be drawn from this review, even though obesity was mentioned in one study[28]. Within the included studies that described characteristics of patients with a SSI, two out of four found a potential correlation with prophylactic antibiotics[22,28]. Since most studies did not report whether or not prophylaxis was standardly administered, it is again hard to draw any conclusions from this. Most likely, prophylactic antibiotics were not used in the other studies, since this is not standard protocol for implant removal, as a "clean procedure"[34]. A recent RCT that investigated the effect of antibiotic prophylaxis on SSI after implant removal below the knee found SSI rates of 13.2% with and 14.9% without antibiotic prophylaxis, which was not a statistically significant difference [38]. Although the current study provides insufficient concrete evidence and further studies are necessary, prophylactic antibiotics are a hot topic and may proof to be beneficial in SSR.

More importantly, with the high infection rate in mind, the additional value of SSR should be carefully evaluated. To prevent this additional procedure, multiple other methods to treat syndesmotic injury have been on the rise. Recent studies point out that when syndesmotic injury shows posterior malleolar involvement, direct fixation of the posterior malleolus reduces the need for separate syndesmotic fixation[47,48]. When it comes to direct syndesmotic fixation, other fixation devices, that do not necessarily require removal, are absorbable screws and suture buttons (e.g. TightRope, Endobutton). However, they too are not entirely without risk. A meta-analysis comparing bio-absorbable to metallic screws found more wound complications in the bio-absorbable group (19.7% versus 5.7%)[49]. Another meta-analysis found similar functional outcome, but a higher incidence of foreign body reactions (RR 6.07, $p<0.001$), although reoperation rate was lower (RR 0.08, $p=0.01$) for bio-absorbable screws[50]. As for suture button devices, multiple systematic reviews suggest similar to better clinical outcomes for suture button devices when compared to screw fixation[51,52]. One of the proposed benefits of the suture button device is the absence of the need for removal, thereby reducing complication rates and costs. However, the most recent systematic review comparing SS and suture button found no difference in complication rate (OR 0.60, $p=0.48$)[52]. Complications that have been described from suture button devices are: skin irritation/granulation, infection, osteomyelitis, aseptic osteolysis, and failed stabilization often resulting in subsequent removal[53–56].

Instead of avoiding SSR by choosing another fixation method, it is also an option to use metallic screws but to leave them in place. Especially when the SS is broken or loosened, thereby not restricting natural movement of the distal tibiofibular syndesmosis, SSR does not necessarily lead to improved functional outcome or ROM[19,57,58]. “On demand removal”, where SSR is based on complaints of the patient instead of routinely planned, may be a better solution. However, this has so far only been suggested based on underpowered or retrospective studies[11,57,59] and the results of a RCT comparing on demand removal to routine removal have not yet been published[60]. On demand removal does require clear instructions for the patient, specifically on what valid indications for implant removal are. To be able to make recommendations on SSR indications, it is important to know the risks of both removal and of retaining syndesmotic screws. At the time there is insufficient high-quality evidence on the risks of retaining syndesmotic screws to make evidence based recommendations on this front. A few retrospective studies on retaining SSs found low removal rates and radiographic findings (e.g. loosening or breakage of SS) aside complication rates were low [61–63]. Complications of retaining SSs are almost exclusively reported in case reports or small series and include “backing-out” of the SS[64,65], malposition of fibula in tibial notch which spontaneously reduces after SSR[66–68] or a stress fracture at SS level[69]. Based on these studies and clinical experience we advise removal of the SS when the patient has complaints of pain or stagnation in functional recovery in combination with one of the following signs on radiographic imaging: 1) SS backing out to the point of threatening/protruding from the skin, 2) malposition of the fibula in the tibial notch in combination with an intact SS. In addition to these, signs of infection, pain/skin irritation specifically located at the SS head, and revision surgery or removal of other implants would be valid reasons for SS removal.

Besides from the options to prevent [complications of] SSR as mentioned above, the indication for and method of syndesmotic fixation are also areas of interest for future research.

Limitations

This review has several limitations, most of them arising from the fact that included studies were mostly retrospective and did not list SSI as a primary outcome. First of all, the overall risk of bias was high, with only 4 studies with a “good” score on more than half of the items of the risk of bias assessment. By performing a risk of bias assessment using the NOS we have tried to make the risk of bias insightful for the individual studies. However, as this assessment is not an objective outcome, it is subjective to a risk of bias on its own. By including the support of judgement for each study and item in the Appendix (online only) we have tried to make our considerations more transparent. To evaluate the effect of the individual study’s risk of bias on our primary outcome, we provided the results for all studies but also separately for studies with a low risk of bias. Secondly, since SSI was not always the primary outcome, some studies did not report the criteria that were used to diagnose a SSI. This makes it hard

to compare the incidences between studies, since definitions may not equal. The same goes for the patient populations that were studied. Although nearly all studies described age and sex, other possibly confounding characteristics were usually not mentioned. It is therefore hard to say if patient populations were comparable. By using the inverse variance weighted average we tried to restrict the effect of heterogeneity. Finally, with the low reporting rate of confounding factors such as BMI, Diabetes Mellitus or smoking it was not possible to identify risk factors for SSI after SSR. However, it is likely that risk factors after this procedure are comparable to those of other orthopedic lower extremity procedures.

CONCLUSION

The SSI rate after SSR found in this review is comparable to that of other foot/ankle procedures and the individual indication for SSR should be carefully considered. Future studies should focus on valid indications for SSR, the influence of prophylactic antibiotics on SSI after SSR and on complications of retaining the syndesmotic screw to enable a fair comparison of benefits and risks between routine removal and retaining/on demand removal of the SS. A sufficiently powered RCT comparing routine and on demand removal would be helpful in answering the questions that remain unanswered by this review.

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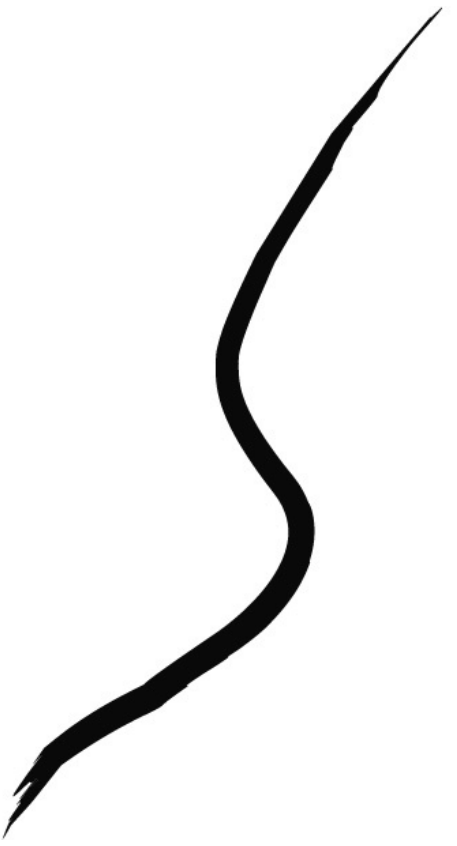
CHAPTER



2

RISK FACTORS FOR SURGICAL SITE INFECTIONS WITH THE SINUS TARSI APPROACH IN DISPLACED INTRA-ARTICULAR CALCANEAL FRACTURES; A PROSPECTIVE COHORT STUDY

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Injury, Jul 2020

ABSTRACT

INTRODUCTION

In the last decade, the sinus tarsi approach (STA) has gained interest over the extensile lateral approach (ELA) in the operative treatment of displaced intra-articular calcaneal fractures (DIACF's), mainly because of the lower rate of surgical site infections (SSIs). However, most studies are small and retrospective. The aim of this study was to evaluate the rate of SSIs of the STA in a large, prospective series of patients and to identify predictors for SSIs.

METHODS

In this prospective cohort study, all consecutive patients who were operatively treated for a DIACF in our Level 1 trauma center between August 2012 and January 2019 were included and followed for at least one year. All operative procedures were performed by two specialized foot and ankle trauma surgeons using the STA. Using multinomial logistic regression, risk factors for SSIs were identified.

RESULTS

A total of 237 calcaneal fractures in 214 patients were included, of which 179 underwent open reduction and internal fixation and 58 a primary arthrodesis. Most patients were male (73.6%) and the mean age was 45.9 years. There were 16 patients that developed a SSI (6.8%), of which 9 (3.8%) were deep and 7 (3%) were superficial infections. The multivariate analysis pointed out that surgery within one week after injury increased the chance of a SSI, as well as an ASA of 2 or higher and more than 150 cc of blood loss during the procedure.

CONCLUSIONS

This study confirms the low risk of SSI in DIACFs treated via STA. Significant predictors for SSIs were surgery within one week after injury, ASA of 2 or higher and blood loss >150cc.

INTRODUCTION

The operative treatment of displaced intra-articular calcaneal fractures (DIACFs) has always been controversial and not without potentially catastrophic infections and wound complications. Since the early nineties, the extended lateral approach (ELA) has been widely used and the results of operative treatment have improved significantly. However, with the arrival of less invasive and minimally invasive surgery in the last decade, the sinus tarsi approach (STA) has regained interest in the operative treatment of DIACFs. This is mainly due to the large advantage over the ELA in terms of the rate of SSIs [1] . Studies have shown an overall percentage of SSI of 3.6%-6.3%, which is significantly lower than the complication rate in the ELA, ranging from 13.3% to 31.2% [2–5] .

Nevertheless, despite the (re)implementation of the STA, prevention of wound complications is still paramount with regards to costs and patient satisfaction. Therefore, it is important to keep investigating risk factors for the development of a SSI to try and identify other controllable factors. Moreover, risk factors for SSI's after the STA might differ from risk factors for SSI's after the ELA. The aim of this study was to evaluate the rate of SSIs of the STA and to identify predictors for SSIs in calcaneal fractures in a large, single-center, prospective database.

METHODS

In this prospective cohort study, all consecutive patients who were operatively treated via a STA for a DIACF in our Level 1 trauma center between August 1st, 2012 and January 31st, 2019 were included and followed up for at least one year. This included patients with open and closed fractures treated by either open reduction and internal fixation (ORIF) or primary subtalar arthrodesis, following reconstruction of overall anatomy, via the sinus tarsi approach. Excluded were patients that were treated surgically via the ELA (n = 3) or percutaneously (n = 2).

All operative procedures were performed by two specialized foot and ankle trauma surgeons using the STA, which is the preferred technique at the present institute since 2013 [10]. The indications for a primary arthrodesis were described previously[6]. In case of a primary arthrodesis, the exact same STA was used including similar reduction and fixation techniques. The only difference being that the articular surfaces were prepared for a fusion. In addition, two large diameter screws were added to stabilize the subtalar joint [26] . Closed suction drains were not used. Patients were followed-up two weeks after surgery for wound check-up and suture removal. According to hospital protocol, after eight weeks, six months and one year there was another check-up with x-ray. After one year, patients were no longer routinely checked and were told to return in case of an infection or symptoms of the implants or other complaints of pain. To determine whether or not a SSI occurred, electronic medical records were screened at least 12 months after surgery of the last included patient. The following data was collected:

1) Patient characteristics: gender, age, BMI (Body Mass Index), ASA (American Society of Anesthesiologists) classification, smoking habits, diabetic status.

2) Fracture characteristics: severity of fracture (Sanders classification [7]), side of fracture, open or closed fracture as classified by Gustilo et al. [8] , date of injury, whether the patient was referred.

3) Surgical characteristics: date of surgery, type of surgery (i.e. plate, screw fixation or primary arthrodesis), tourniquet use (based on preference of the operating surgeon), estimated blood loss (amount of fluid in collection pot of suction device minus estimated amount of irrigation fluid used, adding estimated volume of packed gauzes), post-operative SSIs (diagnosed as superficial or deep wound infections according to Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection [9]).

Statistical analysis

Baseline patient, fracture, and surgical criteria were compared in patients with and without a SSI in univariate analysis according to the characteristics and distribution of data. Categorical values were analyzed with a chi-square and continuous, normally distributed values with a Student's t-test. Continuous, non-normally distributed values were compared with a Mann-Whitney-U test. The continuous variables were evaluated for normality using the Shapiro-Wilk test and Q-Q plots. Continuous values were first transformed into binary variables based on clinical relevance and the optimal cut-off value using the Youden-index (extracted from a ROC-curve) [11] . The following cut-off values were used for continuous variables (value with maximal Youden-index): age: 45 year (Ymax = 43.5), BMI: 27 (Ymax = 27.12), blood loss: 150cc (Ymax = 135), duration of surgery: 60 min (Ymax = 74.5) and time from trauma to surgery: 7 days (6.5). The ASA classification was transformed into two groups: an ASA of 1 and an ASA of 2 or higher. In order to limit bias caused by missing data, multiple imputation was used for variables with (under 50%) missing data. The over- all missing percentage was 5% with a range of missing numbers of 1-40 (Table 1). The variable with the largest amount of missing values was height. Imputation was performed based on predictive mean matching combined using Rubin's rule (10 sets). Imputed variables were height, weight, smoking, Sanders classification, duration of surgery and blood loss. The pooled results of the 10 imputed sets were used to estimate odds ratios and 95% confidence intervals (CI). After imputation, all clinically relevant characteristics and those with a (near-)significant difference between the two groups (P = < 0.3), as well as risk factors described in literature, such as age and diabetes mellitus, were put into a multivariate analysis to determine risk factors for SSI (in general, and then for superficial and deep infections separately). Variables were manually removed based on their addition to the prediction model (least significant variables first), until only significantly predicting variables remained. The following order was used: age, BMI, ASA classification, smoking, bilateral fractures, primary arthrodesis, tourniquet use, blood loss, duration of surgery, time till surgery. Data were analyzed using SPSS, version 25.0 [12].

Table 1 Baseline characteristics

	SSI (N = 16)	No SSI (N = 221)	P-value
Gender, No (%) male	11	160 (72.4%)	.980[a]
Age, mean (SD)	47.5 (13.8)	45.5 (14.9)	.607[b]
Age, years old:			0.535
- **<45**	6	108 (48.9%)	
- **45 or more**	10	113 (51.1%)	
Diabetes Mellitus, No (%)	0	1 (0.5%)	1.0[a]
BMI, median [IQR]	25.5 [20.4-30.1]	23.9 [21.6-26.6]	0.563
BMI*:			.084[a]
- **<27**	7	145 (78.8%)	
- **≥27**	6	39 (21.2%)	
Referred from other hospital, No (%)	12	188 (85.1%)	.475[a]
ASA classification, No (%):			.035[b]
- **1**	6	146 (66.1%)	
- **2**	10	69 (31.2%)	
- **3**	0	6 (2.7%)	
Smoking, No (%)**	10	94 (42.7%)	.201[a]
Bilateral fracture, No (%)	1	45 (20.4%)	.293[a]
Open fracture, No (%)	0	10 (4.6%)	.860[b]
- **Grade 1**		- 5 (2.3%)	
- **Grade 2**		- 1 (0.5%)	
- **Grade 3**		- 4 (1.8%)	
Sanders classification, No (%)**			.047[b]
- **Type 1**	1	1 (0.5%)	
- **Type 2**	12	135 (61.4%)	
- **Type 3**	2	63 (28.6%)	
- **Type 4**	1	21 (9.5%)	
Fixation type, No (%)			.231[b]
- **ORIF**	10	169 (76.5%)	
- **Primary arthrodesis**	6	52 (23.5%)	
Tourniquet use, No (%)	6	129 (58.4%)	.172[a]
Estimated blood loss, median (IQR)***	200 (100 – 287.5)	100 (50 – 200)	.097[b]
Estimated blood loss, cc;			.092[a]
- **<150**	7	139 (67.8%)	
- **≥150**	9	66 (32.2%)	
Duration of surgery in min, mean (SD)**	117.4 (8.695)	88.3 (2.046)	.005[b]
Time till surgery:			.054[a]
- **≤7 days**	5	28 (12.7%)	
- **>7 days**	11	193 (87.3%)	

Abbreviations: IQR: interquartile range, min: minutes, No: number of cases, SD: standard deviation, SSI: surgical site infection

a Continuity correction

b Pearson Chi-Square

* Missing data: 40 (3 SSIs)

** Missing data: 1 (no SSI)

*** Missing data: 11 (no SSIs)

RESULTS

A total of 237 calcaneal fractures in 214 patients were included. Most patients were male (72.2%) and the mean age was 45.7 years (SD 14.8). Most patients were ASA 1 (64.1%) and most fractures were of Sanders type II (62%) (Table 1). Patients were operated within a median of 13 days (IQR 9–15 days) Mean follow-up was 46.5 months (range 14–89 months). All patients were seen in the outpatient clinic at 3 months after surgery, 225 (95%) patients were also seen in the outpatient clinic at 12 months after surgery. As for the remaining 12 patients, their follow-up was on average six months, without any signs of SSI at their last follow-up. ORIF was performed in 179 fractures and primary arthrodesis in 58 fractures (Table 2).

Table 2 ORIF vs primary arthrodesis

	ORIF (N = 179)	Primary arthrodesis (N = 58)	P-value
Gender, No (%) male	133 (74.3%)	38 (65.5%)	.259[a]
Age, mean (SD)	43.1 (13.900)	53.6 (14.755)	.000[b]
Diabetes Mellitus, No (%)	0	1 (1.7%)	.552[a]
BMI*:			.064[a]
- **<27**	117 (65.4%)	34 (58.6%)	
- **>27**	28 (15.6%)	17 (29.3%)	
Referred from other hospital, No (%)	150 (83.8%)	50 (86.2%)	.817[a]
ASA classification, No (%):			.006[b]
- **1**	123 (68.7%)	29 (50%)	
- **2**	54 (30.2%)	25 (43.1%)	
- **3**	2 (1.1%)	4 (6.9%)	
Smoking, No (%)**	80 (44.7%)	24 (41.4%)	.747[a]
Bilateral fracture, No (%)	36 (20.1%)	10 (17.2%)	.772[a]
Open fracture, No (%)			.001[b]
- **Grade 1**	3 (1.7%)	2 (3.4%)	
- **Grade 2**		1 (1.7%)	
- **Grade 3**		4 (6.9%)	
Sanders classification, No (%)**			.011[b]
- **Type 1**	2 (1.1%)		
- **Type 2**	119 (66.5%)	28 (48.3%)	
- **Type 3**	47 (26.3%)	18 (31%)	
- **Type 4**	11 (6.1%)	11 (19%)	
Tourniquet use, No (%)	104 (58.1%)	31 (53.4%)	.639[a]
Estimated blood loss, median (IQR)	100 (50 – 200)	150 (100 – 300)	.001[b]
Duration of surgery in min, mean (SD)	86.1 (31.207)	103.1 (28.888)	.000[b]
Time till surgery:			.119[a]
- **<7 days**	29 (16.2%)	4 (6.9%)	
- **>7 days**	150 (83.8%)	54 (93.1%)	

Abbreviations: IQR: interquartile range, min: minutes, No: number of cases, SD: standard deviation, SSI: surgical site infection. a: continuity correction, b: Pearson Chi-square

* Missing data: 41 (7 PA)

** Missing data: 1 (ORIF)

Differences in the baseline and surgical characteristics of fractures treated with ORIF or with primary arthrodesis are stated in Table 2 . The duration of surgery was significantly longer in patients with a primary arthrodesis (mean 103.1 min vs 86.1 min, P = .000) and there was more blood loss (median 150 cc vs 100 cc, P = .001).

In total, there were 16 SSIs (6.8%), of which 9 (3.8%) were deep and 7 (3%) were superficial infections (Table 1). Superficial infections were treated with local wound care and/or oral antibiotics, deep infections were treated with intravenous antibiotics and in four cases implant removal was eventually necessary to adequately treat the infection.

Possible predictors of SSI as identified in univariate analysis were BMI, ASA classification, smoking, bilateral fractures, Sanders classification, time till surgery, type of fixation, tourniquet use, estimated blood loss and duration of surgery (Table 1). In multivariate analysis, surgery within one week (OR: 5.78, 95%CI: 1.52-21.90, P = .010), ASA classification of 2 or higher (OR: 3.51, 95%CI: 1.18-10.41, P = .024), and more than 150 cc of blood loss during the procedure (OR: 5.11, 95%CI: 1.43-18.32, P = .012) remained as independent predictors of SSI.

DISCUSSION

In the operative treatment of DIACF's the most commonly used approaches to restore intra- and extra-articular anatomy are the STA and the ELA. The ELA used to be the preferred approach, but comes with a high rate of SSIs compared to the STA, leading to a gradual worldwide shift toward the STA[2–5] . In the current study, the incidence of SSIs using the STA was 6.8%. This suggests lower risk of SSIs compared to the risk in ELA, which was described earlier in a systematic review by Backes et al., reporting an infection rate of 14.3% globally and 12.1% in Europe[22]. At our center, a wound complication rate of 31% has been previously described with the use of the ELA[10].

Our results seem to be in line with a recent systematic review and meta-analysis, in which an infection rate of 4.9% is described in the STA[1]. Our slightly higher infection rate may be attributed to the fact that as the STA gains in popularity, more complex fractures and patients with increased risk for wound complications are treated via this approach. Moreover, this study was performed in a tertiary referral center for complex traumatic foot/ankle injuries. This is reflected in our rate of Sanders type IV fractures (9.3%) and patients with ASA II or higher (35.8%).

Surgery within one week after injury was one of the risk factors that were found in this cohort. In our center, calcaneal fractures are preferably treated after the swelling is gone or at least decreasing, when there is a positive wrinkle sign. When treated too soon, when the swelling is still present, the already thin skin covering the fracture can fail to heal sufficiently and increase the risk in wound infections[23]. However, a delay in time until definite fixation

has been described as a risk factor for SSIs after ORIF for DIACFs[13,14,20]. Taking these results into account, we conclude that surgery should take place within a window of one to two weeks after injury, to minimize the risk of SSIs.

Blood loss has been described as a risk factor for SSIs both in the operative treatment of calcaneal fractures and in other surgical fields[15–17,24]. The larger amount of blood loss in this group is likely to be related to more complex injuries and a longer duration of surgery. Ding et al.[15] described blood loss as a risk factor for complications with the ELA as well (200.40 cc with SSIs vs 166.23 cc without SSIs, P = .017) and mentions tourniquet use as a protective factor of SSIs, however they do not describe the use of tourniquet in detail. In our center the joint reconstruction part of the procedure is currently often performed with the use of a tourniquet at the level of the calf, reducing blood-loss to approximately 50-100 cc. However, at the start of this cohort, this was not standard practice.

Backes et al. described ASA classification of 2 or higher as a risk factor for SSIs in DIACFs as well. However, the approach used there was the ELA, whereas in this cohort the STA was used for all ORIFs and primary arthrodesis [25].

Smoking is another well-known risk factor for surgical site infections [14,15,18,19,23]. In this cohort we found a high percentage of smokers (43.9%). Even though it was not identified as a significant predictor, 10 out of the 16 SSIs occurred in people with nicotine abuse.

Limitations

A strength of our study is that it describes a large cohort of patients with calcaneal fractures treated via the STA, based on a prospective database. There were also some limitations in this study. Firstly, two types of treatment were included: primary arthrodesis and ORIF. One could argue that ORIF and primary arthrodesis are different operative procedures, and therefore cause a heterogeneous study population. For a primary arthrodesis, in addition to repositioning of the fractured bone, the cartilage has to be removed, usually resulting in a longer duration of surgery, as can be seen in Table 2. Moreover, due to the severity of their injury, patients undergoing primary arthrodesis might have a higher chance of developing a SSI. However, we were looking for predictors of SSIs after a sinus tarsi approach, which does include both primary arthrodesis and ORIF of the calcaneus. Additionally, in multivariate analysis, primary arthrodesis was not a significantly contributing factor for the risk of a SSI. Therefore, the effect of including both procedures is regarded to be of minimal impact on the validity of the study.

Secondly, this study may be subjected to a selection bias since it was carried out with data of a single center, specialized in complex traumatic foot/ankle injuries. This may have led to a higher overall complication percentage than one would expect. Moreover, due to the single center study design, the number of included patients might not be sufficient to achieve statistical significance. Specifically, to identify predictors, a larger sample size would be beneficial, making it possible to identify factors with a smaller impact. However, since

calcaneal fractures are not very common, and usually surgically treated in specialized centers, achieving large samples sizes is difficult without thereby compromising the homogeneity of the study population.

Finally, although this study was set up as a prospective cohort, not all variables could be collected as protocolled. For example, the measurement of the amount of blood loss as described before is not 100% reliable. Confounding of this measurement due to e.g. irrigation fluids being used during surgery cannot be ruled out. However, this is probably an accurate reflection of daily practice, since also in reality blood loss is often based on the surgeon's estimation.

CONCLUSION

This study confirms the low risk of SSI in DIACFs treated via STA with either ORIF or primary arthrodesis. Moreover, we identified surgery within one week after injury, ASA classification of 2 or higher and blood loss of more than 150cc as significant predictors for SSIs in this cohort. Although not statistically significant, this study also indicated a higher risk of SSIs in patients who smoke. This data may be helpful in the identification of patients with a higher risk of SSI after a DIACF operating with STA. These ‘high-risk’ patients may benefit from risk-limiting interventions, such as negative pressure wound therapy on the incision, which has shown promising results[21]. Furthermore, the results of this study can be combined with future studies on risk factors of SSI after DIACFs, aiming to get a clearer picture of which patients should be defined as ‘high risk’.

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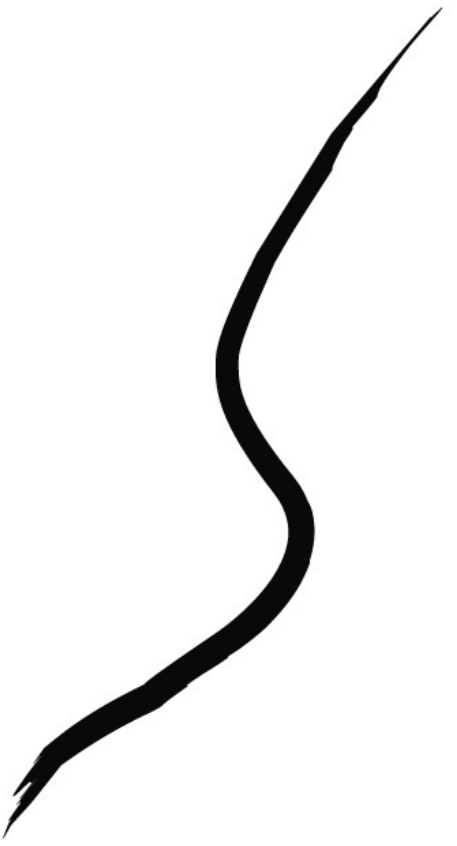
CHAPTER



3

SEASONAL EFFECT ON THE INCIDENCE OF POST-OPERATIVE WOUND COMPLICATIONS AFTER TRAUMA-RELATED SURGERY OF THE FOOT, ANKLE AND LOWER LEG

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ABSTRACT

INTRODUCTION

Post-operative wound complications remain among the most common complications of orthopedic (trauma) surgery. Recently, studies have suggested environmental factors such as season to be of influence on wound complications. Patients operated in summer are reported to have more wound complications, compared to other seasons. The aim of this study was to identify if "seasonality" was a significant predictor for wound complications in this cohort of trauma-related foot/ankle procedures.

MATERIALS AND METHODS

This retrospective cohort study included all patients undergoing trauma-related surgery (e.g. fracture fixation, arthrodesis, implant removal) of the foot, ankle or lower leg. Procedures were performed at a Level 1 Trauma Center between September 2015 until March 2019. Potential risk factors/confounders were identified using univariate analysis. Procedures were divided into two groups: (1) performed in summer (June, July or August), (2) other seasons (September–May). The number of surgical wound complications (FRIs, SSIs or wound dehiscence) was compared between the two groups, corrected for confounders, using multivariate regression.

RESULTS

A total of 599 procedures were included, mostly performed in the hindfoot (47.6%). Patients were on average 46 years old, and mostly male (60.8%). The total number of wound complications was 43 (7.2%). Age, alcohol abuse, open fracture and no tourniquet use were independent predicting factors. No difference in wound complications was found between summer and other seasons, neither in univariate analysis [4 (3.2%) vs 39 (8.2%), $p = 0.086$] nor when corrected for predicting factors as confounders ($p = 0.096$).

CONCLUSIONS

No seasonality could be identified in the rate of wound complications after trauma surgery of the lower leg, ankle and foot in this cohort. This lack of effect might result from the temperate climate of this cohort. Larger temperature and precipitation differences may influence wound complications to a larger extent. However, previous studies suggesting seasonality in wound complications might also be based on coincidence.

INTRODUCTION

The incidence of surgical site infections (SSIs) following orthopedic trauma surgery of foot and ankle has been reported as ranging from 0 to 9.4% [1]. In complex foot injuries, this percentage can even increase up to 25% [2]. This incidence is much higher compared to most other surgical procedures and is most likely related to the thin soft-tissue envelope and damage to vascularization during the injury [3]. Moreover, the fact that a fracture is involved, could have implications for the odds of developing surgical wound complications or, in recently defined terminology: "fracture related infection (FRI) [4]. Surgical wound complications, including FRIs and other SSIs can cause longer hospital stay or readmission, increased use of antibiotics and revision surgery, resulting in higher healthcare costs [5]. With the increasing rate of antibiotic resistance, preventing these complications is becoming even more important.

Various risk factors for developing surgical wound complications have been described. Risk factors can be divided in patient-related factors, injury-related factors, procedure-related factors and other risk factors [6]. The last group contains environmental factors such as geographical region, socioeconomic status of the country and season [7, 8]. A seasonal effect on the incidence of infectious complications after different types of surgery has been increasingly described in recent literature [8–18]. Numerous publications have documented a significantly higher incidence of wound complications during the summer months [10, 16, 19–21]. The suggestion is that in summer, the warmer temperatures and higher humidity of the air, provide optimal conditions for proliferation of bacteria outside of the operation room. Moreover, when the surface of the skin is moist and warm, bacterial growth is stimulated [22]. Considering the development of global warming, we also might have to anticipate on a growing number of wound complications. If this seasonal effect is indeed present for all types of surgery, it could be used to lower the overall rate of wound complications by for example planning of elective procedures.

The purpose of this study was to identify if there is a seasonal difference in the number of surgical wound complications after orthopedic trauma-related foot/ankle surgery. The hypothesis was that there are significantly more wound infections during the summer months.

MATERIALS AND METHODS

In this retrospective cohort study, all patients undergoing trauma-related surgery of the foot, ankle or lower leg, were included. Data were anonymously collected from electronic patient records operated between September 2015 and March 2019 at a single level-1 trauma center in the Netherlands. The surgical procedures performed included open fracture

reduction and fixation (ORIF), primary and secondary arthrodesis, repairing of acute tendon ruptures, and implant removal. Both acute and elective surgeries were included, as long as the initial diagnosis was trauma-related. Follow-up after surgery had to be at least 90 days for a patient to be eligible.

Permission for the use of data was acquired from all eligible patients. The study protocol was checked by the hospital's privacy advisor and the study was registered at the Central Register for Data Processing. Exclusion criteria were: age below 18 years old, preexistent wound complication before surgery, and one of the following surgical procedures: external fixation, percutaneous wire fixation only, decompression of acute compartment syndrome, and treatment of Charcot arthropathy. In addition, non-trauma related procedures like amputations (toe, foot or lower leg), exostosis operations and arthroscopy were also excluded.

Methods

Baseline patient, injury and surgical characteristics were collected based on procedure. If one patient had multiple surgical procedures in the study period, these were counted separately. Bilateral surgery was also counted as two separate procedures since there would be two incisions with the potential to infect. The following patient's baseline characteristics were collected: gender, age, height, weight, American Society of anesthesiologists (ASA) classification, immune disorders or use of immunosuppressive medication, severe comorbidities (including Diabetes Mellitus, severe kidney failure defined as eGFR < 20), and intoxications (smoking, alcohol and drugs abuse).

The injury characteristics collected for fractures were: open/closed fracture, Gustilo classification and type of fracture, and for all injuries the inflicted body part:

- *Forefoot* Metatarsal fracture.
- *Midfoot* Navicular fracture, Cuboid fracture, Lisfranc and Chopart dislocation/fracture.
- *Hindfoot* calcaneus fracture, talus fracture.
- *Lower leg* Tibia plateau fracture, tibia fracture, Cruris fracture, fibula fracture, tendon injury.
- *Ankle* Pilon fracture, Maisonneuve fracture, Weber A/B/C fracture, tendon injury.

Surgical characteristics were: previous procedure in same area, type of procedure (ORIF, arthrodesis, implant removal, other), the amount of days between trauma and procedure (for acute procedures only), duration of surgery in minutes, tourniquet use, the use/dose of prophylactic antibiotics, type of fixation (plates, nails and/or screws), use of bone void fillers, and amount of blood loss in ml. Post-surgical characteristics included the use of antibiotics, type of wound dressing (plaster cast, pressure bandage, vacuum system) and time to mobilization.

All procedures were categorized in the month of surgery and then coded as summer (June–July–August) or other seasons (September–May). Weather conditions for that time of year

were obtained from the Dutch Weather Institute or "Koninklijk Nederlands Meteorologisch Instituut" (KNMI). Conditions entailed average temperatures, precipitation and hours of sun.

Outcome

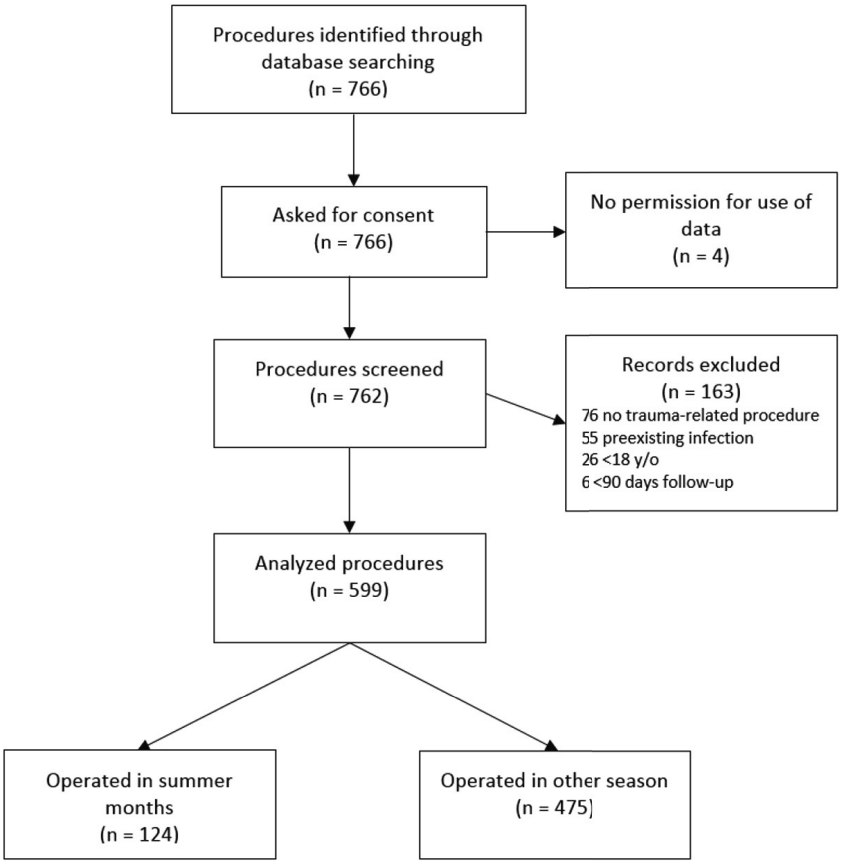
The primary outcome was the incidence of wound complications, defined as a SSI according to US Centers for Disease Control and Prevention (CDC) criteria [23] or another surgical wound healing complication (wound dehiscence), developed within 90 days after the surgical procedure. The term FRI was not used as a primary endpoint since this study also includes data from secondary/elective procedures (sometimes years after the initial fracture occurred) and the definition of FRI does not clearly describe a time frame for the diagnosis. Wound complications were diagnosed during follow-up visits, protocolled at 2 weeks, 6 weeks and 3 months after discharge from the hospital and retrospectively retrieved from the medical records. All patients were instructed upon discharge to contact the hospital sooner in case of suspicion of wound complications. In case of a complication, treatment was recorded as well, categorized as expectative treatment (wait and see), vacuum system, wound reopened (at outpatient clinic or ward), oral antibiotics, i.v. antibiotics or revision surgery.

Statistical analysis

Data were collected and analyzed using SPSS, Version 25.0 [24]. All clinically relevant patient, injury and (post-)surgical variables were univariably analyzed for differences between patients with and without wound complications to identify possible confounders. Chi-square analysis was used to identify differences for categorical variables. For continuous data that were normally distributed a student's T-test was used, and when not normally distributed, a Mann Whitney U test. All (nearly) significantly differing variables ($p < 0.2$) were included in multivariate analysis to identify individual predictors for wound complications with manual backwards selection. To limit bias caused by missing data, multiple imputations was used for variables with (under 50%) missing data. Imputation was performed using predictive mean matching with 10 sets. Imputed variables were: height, weight, smoking, alcohol abuse, drugs abuse, ASA classification, previous surgery, prophylactic antibiotics, duration of surgery, tourniquet use, primary closure, wound dressing and days between injury and surgery (for acute procedures). The amount of blood loss was not imputed because of too many missing values. After imputation, the remaining individual predictors were added to multivariable logistic regression analyzing the effect of season of the number of wound complications. The pooled results of the ten imputed sets were used to estimate odds ratios and confidence intervals.

Statistical significance was defined as $p < 0.05$. Due to practical considerations regarding the implementation of the electronic medical record system in 2015, all data was collected from that point onwards and no sample size calculation was performed before the start of the study.

Figure 1. Flow diagram of patient selection



RESULTS

A total of 766 surgical procedures were reviewed for this study. Based on the exclusion criteria and the possibility for the patient to object, a final 599 procedures in 498 patients were included for analysis (Fig. 1). In this cohort, the majority was male (60.8%), the mean age was 46 (IQR 31–57) and most procedures were located in the hindfoot (45.1%) followed by the ankle (22.7%). Some 43 patients (7.2%) developed a surgical wound complication, of which 22 were deep infections, 10 superficial infections and 11 wound dehiscence. Excluded cases did not differ in gender or age but had Diabetes Mellitus more often and were less likely to be smoking tobacco or using drugs (Table 5 of "Appendix").

Of all patients (n = 124) operated during the summer months, 4 (3.2%) developed a wound complication. In the other months (n = 475) the number of wound complications was 49 (8.2%). Table 1 shows wound complications for each season individually.

Table 1. Number of wound complications per season

	Winter (n = 186)	Spring (n = 123)	Summer (n = 124)	Fall (n = 166)
Complications:	17 (9.2%)	9 (7.3%)	4 (3.2%)	13 (7.8%)
Deep SSI	8 (4.3%)	7 (5.7%)	4 (3.2%)	3 (1.8%)
Superficial SSI	5 (2.7%)	1 (0.8%)	0	4 (2.4%)
Dehiscence	4 (2.2%)	1 (0.8%)	0	6 (3.6%)

Abbreviations: SSI: surgical site infection

Tables 2 and 3 contain patient, injury and surgical characteristics of all included patients. When comparing these characteristics between cases resulting in a wound complication and cases who did not, age, ASA classification, alcohol abuse, the number of open fractures, and tourniquet use differed significantly. In addition, gender, duration of surgery and amount of blood loss were not significantly differing but had a p value below 0.2, therefore, also qualifying for inclusion in multivariate analysis. Because the amount of blood loss was missing in over 50% of procedures (317), this variable was not imputed or included in multivariate analysis. After backwards selection, the variables age, alcohol abuse, open fracture and tourniquet remained as independent predictors of wound complications. As shown in Table 4, correcting for these variables as confounders, there was no statistically significant relation between season of surgery and wound complications (p = 0.096).

Figures 2 and 3 show the average temperatures, amount of sun and precipitation of each season during the study period compared to the amount of wound complications in that time frame.

DISCUSSION

Key results

The aim of this study was to identify whether the season of surgery has an influence on the incidence of wound complications following trauma surgery of the lower leg, ankle and foot. This seasonality could not be confirmed in this study, contradictory to our hypothesis. No significant difference was found in the number of surgical wound complications between seasons. Moreover, in this cohort a (non-significant) peak of wound complications was seen in winter instead of summer.

Previous literature

To the best of our knowledge, there is only one other study which investigated seasonal effects in foot/ankle surgery. They retrospectively analyzed a large cohort of 17,939 patients undergoing orthopedic foot/ankle surgery and could not identify a statistically significant difference in wound complications between seasons, without any large confounding factors being present [15].

Previous literature on seasonality in orthopedic/trauma surgery has led to varying conclusions. Anthony et al. performed a large national retrospective cohort study on seasonal influence on 30 day infection rates after total knee (TKA) and total hip replacement (THA) surgery in the United States of America (USA). With over 750,000 included procedures, they concluded that the incidence of wound complications was highest in summer with an increase of SSIs of 24% in June compared to December, corrected for comorbidities and socioeconomic status [10]. Multiple authors have supported these findings in orthopedic and trauma surgery [9, 12, 14, 25]. However, there are also authors who did not find a difference in wound complication rates in orthopedic surgery [8, 20, 26]. This raises the question of whether or not the found effects of season are clinically relevant, even when they are statistically significant. Most of the mentioned studies reported on large populations, making it perhaps too easy to achieve statistical significance.

Table 2. Patient characteristics

	No wound complication (n = 556)	**Wound complication (n = 43)**	**Significance**
Gender, No(%) male	343 (61.7%)	21 (48.8%)	0.133
Age, Median [IQR]	45 [31 – 57]	54 [39 – 61]	0.008*
BMI, Median [IQR][a]	24.8 [22.7 – 28.1]	25.5 [23.3 – 29.2]	0.433
Diabetes, No(%)	16 (2.9%)	1 (2.3%)	1.000
Immunocompromised, No(%)	11 (2.0%)	2 (4.7%)	0.538
ASA-classification[b]			0.008*
I – II	522 (94.9%)	36 (83.7%)	
III – IV	28 (5.1%)	7 (16.3%)	
Smoking, No(%) of smokers[c]	170 (38.0%)	16 (50.0%)	0.248
Alcohol abuse (>2units/day), No(%)[d]	36 (9.0%)	7 (22.6%)	0.034*
Drug use, No(%)[e]	40 (10.1%)	3 (9.7%)	0.1000

Abbreviations: IQR: inter quartile range, n: number of included procedures, No: number, %: percentage of, >: more than

a Missing 124 (114 in no wound complication, 10 in wound complication)
b Missing 6 (in no wound complication)
c Missing 120 (109 in no wound complication, 11 in wound complication)
d Missing 168 (156 in no wound complication, 12 in wound complication)
e Missing 170 (158 in no wound complication, 12 in wound complication)

Table 3. Injury and surgical characteristics

	No wound complication (n = 556)	Wound complication (n = 43)	Significance
Open fracture, No(%)	49 (8.8%)	9 (20.9%)	0.020*
Part of leg[a]			
Forefoot	23 (4.1%)	1 (2.3%)	0.691
Midfoot	77 (13.8%)	4 (9.3%)	
Hindfoot	250 (45.0%)	20 (46.5%)	
Ankle	127 (22.8%)	9 (20.9%)	
Lower leg	79 (14.2%)	9 (20.9%)	
Previous surgery, No(%)[b]	124 (23.1%)	9 (22.0%)	1.000
Acute operation			
Acute	347 (62.4%)	28 (65.1%)	0.849
Elective	209 (37.6%)	15 (34.9%)	
Type of surgery			
Osteosynthesis	343 (61.7%)	25 (58.1%)	0.694
Arthrodesis	91 (16.4%)	7 (16.3%)	
Implant removal	94 (16.9%)	7 (16.3%)	
Other procedures	28 (5.0%)	4 (9.3%)	
Days between injury and operation, Median [IQR][c]	7 [3 – 14]	7 [1 – 16]	0.732
Duration of surgery, Median [IQR][d]	75 [55 – 110]	89 [60 – 138]	0.101
Tourniquet use, No(%)[e]	228 (41.1%)	7 (16.3%)	0.002*
Prophylactic antibiotics[f]			
Yes	456 (82.9%)	34 (79.1%)	0.203
No	92 (16.7%)	8 (18.6%)	
Therapeutic	2 (0.4%)	1 (2.3%)	
Blood loss in mL, Median [IQR][g]	100 [50 – 200]	200 [75 – 375]	0.036*
Primary closure[e]	550 (99.1%)	43 (100%)	1.000
Post-surgical dressing[h]			0.525
Pressure bandage	344 (63.8%)	26 (61.9%)	
Cast	146 (27.1%)	10 (23.8%)	
Negative pressure system	49 (9.1%)	6 (14.3%)	

Abbreviations: IQR: inter quartile range, n: number of included procedures, No: number, %: percentage of
a Missing: 1 (in no wound complication, crush injury)
b Missing 21 (19 in no wound complication, 2 in wound complication)
c Only for acute injuries, missing: 9 (5 in no wound complications, 4 in wound complication), N = 366
d Missing 57 (56 in no wound complication, 1 in wound complication)
e Missing 1 (in no wound complication)
f Missing 6 (in no wound complication)
g Missing 317 (291 in no wound complication, 26 in wound complication)
h Missing 18 (17 in no wound complication, 1 in wound complication)

Table 4. Multivariable regression

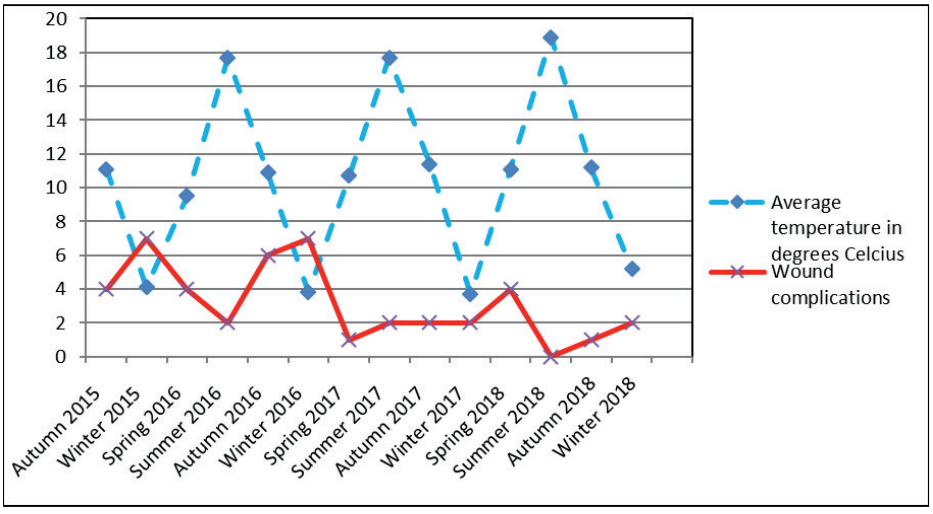
	Odds ratio	95% CI	p-value
Age	1.029	1.007 – 1.051	0.010
Alcohol abuse	2.680	1.065 – 6.747	0.037
Open fracture	2.559	1.109 – 5.904	0.028
Tourniquet	0.297	0.128 – 0.690	0.005
Summer season	2.485	0.851 – 7.258	0.096

Abbreviations: CI: confidence interval, %: percentage of

Rational behind seasonality

Possible seasonality in wound complications has been ascribed to skin colonization associated with warm weather [21, 25]. The incidence of gram positive but especially gram negative bacteria such as Escherichia coli or Klebsiella seems to correlate well with the temperature, with a higher incidence in warmer months [27–31]. Sagi et al. compared the rate of wound complications in open fractures in seven different climate regions within the USA. With results of all seven regions combined they could not identify a difference in wound complications between seasons. For two out of seven regions a significant seasonal difference was found, with fall having the highest number of wound complications. Interestingly, the overall incidence of wound complications did vary significantly between climate regions (corrected for patient and injury characteristics) [19]. This leads to the hypothesis that a seasonal effect can only be found in certain climate regions. This theory is supported by Haws et al. who did not identify an overall difference in wound complications but did find an effect when comparing the wet season with other seasons in tropical areas [26]. The temperate climate of the Netherlands might be an explanation for the fact that this study could not detect a seasonal difference in wound complications. Seasonality might only exist in climate zones with more extreme weather conditions.

Figure 2. Average temperatures in degrees Celcius and amount of wound complications during the study period (KNMI)



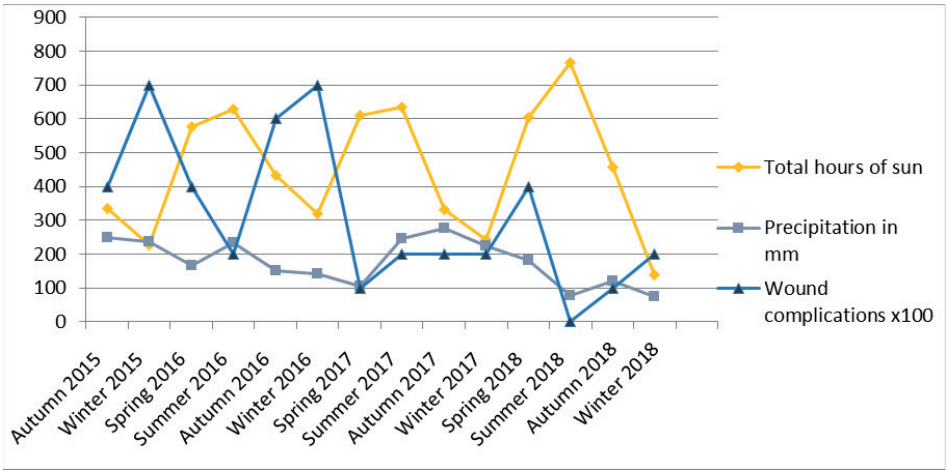
KNMI: Koninklijk Nederlands Meteorologisch Instituut

Another possible explanation is the “July-effect”, a description for the start of the academic year when new (inexperienced) surgeons in training start. Previous studies have concluded that there is a significant difference in the amount of complications, morbidity, outcomes and mortality at the beginning of the academic year [32]. However, the same “July-effect” was also found in non-teaching hospitals, making training status less likely as a cause for the higher number of wound complications in summer [21]. In the presently studied hospital,

surgeons in training start at varying time points during the year, making a “July-effect” unlikely to occur.

However, the reason for a difference in the incidence of wound complications between seasons is most likely multifactorial. Besides changes in temperature and bacterial flora of the skin, diet change, clothing, sunlight exposure (influence vitamin D or skin flora), exercise, amount of time spent inside with other people, duration and quality of sleep, exposure to diseases could also influence wound complications. Also the number of admissions of trauma surgery may vary due to weather influence such as temperature or precipitation [33].

Figure 3. Amount of sun, precipitation and wound complications during the study period (KNMI)



KNMI: Koninklijk Nederlands Meteorologisch Instituut

Limitations

Some limitations can be mentioned in this study. The first limitation is the retrospective study design, which limits the number of variables that can be reliably extracted from electronic patient records. This may have led to underreporting of confounding factors (such as “amount of blood loss”) but also of the primary outcome measure “wound complications”. Especially superficial SSIs or other minor wound healing problems may have been treated by a general practitioner and, therefore, not mentioned in patient’s hospital records. However, major wound complications needing re-admission or additional surgery were well documented. Another limitation is the heterogeneity of the study population. Although included patients have been limited to patients undergoing trauma-related surgery of foot, ankle or lower leg, there is still variation in the risk of wound complications between these locations of injury. Moreover, this study includes both elective and acute procedures and open as well as closed fractures. By reporting all potential risk factors and confounders of wound complications and incorporating them in the multivariate analysis we have tried to make it more transparent and limit the effect on the main research question.

This study may be subjected to a selection bias since it was carried out with data of a single center, specialized in complex foot/ankle traumas. This may have led to a higher overall complication percentage than one would expect. A single center study in a small country does have the advantage of similar weather conditions for each patient. Finally, due to the single center study design, the number of included patients might not be sufficient to achieve statistical significance. However, the odds that our findings with more wound complications in winter than in summer are purely coincidental and that with sufficient power we would have found an opposite effect (more wound complications in summer) are slim.

CONCLUSION

Despite limitations, this study was able to confirm previous evidence and demonstrated that there is no seasonal influence on the number of wound infections in trauma-related foot/ ankle surgery. Moreover, this effect of the season remained absent after correcting for multiple patient and surgery-related factors. As seasonality is multifactorial, it would be more beneficial to identify specific climate/season related factors that are of influence. Future research should focus more on these specific “sub-factors” which may be influenced (e.g. diet, sunlight/ high-temperature exposure, exercise) to hopefully reduce the number of surgical wound complications. Besides season, weather conditions in the days after surgery, should, therefore, also be reported in studies on this topic.

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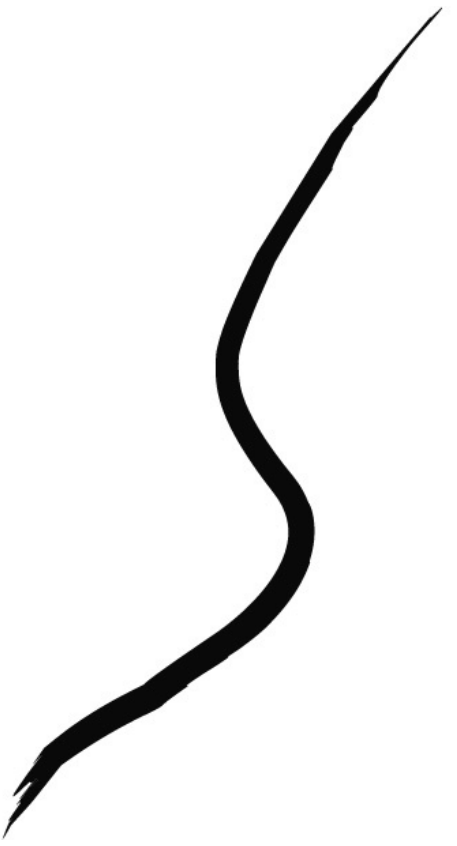
PART 2

PROPHYLACTIC ANTIBIOTICS TO PREVENT SURGICAL SITE INFECTIONS

CHAPTER



4

TARGET SITE ANTIBIOTIC CONCENTRATIONS IN ORTHOPEDIC/TRAUMA EXTREMITY SURGERY; IS PROPHYLACTIC CEFAZOLIN ADEQUATELY DOSED? A SYSTEMATIC REVIEW AND META-ANALYSIS

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Acta Orthopaedica, Apr 2019

ABSTRACT

BACKGROUND

The incidence of surgical site infections (SSIs) in trauma/orthopedic surgery varies between different body parts. Antibiotic prophylaxis (e.g., with cefazolin) lowers infection rates in closed fracture surgery and in primary arthroplasty. For prophylactic antibiotics to prevent infections, sufficient concentrations at the target site (location of surgery) are required. However, dosage recommendations and the corresponding efficacy are unclear. This review assesses target site cefazolin concentrations and the effect of variation in dose and location of target site during orthopedic extremity surgery.

METHODS

For this meta-analysis and systematic review, the literature was searched using the following keywords: “cephalosporins,” “orthopedic,” “extremity,” “surgical procedures,” and “pharmacokinetics”. Trials measuring target site antibiotic concentrations (bone, soft tissue, synovia) during orthopedic surgery after a single dose of cefazolin were included.

RESULTS

The search identified 14 studies reporting on concentrations in the shoulder (n = 1), hip (n = 8), knee (n = 8), or foot (n = 1). A large variation was seen between studies, but the pooled results of 4 studies showed higher concentrations in hip than in knee (mean difference: 4 ug/g, 95% CI 0.8–7). Articles comparing different doses of cefazolin reported higher bone concentrations after 2 g than before, but pooling results did not lead to a statistically significant difference.

CONCLUSION

Although not all results could be pooled, this study shows that cefazolin concentrations are higher in the hip than in the knee. These findings suggest that the dose of prophylactic cefazolin might not be sufficient in distal parts of the extremity. Further research should investigate whether a higher dose of cefazolin can lead to higher concentrations and fewer SSIs.

INTRODUCTION

A surgical site infection (SSI) is one of the most common complications of surgical interventions of the extremity, especially when implants are involved. The infection rate ranges from 1.3%-10% in hip and knee procedures[1,2] to 12.2%-24.6%[3–5] in foot and ankle surgery. Antibiotic prophylaxis is widely used in surgical and orthopedic interventions and has been shown to lower infection rates in closed fracture surgery[6,7], as well as in primary arthroplasty[8,9]. Because of their broad-spectrum effect on methicillin sensitive staphylococci and streptococci and relatively low costs, first generation cephalosporins (e.g. cefazolin, cephradine or cephalexin) are the recommended prophylactics in orthopedic/trauma surgery[10,11]. However, there is limited evidence to support dosage recommendations in this field. The studies that form the foundation for the dosage, as mentioned in several international guidelines on surgical prophylaxis, do not include patients undergoing fracture/implant surgery[12–14].

For a prophylactic antibiotic to exert its antimicrobial effect it is necessary to achieve concentrations that exceed the minimum inhibitory concentration (MIC) of the targeted pathogen for at least the time between incision and closure of the wound[15]. The MIC is the serum concentration that an antibiotic should exceed to inhibit a certain pathogen (e.g. MIC of cefazolin for s. Aureus is 0.5-2 ug/l, meaning that a cefazolin concentration in serum of 0.5-2 ug/l is necessary for adequate inhibition of s. Aureus). Because drugs are not evenly distributed through the body, it is important to know that an antibiotic achieves sufficient concentrations not only in serum but also at the target site (location of surgery)[16]. Data on target site concentrations of cefazolin during orthopedic surgery of the extremities could provide us with necessary information to assess and improve the efficacy of prophylactic cefazolin.

The aim of this systematic review was to answer the following questions:
1. What are the target site concentrations of cefazolin in the extremities during orthopedic surgery?
2. What is the influence of location of the target site and dose of cefazolin on the target site concentration?

METHODS

Search Strategy and Criteria

This meta-analysis and systematic review was performed according to the PRISMA statement[17] and registered in PROSPERO (nr CRD42018093697). A search was performed in MedLine (PubMed), EMBASE (Ovid) and the Cochrane Library. A clinical librarian was consulted on the search strategy. The full search is presented in the Appendix, but it included the following keywords: ‘cephalosporins’, ‘orthopedic’, ‘extremity’, ‘surgical procedures’ and

'pharmacokinetics'. The last search was run on 15-1-2018. In addition to the databases, bibliographies were checked for additional articles.

Eligible for inclusion were randomized controlled trials or prospective cohort studies investigating 'target site' antibiotic concentrations in human, adult subjects who received prophylactic cefazolin in a single, intravenously administered dose before orthopedic/trauma surgery of the extremity. 'Target site' concentrations were defined as concentrations measured in soft-tissue, bone, synovia of wound/drain fluid at or near the site of surgery. To be able to compare dosages, we chose to limit the type of administered prophylaxis to cefazolin only, the most widely studied first generation cephalosporin. No publication date or language restrictions were imposed.

Study selection

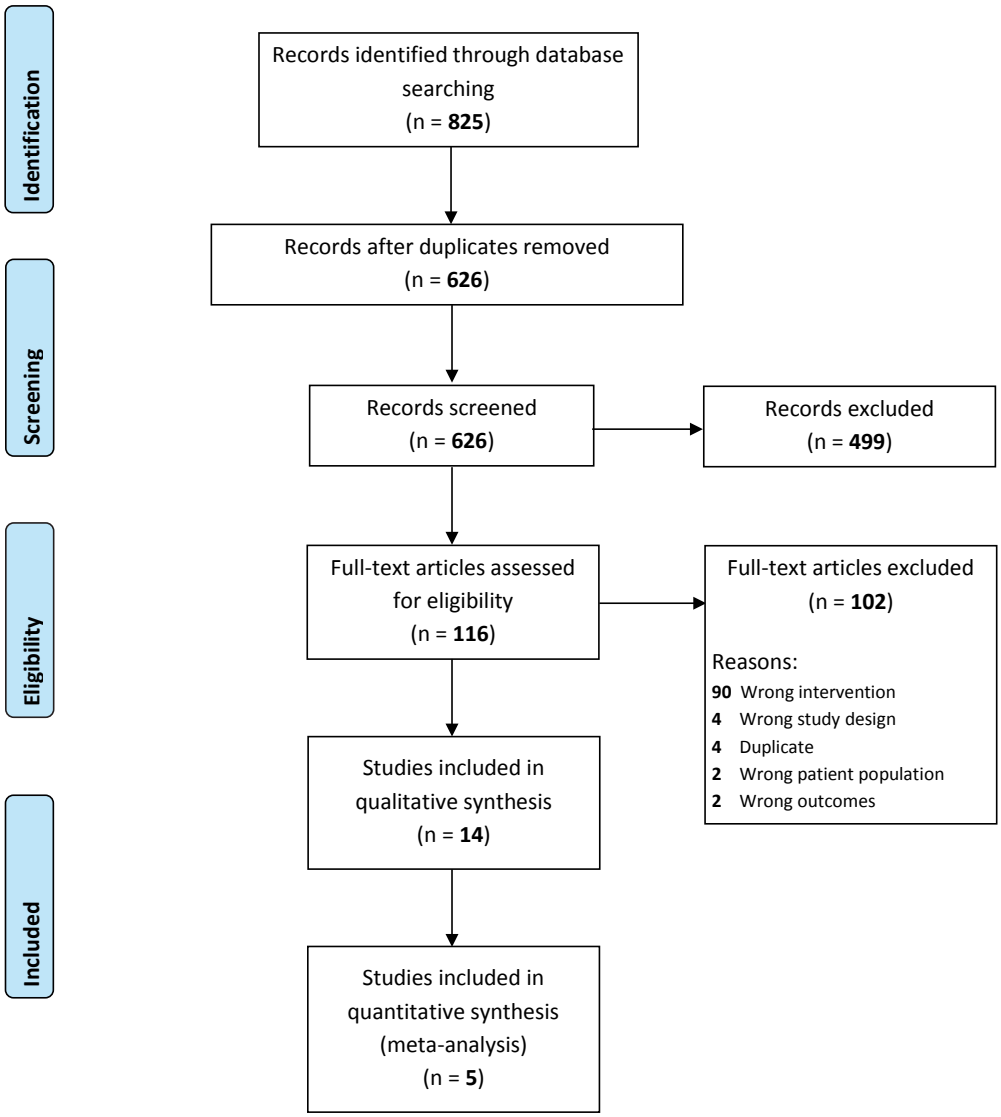
All identified studies were screened for relevance based on title and abstract by 2 reviewers (TS and FS). The remaining studies were independently screened for eligibility based on full-text reading by the same reviewers and were included if none of the exclusion criteria were met. Studies were excluded based on; intervention (cephalosporin that was not cefazolin), study design (reviews or articles only available as abstract), population (when included patients received therapeutic antibiotics up until a week before surgery or had peripheral vascular disease) and outcome (solely serum concentrations measured). Conflicts were discussed until consensus was reached.

The literature search identified 825 articles, of which 626 were assessed for eligibility and a final number of 14 studies were included in the systematic review after full text screening. Five studies were also included in the meta-analysis (4 in the comparison of different target sites, 1 in the comparison of different cefazolin dosages, 1 in both). The number of records identified, included, and excluded (with reasons) are depicted in a PRISMA Flow Diagram (Figure 1).

Data collection

Data was extracted using a customized extraction sheet (based on the Cochrane data extraction template), which was pilot-tested on 5 articles randomly selected from the included articles and adjusted accordingly. One reviewer (FS) extracted the data and the other reviewer (TS) verified it. Duplicate publications were filtered out by juxtaposing author names and carefully reviewing study designs and treatment combinations. In case of multiple publications on one trial, the published information was combined to ensure comprehensiveness of data. Collected information included 1) study characteristics (study design, number of patients included, in/exclusion criteria and year published), 2) patient characteristics (sex, age, weight, type of procedure, given demographic or disease specifics), 3) type of intervention(s) (dose, timing of administration, comparative), 4) outcome (site of measurement, timing of measurement, unit presented as, type of analysis, results).

Figure 1. PRISMA flow diagram of inclusion



Study Quality

Studies were screened for quality and risk of bias using the Newcastle-Ottawa Scale (NOS), designed to assess the quality of nonrandomized cohort studies[18]. Using this scale studies were judged on nine items within three domains (selection, comparability and outcome) as either good, poor or unclear, a "good" score counting as one point, with a maximum of nine points. The rating sheet was adjusted to this review using topic-specific rating criteria (shown in Annex). Quality screening was performed by one reviewer (FS) and subsequently checked by another reviewer (TS).

Due to heterogeneity of location of measurements, cefazolin dosages and measurement methods, assessment of publication bias using for example a funnel-plot, was not possible.

Statistical analysis

All statistical analyses were performed using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Mean target site antibiotic concentrations were compared between different locations of the target site and between different dosages of cefazolin. To compare these groups, while taking the heterogeneity between studies into account, only studies describing two different doses/measuring sites were included in the meta-analysis. Only concentrations measured in bone were included for meta-analysis, since soft tissue samples were not comparable (different locations). Antibiotic concentrations were expressed as weighted mean difference with the corresponding 95% confidence interval (95% CI) and p-value. Statistical analyses were performed using a random-effects model, considering the heterogeneity of included trials(19). The I2 was used as a measure for consistency of data. To incorporate the heterogeneity in the estimation of difference in concentrations between hip and knee, a 95% prediction interval was also computed. Where a 95% CI only represents the average of study effects, a 95% prediction interval presents the range of expected results for 95% of similar studies that might be conducted in the future[20]. However, as Partlett and Riley (2017) recently concluded, prediction intervals perform best when heterogeneity is high but when there is also a minimum of 5 included studies(21). With a smaller amount of studies, the prediction interval tends to be too wide, and should not be interpreted as true effect. Statistical significance was defined as $p < 0.05$.

Table 1. Study characteristics

Author (year)	Study design	N	Intervention (n)	Comparison (n)	Age, mean (SD)*	Sex (% male)	Weight*	Type of surgery (n)	Tourni-quet use	Timing AB administration	MIC reported
Angthong (2015)	PC	18	Cefazolin 1g iv (12) Cefazolin 2g iv (6)	-	70.1(4.6) 68.4 (3.0)	25% 16.7%	61.2 (8.4) 62.0 (8.2)	TKA (18)	Yes	< TQ / incision	30 ug/ml
Bryan (1988)	Double blind RCT	97	Cefazolin 1g iv (48)	Cefamandole 2g iv (49)	58.9 (12.1)	45.8%		THA (37)/ TKA (11)	NR	30-60 min < anesthesia	NR
Cunha (1977)	PC	71	Cefazolin 1g iv (?)	Cephradine 1g iv (?) Cephalothin 1g iv (?)	NR	NR	NR	THA	No		NR
Cunha (1984)	PC	35	Cefazolin 1g iv (13)	Cephradine 1g iv (?)	[61-88]	NR	NR	TKA	Yes	10-225 min < bone removal	0.5 ug/ml
Deacon (1996)	PC	25	Cefazolin 1g iv (25)	-	<55	NR	NR	Bunionec-tomy	Yes	60 min < TQ	0.5-1.0 ug/ml
Friedman (1990)	RCT	24	Cefazolin 1g 1min<TQ (8) 2min< TQ (8) 5min< TQ (8)	-	 67 (8) 63 (10) 60 (8)	52.2%	 94 (18) 98 (22) 90 (25)	TKA	Yes	until 1, 2 or 5 min < TQ	1 ug/ml
Miller (2004)	PC	15	Cefazolin 1g iv (7)	Cefazolin 1g iv+regional (8)	49.3 [29-77] *51.4 (13.9)*	57.1%	NR	Shoulder surgery	No	20 min < incision	NR
Parsons (1978)	PC	7	Cefazolin 4g iv (7)	-	61.4 (1.3)	57.1%	64.8 (5.3)	THA	No	Immediately < anesthesia	0.25-4 ug/ml
Polk (1983)	PC semi-randomized	20	Cefazolin 10mg/kg (9)	Cefazolin 10mg/kg (11)	[27-82]	65.0%	[51-83]	THA	No	Shortly after anesthesia	NR

Sharareh (2016)	PC	34	Cefazolin 1g/2g (<70kg/>70kg) (31)**	-	66.8 [38-86] *64.4 (12)*	44.1%	82.5 [50.4-124.7] *85.0 (18.6)*	THA (12)/ TKA (22)	Yes (in TKA)	60 min < incision /< TQ	2 ug/ml
Sorensen (1978)	PC	20	Cefazolin 1g iv (1)***	Erythromycin (8) Methicillin (6)	75 [48-92]† *72.5 (11)*	40.0%†	NR	Fixation femur fracture	No	< surgery	0.5-3 ug/ml
Williams (1983)	PC	125	Cefazolin 1g iv (17) Cefazolin 2g iv (6)	Cephalothin 1/2g (38) Cefamandole 2g (13) Cefoxitin 1/2g (37) Ceforanide 1/2g (14)	65 [13-91] † *58.5 (13)*	NR	NR	THA (13) /TKA (10)	Yes (in TKA)	30 min < TQ	0.5-7 ug/ml
Yamada (2011)	PC	43	Cefazolin 2g iv (43)	-	74.8 (7.9)	16.3%	55.4 (8.2)	THA (16) /TKA (27)	Yes (in TKA)	< TQ / incision	1-100 ug/ml
Young (2013)	RCT	22	Cefazolin 1g iv (11)	Cefazolin 1g io (11)	65.3 [48-83] *65.4 (10.1)*	36.4%	BMI 29.1 [23.1-35]	TKA	Yes	10-30 min < TQ	0.5-100 ug/ml

Characteristics are reported for intervention groups (patients receiving cefazolin iv. only) unless reported otherwise

Abbreviations; AB: antibiotic, io: intra-osseously administered, iv: intravenously administered, min: minute, n: number of patients, PC: prospective cohort trial, RCT: randomized controlled trial, TQ: tourniquet

* when only median [range] are reported, values were transformed into estimated mean and standard deviation by using the calculations from Hozo et al.(38) , estimations are printed in italica.
** 3 patients did not receive cefazolin because of allergy, 4 got 1g, 27 got 2g
*** 6 patients received cefazolin, 3 excluded because of receiving >1 dose, 2 no detectable levels
† for all patients, not just intervention group

RESULTS

Included trials were mostly prospective cohorts[22–32], except for three randomized controlled trials[33–35]. Patient and study characteristics are specified in Table 1. Most studies included patients undergoing elective total hip replacement (n=3)[23,28,29], total knee replacement (n=4)[17,29,30] or both (n=5)[24,25,30,32,33] (of which Cunha et al.[25] compared their results in the knee with results in the hip from a previously reported trial[23] in their most recent article) and one each included patients with a femur fracture[31], shoulder surgery[27] or bunionectomy[26]. Table 2 (see Supplementary data) gives an overview of the different target sites and given dose of cefazolin described by each study.

All studies reported target site antibiotic concentrations in bone and some also measured concentrations in soft-tissue (n=4)[27,28,34,35] or synovial fluid (n=1)[25]. Target site concentrations were reported as a mean value in ten studies[22,24,26–30,32,33,35], as mean peak value in two studies[23,25], as separate values per patient in one study[31], and as percentage of patients with values above the MIC in two studies[30,34]. Due to the heterogeneity of included studies regarding cefazolin doses, sampling and analysis methods, the majority of data could not be pooled.

Quality assessment

Although a minimal score on the NOS suggesting good quality has not been established, the overall risk of bias in the included studies seemed high, with only five studies scoring five or more out of nine points on the NOS[18]. The studies used in meta-analysis scored relatively high with two studies scoring seven stars and one each scoring six, five and four points. The full quality assessment is shown in Figure 2 (see Supplementary data).

Target site concentrations

Bone concentrations

Overall, target site antibiotic concentrations in the bone ranged from 0.64 ug/g to 87.7 ug/g, but the variation of concentrations between different administered dosages of cefazolin and location of measurement was quite large. All of the ten studies reporting a MIC (Table 1), reported mean target site concentrations higher than the minimum concentration for S. Aureus (0.5-2 ug/ml). However, most studies also described MICs for other organisms, usually requiring higher concentrations of cefazolin. In five studies, mean cefazolin concentrations were higher than all of the MICs they reported for different pathogens/resistance patterns, ranging from 0.5 ug/ml for s. Aureus, to 3-4 ug/ml for E. Coli and Klebsiella species[25,26,28,30,31]. Two studies specifically reported the percentage of patients achieving bone concentrations higher than the MIC. Friedman et al. (1990) reported that 40.3% of patients achieved bone concentrations higher than a MIC of 4 ug/ml, at 30 minutes after administering 1g of cefazolin. Sharareh et al. (2016), using a MIC of 2ug/ml, found that

in the group receiving 1g of cefazolin, 75% reached the MIC compared to 92.6% in the group receiving 2g.

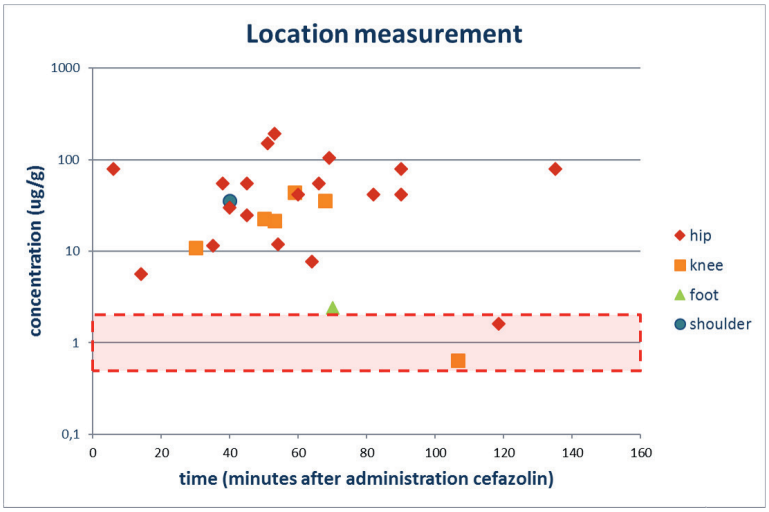
Soft tissue concentrations

Cunha et al. (1984) took samples of the synovia of the knee and found mean peak levels of 8mg/l, which cannot be compared to measurements in bone due to the unit (mg/l vs ug/g) and absence of standard deviations (Table 3, see Supplementary material). Miller et al. (2004) found a mean cefazolin concentration of 10.7 ug/g in the soft tissue of the shoulder (SD not reported), which was lower than the 35.8 ug/g they found in bone at the same time-point. Young et al. (2013) found values between 7.2 ug/g and 12.8 ug/g in fat around the knee joint on different time-points, comparable to the values measured simultaneously in bone. Friedman et al. (1990), on the contrary, reported a higher percentage of patients with concentrations above the MIC (4ug/g) in soft-tissue than in bone of the knee at each time-point. Parsons et al. (1978) also found higher levels in the hip capsule than in bone with mean concentrations of 35.2 ug/g (SD 7.2) and 14.4 (2.3) respectively.

Location of target site

Mean (peak) antibiotic concentrations for different measuring sites were ranging from 1.6 ug/g to 87.7 ug/g in the hip, from 0.64 ug/g to 39.8 ug/g in the knee, 2.39 ug/g in the foot and 35.8 ug/g in the shoulder, measured at varying time-points. The results of each individual study are visualized in Figure 3-6. Figure 3 shows that although concentrations in the knee were lower than in the hip, nearly all measured concentrations were higher than the MIC of S. Aureus. The concentrations that were lower or only just above the MIC were measured either more than 100 minutes after administration or in the foot. In five studies concentrations in the hip and knee were compared [24,25,30,32,33]. All reported higher concentrations measured in the hip than in the knee, statistically significant in two[30,32]. The other three studies either did not compare knee and hip directly, or did not perform statistical testing for this comparison.

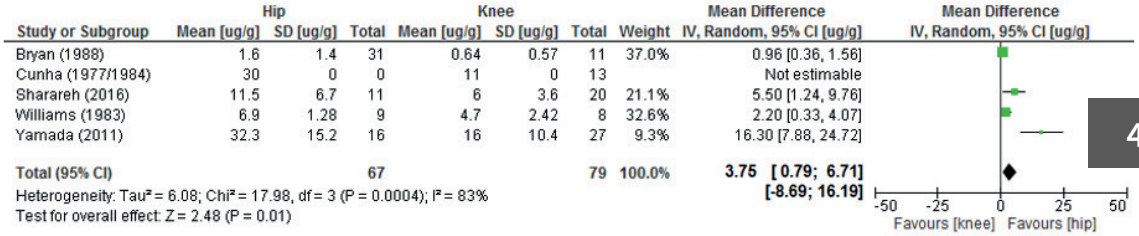
Figure 3. Bone concentration per location



Mean or maximum target site concentrations of all included studies. When reported separately for individuals or for multiple time points, the se are depicted separately. Bar represents MIC90 of Staphylococcus Aureus (0,5-2,0 ug/l)

Out of the five studies measuring antibiotic concentrations at different target sites, four[24,30,32,33] could be pooled. The results from Cunha et al. (1984) could not be included into the meta-analysis due to the fact that no standard deviations were provided. When pooled, target site cefazolin concentrations were significantly higher in the hip (acetabulum, femoral head or proximal femur) than in the knee (distal femur or proximal tibia) with a mean difference of 3.75 ug/g, 95% CI: [0.79 – 6.71] (Figure 4). Although the time-points at which concentrations were measured differed between studies, the time-points of measurements in hip and knee within each study were similar. Heterogeneity between the studies is high, with an I2 of 83%.

Figure 4. Pooled mean target site concentrations comparing location of measurement

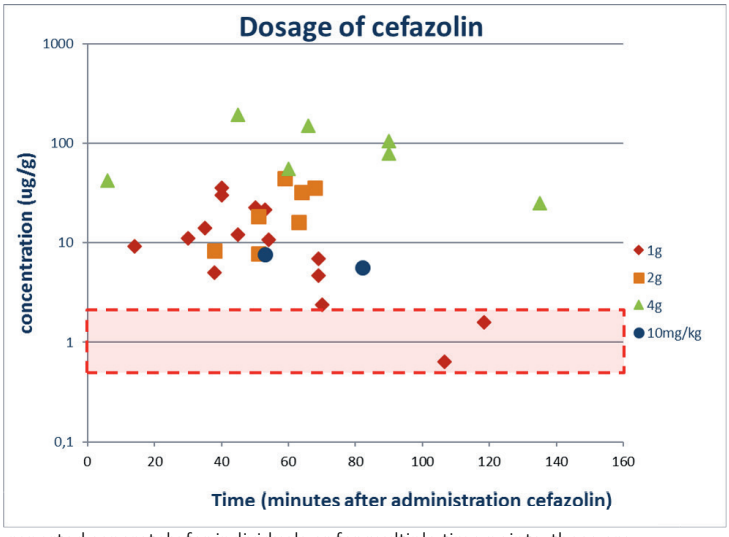


4

Dose of cefazolin

Bone concentrations were ranging from 0.64 ug/g to 35.8 ug/g when 1g of cefazolin was given, 8.3 ug/g to 39.8 ug/g in 2g, 10.2 ug/g to 87.7 ug/g in 4g and 7.7 ug/g in the study administering 10mg/kg (Figure 5). Three studies compared target site concentrations according to the given dose of cefazolin (either 1g or 2g)[22,30,32]. All of these studies report higher levels for the group receiving 2g of cefazolin, but only in one study statistical significance was achieved[22] (Figure 6). Figure 5 shows that the concentrations lower or just above the MIC were all measured after administration of 1g of cefazolin. Only two studies[22,30] could be used for meta-analysis, because of missing standard deviations in the study by Williams et al. (1983). As shown in Figure 6, pooling the results did not lead to a statistically significant

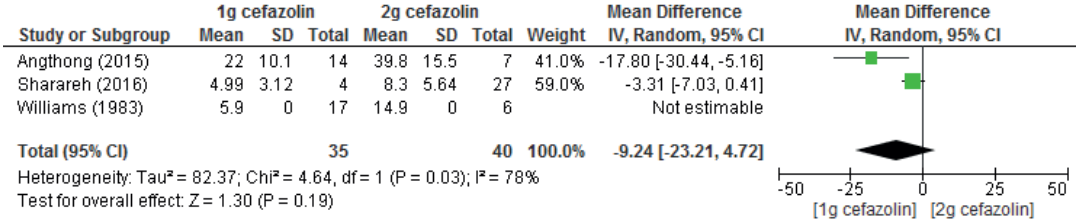
Figure 5. Bone concentration per dosage



reported separately for individuals or for multiple time points, these are depicted separately. Bar represents MIC90 of Staphylococcus Aureus (0,5-2,0 ug/l)

difference in target site concentration (mean difference -9.24, 95% CI [-23.2 – 3.7]). Time-points of the measurements were similar both between and within the different studies. Nonetheless, heterogeneity between the studies was high with an I2 of 78%.

Figure 6 Pooled results: mean target site bone concentrations compared by dose



Due to the small number of studies for this outcome, no predictive interval was computed

DISCUSSION

Because of the large clinical implications of SSIs in orthopedic trauma surgery, prophylactic antibiotics are widely instated. However, dosage recommendations and corresponding efficacy remain unclear, partly because of the unequal distribution of drugs throughout the body. Sufficient concentrations of antibiotics at the target site (location of surgery) are required for optimal infection prevention. Therefore this meta-analysis focused on the target site concentrations of the most commonly used prophylactic in orthopedic trauma surgery, cefazolin. It aimed to answer the following questions: 1) What are the target site concentrations of cefazolin in the extremities during orthopedic surgery? 2) What is the influence of location of the target site and dose of cefazolin on the target site concentration?

A few limitations can be pointed out for this review and the available literature. First of all, the quality of the individual studies included in this systematic review varied. Most studies presented data that was collected before the year 2000, which often resulted in incomplete reporting and possibly outdated analyzing methods. Also, given the fact that most studies included only elective orthopedic surgery, selection bias, by including only relatively healthy patients, may have occurred. Secondly, given the large heterogeneity in methods used for sampling, timing of the samples, processing and analyzing, less than half of the results could be pooled. Thirdly, target site concentrations of an antibiotic may also be influenced by other patient or surgical characteristics such as renal function, obesity, bleeding or tourniquet use. Although most of these characteristics do not seem to differ between location of surgery or dose within one study, tourniquet use could have an influence on the comparison between samples of hip and knee. Another limitation is the fact that all of the individual studies measured concentrations in samples of bone/soft-tissue, the so called ‘whole tissue concentration’. As described by Mouton et al. (2008), these concentrations are only an estimate of the ‘unbound’ or active part of the drug and cannot be credibly compared to the

MIC, which is the total (unbound plus plasma protein bound) concentration in serum. Moreover, homogenizing or grinding up whole tissue samples, leads to dilution of the drug by mixing intracellular and extracellular fluids, resulting in, depending on the type of drug, under or overestimation of its concentrations[36]. Nevertheless, simply using the serum concentration as a surrogate might not be sufficient for estimating effect, since the distribution of drugs throughout the body is not homogenous[16]. Finally, regarding the clinical implications of antibiotic prophylaxis, more than the concentration itself, the time that the concentration is higher than the MIC (T>MIC) is important. The T>MIC should at least overlap with the "decisive period". This is the period that starts at incision and ends after 3 hours, during which antibiotics can effectively suppress the development of a wound infection[15]. Instead of reporting this T>MIC, all included studies solely measured antibiotic concentrations at individual moments in time. When samples are taken at multiple time points, they can be used to predict levels of antibiotics in tissue over a course of time, using population kinetics, like Gergs et al. (2014). With population kinetics, model predicted time-concentration curves for each patient can be fabricated, which allows the evaluation of the T>MIC, and therefore a more precise estimate of clinical efficacy.

We found a large variation in target site cefazolin concentrations of the extremity between different studies. In general, the achieved concentrations in bone surpassed the minimal inhibitory concentration (MIC) for S. aureus, the most common pathogen of a SSI. However, when stratifying the results on the location of the target site and dose of cefazolin, some measurements did not reach this MIC.

Regarding the association between location of the target site and antibiotic concentrations, the present study showed that the same dosage of cefazolin resulted in significantly lower concentrations in the knee than in the hip. Although, with just a single study in the foot[26], no definite conclusions can be drawn, this could mean that for surgery of the more distal parts of the extremity (e.g. foot/ankle), 1g of cefazolin is not sufficient as prophylaxis. Whether or not a higher dose is beneficial in this area is yet to be determined.

As for the relationship between cefazolin dose and concentration, all three articles that compared different dosages found higher concentrations when 2g was given instead of 1g, although only one with statistical significance. A visualization of these concentrations, including also the studies investigating only one dose, suggests that the higher the dose, the higher the concentration (Figure 5). However, even though concentrations seemed increasingly high, the clinical implications of this phenomenon have not been investigated. A ceiling effect, where higher concentrations would not lead to less SSIs, is likely to occur at a certain time and could pave the way for antimicrobial resistance.

This first systematic review on target site concentrations of prophylactic antibiotics has provided valuable insights. The results of this study show that there is a large variation in

target site cefazolin concentrations of the extremity between different studies. In general, the achieved concentrations in bone surpassed the minimal inhibitory concentration (MIC) for S. aureus, the most common pathogen of a SSI. Most importantly, we found that the local concentration of cefazolin is associated with the location of the target site. Although no definite conclusions can be drawn based on this study, a higher dose of cefazolin seems to produce higher whole tissue concentrations. These insights could be very helpful in the path towards more efficient use of antibiotics. In particular, this study gives rise to the question whether the dose of prophylactic cefazolin needs to be adjusted to the location of the target site. To make any recommendations for the dose of prophylactic cefazolin in orthopedic/trauma surgery of the extremity however, additional prospective research is needed. We believe that a preclinical trial, comparing multiples dosages and locations of measurement in the extremity, is necessary before further investigating the efficacy of prophylactic cefazolin in preventing SSIs.

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SUPPLEMENTARY DATA

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Searches Results 1 exp cephalosporin derivative/ or (cephalospor* or kefzol or cefazolin or cephazolin or cefamandole or cefuroxime or duricef or keflex or Cefadroxil or velosef or biocef or panixine or cephalexin or ancef or cephradine or ultracef). ti,ab,kw. 207,766 2 exp lower limb/ or exp upper limb/ or podiatry/ or exp ankle fracture/ or exp "bones of the leg and foot"/ or exp "bones of the arm and hand"/ or exp joint/ or (orthopedic* or orthopaedic* or joint* or lower extremit* or upper extremit* or lower limb* or upper limb* or ankle* or foot or feet or knee* or hip* or femor* or femur or tibia* or fibula* or calcane* or shoulder* or arm or arms or elbow* or wrist* or hand or hands or leg or legs).ti,ab,kw. 2,376,346 3 exp surgery/ or su.fs. or exp orthopedic surgery/ or exp total arthroplasty/ or exp knee replacement/ or (invasive procedure* or orthopedic* or orthopaedic* or arthroplast* or knee replac* or surger* or operat* or preoperat*). ti,ab,kw. 5,840,574 4 exp pharmacokinetics/ or pharmacokinetics. fs. or tissue distribution/ or (concentration* or tissue distribution* or tissue locali* or pharmacokinetic* or pharmaco-kinetic* or absorption* or kinetic* or drug body relation*). ti,ab,kw. 3,236,447 5 1 and 2 and 3 and 4 588

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ID Search #1 cephalospor* or kefzol or cefazolin or cephazolin or cefamandole or cefuroxime or duricef or keflex or Cefadroxil or velosef or biocef or panixine or cephalexin or ancef or cephradine or ultracef:ti,ab,kw (Word variations have been searched) #2 MeSH descriptor: [Podiatry] explode all trees #3 orthopedic* or orthopaedic* or joint* or lower extremit* or upper extremit* or lower limb* or upper limb* or ankle* or foot or feet or knee* or hip* or femor* or femur or tibia* or fibula* or calcane* or shoulder* or arm or arms or elbow* or wrist* or hand or hands or leg or legs:ti,ab,kw

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TABLES

Table 2. Cefazolin dose and site of measurement of included studies

	Cefazolin 1g	**Cefazolin 2g**	**Other***
Hip	Bryan (1988) Cunha (1977) Sharareh (2016) Sorensen (1978) Williams (1983)	Sharareh (2016) Williams (1983) Yamada (2011)	Parsons (1978) Polk (1983)
Knee	Angthong (2015) Bryan (1988) Cunha (1984) Friedman (1990) Sharareh (2016) Williams (1983) Young (2013)	Angthong (2015) Sharareh (2016) Williams (1983) Yamada (2011)	
Foot	Deacon (1996)		
Shoulder	Miller (2004)		

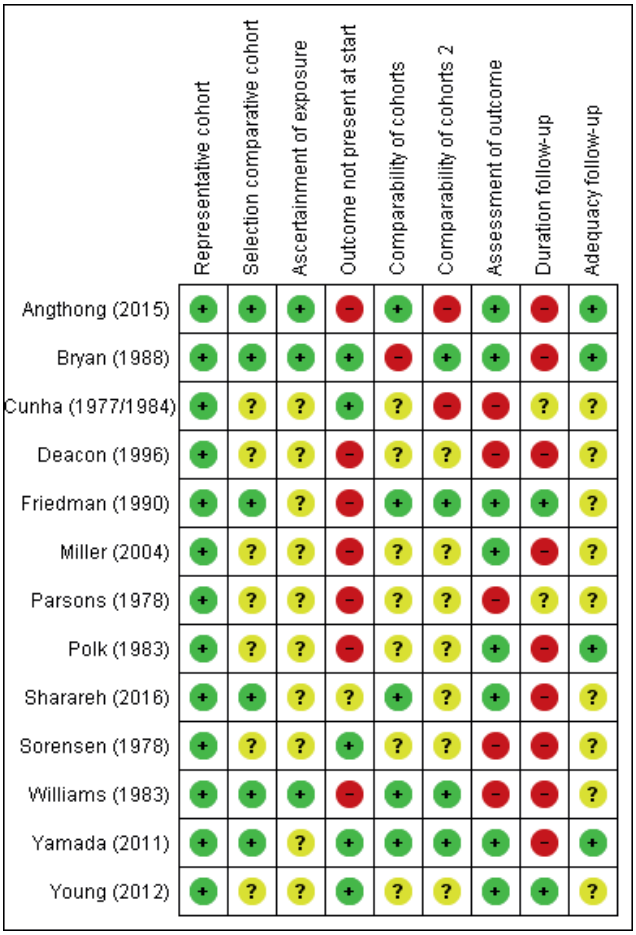
Table 3. Soft tissue target site cefazolin concentrations

Site **Author (year)**	**n/dose**	**Time of sample, min (SD)**	**Concentration, µg/g (SD)**
Hip capsule			
Parsons (1978)	6/4g	64 (26)	35 (24)
Knee			
Cunha (1984)	13/1g	ND	8 mg/L
Friedman (1990)*	24/1g	10	75%
		30	57%
		60	54%
Young (2013)	11/1g	26 (23)	11 (2.4)
Shoulder			
Miller (2004)	7/1g	40	11

ND: no data
*Results in percentage of patients achieving a concentration > 4 µg/g (MIC).

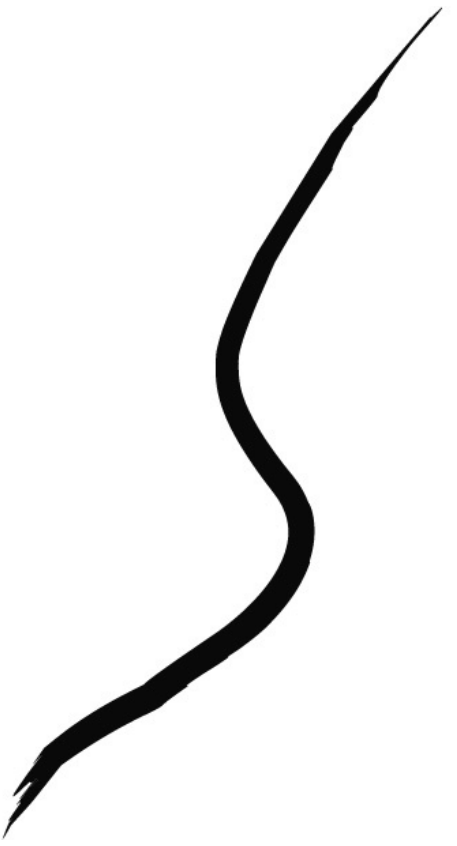
FIGURES

Figure 2. Quality assessment



+: low risk of bias/good quality, -: high risk of bias/poor quality, ?: unknown risk of bias/unclear or not-applicable (e.g. comparability of cohorts in studies where only one group received intravenously administered cefazolin). A green '+' matches with a star on the NOS.

CHAPTER



5

COMPARISON OF 2G VS 1G OF PROPHYLACTIC CEFAZOLIN IN SURGICAL SITE INFECTIONS IN TRAUMA SURGERY BELOW THE KNEE

Sanders FRK, Kistemaker RMG, van ‘t Hul M, Schepers T

Foot Ankle International, May 2020

ABSTRACT

BACKGROUND

The rate of surgical site infections (SSIs) after foot or ankle surgery remains high, despite the implementation of antibiotic prophylaxis. Recently, guidelines suggest a single dose of 2 g instead of 1 g of cefazolin for implant surgery; this decision is largely based on pharmacokinetic studies. However, the clinical effect of this higher dose has never been investigated in foot and ankle surgery. This retrospective cohort study investigated the effect of 2 g compared with 1 g of prophylactic cefazolin on the incidence of SSIs in foot and ankle surgery.

METHODS

All patients undergoing trauma-related surgery of the foot, ankle, or lower leg between September 2015 and March 2019 were included. The primary outcome was the incidence of an SSI. SSIs were compared between patients receiving 1 g and 2 g of cefazolin as surgical prophylaxis, using a propensity score to correct for possible confounders.

RESULTS

A total of 293 patients received 1 g and 126 patients received 2 g of cefazolin. The overall number of SSIs was 19 (6.5%) in the 1-g group and 6 (4.8%) in the 2-g group. Corrected for possible confounders, this was not statistically significant (OR, 0.770; *P* = .608).

CONCLUSION

Even though the decrease in SSI rate from 6.5% to 4.8% was found not to be statistically significant, it might be clinically relevant considering the reduction in morbidity, mortality, and healthcare costs. Research linking pharmacokinetic and clinical results of prophylactic cefazolin is needed to establish whether or not the current recommendations and guidelines are sufficient for preventing SSIs in foot and ankle surgery.

INTRODUCTION

Despite the implementation of prophylactic antibiotics, the rate of surgical site infection (SSI) in foot and ankle surgery has been reported as ranging from 0 to 9.4%, with the highest percentages in trauma-related surgery[1]. SSIs, both superficial and deep osteomyelitis, negatively affect the functional outcome after foot/ankle surgery and cause an increase of morbidity and mortality[2–4]. In addition, higher health costs due to prolonged hospital stay, reoperation and increased use of antibiotics can be attributed to SSIs.

In line with the WHO Global Action Plan on Antimicrobial Resistance; evidence-based prescription of antibiotics should be a priority in health care[5]. This plan states that there is compelling evidence that antimicrobial resistance is driven by the large volume of antimicrobial agents being used. According to the European Centre for Disease Control and Prevention, drug-resistant bacteria are responsible for 25,000 deaths annually and extra healthcare costs and lost productivity amounting to at least €1500 million in the European Union alone[6]. The Joint Commission International hospital manual advices avoiding of prolonged use of prophylactic antibiotics and prescribing a narrower-spectrum agent when possible[7]. It has also been argued that with a higher, more effective starting dose, one may avoid opportunities for resistant subpopulations to amplify[8].

Based on pharmacokinetic studies, guidelines have altered their policy on antibiotic prophylaxis and now advice 2g instead of 1g of cefazolin for implant surgery[9,10]. However, the clinical effectiveness of a higher dosage has, to the best of our knowledge, not been proved in trauma or orthopedic surgery.

The aim of this study was to retrospectively evaluate the clinical effect of a single dose of 2g compared to 1g cefazolin administered prophylactically in trauma-related foot/ankle surgery.

METHODS

This retrospective observational cohort study was conducted at a single level-1 trauma center with tertiary referral for complex foot/ankle injuries.

Patients and Data Collection

All patients undergoing trauma related foot and ankle surgery between September 2015 and March 2019 were extracted from the electronic patient data system, using a series of surgical procedure codes and selecting on specialized trauma surgeons and residents. Ethical permission was not required given the retrospective, non-invasive nature of this study. Informed consent was obtained by means of an information letter accompanied by an objection form on which patients could object to the use of their data for research. After permission was obtained records were screened for eligibility and data was retrospectively collected from the digital medical files. All (post-)traumatic surgical procedures warranting

antibiotic prophylaxis were included, entailing acute and reconstructive implant surgery as well as tendon repairs. Acute implant surgery was defined as open reduction and internal fixation (ORIF) of fractures either with or without arthrodesis within 30 days of trauma. Reconstructive implant surgery consisted of all secondary or planned procedures, longer than 30 days following trauma, such as secondary subtalar arthrodesis or correction osteotomies after malunion. Only metal, non-absorbable implants made of either stainless steel or titanium were used and all procedures were performed by a foot ankle specialized trauma surgeon.

After reviewing 777 surgical procedures, a final 419 procedures in 375 patients were included in this study. Patients who objected to the use of their medical records (N = 4) were excluded from all analysis. All other cases were reviewed and excluded when SSI was pre-existing at time of surgery (N = 57), other prophylactic/therapeutic antibiotics than cefazolin were administered perioperatively (N = 52), patient's age was <18 at time of surgery (N = 26) or when the patient was lost to follow-up within 30 days after surgery (N = 23). The following surgical procedures were also excluded because antibiotic prophylaxis was not warranted or because of an altered chance of SSI: implant removal (N = 108), percutaneous fixation (Kirschner wire/external fixator, N = 49), not trauma-related procedures (arthroscopy/Charcot amputations/exostosis removal, N = 39).

The following patient characteristics were collected: gender, age, height, weight, ASA score (American Society of Anesthesiologists), comorbidities such as diabetes mellitus, (iatrogenic) immunodeficiency, intoxications: (history of) smoking, more than two glasses of alcohol a day and other substance abuse. Location and type of injury were coded, including Gustillo classification in open fractures. The following surgical characteristics were collected: previous procedure or treated infection in operation area, time between initial trauma and surgery, procedure performed by specialist or resident, duration of surgery in minutes, tourniquet use, estimated blood loss, fixation material, use and type of bone filling, primary closure of skin and dosage of cefazolin. Additionally, type and duration of wound dressing, time to mobilization in weeks and prescription of antibiotic treatment were recorded. When a SSI was present, information on the treatment was recorded.

Treatment

Procedures were divided into two groups; group 1 constituted of patients receiving a dose of 1g of cefazolin and group 2 of those receiving 2g of cefazolin. Following national guidelines, the hospital's antimicrobial prophylaxis protocol was changed in March 2018, recommending a single dose of 2g of cefazolin. Before implementing the new guideline patients standardly received 1g of cefazolin. An additional dose was administered intraoperatively if the duration of the procedure was over 4 hours; in those cases the dosage administered before incision was noted. Patients who received 2g of cefazolin before the implementation of the new protocol were analyzed in group 2. Standard follow-up appointments in the outpatient clinic

were at two weeks, six weeks and three months after surgery. All patients were instructed to contact the hospital sooner in case of a suspected infection.

Outcome and analysis

The primary outcome variable was the incidence of a SSI after trauma related orthopedic surgery as defined by the criteria applied by the Centers for Disease Control[11]. SSIs were classified as superficial (limited to skin of subcutaneous tissue, diagnosed within 30 days after surgery) or deep (involving deeper tissue or bone, diagnosed within 90 days after surgery) and diagnosed at the standard follow-up appointments. SSIs were treated with drainage of the wound and/or oral antibiotics when superficial and i.v. antibiotics with or without surgical debridement when deep. In addition to SSIs, other complications related to wound healing (e.g. wound dehiscence) were recorded.

Collected data was analyzed using IBM SPSS Statistics for Windows, Version 25.0[12]. Descriptive statistics were used to report baseline characteristics of in- and excluded cases. To identify possible confounders, patient- injury- and surgical characteristics were compared between group 1 and 2 and between cases that did and did not develop an SSI. Differences were calculated using Fisher's Exact test (categorical) and Mann-Whitney U test (continuous, non-normal distribution). Exact significances were used and all variables with a (near) significant difference ($p < 0.2$) between group 1 and group 2 were identified as possible confounders and used to calculate a propensity score. This propensity score was subsequently entered into a multivariable logistic regression analysis together with group (1g or 2g) with SSI as the dependent variable, thereby correcting for confounders. In order to limit bias caused by missing data, multiple imputation was used for variables with (under 50%) missing data. The overall missing percentage was 9.6% with a range of missing numbers of 1 – 190 (Table 1). The variable with the largest amount of missing values was "blood loss". Imputation was performed based on predictive mean matching combined using Rubin's rule (10 sets)[13]. Imputed variables were: height, weight, smoking, alcohol abuse, drugs abuse, ASA classification, fixation type, duration of surgery, amount of blood loss, primary closure, wound dressing, therapeutic antibiotics.

The pooled results of the 10 imputed sets were used to estimate odds ratios and 95% confidence intervals (CI).

RESULTS

The majority of patients in this cohort was male (63%), with a median age of 47, [IQR: 33-57] years. Most injuries within this cohort were located in the hindfoot (47%), followed by the ankle (24%) and the majority of procedures were acute (77%) as compared to reconstructive. Excluded cases only differed from the included cases in amount of drug abuse and location of injury (Appendix, Table 5). Median follow-up duration (number of days between surgery and

last follow-up visit) of included patients was 169 days, ranging from 30 to 960 days. In 293 cases patients received 1g of cefazolin prophylactically; in 126 cases patients received 2g of cefazolin. Four patients received 2g of cefazolin before official instatement of the new protocol. In one case this was 2 weeks before implementation, the others were earlier and based on surgeons judgement.

Group 1 and group 2 did not differ significantly in gender, age, weight, BMI, co-morbidities or location of injury. There were however differences in the type of surgery performed, type of fixation and the type of wound dressing used, so these variables were used for the propensity score (Table 1). Although not differing significantly, number of patients with alcohol (>2 units/day) or substances abuse and open fractures, also qualified for inclusion in the propensity score because of a difference between groups with a p value below 0.2. In addition to these, smoking, tourniquet use and blood loss were added to the propensity score because of their clinical relationship with SSI and significant differences of these variables in patients with/without a SSI (Table 2). Weight and BMI were not regarded as possible confounders because they did not differ between groups nor in patients with/without a SSI. In both groups, no severe (allergic) reactions to cefazolin were reported.

The overall number of SSIs was 19 (6.5%) in the 1g group and 6 (4.8%) in the 2g group, as further specified in Table 3. After correction for confounders, no statistically significant difference (OR 0.770, 95%CI 0.284 – 2.087, p = 0.608) was found in the occurrence of SSIs between group 1 and group 2 with the numbers available.

A post-hoc analysis was performed, with all wound complications (including wound dehiscence) as the dependent variable, since it might be argued that these complications are the result of a low grade infection. Results of this analysis could also not demonstrate an effect of 2g of cefazolin (OR 0.433, 95%CI 0.179 – 1.045, p = 0.06). A post-hoc power analysis showed that if we take this difference in SSIs (6.5% vs 4.8%) as the smallest clinically important difference, and we would like to demonstrate an effect with 80% power and an α of 0.05, 2893 patients per group would be necessary. Out of all 25 SSIs, a causative pathogen was found in 21 cases; this was a Staphylococcus Aureus in most cases (N = 12). In two cases, no growth was detected and in two cases no material for culture was obtained. The difference in cultured microorganisms between group 1 and group 2 is shown in Table 4.

Table 1. Baseline and Surgical Characteristics per Group

	1g (n=293)	2g (n=126)	Sign.
Gender, No males (%)	182 (62.1%)	83 (65.9%)	0.51
Age, median [IQR]	47 [33 – 58]	46 [33 – 56]	0.51
ASA score, No (%)			1.00
1/2	272 (93.5%)	114 (93.4%)	
3/4	19 (6.5%)	8 (6.6%)	
Weight, No (%)			0.29
< 80 kg	140 (51.7%)	43 (43.0%)	
80 – 100 kg	103 (38.0%)	44 (44.0%)	
100 – 120 kg	25 (9.2%)	10 (10.0%)	
> 120 kg	3 (1.1%)	3 (3.0%)	
BMI, median [IQR]*	25 [23 – 28]	25 [23 – 28]	0.72
Diabetes Mellitus, No (%)	5 (1.7%)	4 (3.2%)	0.46
Immunocompromised, No (%)	6 (2.0%)	1 (0.8%)	0.68
Current smoker, No (%)	96 (40.3%)	39 (38.2%)	0.81
Alcohol abuse, No (%) (>2 units daily)	20 (9.7%)	16 (16.8%)	0.087
Use of other substances, No(%)	20 (9.6%)	16 (17.2%)	0.082
Location of injury, No(%)			0.41
Lower leg	36 (12.3%)	22 (17.5%)	
Ankle	67 (22.9%)	32 (25.4%)	
Hindfoot	146 (49.8%)	51 (40.5%)	
Midfoot	37 (12.6%)	18 (14.3%)	
Forefoot	7 (2.4%)	3 (2.4%)	
Open fracture, No(%)	26 (8.9%)	19 (15.1%)	0.084
Days between injury and surgery, median [IQR]**	8 [3 – 15]	7 [5 – 13]	0.80
Type of surgery, No(%)			0.002
ORIF	211 (72.0%)	109 (86.5%)	
Arthrodesis	67 (22.9%)	16 (12.7%)	
Other	15 (5.1%)	1 (0.8%)	
Type of fixation, No(%)			0.004
Screws only	126 (43.3%)	35 (28.0%)	
Plate	151 (51.9%)	82 (65.6%)	
Intramedullary	9 (3.1%)	8 (6.4%)	
Other	5 (1.7%)	0	
Duration of surgery in minutes, median [IQR]***	85 [65 – 120]	90 [63 – 130]	0.21
Use of tourniquet, No(%)	133 (45.4%)	65 (51.6%)	0.29
Blood loss in mL, median [IQR] †	100 [58 – 200]	100 [50 – 200]	0.23
Primary closure, No(%)	290 (99.3%)	124 (98.4%)	0.59
Type of wound dressing, No(%)			0.000
Pressure bandage	160 (56.5%)	58 (46.8%)	
Cast	81 (28.6%)	61 (49.2%)	
VAC	42 (14.8%)	5 (4.0%)	

Abbreviations: ASA score: America Society of Anesthesiologists classification, g: gram(s), IQR: interquartile range, mL: milliliters, No: number of cases, VAC: Vacuum Assisted Closure

* missing: 53 in 1g, 41 in 2g
** missing: 88 in 1 g, 15 in 2 g, only displayed for "acute surgical procedures"
*** missing: 29 in 1g, 5 in 2g
† missing: 127 in 1g, 63 in 2g

Table 2. Baseline and Surgical Characteristics for Patients With or Without SSI

		No SSI (n=394)	SSI (n=25)	Sign.
Patient characteristics	Gender, No males(%)	251 (63.7%)	14 (56.0%)	0.52
	Age, median [IQR]	46 [32.75-57.0]	53 [36.5-61]	0.12
	Weight, kg, No(%)			0.52
	<80	172 (49.4%)	11 (47.8%)	
	80-100	137 (39.4%)	10 (43.5%)	
	100-120	34 (9.8%)	1 (4.3%)	
	>120	5 (1,4%)	1 (4.3%)	
	BMI, median [IQR]*	25 [23 – 28]	26 [22 – 28]	0.79
	ASA score, No(%)			0.071
	1 or 2	365 (94,1%)	21 (84.0%)	
	3 or 4	23 (5,9%)	4 (16.0%)	
	Diabetes Mellitus, No(%)	9 (2,3%)	0	1.00
	Immunocompromised, No(%)	5 (1,3%)	2 (8.0%)	0.060
	Current smoker, No(%)	124 (38.4%)	11 (64,7%)	0.041
	Alcohol use (>2 units daily), No(%)	32 (11.2%)	4 (26,7%)	0.090
	Use of other substances, No(%)	35 (12.2%)	1 (6,3%)	0.70
Injury characteristics	Location of injury, No(%)			0.42
	Lower leg	52 (13.2%)	6 (24.0%)	
	Ankle	96 (24.4%)	3 (12.0%)	
	Hindfoot	184 (46.7%)	13 (52.0%)	
	Midfoot	52 (13.2%)	3 (12.0%)	
	Forefoot	10 (2.5%)	0	
	Open fracture, No(%)	39 (9,9%)	6 (24.0%)	0.040
Surgical characteristics	Timing surgery, No(%)			0.47
	Acute	302 (76.6%)	21 (84.0%)	
	Elective	92 (23.4%)	4 (16.0%)	
	Time injury - surgery, days, median [IQR]**	8 [4-15]	7 [3-12]	0.54
	Previous surgery, No(%)	64 (16.7%)	4 (16.7%)	1.00
	Type of surgery, No(%)			0.92
	ORIF	300 (76.1%)	20 (80.0%)	
	Arthrodesis	79 (20.1%)	4 (16.0%)	
	Other	15 (3.8%)	1 (4.0%)	
	Type of fixation, No(%)			0.078
	Screws only	151 (38.6%)	10 (40.0%)	
	Plate	222 (56.8%)	11 (44.0%)	
	Intramedullary	14 (3,6%)	3 (12.0%)	
	Other	4 (1,0%)	1 (4,0%)	
	Duration of surgery in min, median [IQR]***	87.5 [60.0-120.0]	100 [80-165]	0.065
	Use of tourniquet, No(%)	192 (48.7%)	6 (24.0%)	0.022
	Blood loss in ml, median [IQR] †	100 [50-200]	300 [100-500]	0.021
	Primary closure, No(%)	389 (99.0%)	25 (100%)	1.00
	Type of wound dressing, No(%)			0.024
	Pressure bandage	202 (52.7%)	16 (66,7%)	
	Cast	139 (36.3%)	3 (12,5%)	
	VAC	42 (11.0%)	5 (20,8%)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; ORIF, open reduction and internal fixation; SSI, surgical site infections; VAC, vacuum-assisted closure.

*missing: 87 in No SSI, 7 in SSI
** missing: 125 in No SSI, 9 in SSI, only for "acute surgical procedures"
*** missing: 3 in No SSI
† missing: 176 in no SSI, 14 in SSI

DISCUSSION

Prophylactic antibiotics are widely used in implant surgery, because of the important clinical implications of SSIs. However, the optimal dose is still debated and guidelines have been subjected to some changes over the past few years. This retrospective cohort study sought to compare the clinical effect of 1g of cefazolin and the recently recommended dose of 2g in patients undergoing orthopedic trauma surgery of the foot, ankle or lower leg. We found a lower rate of SSIs in patients receiving 2g (4,8%) compared to the group receiving 1g (6.5%) as antibiotic prophylaxis. However, with the numbers available, when corrected for confounders, this difference was not statistically significant (p = 0.705). Because of the small sample size of this study, the results should be considered as exploratory point estimates. The "true" point estimate may vary, and would then have substantial implications for sample size calculations of future research based on this study. To give some insight in how the necessary sample size for a RCT would vary while using other point estimates, we have subtracted a few incidents from both groups. We chose to make the rate of SSIs of the 2g group resemble that of the mean SSI incidence rates of the systematic review by Modha et al.[1] (1.3% in group receiving antibiotic prophylaxis). This would mean subtracting 4 events from both groups, leading to a SSI rate of 1.6% in the 2g group and 5.1% in the 1g group. With an α of 0.05, 460 per group would be required to achieve 80% power. If the number of events would not deviate that much from our results, for example by subtracting 2 SSIs from the 2g group, this would reduce the needed sample size to around 570 per group.

Table 3 Wound complications and treatment

	Deep SSI		**Superficial SSI**		**Dehiscence**	
	1g	2g	1g	2g	1g	2g
N (%)	12 (4.1%)	5 (4.0%)	7 (2.4%)	1 (0.8%)	14 (4.8%)	1 (0.8%)
Treatment						
Watchful waiting					9	
VAC					2	1
Drainage of wound					1	
Oral AB			6	1	2	
IV AB		1	1			
IV AB + Surgery	12	4				

Abbreviations: AB: antibiotics, g: gram(s), IV: intravenously administered, SSI: surgical site infection, VAC: Vacuum Assisted Closure

This is, to our knowledge, the first study on the clinical efficacy of different cefazolin dosages in implant surgery below the knee. In a similar study design, Peppard et al.[14] evaluated the efficacy of 2g vs. 3g in obese patients in both general surgery, orthopedic and neurosurgical procedures. In that study of 436 surgical patients weighing >100kg, increased dosage of cefazolin did not alter the rate of SSI (7,2% vs. 7,4%). In contrast, Abdel Jalil et al.[15] found that a higher, weight-adjusted dose of 2g cefazolin, was associated with lower SSIs risk (OR 0.967) in a cohort of 1173 women undergoing ceasarean section. In orthopedic/trauma

surgery, only pharmacokinetic studies have investigated different dosages of cefazolin without reporting clinical outcome measures. Such as Angthong et al. who, without incorporating clinical effectiveness, found significantly higher intraosseous concentrations for 2g of cefazolin, compared to 1g, when measured during total knee arthroplasty although they could not correlate this to higher inhibitory effects[10]. A possible explanation for this is provided by Blum et al. who argued that cefazolin displays time-dependent killing kinetics, and therefore as long as the MIC is reached, higher concentrations will not lead to an enhanced effect[16]. However, a recently performed systematic review and meta-analysis showed significantly lower concentrations in the more distal parts of the lower extremity, indicating that a higher dose might be necessary to reach the MIC at the most distal parts of the body[17]. In that review, all studies did report mean target site concentrations exceeding the MIC for S. aureus (0.5-2 mcg/mL) for both doses. However, the time that these concentrations remained above the MIC was not described.

Previously reported as pathogens of SSIs in foot/ankle surgery are S. aureus, Pseudomonas and S. epidermidis; all associated with the formation of a biofilm on foreign material[1,18,19]. Since Cephalosporins are effective in preventing Staphylococcus infections; cefazolin is the most often used prophylactic antibiotic in a variety of surgical procedures and is recommended for implant surgery by multiple guidelines[20,21]. The most common pathogens causing SSI in this study were S. aureus and E. Cloacae. Although it was not a statistically significant difference with the numbers available, the percentage of S. aureus as causative microorganism in group 1 was double of that in group 2. This suggests that in this cohort 2g of cefazolin might in fact have been more effective in preventing S. aureus infections.

Table 4. Microorganisms cultured from SSIs

	SSIs group 1 (N = 15)	SSIs group 2 (N = 6)
Staphylococcus Aureus	10	2
Enterobacter Cloacae	4	1
Enterococcus Faecalis	1	1
Pseudomonas	0	1
Staphylococcus Epidermidis	0	1

Abbreviations: SSI: surgical site infection

Limitations

This study had some limitations. First of all, this study may be subjected to a selection bias since it was carried out with data of a single center, specialized in complex foot/ankle trauma. This may have led to a higher overall complication percentage due to the referral of more complex patients. Moreover, due to the single center study design, the number of included patients might not be sufficient to achieve statistical significance. However, even though the findings should to be interpreted with caution; a decrease in SSI rate from 6,5% to 4.8% with a

2g dose (26,1% relative difference) might be clinically relevant. Secondly, the retrospective study design has inherent limitations. Data extraction from medical records not written for research purposes leads to missing data and might also have caused an underestimation of the total number of SSIs. Especially superficial infections may have been underreported in the outpatient clinic, because they were treated by the general practitioner. In this study, missing data was limited (9.6%) to the extent that imputation was still feasible and reliable. Moreover, by identifying and correcting for confounders we have tried to limit the confounding bias that may be present. Thirdly, the cohorts that were compared in this study were largely consecutive instead of simultaneous (except for the 4 cases which received 2g instead of 1g before official instatement of new protocol). This may be both an advantage and a type of bias. Because the only factor that decided which dose of cefazolin a patient received was time, selection bias is minimal. However, in addition to the dosage change, other influencing factors also may have changed over time (e.g. operation technique, OR policies), leading to bias. By correcting for the identified confounders, we have tried to limit the influence of this type of bias. Moreover, there have not been any major changes in protocol or surgical approach during the time of this study.

CONCLUSION

In conclusion, despite some limitations the findings of this study do shed light on the question of the clinical efficacy of the recommended dosage of prophylactic cefazolin in implant surgery. Even though the decrease in SSI rate from 6.5% to 4.8% was found not to be statistically significant with the numbers available, if this is the true reduction and the results are not based on coincidence, it might be clinically relevant. Even a small reduction in SSIs can cause a considerable reduction in morbidity, mortality and healthcare costs[2–4]. Also considering the little side effects that cefazolin has there seems to be no reason to set aside the 'Clinical practice guidelines for antimicrobial prophylaxis in surgery'. However it is evident that further (prospective) research is needed on this topic. Specifically in the foot/ankle area, more research is necessary on the optimal dose and formulation of prophylactic antibiotics. Locally applied antibiotics might be necessary to achieve sufficiently high antibiotic concentrations in this area. A study linking pharmacokinetic and clinical results of prophylactic cefazolin is needed to establish whether or not the current recommendations and guidelines are sufficient for preventing SSIs in foot/ankle surgery.

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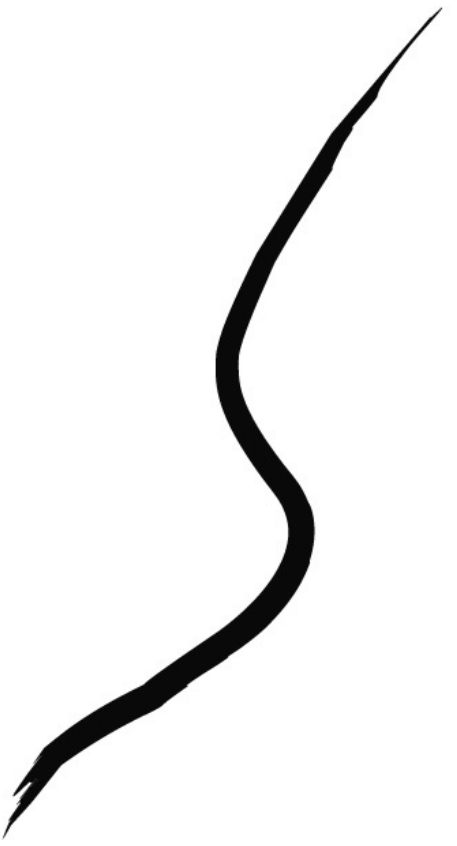
CHAPTER



6

WOUND INFECTION FOLLOWING IMPLANT REMOVAL OF FOOT, ANKLE, LOWER LEG AND PATELLA; PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL INVESTIGATING THE (COST-)EFFECTIVENESS OF 2G OF PROPHYLACTIC CEFAZOLIN COMPARED TO PLACEBO (WIFI-2 TRIAL)

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Submitted

ABSTRACT

BACKGROUND

Elective implant removal (IR) after fracture fixation is one of the most common procedures within orthopedic/trauma surgery. The rate of surgical site infections (SSIs) in this procedure is quite high, especially below the level of the knee. Antibiotic prophylaxis is not routinely prescribed, even though it has proved to lower SSI rates in other orthopedic trauma surgical procedures. The primary objective is to study the effectiveness of a single intravenous dose of 2g of cefazolin on SSIs after IR following fixation of foot, ankle and/or lower leg fractures.

METHODS

This is a multicenter, double-blind placebo controlled trial with a superiority design, including adult patients undergoing elective implant removal after fixation of a fracture of foot, ankle, lower leg or patella. Exclusion criteria are: an active infection, current antibiotic treatment, or a medical condition contraindicating treatment with cefazolin including allergies. Patients are randomized to receive a single preoperative intravenous dose of either 2g of cefazolin or a placebo injection (NaCl). The primary analysis will be an intention-to-treat comparison of the proportion of patients with a SSI at 90 days after IR in both groups.

DISCUSSION

If 2g of prophylactic cefazolin proves to be both effective and cost-effective in preventing SSI, this would have implications for current guidelines. Combined with the high infection rate of IR which previous studies have shown, it would be sufficiently substantiated for guidelines to suggest protocolled use of prophylactic antibiotics in IR of foot, ankle, lower leg or patella.

TRIAL REGISTRATION

Nederlands Trial Register (NTR): NL8284, registered on 9th of January 2020.

BACKGROUND

In the Netherlands, each year, about 18,000 surgical implants are removed after fracture healing[1]. Most fracture implant removals (IR) are performed in the lower extremity (85.7% of all IR surgeries) and the removal rate is the highest in foot and ankle[2, 3]. A surgical site infection (SSI) is one of the most common complications of surgical interventions of the lower extremity, especially when implants are involved. The infection rate ranges from 1.3%-10% in hip and knee procedures[4, 5] to 4.5-24.6% in foot and ankle surgery[6–8]. SSIs are not only responsible for prolonged hospital stay and a significant increase in healthcare costs, the functional outcome of patients who suffered from an infection is also relevantly decreased[9]. Even though IR is regarded a "clean procedure" according to the Centers for Disease Control and Prevention (CDC) classification of surgical wounds[10], and it usually is a relatively short procedure (< 1 hour), the infection rate of 8%-20%[11, 12] is at least as high as in procedures where orthopedic implants are placed.

As IR is classified as a "clean procedure" in current guidelines, prophylactic antibiotics are not routinely administered[13]. Previously, a randomized controlled trial (WIFI trial) investigated the effect of 1g of cefazolin on SSIs in IR below the level of the knee and found that overall infection rates did not significantly decrease (14.9% vs. 13.2%)[14]. However, there was a trend towards a lower rate of deep SSIs with resp. 2.9% in placebo and 0.4% in the cefazolin group.

Recently, guidelines on general surgical prophylaxis have been revised, now suggesting 2g instead of 1g of cefazolin for implant surgery of longer than 1 hour and 3g for obese individuals (Body Mass Index (BMI) > 40)[13, 15]. The decision to increase the dosage from 1g to 2g was mostly based on pharmacological studies[16, 17]. Although the difference in tissue concentrations between the two dosages has also been investigated in orthopedic trauma surgery, the clinical effect of a higher dosage remains unclear[18]. To the best of our knowledge, only one recent retrospective cohort study compared 2 g with 1 g of prophylactic cefazolin on the incidence of SSIs in foot and ankle surgery. This study could not demonstrate a statistically significant difference with 4.8% vs. 6.5% SSIs, but did conclude that the difference might be clinically relevant. In gynecology, a large retrospective study reported that 2g was associated with a significantly lower risk of SSI compared to 1g of cefazolin (OR 0.967, 95% CI 0.94-0.99)[19].

The hypothesis is that prophylactic cefazolin in a dose of 1g does not sufficiently penetrate the more distal parts of the lower extremity[18]. This hypothesis is supported by studies measuring cefazolin concentrations in both hip and knee bone, which found significantly lower values in the knee than in the hip after prophylactically administered cefazolin[20, 21]. Deacon et al. reported even lower concentrations in the foot[22]. A single dose of 2g of cefazolin would increase not only the duration of adequate coverage but also the peak concentration.

Given the high rate of SSIs in IR and evidence that higher dosages are required below the level of the knee, we feel that there are sufficient arguments to evaluate whether 2g of cefazolin is effective as prophylaxis. Therefore, primary objective of this randomized controlled superiority trial is to study the effectiveness of a single intravenous dose of 2g of cefazolin on SSIs prior to IR following fixation of foot, ankle, lower leg or patella fractures.

Secondary objectives are to study the cost-effectiveness of 2g of cefazolin preventing SSIs after IR (only when a statistically significant effect is found); to elucidate the underlying mechanism of antibiotic prophylaxis by measuring target-site concentrations of cefazolin; to identify possible underlying infections (before IR); and to identify independent predictors of SSI.

METHODS

This is a multicenter, randomized double-blind placebo controlled intervention trial with a superiority design, comparing 2g of cefazolin as antibiotic prophylaxis to placebo with a 1:1 allocation ratio.

Participants

The trial will run in approximately 20 hospitals in the Netherlands, both academic and non-academic centers. A list of participating sites can be found on the trial website: https://www.amc.nl/web/research-75/trials-collaborations/wifi-2.htm
All consecutive patients (age 18-75), scheduled for elective IR in foot, ankle, lower leg or patella are eligible for inclusion.
Exclusion criteria are:
- Removing and re-implanting material for osteosynthesis in the same session
- Active wound infection or antibiotic treatment (for any reason) at time of IR
- A medical history of serious peripheral vascular disease, severe renal insufficiency
- Allergy for cephalosporin, or severe allergy for penicillin/other beta-lactam antibiotic
- Treatment with probenecid or immunosuppressants
- Pregnancy
- Insufficient comprehension of Dutch/English language

Randomization

After signing informed consent forms, patients will be randomly assigned to the intervention or control group (1:1 allocation, random block sizes of 2, 4 or 6), using a computerized randomization module stratified by academic/non-academic center to ensure allocation concealment. Randomization will be performed preoperatively by the coordinating investigator using a dedicated, password protected, SSL–encrypted website (Castor) and the responsible anesthesiologist will be notified of the result, while being unaware of allocation

sequence. If the electronic randomization module fails for any reason, randomization will be performed by tossing a coin (head signifying cefazolin and tails placebo).

Blinding

The patient, operating (orthopedic) surgeon and outcome assessors will all be blinded for the result of randomization. Unblinding will not be performed until the end of the trial. If the attending physician does decide that unblinding is necessary, (s)he will make every effort to contact the coordinating investigator before unblinding to discuss options. Statistical analysis will be performed by an independent researcher, blinded for the randomization result. The randomization code will be unblinded after complete analysis of the study results.

Interventions

If patients are allocated to the intervention group, they will receive a single dose of either 2000 mg or 3000 mg of cefazolin solved in 10 cc of Sodium chloride (NaCl) 0.9% through a peripheral intravenous (iv) catheter. The actual dose is dependent on the patient's BMI; patients with a BMI over 40 will receive 3000 mg of cefazolin, the remainder receives 2000 mg. The drug will be prepared by the anesthesiologist or his/her assistant and administered in the theatre/holding within 60 minutes prior to surgery. When allocated to the placebo/control group, the patient receives a single dose of 10 cc of Sodium chloride (NaCl) 0.9% in the same manner. Both will be administered in absence of the surgeon to avoid unblinding. The anesthesiologist/assistant then fills out a form containing: randomization number, date, placebo/ cefazolin dose (2g/3g), LOT number, expiration date and the initials of the anesthesiologist. This form will be sealed in a closed envelope and sent to the coordinating investigator. The envelope will remain sealed until the end of the study period and is opened at the time of analysis to check whether the patient received the allocated drug/correct dosage.

The exact timing of antibiotic administration and surgical technique and characteristics are not predefined, since this is a pragmatic trial, designed to resemble daily practice as much as possible. However, these characteristics are all collected to use in the multivariable analysis predicting the risk of SSI.

Outcomes

The primary outcome parameter is SSI within 90 days, as defined by the criteria used in the latest CDC guideline for the prevention of SSI (Table 1). The criteria for a superficial infection will however be modified to the extent where diagnosis by surgeon/attending will have to be confirmed by an independent expert. Therefore, a picture and description of the wound will be required when the physician suspects an infection.

Secondary outcomes are:

- Other infectious outcomes possibly related to the surgical procedure. These include wound dehiscence (without qualifying as a superficial SSI) and S. aureus bacteremia (which

does not qualify as a SSI after extensive assessment for a focus of infection). This outcome does not include hospital acquired infections such as pneumonia or urinary tract infections.

- Cost-effectiveness of intervention: measured with health care resource utilization and costs (iMCQ, iPCQ); at baseline, 6 weeks, 3 months and 6 months after surgery. Cost effectiveness will be measured as cost per patient free of SSI and the cost utility analysis will be described as cost per quality adjusted life years (QALY's). QALYs will be measured by the 5-level EuroQuality of Life-5D (EQ-5D-5L); at baseline, 2 weeks, 6 weeks, 3 months and 6 months after surgery.
- Target-site antibiotic concentrations: The time that target site concentrations of prophylactic cefazolin (µg/L) stay above the minimal inhibitory concentration needed to adequately prevent SSIs (T>MIC) will be measured during surgery from at least two samples at varying time points in blood and soft tissue from incision site. In addition, the concentration of cefazolin will be measured in serum, to construct a multi-compartment pharmacokinetic model (only selected patients).
- Subclinical low-grade infections: diagnosed by analyzing the presence of pathogens on removed implants, determined by culture of removed material (only Amsterdam UMC); directly following surgery.
- Independent predictors of SSI, measured by a multivariate regression analysis/subgroup analysis of patient and treatment characteristics (e.g. weight, smoking).

Data collection

Invasive procedures

To administer the antibiotics or placebo intravenously, a peripheral intravenous (iv) catheter is required. However, this is standard procedure during surgery because the iv-catheter is already used for either sedatives, muscle relaxants and/or pain medication.

For the additional measurements, in a selection of patients from the Amsterdam UMC, location AMC only, samples are acquired during the procedure to measure antibiotic concentrations. Samples will be taken from:

- Serum (from IV catheter, 3-4 samples at different time intervals)
- Soft tissue (from target-site, 2 samples at different time intervals)
- Blood (from target-site, 2 samples at different time intervals)

The serum samples are drawn from a second iv catheter, placed under general anesthesia. Samples from the target-site (operated foot/ankle) will be taken after incision. They are comprised of "fresh" blood that spontaneously surfaces from the bone during surgery and soft-tissue nearest to the incision. Serum will be separated from blood cells within one hour after withdrawal and stored at -80°C until analysis. By measuring concentrations in the samples at varying time intervals through a validated laboratory analysis, we will be able to construct individual time-concentration curves of cefazolin. Based on a pharmacokinetic multi-compartment model, fT>MIC at the target-site (secondary outcome measure) can be extracted.

Questionnaires

As shown in Figure 1, after informing the patient about the study and obtaining informed consent in the outpatient clinic, patients will be asked for a pre-operative, baseline assessment 14 - 1 day(s) before IR by means of 3 questionnaires they will receive by (e-)mail. Additionally, patients will fill out questionnaires at 2 weeks, 6 weeks, 3 months and 6 months after IR. These questionnaires consist of the 5-level EuroQuality of Life-5D (EQ-5D-5L) and the Dutch iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ). In addition to these validated questionnaires, patients will be asked if they have any complaints that could suggest wound complications (combined with questionnaires at 2 weeks, 6 weeks and 3 months) or side-effects of the investigational product (only at 2 weeks).

Additional data collection

Patient, fracture and surgical characteristics will be collected and documented in the online, password protected, SSL–encrypted database(Castor EDC[23]). Patient characteristics comprise age, gender, weight, BMI, American Society of Anesthesiologists (ASA)-classification, substance abuse (smoking, alcohol, drugs) and medical history (including diabetes mellitus). Fracture characteristic comprise the type of fracture and the conditions of the soft tissues (open/closed) prior to fixation. Surgical characteristics comprise timing of administration of cefazolin/placebo, duration of surgery, use of a tourniquet, placement of implants, type of implants and wound closure technique. Moreover, patients and the operating surgeon will be asked for the reason for IR.

Sample size

A total SSI rate of 14.9% is assumed in the control group, as was found in the WIFI-trial[14]. In the intervention group we aim for a 50% reduction to 7.45%, based on the Dutch Trauma Trial[24], who showed a reduction of SSIs of over 50% in a large cohort of 2195 patients with fractures of the extremity (control group: 8.3%, antibiotic prophylaxis group: 3.6%). In total, 554 patients are required to have an 80% chance of detecting a reduction from 14.9% in the control group to 7.45% in the experimental group with a chi-square test with a two sided alpha level of 0.05. However, the WIFI-1 trial had insufficient power to demonstrate a significant difference in deep SSIs[14]. Because deep SSIs often have the most serious consequences, an intervention that reduces these infections (even if they are less common) may still be cost-effective. Therefore, we chose to expand the number of included patients in order to have sufficient power to demonstrate a difference in deep SSIs as well. Combining the number of deep SSIs of the WIFI-1 trial and an RCT by Dong et al.[25] leads to a mean of 0.85% deep SSIs with cefazolin and 4.15% deep SSIs without. To detect this difference with a chi-square test with 80% power and a two-sided alpha of 0.05, 348 patients per group are required (696 in total). The loss to follow up of the WIFI-1 trial was only 1.5%. To be sure, a loss to follow up of 5% will be incorporated, coming down to a total of 732 patients.

In the absence of data for a reliable sample size calculation for the antibiotic concentration measurements we will conduct of a pilot study using 40 participants (around 20 per group). This should be sufficient to estimate the pharmacokinetic (PK) parameters; clearance and volume of distribution, the mean value, and its inter-individual variability. The availability of these population PK parameters allows Monte Carlo simulations in which T>MIC can be simulated for different MIC values and varying doses.

Recruitment feasibility and consent

Since the WIFI-1 trial[14] was performed in the same centers and patients, we have a realistic estimation of the number of included patients each center will contribute and the amount of time it will take. In the WIFI-1 trial, it took 22 months to include 500 patients (from the start of inclusion), including a warm-up period. With largely the same hospitals participating in this trial and 21 that have already agreed to participate, the expectation is that it will take 32 months to include 732 patients. These participating centers have proved to be reliable partners in recruiting patients for previous multicenter trials[14, 26]. Moreover, taking the nature of the intervention into account, the patients' willingness to participate is expected to be high. They are after all not exposed to risks other than in current practice and could potentially have a direct benefit from the intervention. The exclusion criteria are not different from those of the previously performed WIFI-1 trial, and are therefore not expected to make a difference in number of included patients.

To ensure sufficient time to consider participation, the patient will be informed about the trial as soon as it is clear that there is an indication for IR surgery. This will be either in the emergency room or in the outpatient clinic. Documents are handed to the patient and the patient is asked to read the patient information letter. On the day of the surgery the patient will be asked to sign the informed consent form if not signed before that time.
Surgeons are asked by the coordinating investigator/project leader to check whether patients are included in the trial during the pre-operative assessment a day prior to surgery. Randomization is only performed after informed consent has been obtained.

Statistical analysis

Descriptive methods will be used to assess quality of data, homogeneity of treatment groups and endpoints. Normality of the data will be assessed by visually inspecting the histograms and boxplots. Outcome measures will be analyzed using either a t-test or Mann-Whitney U test for continuous data according to the distributing of the data and a Chi-Square test for categorical data. Missing data will be handled through multiple imputation with predictive mean matching for variables with less than 50% missing data.

Primary outcome

The primary analysis will be an intention-to-treat comparison of the proportion of patients with a SSI (90 days after IR) expressed as an absolute risk reduction between intervention and

control group, using a chi-square test. A sensitivity analysis will be performed correcting for stratification of academic/non-academic center, using logistic regression. Furthermore a weight will be performed using the following subgroups: <80kg, 80-120kg and >120kg. A two-sided p-value <0.05 will be considered statistically significant. In all analyzes statistical uncertainties are expressed with 95% two-sided confidence intervals. Data-analysis will be performed blinded for the type of intervention.

Secondary outcomes

- Cost-effectiveness and cost utility analysis: If a statistically significant difference in number of SSIs is found, cost-effectiveness of the intervention will be analyzed. The primary outcome in the CEA will be costs per patient free of SSI's. The primary outcome in the CUA will be costs per quality adjusted life year (QALY), which is a suitable outcome measure for health care policy making across interventions, patient populations, and health care settings. Both analysis will be performed from a societal perspective with a time horizon of 6 months, because we expect that differences in health outcomes and costs will be presented in the first 6 months after IR. No discounting on effects and costs will be done. To account for uncertainties a probabilistic sensitivity analysis will be performed. Incremental cost-effectiveness ratios will be calculated as the difference in costs per patient free of SSI and per QALY. Sampling variability in the CEA and CUA will be accounted for by bias corrected and accelerated non-parametric bootstrapping. Results will be reported along with their 95% confidence intervals and displayed graphically with cost-effectiveness planes and with cost-effectiveness acceptability curves. One-way and multi-way sensitivity analyzes will be done for the unit costs of health care, ratio of superficial to deep SSI. Some missing data can be expected, if missing data is at random this will be handled through multiple imputations with predictive mean matching.
- Antibiotic concentrations: The T>MIC will be computed for each individual patient. Furthermore population PK analysis allows Monte Carlo simulations in which T>MIC can be evaluated for different doses and varying MIC values; e.g. 1, 2 and 8 mg/L.
- Underlying infections: The presence of pathogens on implants will be displayed using descriptive statistics.
- Independent predictors of SSI: Possible predictors will be identified by comparing baseline/surgical characteristics of patients with and without a SSI in univariate analysis (depending on type and distribution of data). Only characteristics clinically identified as possible risk factors will be included. These are: age, sex, weight, intoxications, comorbidities (such as Diabetes Mellitus or auto immune disorders), antibiotic prophylaxis, previous SSI, duration of surgery, tourniquet use, incomplete implant removal, wound dressing and weight-bearing policy. All relevant characteristics ($p<0.2$ in univariate analysis) identified in univariate analysis will be included in a multivariable logistic regression with stepwise backward selection using SSI as the dependent variable, to determine individual predictors of SSI.

Handling and storage of data and documents

After randomization, patients will receive a numeric study identification number (anonymized). A subject identification code list will be solely accessible for the principal investigator and study coordinator. Furthermore, possibly identifying baseline characteristics are kept in an online, password protected database (Castor EDC[23]) with an audit trail. The source data will be stored after publication of results of the trial and kept by the project leader for 15 years after the inclusion of the last patient.

Monitoring

The study will be monitored by the Clinical Research Unit of the Amsterdam UMC according to ICH-GCP guidelines throughout its duration by (a) BROK or GCP-certified monitor(s) according to the Monitoring Plan (Appendix). The assigned monitor is not involved in the clinical trial as part of the trial site staff. The monitor's qualifications, including the received GCP-training, are documented.

In addition, a Data Safety Monitoring Board (DSMB) is assigned, consisting of three independent professionals with complementing expertise (1 general surgeon, 1 anesthesiologist and 1 clinical epidemiologist).

The specific responsibilities of the DSMB are to:

- Monitor evidence for treatment harm (e.g. toxicity data, SAEs, deaths)
- Monitor efficacy data to guide recommendations for continuation of the study or early termination because of clear benefit, harm or futility
- Monitor planned sample size assumptions

An interim analysis will not be performed and there are no pre-specified stopping rules. A recommendation from the DSMB to terminate the study due to clear harm will be based on data showing a notably increase of (serious) adverse events in the intervention group. The justifications for a recommendation to terminate the study due to clear benefit will be based on the judgement of the DSMB and principal investigator.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Harms

Adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. The investigator will appreciate the severity of an event and consider whether the event is related to the study medication or not. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the

temporal relationship of the event to the study medication will be considered and investigated. AEs unrelated to the study will be reported in the medical records, but not in the database.

Serious adverse events
A serious adverse event is any untoward medical occurrence or effect occurring within 14 days after administration of the investigational product/placebo that:

- results in death
- is life threatening (at the time of the event)
- requires hospitalization or prolongation of existing inpatients' hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator

An elective hospital admission will not be considered a serious adverse event. The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs through the web portal 'ToetsingOnline' to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening, followed by a period of maximum of 8 days to complete the initial preliminary report.
The following SAE's will be listed in an overview list that will be submitted in an annual safety report to the METC and DSMB:

- Allergic reactions
- Surgical site infections requiring (re)admission or surgery
- Re-admission or revision surgery related to the implant removal (diastasis of ankle joint, deep venous thrombosis)
- Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) and has not increased in severity or frequency as judged by the clinical investigator

All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Dissemination and implementation of results

The results of the primary analysis will be shared with all main investigators in order to discuss results and subsequent conclusions and implications for clinical practice. After reaching consensus on trial results and conclusions, these are communicated to participants in-short and in clear language. To assure implementation of results an implementation plan has been made, focusing on the target group of trauma surgeons, orthopedic (trauma) surgeons, as well as microbiologists, anesthesiologists and pharmacists. Partly based on our previous experiences, we will use a combination of three implementation strategies: 1. an "informing

strategy", 2. a "motivational strategy" and 3. an "organizational strategy" would be most fitting for this intervention.

1. To inform the target group we will largely rely on the conventional means of implementation, such as publication in an international journal and presenting on conferences. However, also a press release will be issued if the intervention proves to be effective, following up on the earlier article following the initial WIFI trial. Moreover, the participation of many centers (academic/non-academic) throughout the Netherlands will facilitate wide-spread knowledge and implementation of the results. With the multidisciplinary involvement in the development and conduction of this trial (trauma/orthopedic surgeons, anesthesiologists, medical microbiologists, pharmacists) we can raise awareness in different fields of health care.
2. To combine the motivational and organizational strategy, both the personal contact with main investigators and the electronic medical record system can be used. Nowadays, every hospital has a mandatory pre-operative checklist to confirm the correct patient, procedure but also the antibiotic prophylaxis ("time-out procedure"). This forces not only the surgeon and surgical staff, but also the anesthesiologist to think about the need for antibiotic prophylaxis. Since this procedure is documented in the electronic medical records, it can be used both to embed the results of this trial (pop-up with reminder to prescribe antibiotic prophylaxis) and for performance feedback.

Authorship and publication

The study coordinator(s) will be first author on the primary manuscript and included in the list of authors in any subsequent manuscripts. The last authorship is reserved for the principal investigator. All other authors will be listed in alphabetical order. For purposes of abstract presentation and publication, any secondary publication will be discussed with all locally participating principal authors.

Publications will be in accordance with international recognized scientific and ethical standards concerning publications and authorship, including the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors. Copyrights concerning publications of the Clinical Study remain with the authors of the publication, regardless of any other provisions regarding intellectual property rights. Further specifications will be adapted to each individual study site.
The funding party will be mentioned on all publications of primary/secondary results of the trial.

DISCUSSION

Although previous trials[14, 25] investigating the effect of prophylactic antibiotics in implant removal were accurately designed based on the formerly active protocols, guidelines have changed. Two grams of cefazolin is the currently recommended dose of prophylaxis, mostly based on new insights in weight-based dosing. Moreover, a recent meta-analysis shows that antibiotic concentrations are lower when measured more distally in the extremity, indicating that 1g might not be sufficient below the level of the knee[18]. If the hypothesis that 2g of prophylactic cefazolin is effective in preventing SSI is supported by the results of this study, this would have implications for current guidelines. Combined with the high infection rate of IR which has already been proved in previous studies[2], it would be sufficiently substantiated for guidelines to suggest protocolled us of prophylactic antibiotics in IR of foot, ankle, lower leg or patella. Moreover, if antibiotic prophylaxis proves to be effective in reducing SSIs, it is likely to be cost-effective, since it is a relatively cheap intervention. If antibiotic prophylaxis does not turn out to be effective, the target-site concentrations of measured in this trial will hopefully provide us with an explanation.

DECLARATIONS

Ethics approval and consent to participate

Ethical approval was obtained on the 23th of December 2019 from the Medical Ethics Review Committee of the Academic Medical Center (METC AMC, reference: “METC 2019_206”). All substantial protocol amendments will be notified to the METC and to the competent authority. Non-substantial amendments (typing errors and administrative changes) will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

Funding

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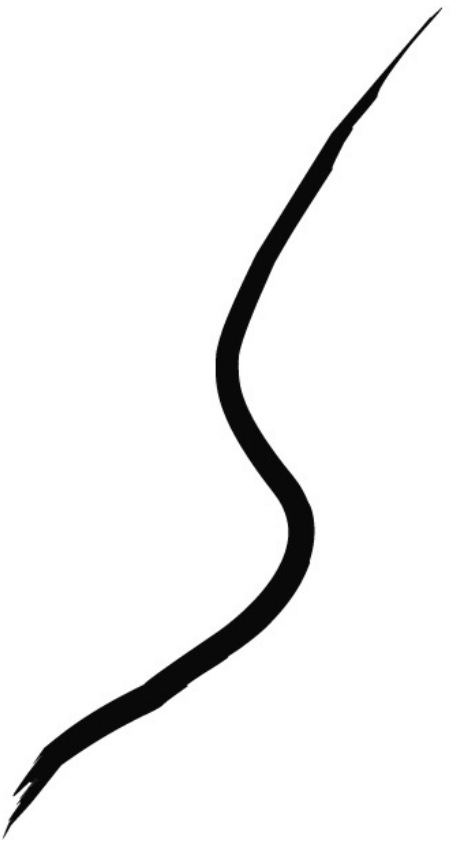
PART 3

PATIENT REPORTED OUTCOME

CHAPTER



7

FUNCTIONAL OUTCOME OF IMPLANT REMOVAL FOLLOWING FRACTURE FIXATION BELOW THE LEVEL OF THE KNEE

Sanders FRK, Backes M, Dingemans SA, Hoogendoorn JM, Schep NWL, Vermeulen J, Goslings JC, Schepers T

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ABSTRACT

AIMS

The aim of this study was to evaluate the functional outcome in patients undergoing implant removal (IR) after fracture fixation below the level of the knee.

PATIENTS AND METHODS

All adult patients (18 to 75 years) undergoing IR after fracture fixation below the level of the knee between November 2014 and September 2016 were included as part of the WIFI (Wound Infections Following Implant Removal Below the Knee) trial, performed in 17 teaching hospitals and two university hospitals in The Netherlands. In this multicenter prospective cohort, the primary outcome was the difference in functional status before and after IR, measured by the Lower Extremity Functional Scale (LEFS), with a minimal clinically important difference of nine points.

RESULTS

A total of 179 patients were included with a median age of 50 years (interquartile range (IQR) 37 to 60), of whom 71 patients (39.7%) were male. With a median score of 60 before IR (IQR 45 to 72) and 66 after IR (IQR 51 to 76) on the LEFS, there was a statistically significant improvement in functional outcome ($p < 0$ .001). A total of 31 surgical site infections (17.3%) occurred.

CONCLUSION

Although IR led to a statistically significant improvement of functional outcome, the minimal clinically important difference was not reached. In conclusion, this study shows that IR does not result in a clinically relevant improvement in functional outcome. These results, in combination with the high complication rate, highlight the importance of carefully reviewing the indication for IR.

INTRODUCTION

Implant removal (IR) after fracture fixation used to be standard practice, mostly due to perceived risks of corrosion, carcinogenesis, and allergic reactions[1]. Since the introduction of improved alloys and new materials, however, these complications have not been described. Attention has therefore recently been shifting towards the risks of IR. Although it is a frequently performed procedure that rarely takes more than one hour, it has proved not to be without risk.[2]. In addition to the fact that it is not always easy to remove implants[3], surgical site infection (SSI) occurs in up to 20% of cases following IR[4-6]. The removal of implants below the level of the knee has, in particular, been associated with high rates of SSI[2].

Currently, indications for elective IR are mostly patient-reported symptoms such as skin irritation, limited range of movement, and/or pain[7]. It can therefore be argued that the improvement of function and pain relief are the most important goals of IR and this is reflected by the focus on patient-reported outcome measures (PROMs) in recent literature on IR. Most publications, however, are surveys[8,9]. or report only pain[5,10]. The studies that do report other PROMs form a heterogeneous group, describing the procedure in a limited number of patients and in varying parts of the body[6,11-14].

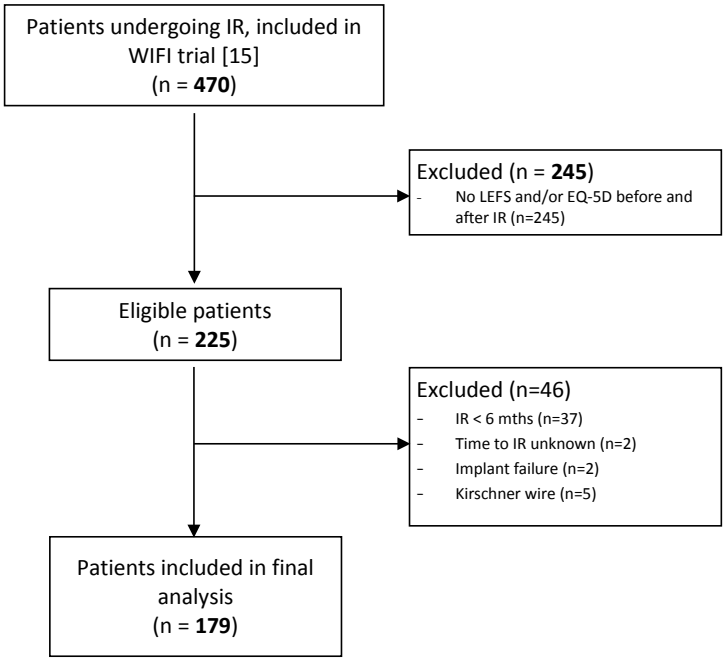
In this prospective cohort study, we sought to quantify the effect of IR on both functional outcome and quality of life (QoL) in patients undergoing removal of implants below the level of the knee following fracture fixation, with the hypothesis that the removal of implants following successful fracture healing leads to a clinically relevant improvement of functional outcome.

PATIENTS AND METHODS

Patient data were collected for the purpose of a randomized controlled trial, the WIFI (Wound Infections Following Implant Removal Below the Knee) trial, investigating the effect of prophylactic antibiotics on the risk of wound infection following IR below the knee[15]. The WIFI trial was performed in 17 teaching hospitals and two university hospitals in The Netherlands. Patients aged 18 to 75 years, undergoing IR below the level of the knee, for any reason, between November 2014 and September 2016 were eligible. Exclusion criteria were an active infection, fistula or antibiotic treatment at the time of IR, re-implantation of material in the same session, an allergy to cephalosporins, a known kidney disease, immunosuppressant use, and/or pregnancy. The full protocol has been published elsewhere[15]. The study, including the informed consent procedure, was conducted according to the principles of the Declaration of Helsinki[16], and in accordance with the Medical Research Involving Human Subjects Act.

Patients were included in this study if they completed both the baseline (preoperative) and postoperative questionnaire for functional outcome or QoL (n = 225). Baseline questionnaires were filled out preoperatively, as described in the WIFI study protocol published earlier[15]. The postoperative questionnaires were filled out after six months. Patients received the questionnaires by email and were seen within 28 days postoperatively in the outpatient clinic for a postoperative check and wound examination. Patients with an unknown period of time elapsing between fixation and IR (n = 2) or undergoing IR within six months of fixation (n = 37) were excluded. This removal was usually as part of a staged treatment strategy such as bridge plating in Lisfranc injuries, percutaneous wiring, or for implant failure. There is also more validity to assessing functional outcome after at least six months, thereby limiting the confounding effect of fracture healing on functional outcome measures. Patients whose implants were removed after the six-month point, but where those implants were wires (n = 5) or were removed for failure (n = 2), were also excluded. A response to the questionnaire was received from 52.1% of patients. The final number of included patients was 179 (Fig. 1).

Figure 1. Flowchart of included patients



Abbreviations: IR: implant removal, LEFS: Lower Extremity Functional Scale, EQ-5D: EuroQol-5D

Outcome

The primary outcome measure was the Lower Extremity Functional Scale (LEFS), a PROM that consists of 20 questions concerning physical activities, each scored by a five-point scale ranging from 'extreme difficulty/unable to perform'(0) to 'no difficulty' (4)[17]. The points for each question are calculated to give a total score between 0 and 80 points, where 80 is the best possible score. The minimal clinically important difference (MCID) of the LEFS is nine points, so any change less than this would not be clinically relevant[17].

Secondary outcomes were the EuroQol 5-dimension questionnaire (EQ-5D-3L)[18], and a patient-reported health status using a visual analogue scale (VAS), as well as predictors of an improved functional outcome as identified by a multivariable analysis.

Baseline patient characteristics and surgical characteristics were collected from all patients (Tables 1 and 2). Patient characteristics included: gender, age, body mass index (BMI), smoking, alcohol (more than three units a day) or drug abuse, relevant medical history, and treatment satisfaction. Surgical characteristics were: hospital, surgeon, time between fixation with and removal of implant, reason(s) for removal (multiple answers possible), location of the implant, type of implant, and occurrence of a SSI.

Statistical analysis

Descriptive statistics were used to report baseline characteristics (Table I). Baseline characteristics of excluded patients were compared with those of included patients with a chi-squared test (categorical), unpaired Student's *t*-test (normal distribution), or Mann–Whitney U test (non-normal distribution), as appropriate. Patient-reported outcome measure responses were evaluated for normality using the Shapiro–Wilk test and Q–Q plots. If normally distributed, the primary (LEFS) and secondary outcomes (EQ-5D and VAS) were analyzed by a paired-samples Student's *t*-test. If not normally distributed, the PROMs were compared, before and after IR, using a Wilcoxon's signed-rank test for paired values. A subgroup analysis was performed using the same statistics for patients with IR on the patient's request, and separately for patients with "pain" as reason for removal.

Predictors of functional outcome were identified using multivariable linear regression. All relevant baseline characteristics were evaluated as possible predictors, using a univariate linear regression with LEFS improvement (difference between LEFS before and after IR) as dependent variable. All characteristics with a p-value below 0.3 were entered into the multivariable analysis and eliminated backwards, until only significant contributors to the prediction model remained. Analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, New York). In all analyses, a p-value < 0.05 was considered to be of statistical significance.

To check for sufficient power to detect a clinically significant effect, a power calculation was performed. We used data from Garner et al.[14] for the standard deviation of the LEFS and

MCID of the LEFS (nine points)[17] as the non-inferiority limit. To demonstrate a clinically significant difference in functional outcome before and after IR with 90% power and a significance level of 2.5%, 74 patients were required.

RESULTS

Baseline characteristics

Baseline and surgical characteristics of the 179 included patients are displayed in Tables 1 and 2. Median age was 50 years (IQR 37 to 60), 71 patients (39.7%) were male, and the most frequent comorbidity was hypertension (10.6%). Polytrauma patients were not included in this study. The reason for IR was mostly patient-driven, with the most reported reason being pain (82.7%), followed by functional problems (7.8%). Baseline questionnaires were filled out at a median time of 13 months after fracture fixation, and postoperative questionnaires represent the functional outcome six months after IR (19 months after fracture fixation).

Table 1. Patient characteristics

Characteristic	Missing cases (incl:excl)	Included patients (n=179)	Excluded patients (n= 291)	p-value
Male:female ratio, n (%)	0:0	71:108 (39.7:60.3)	128:163 (44.0:56.0)	0.41*
Median age, yrs (IQR)	0:0	50 (37 to 60)	41 (29 to 53)	< 0.001†
Median BMI, kg/m^2 (IQR)	20:25	26.2 (23.1-29.0)	26.2 (22.7 to 29.4)	0.86†
Smoking, n (%)	11:22	29 (17.3)	89 (33.1)	0.001*
Alcohol abuse, n (%)	12:23	46 (27.5)	76 (28.4)	0.94*
Drugs abuse, n (%)	13:23	4 (2.4)	12 (4.5)	0.40*
Medical history, n (%)	0:0			
Diabetes mellitus		2 (1.1)	10 (3.4)	0.21*
Pulmonary disease		3 (1.7)	10 (3.4)	0.40*
Hypertension		19 (10.6)	27 (9.3)	0.75*
Cardiac disease		8 (4.5)	3 (1.0)	0.038*
Peripheral vascular disease		1 (0.6)	3 (1.0)	0.98*
Median VAS treatment satisfaction (IQR)	9:230	8.25 (7-9)	8 (7-10)	0.95†

Abbreviations: IQR, interquartile range; BMI, body mass index; VAS, visual analogue scale
*Chi-squared test
†Mann–Whitney U test

Excluded patients

Excluded patients differed significantly in both patient characteristics (Table 1) and surgical characteristics (Table 2). Excluded patients were significantly younger, with a median age of 41 years (IQR 29 to 53) compared with 50 years (IQR 37 to 60) ($p < 0.001$), were more often smokers ($p = 0.001$), and suffered more often from cardiac disease ($p = 0.038$). With respect to surgical characteristics (Table 2), time to IR was significantly shorter ($p < 0.001$), the reason for IR differed, the duration of surgery was shorter ($p = 0.007$), and the type of implant that

was removed differed significantly ($p < 0.001$). Other variables did not show a statistically significant difference.

Table 2. Surgical characteristics

Characteristic	Missing cases (incl:excl)	Included patients (n = 179)	Excluded patients (n = 291)	p-value
Median time to IR, mths (IQR)	0:2	13 (9 to 20)	10 (5 to 15.5)	< 0.001*
Reason for IR, n (%)†	0:0			
Pain		148 (82.7)	197 (67.7)	0.001‡
Patient's request		100 (55.9)	124 (42.6)	0.007‡
Functional problem		14 (7.8)	13 (4.5)	0.19‡
Planned by surgeon		4 (2.2)	44 (15.1)	<0.001‡
Implant dysfunction		0 (0.0)	15 (5.2)	0.005‡
Initial injury, n (%)	0:0			
Proximal tibia/tibial plateau fracture		23 (12.8)	26 (8.9)	0.054‡
Tibial shaft/cruris fracture		20 (11.2)	44 (15.1)	
Distal tibia/pilon fracture		14 (7.8)	9 (3.1)	
Ankle fracture		88 (49.2)	162 (55.7)	
Calcaneal fracture		15 (8.4)	17 (5.8)	
Chopart injury		0 (0.0)	6 (2.1)	
Talus fracture		1 (0.6)	2 (0.7)	
Lisfranc/metatarsal fracture		18 (10.1)	25 (8.6)	
Surgeon, n (%)	0:1			0.36‡
Specialist		54 (30.2)	75 (25.9)	
Resident		125 (69.8)	215 (74.1)	
Median duration of surgery, min (IQR)	19:32	34 (25 to 47)	30 (18 to 45)	0.007*
Tourniquet, n (%)	4:4	20 (11.4)	39 (13.6)	0.60‡
Location IR, n (%)	0:0			0.95‡
Foot		11 (6.1)	16 (5.5)	
Tarsus		23 (12.8)	36 (12.4)	
Ankle		101 (56.4)	172 (59.1)	
Proximal tibia		44 (24.6)	67 (23.0)	
Type of implant, n (%)	0:2			<0.001‡
K-wire		0 (0)	15 (5.2)	
Screw		35 (19.6)	66 (22.8)	
Syndesmotic screw		7 (3.9)	34 (11.8)	
Plate and screws		123 (68.7)	153 (52.9)	
Intramedullary nail		14 (7.8)	21 (7.3)	
Removal of all implants, n (%)		137 (76.5)	205 (70.4)	0.18‡
Surgical site infection, n (%)	0:0	31 (17.3)	35 (12.0)	0.14‡
Superficial		25 (14.0)	33 (11.3)	0.49‡
Deep		6 (3.4)	2 (0.7)	0.072‡

Abbreviations: excl: excluded, incl: included, IR: implant removal, IQR: interquartile range, n: number of included patients

*Mann–Whitney U test
†Multiple answers possible
‡Chi-squared test

Functional outcome and quality of life

With a median score of 60 before the IR (IQR 45 to 72) and 66 after the IR (IQR 51 to 76), the functional outcome measured by the LEFS improved statistically significantly (Z = -5.0; p < 0.001) in patients with IR after at least six months (Table 3). The MCID of nine points was not reached. The EQ-5D score after IR (median 0.81, IQR 0.73 to 1.00) was also higher than the EQ-5D score before IR surgery (median 0.81, IQR 0.73 to 0.84) (Z = -3.2; p = 0.002), although the median did not change. Median patient-reported health did not improve significantly, with a median VAS of 80 (IQR 70 to 90) before and after IR (Z = -0.2; p = 0.81).

Table 3. Patient-reported outcome measures (PROMs)

Median PROM score (IQR)	Before IR	After IR	p-value*
LEFS (n = 177) †	60 (45 to 72)	66 (51 to 76)	< 0.001
EQ-5D (n = 176) ‡	0.81 (0.73 to 0.84)	0.81 (0.73 to 1.00)	0.002
VAS self-reported health (n = 172)§	80 (70 to 90)	80 (70 to 90)	0.81

Abbreviations: IQR, interquartile range; IR, implant removal; LEFS, Lower Extremity Functional Scale; EQ-5D, EuroQol-5D; VAS: visual analogue scale

*Wilcoxon's signed-rank test for paired values
†Two patients with missing LEFS after IR
‡Three patients with missing baseline EQ-5D
§Four patients with missing baseline and seven patients with missing VAS after IR

Subgroup analyses

As shown in Table IV, a subgroup analysis of only the patients with removal on the patient's request (n = 100) had a median LEFS of 63.0 before IR (IQR 50 to 72) and 69.0 after IR (IQR 53 to 76) (Z = -3.05; p = 0.002). Patients with removal due to pain (n = 148) had a median LEFS before IR of 59.5 (IQR 43.3 to 71.5) and 66.0 (IQR 51.0 to 76.0) after IR (Z = -5.0; p < 0.001). A *post hoc*, subgroup analysis of the functional outcome for different locations of implants showed a statistically significant improvement of functional outcome after removal of implants from the ankle. More specifically, when plate and screws were removed from the ankle, this resulted in a statistically significant improvement of the LEFS (Table IV).

Predictors of functional outcome

Possible predictors of an improvement in functional outcome, as identified by univariate analysis, were: no history of drug abuse, pain as the reason for IR, patient choice as the reason for removal, removal of all implants, and a shorter time between fracture fixation and removal. Since previous studies had identified SSI as a predictor for worse functional outcome[19], this variable was added to the equation, although it was not identified in univariate analysis. The variable "antibiotic prophylaxis" was not included, since the original randomized controlled trial (RCT) found no effect of antibiotic prophylaxis on the number of SSIs, and antibiotics themselves are not considered to influence functional outcome. When all

possible predictors were entered into multivariable regression with backwards elimination, no predictors for improvement in functional outcome remained.

Table 4. Subgroup analyses of primary outcome (LEFS)

LEFS	Median score before IR (IQR)	Median score after IR (IQR)	p-value*
Reason for IR			
Patient's request (n = 100)	63.0 (50 to 72)	69.0 (53 to 76)	0.002†
Pain (n = 148)	59.5 (43 to 72)	66.0 (51 to 76)	< 0.001†
Location of IR			
Foot (n = 11)	54 (34 to 63)	57 (49 to 65)	0.62
Tarsus (n = 23)	47 (32 to 61)	57 (33 to 69)	0.11
Ankle (n = 100)‡	63 (54 to 73)	71 (59 to 77)	< 0.001†
Proximal tibia (n = 43)‡	52.5 (40.25 to 71.5)	63 (46 to 76)	0.008
Type of implant (within ankle)			
Plate and screws (n = 79)‡	63 (49.25 to 72)	71 (57 to 76)	< 0.001†
Screw (n = 13)	70 (61 to 77)	76 (64.5 to 80)	0.055
Syndesmotic screw (n = 7)	62 (54 to 73)	72 (59 to 78)	0.34
Intramedullary nail (n = 1)	57	51	N/A

Abbreviations: IR: implant removal, IQR: interquartile range, LEFS: Lower Extremity Functional Scale, N/A: not applicable

*Using the Bonferroni method (correction for multiple testing), a p-value below 0.004 was considered statistically significant (0.05/12, based on the analysis of LEFS, EuroQol (EQ)-5D, and visual analogue scale (VAS) in general (3), and all subgroup analyses (9))
†Statistically significant
‡One patient with missing LEFS after IR

Complications

The number of patients with a surgical site infection was 31 (17.3%), of whom 25 (14.0%) were superficial and six (3.4%) were deep. The number of SSIs was not related to the administration of antibiotic prophylaxis, with 17.3% developing an SSI in the group receiving cefazolin (13/75) as well as in the placebo group (18/104). Superficial infections were all treated with oral antibiotics, except for those in two patients who did not receive antibiotics and one who received intravenously administered antibiotics. Of the patients with a deep infection, all were treated with antibiotics (five intravenously, one orally) and four were also surgically treated.

DISCUSSION

This study is, to our knowledge, the largest published series on functional outcome after removal of implants, and we found that the procedure leads to a statistically significant improvement in both functional outcome and quality of life. We did not find, however, that this was clinically significant as the MCID for the LEFS was not met. This was also true of the subgroup analysis limited to patients with removal either at the patient's request or because of pain. Additionally, predictors for improvement in functional outcome could not be identified in this study.

The results of this study are in line with previous literature on the topic but the evidence, so far, has been limited. Below the level of the knee, two recent articles report functional outcome after removal of implants. Garner et al.[14] reported a prospective cohort study of all patients undergoing surgical fixation for tibial plateau fractures, and compared multiple PROMs in patients who opted for removal before and after IR (n = 39). They found an improvement in functional outcome of 8.1 points on the LEFS (median 80.0% *vs* 71.9%; $p < 0.05$), but not in QoL, measured by the 36-Item Short-Form Health Survey questionnaire (SF-36). They concluded that patients who choose the option of removal of surgical implants should expect an improvement in clinical outcomes, although they did not reach the MCID for the LEFS[17]. Williams et al[13] retrospectively studied 43 patients following internal fixation of ankle fractures. They found an improvement of 4.1 points on the Short Musculoskeletal Function Assessment (SMFA) after IR, which was statistically significant. The article did not report an MCID for the SMFA but, elsewhere in the literature, MCIDs are reported to range from 4.4 to 10 points[20,21], neither of which are reached in the cohort reported by Williams et al.[13].

Brown et al[7] did not study IR specifically, but rather prospectively followed a cohort of 126 patients with surgically fixed ankle fractures. They found that patients with persistent pain after fracture fixation had a lower score on PROMs (measured by the SMFA and SF-36). They were not able to demonstrate a difference in SMFA and SF-36 in patients who had their implants removed or retained. Although the results of these previous studies are similar to the results of this study, their conclusions are mostly based on statistically, instead of clinically, significant outcomes. Moreover, the number of patients included in these studies was small, resulting in insufficient power to detect a clinically relevant difference.

Complication rates following IR have been described to be up to 37%[4]. When focusing only on SSIs as a postoperative complication, rates are found to be between 0% and 20%[2,4-6]. This study confirms this relatively high rate with a total of 31 SSIs (17.3%: 14.0% superficial, 3.4% deep). A possible explanation for these high infection rates might be the need to operate through scar tissue or the short period within which most patients return to weight-bearing and mobility compared with after fracture fixation.

A subgroup that is particularly of interest in this trial is the group of patients with a 'relative' indication for IR, such as "the implant does not belong in my body" or complaints of pain or functional impairment that cannot necessarily be attributed to the implant. In these patients, it is especially important to carefully weigh the benefits and risks of the procedure. By performing a subgroup analysis on patients who had their implant removed at their own request, we tried to show the results for patients with a 'relative' indication. However, multiple reasons for IR could be given in the questionnaire, and the answer "at patient's request" often overlapped with "pain". It was not, therefore, possible to completely separate patients with an unspecific reason for IR from the patients with pain as reason for removal. Results of the subgroup analysis can therefore not be interpreted specifically for patients with a wish for IR without accompanying pain.

Limitations

The results are based on the improvement in functional outcome before and after IR, without offering a control group. Although we tried to rule out the influence of the 'natural healing process' by including only patients who had IR after more than six months, results cannot be compared with patients who retained their implant. Because most studies reporting on functional outcome after fracture fixation have a maximum follow-up time of 12 months, it is unclear whether a control group would still have improvement of functional outcome after this time. The LEFS of included patients after IR was, however, comparable with the LEFS in healthy individuals with a history (more than one year ago) of lower limb fracture[22], suggesting that further improvement in functional outcome would not be expected.

Selection bias may have occurred; since the data for this study were collected within the scope of a clinical trial with SSI as the primary outcome, the inclusion and exclusion criteria of that trial influenced our population. Patients with a known infection, pregnancy, or severe kidney disease, for example, were excluded from this database. Another cause of selection bias might be that only 225 out of 470 patients filled out both baseline and postoperative questionnaires, and were therefore eligible for inclusion. By reporting the statistically significant differences in baseline and surgical criteria between the included and excluded patients, we aimed to provide the reader with the information necessary to assess the risk of bias caused by applying these exclusion criteria. Moreover, Juto et al[23] recently showed that functional outcome did not differ between responders and non-responders when corrected for age and gender (in patients with an upper limb fracture). An effect of the missing patients on functional outcome, considering the age difference in included and excluded patients, cannot be ruled out.

The LEFS and EQ-5D are both questionnaires that are not validated specifically for this population. Although this approach allows for a better comparison with existing literature, it may also cause under-reporting of functional complaints.

Another limitation is that, although a subgroup analysis for IR due to pain was performed, the type of pain was unknown. It would have been interesting to further subdivide pain into diffuse/localized and continuous/movement-related pain, since implant-localized pain is more likely to improve than non-specific or diffuse pain. Unfortunately, these data were not collected, although it would be a good subject for future research.

Finally, the *post hoc* power calculation showed that the number of patients needed to find a clinically important difference was less than half of the number of patients included in this trial. Due to the fact that the number of patients included in this study can show a relatively small difference between groups, any statistically significant outcomes discovered would not necessarily be clinically relevant.

The large number of included patients from different hospitals did result in sufficient power to be able to detect a clinically significant difference, if there was one. Moreover, the fact that multiple university and non-university hospitals throughout The Netherlands contributed to this study enlarges the external validity of the results. This is also true for the variety of injuries and locations of IR in the included patients. By using the LEFS as a primary outcome value, this study comments not only on statistical significance, but also on clinical relevance, since the MCID for the LEFS has been defined[17].

Regardless of the limitations of this study, it has important implications for current clinical practice. It underlines the importance of carefully reviewing the indication for IR, especially since the most common indication for removal was patient choice. Expectation management is an important part of shared decision making, and when patients are adequately informed about the chances of functional improvement *versus* the risks of surgery, this might reduce the number of patients requesting their implants be removed. The absence of a clinically relevant improvement in combination with the large risk of an SSI[2], in addition to other risks of surgery, should be incorporated into the surgeon's advice. Moreover, we do not recommend standard removal of implants in the absence of a firm indication.

In conclusion, IR below the level of the knee following fracture fixation does not result in a clinically relevant improvement in functional outcome or quality of life. Patients who wish to have their implant removed should be advised that the procedure may not lead to improved functional outcome, and that the risks are not negligible.

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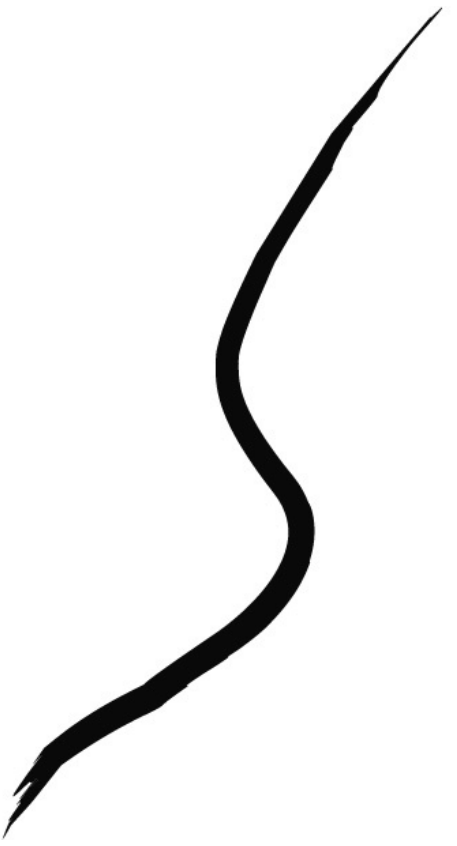
CHAPTER



8

FUNCTIONAL OUTCOME OF ROUTINE VERSUS ON DEMAND REMOVAL OF THE SYNDESMOTIC SCREW; A MULTICENTER RANDOMIZED CLINICAL TRIAL

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Submitted

ABSTRACT

BACKGROUND

The preferred surgical treatment of syndesmotic injuries is a syndesmotic screw (SS), which is traditionally removed after 8-12 weeks. However, implant removal does not always improve functional outcome, and complication rates are high. Therefore, the aim of this study was to investigate whether "on demand removal" is non-inferior to routine removal of the SS regarding functional outcome.

METHODS

In this multicenter RCT with a non-inferiority design, all consecutive adult patients with syndesmotic injury (isolated or with fracture) were randomized between routine removal (RR) after 8-12 weeks and on demand removal (ODR), retaining the SS unless there were complaints warranting removal. Primary outcome was functional outcome at 12 months after SS placement, measured by the Olerud-Molander Score (OMAS). The non-inferiority limit (δ) was a 10 points difference in OMAS (in both intention-to-treat and per-protocol analysis).

RESULTS

There were 152 patients included in final analysis (73 patients in RR and 79 patients in ODR group), 59.2% male, mean age: 46.9 (SD 14.6). Median OMAS at 12 months after syndesmotic fixation was 85 (IQR: 60-95) for RR and 80 (IQR: 65-100) for ODR. The non-inferiority test indicated that the observed effect size was significantly within the equivalent bounds of -10 and 10 scale points ($p<0.001$), meaning ODR was not inferior to RR. In the per-protocol groups the median OMAS was 85 (IQR: 62.5-95) for RR and 82.5 for ODR (IQR: 65-96.3) at 12 months, which was also non-inferior ($p=0.001$). There were significantly more complications in the RR group (12/73) than in the ODR group (1/79), $p=0.007$.

CONCLUSIONS

On demand removal of the syndesmotic screw is not inferior to routine removal when it comes to functional outcome. , this offers a strong argument to adopt ODR as standard practice of care after syndesmotic screw fixation.

TRIAL REGISTRATION

Netherlands Trial Register (NTR5965) and Clinicaltrials.gov (NCT02896998) on July 15th 2016.

BACKGROUND

Syndesmotic injuries are common, being present in approximately 15-20% of surgically treated ankle fractures[1,2]. The preferred surgical treatment of syndesmotic injuries is a syndesmotic screw (SS), which is traditionally removed after 8-12 weeks, as it is thought to hamper ankle function and cause pain when in place during weight-bearing[3–5]. It has also been argued that removing the SS is necessary to achieve final anatomical reduction[6]. Other studies found that syndesmotic screw removal (SSR) does not necessarily result in improvement of functional outcome or range of motion (ROM)[7-11]. In case of a broken or loosened SS, restrictions of natural movement of the distal tibiofibular syndesmosis would no longer be present[8,10,11].
SSR is a procedure that rarely takes more than an hour. Prophylactic antibiotics are not routinely used. Nevertheless, infectious complications are not uncommon, with surgical site infection (SSI) rates of up to 9%[11-14]. With the relatively high complication rate of SSR in mind it could be beneficial to retain SSs or to remove if the patient experiences complaints. We therefore aimed to investigate the effect of "on demand removal" of the SS on functional outcome. The hypothesis was that functional outcome at 12 months after syndesmotic fixation is comparable in patients with on demand removal (ODR) and routine removal (RR).

METHODS

The ROutine vs. on DEmand removal Of the syndesmotic screw (RODEO) trial, was a pragmatic international multicenter randomized controlled trial, comparing on demand and routine removal of the SS. The study was registered at ClinicalTrials.gov (NCT02896998) and the study protocol was published[15]. The trial was conducted in 17 centers, of which 14 were teaching hospitals and 3 were academic, level 1 trauma centers.

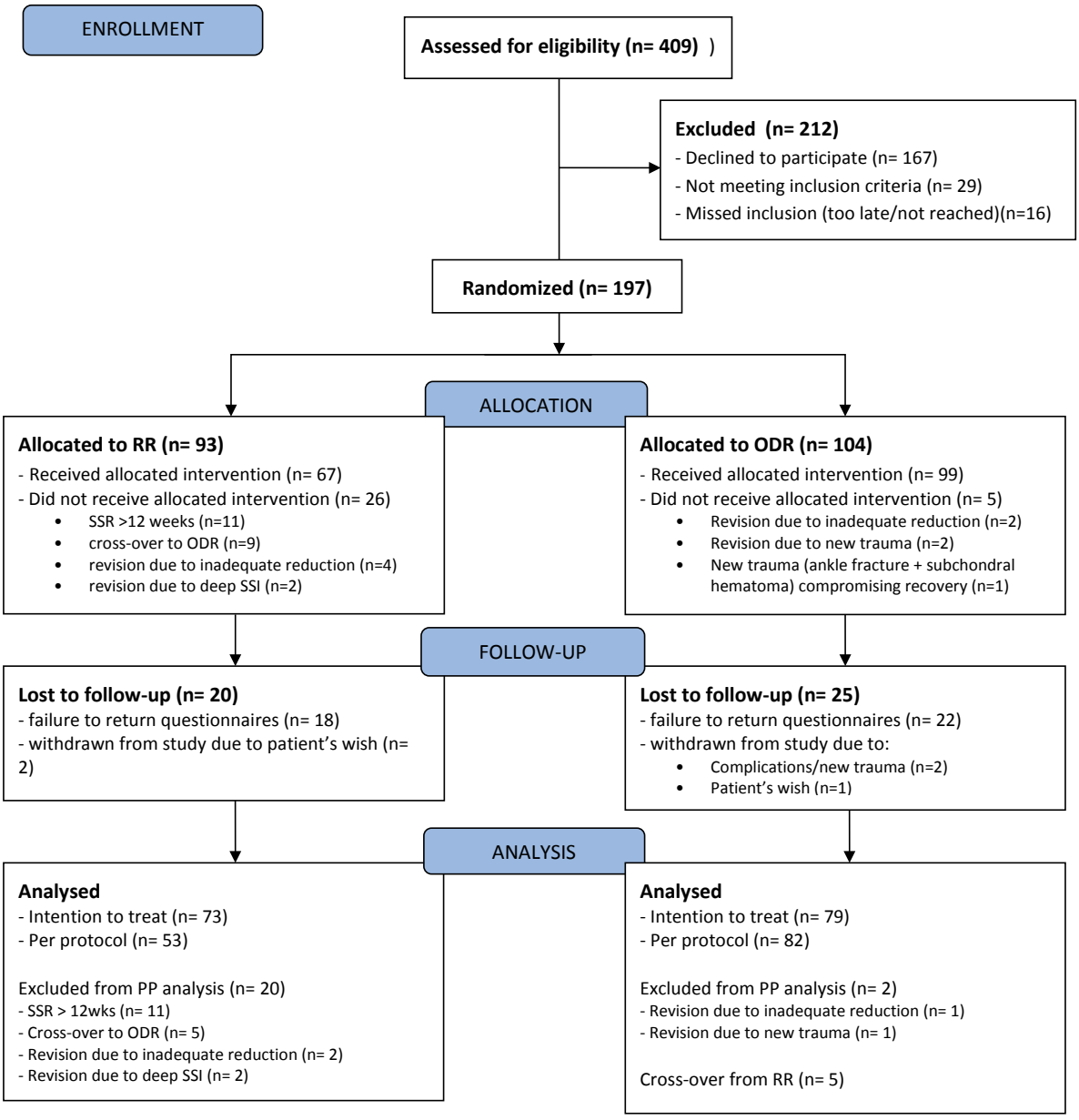
Participants

All adult patients (>17 y/o) with traumatic syndesmotic injury surgically treated within 2 weeks of trauma using 1 or 2 SSs were eligible for inclusion. Both unstable ankle fractures with syndesmotic disruption and isolated syndesmotic injuries were included. Exclusion criteria were; an ISS score >15, insufficient physical condition (to allow for potential SSR), concomitant injury of the ipsi- or contralateral side or other medical conditions hampering rehabilitation, and insufficient comprehension of Dutch or English language.

Interventions

Patients randomized for RR underwent SSR at 8-12 weeks after definite syndesmotic fixation according to protocol(15). If the screw(s) were already broken at that time, surgeons were advised not to remove them unless they caused complaints. The exact timing of removal (within window of 8-12 weeks) and postoperative treatment routine was left to the judgement of the treating surgeon and hospital protocol. Patients were seen at the outpatient clinic by their treating surgeon and the coordinating investigator at 3 months, 6

Figure 1. CONSORT Flow Diagram of Included Patients



months and 12 months after syndesmotic fixation. During each of these visits ROM was measured, and the patient filled out functional outcome questionnaires (see "Outcomes"). Additionally, at 3 month follow-up, wound inspection and radiographic imaging (Mortise view) were performed. Patients randomized for ODR were seen according to the same follow-up schedule and were closely monitored for complaints. ODR was defined as retaining the syndesmotic screw unless there were complaints warranting removal (e.g. localized pain, screw backing out causing skin irritation, infection). Patients (or surgeon) could opt for SSR at any time, but were usually advised to wait, at least until fracture healing allowed for any additional implants to be removed (if necessary), in order to combine these procedures in case of clinically relevant hardware complaints. Time of removal and whether or not additional material was removed was recorded for all patients.

Objectives

The objective of this pragmatic RCT was to investigate the functional outcome of ODR compared to RR of the syndesmotic screw, placed in acute syndesmotic injuries. The hypothesis was that ODR would result in a non-inferior functional outcome when compared to RR.

Outcomes

The primary outcome was functional outcome at 12 months after syndesmotic fixation, as measured by the Olerud-Molander ankle score (OMAS), a patient reported outcome measure with a final score of 0-100, with 100 indicating full functioning(16). The OMAS was also filled out at 3 and 6 months after fixation. Secondary outcomes were: 1) functional outcome using the American Orthopedic Foot and Ankle Hindfoot Score (AOFAS); 2) pain, using a ten-point Visual Analog Scale (VAS); 3) active ROM, reported as the difference in absolute number of degrees (flexion + extension) between injured and healthy side; and 4) complications. Specifically enquired after during follow-up visits were wound healing problems, such as wound dehiscence or SSIs (according to CDC criteria(17)) and recurrent diastasis (diagnosed based on complaints and radiographic imaging). Other complications (e.g. deep venous thrombosis, malreduction, non-union) were reported to the coordinating researcher at the time they occurred. All charts were screened at least 12 months after inclusion of the final patient in order not to miss any unreported complications or revision procedures.

All mentioned outcomes were measured at 3, 6 and 12 months after syndesmotic fixation. Furthermore, baseline patient, fracture and surgical characteristics were collected, as well as the immobilization and weight-bearing policy. Status of the SS was documented as the last date it was reported to be intact and the first date it was found to be broken, using radiographic imaging and surgical documentation.

Sample size

The sample size calculation was based on a non-inferiority design, using the OMAS at 12 months as primary outcome measure. With a one-sided significance level (α) of 0.025, 90% power (ß), standard deviation (SD) of 19 points and a non-inferiority limit of 10 points on the OMAS, 152 subjects were required. In order to conduct a subgroup analysis based on age (<60/≥60 y/o) with the same power, lower standard deviations, and incorporating a lost to follow-up of 10%, a total of 196 patients was required to prove non-inferiority(15).

Randomization

Patients were randomized 1:1 to either RR or ODR, using variable blocks of 4, 6 and 8, stratified per institute and by age category (≥60 or <60 years old). Randomization was performed centrally by the coordinating investigator, who then notified the patient and treating (orthopedic) surgeon. The randomization sequence was generated by a dedicated computer randomization software program (Castor EDC18), ensuring allocation concealment.

Blinding

Considering the nature of the intervention, blinding of patient, surgeon or outcome assessor was not possible.

Statistical methods

Descriptive methods were used to assess distribution of data and homogeneity of treatment groups. The primary outcome was analyzed according to the intention-to-treat as well as the per-protocol principle, non-inferiority only being declared if both analyses proved non-inferiority of ODR compared to RR. In per-protocol analysis, cross-overs were analyzed in the group they crossed over to and patients not treated according to the protocol of either group were excluded, as well as patients where syndesmotic fixation was revised (due to a new trauma or complication). The primary outcome was presented as median and IQR and tested for non-inferiority using a one-sided TOST equivalence test based on Student's t-test[19], with an alpha of 0.025, equal variances assumed and equivalent bounds of -10 and 10 scale points. Secondary outcomes were analyzed using either a t-test or Mann-Whitney U test for continuous data, according to distribution, and a Chi Square test for categorical data. Possible predictors of functional outcome were identified using a univariable linear regression. All variables with a (near) significant relationship with the 12 month OMAS ($p < 0.2$) were added to multivariable linear regression in order to identify independent predictors of functional outcome. All analyses were performed using SPSS, version 26.0.

RESULTS

Participants

Out of 409 eligible patients, 197 were randomized (Figure 1). As shown in Figure 1, 45 patients did not have complete primary outcome data, leaving 152 (73 patients in RR and 79

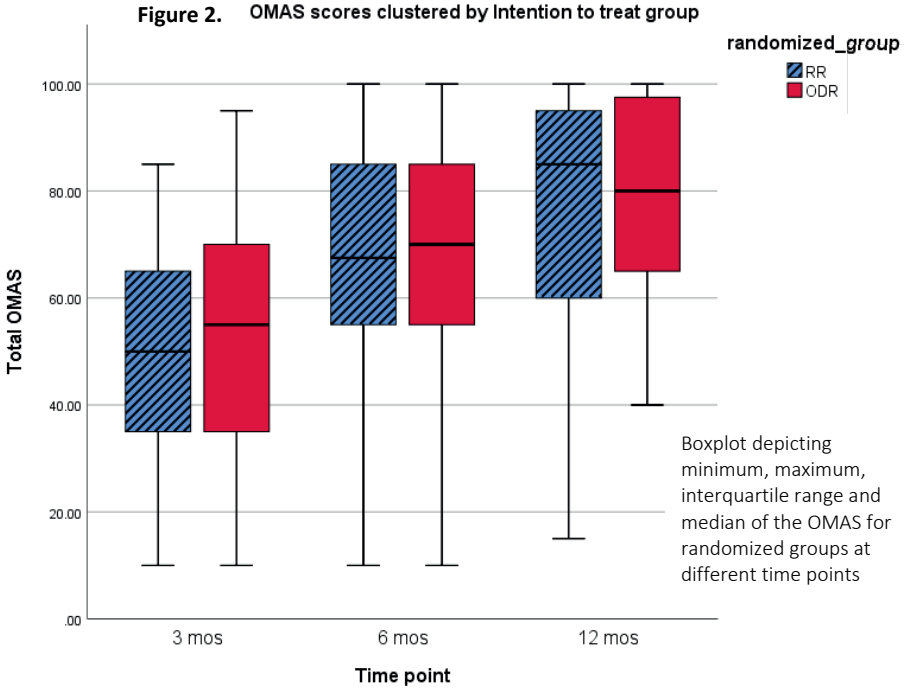
patients in ODR group) for inclusion in final analysis. Of all included patients, 59.2% was male and the mean age was 46.9 (SD: 14.6). The distribution of patients over the age groups was 120 (RR: 59/ODR: 61) in the < 60 y/o group and 32 (RR: 14, ODR: 18) in the ≥ 60 y/o group. Baseline characteristics were similar between randomization groups (Table 1), as well as between included patients and those lost to follow-up (Table 1 of Supplemental material). The per-protocol groups consisted of 53 and 82 patients for RR and ODR respectively (Figure 1).

In the RR group, SSR was performed in 67 of 73 cases (5 cross-overs, 1 revision surgery) at a mean of 11 weeks (SD 2.4) after syndesmotic fixation, with a range from 8 to 18 weeks. In nine cases, the screw was already broken at time of removal. The number of removals (within 12 months) in the ODR group was 18 (23%) at a mean of 33 weeks (SD 10.1), ranging from 13 to 49 weeks after syndesmotic fixation. Reasons for removal were pain (n= 7), limited ROM (n= 4), stiffness (n=2), revision surgery where new syndesmotic fixation was indicated (n= 2), skin reaction to implants (n= 1), screw starting to back out (n= 1), patient's wish not otherwise described (n= 1). None of the five patients who crossed over from RR to ODR had their screw removed. Of the 61 ODR patients who retained their SS, 19 broke their screw within 12 months (13 after >12 weeks). Out of the 18 ODR patients who underwent SSR, the screw was already broken in 10 cases. In addition, two out of the five cross overs broke their screw.

Primary outcome

The median OMAS at 12 months after syndesmotic fixation was 85 (IQR: 60-95) for the RR group and 80 (IQR: 65-100) for the ODR group (Figure 2). The non-inferiority test indicated that for the intention-to-treat analysis the observed effect size was significantly within the equivalent bounds (t(150) = -3.56, p<0.001), meaning ODR was not inferior to RR. In the per-protocol groups the median OMAS was 85 (IQR: 62.5-95) for RR and 82.5 for ODR (IQR: 65-96.3) at 12 months, which was also non-inferior (t(133) = -3.14, p = 0.001).

Figure 2. **OMAS scores clustered by Intention to treat group**



Boxplot depicting minimum, maximum, interquartile range and median of the OMAS for randomized groups at different time points

Table 1. Baseline patient and surgical characteristics

	Routine Removal (N = 73)	On Demand Removal (N = 79)
Sex, men	47 (64.4%)	43 (54.4%)
Age, mean (SD)	45.3 (15.0)	48.3 (14.1)
<60 y/o	59 (80.8%)	61 (77.2%)
>/=60 y/o	14 (19.2%)	18 (22.8%)
Weight, kg, mean (SD)	84.6 (14.4)	88.1 (17.9)
Missing		2
BMI, mean (SD)	27.3 (4.3)	28.6 (5.7)
Missing	4	2
Nicotine use	17 (25.4%)	18 (24.0%)
Missing	6	4
Alcohol abuse (>2units/day)	6 (8.8%)	8 (10.7%)
Missing	5	4
Illegal drug use	8 (11.6%)	1 (1.3%)
Missing	4	4
Diabetes Mellitus	3 (4.1%)	4 (5.1%)
- **Type 1**	1	0
- **Type 2**	2	4
COPD	0	3 (3.8%)
PAD	0	1 (1.3%)
Injury		
Weber B	17 (23.6%)	18 (22.8%)
Weber C	41 (56.9%)	39 (49.4%)
Maisonneuve	11 (15.3%)	22 (27.8%)
Isolated synd.	2 (2.8%)	0
Other	1 (1.4%)	0
Missing	1	
ASA classification		
I	38 (52.8%)	28 (36.4%)
II	33 (45.8%)	41 (53.2%)
III	1 (1.4%)	8 (10.4%)
Missing	1	2
Duration surgery, min.	64.8 (38.3)	62.5 (35.9)
Missing	7	8
Tourniquet use	21 (40.4%)	18 (29%)
Missing	21	17
# Screw(s):		
1	50 (69.4%)	51 (64.6%)
2	22 (30.6%)	28 (35.4%)
Screw diameter:		
3.0 mm	3 (4.2%)	1 (1.3%)
3.5 mm	64 (88.9%)	74 (93.7%)
4.0 mm	1 (1.4%)	1 (1.3%)
4.5 mm	4 (5.6%)	3 (3.8%)
Missing	1	

Cortices:		
3	57 (79.2%)	62 (78.5%)
4	15 (20.8%)	17 (21.5%)
Missing	1	
Level, mm*	23.6 (7.2)	22.5 (9.2)
Missing	4	3
Cast after surgery		
Weeks	5.4 (1.5)	5.3 (1.7)
Missing	9	9
Complication of fixation, No.(%)	16 (22%)	12 (15.2%)
Missing	1	
Weight bearing		
Weeks to full	4.8 (1.8)	4.9 (1.8)
Missing	2	1

Abbreviations: ASA: American Society of Anesthesiologists, BMI: body mass index (weight/(height^2)), COPD: Chronic Obstructive Pulmonary Disease, PAF: Peripheral Artery Disease

*measured from tibial plafond to most distal syndesmotic screw
** of which 2 combined with non-union and 1 with bad reduction

Secondary Outcomes

OMAS scores of three and six months after syndesmotic fixation were comparable between randomization groups, as illustrated in Figure 2. Functional outcome as measured by the AOFAS also did not differ between RR and ODR at any time point. At three months, median scores were 77 (IQR: 61.3-82) and 78 (IQR: 67-86) for RR and ODR respectively (p=0.138), for six months this was 81 (IQR: 71.8-88) and 85 (IQR: 75-90) (p=0.103) and for 12 months 87 (IQR: 84-98) and 85 (IQR: 80-100) (p=0.787). When zooming in on the sub-scores of the AOFAS, the sub-score "function" was marginally higher for the ODR group at three and six months compared to the RR group (Figure 1 of Appendix).

Neither ROM nor the VAS pain scores differed significantly at any time point (Figure 3).

Complications

There were significantly more complications in the RR group (12/73) than in the ODR group (1/79), p=0.007. The 12 complications in the RR group comprised; wound dehiscence (n=5), superficial SSI (n=2), deep SSI (n=2), diastasis after removal (n=1), synovitis (n=1), increase in stiffness after removal (n=1). Four of 12 patients had a complication of the syndesmotic fixation as well; two deep infections (one resulting in a flare-up after SSR, one in diastasis after SSR), one superficial SSI (wound dehiscence after SSR) and a synovitis (persisting after SSR). In addition, within lost-to-follow-up group, three complications occurred consisting of one deep SSI, one superficial SSI and one diastasis. In the ODR group, there was only one complication; a superficial SSI after removal of all implants, seven months after syndesmotic fixation. In the cross-over patients, no complications arose. In one lost-to-follow-up patient,

who would have crossed over to ODR, the retained SS started to back out 14 months after placement, ultimately resulting in a fistula, after which the screw was removed.

Figure 3a. Mean ROM difference (flexion + extension) between healthy and injured ankle

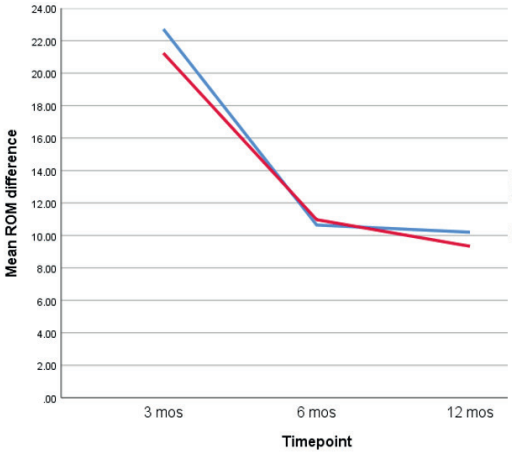
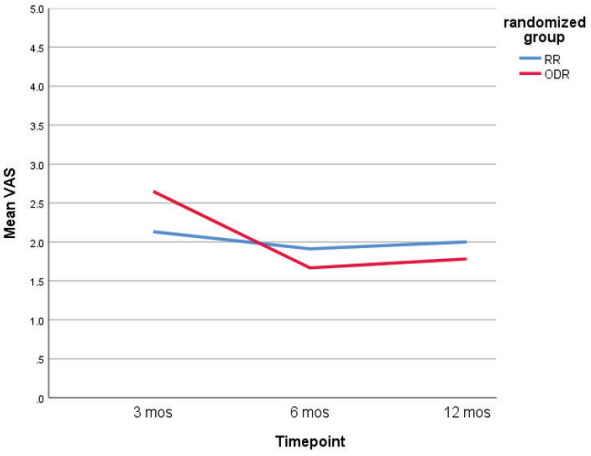


Figure 3b. Mean pain levels (VAS)



Abbreviations: RR: routine removal, ROM: range of motion, ODR: on demand removal, VAS: visual analogue scale

Predictors of functional outcome

Possible predictors for functional outcome were: age, sex, alcohol abuse, illegal drugs abuse, previous fracture, ASA classification, type of fracture, duration of fixation surgery, diameter of SS, cast treatment (after syndesmotic fixation), status of SS (broken/intact/removed), complication of syndesmotic fixation surgery, complication of RR/ODR, and revision surgery. In multivariable analysis; female sex, longer duration of surgery, complication of fixation, and complication of RR/ODR remained as independent predictors of outcome with a negative impact on 12 month OMAS (Table 3 of Appendix).

Subgroup analyses

For the subgroup of patients under 60 years old median 12-month OMAS in ODR was non-inferior (p=0.001), with medians of 85 (IQR: 65-95) in RR and 85 (IQR: 62.5-100) in ODR. For patients over 60 years old this was 77.5 (IQR: 55-96.3) in RR and 80 (IQR: 63.8-92.5) in the ODR group, which was also non-inferior (p=0.041).

In Table 2, results were compared between all patients who had their SS removed at 12 months, patients with a retained screw that was confirmed to be intact and a retained screw that was confirmed to be broken, regardless of randomized group. No significant differences were found between these groups in functional outcome, ROM or pain.

A post-hoc power analysis showed that with the current pooled standard deviation of 21, 93 patients per group would be required for 90% power. However, in order to achieve 80% power, 70 patients per group are sufficient.

Table 2 Subgroup analyses based on SS state

	Removed (n= 75)	Intact (n= 11)	Broken (n= 30)	Statistical sign.
OMAS, median [IQR]	85 [60-95]	70 [45-90]	85 [60-90]	p= 0.405
AOFAS, median [IQR]*	85 [81-97.5]	83 [67.8-87]	86 [81.5-100]	p= 0.239
VAS, median [IQR]**	1 [0-3]	1 [1-4]	2 [1-4]	P= 0.611
ROM, mean (SD)***	11.2 (11.0)	8.8 (11.3)	6.5 (8.8)	p= 0.403

For this analysis, patients with revision syndesmotic fixation and unsure status of the screw were excluded

Abbreviations: OMAS (Olerud Molander Ankle Score), AOFAS, VAS in median [IQR], ROM in mean (SD) degrees difference between injured and healthy side

*missing: 34 in removed, 1 in intact, 16 in broken group
** missing: 32 in removed, 2 in intact and 15 in broken group
*** difference between healthy and injured side (in degrees of total flexion plus extension), compared using Oneway ANOVA. missing: 45 in removed, 3 in intact, 18 in broken group

DISCUSSION

In this multicenter, randomized controlled trial we found that ODR of the syndesmotic screw was non-inferior to RR with regard to functional outcome. Additionally, no differences were identified in pain or ROM at any given time point between the two groups.

Functional outcome scores found in this trial were comparable to previous literature. Two systematic reviews have appeared discussing differences in functional outcome after removing or retaining the SS[21,22]. Both concluded that RR is not indicated; an advise based on low quality, mostly retrospective studies. The one RCT that was included in both reviews, found an OMAS of 82.4 in the group retaining the SS and 86.7 in the removal group (p=0.367)[11]. In the other RCT by Hoiness et al., the RR group received one quadricortical screw and the ODR group two tricortical screws[23]. They found significantly better outcomes of the ODR group at three months, but no statistically significant difference in mean OMAS after 12 months with 88.8 points for ODR and 83.3 for RR[23].

Even though multiple studies have already carefully concluded that routine removal of the SS is not indicated, especially when broken, the opinion is still that intact, retained screws do cause limitations in ROM and functional outcome. This opinion was supported by Manjoo et al. who found significantly lower OMAS results in patients with intact retained screws (46.5) compared to patients with a broken screw (62.2) or RR (66.8)[8]. In the current trial however,

we did not find any statistically significant differences between patients with removed, intact or broken screws at 12 months (Table 2). Although the OMAS seemed lower in patients with an intact screw, the AOFAS was not, pain scores were similar and ROM even seemed to differ less from the healthy side in intact screws when compared to removed screws. A likely explanation for the lack of difference in outcome is that retained SSs either break, or (when intact) start loosening within the bone, thereby regaining the initially impaired ROM. However, no firm conclusions can be drawn, since the position of the screw may also be of influence on where it breaks and whether it causes complaints[24], and in the current trial there were no rules as for the level of SS insertion.
Significantly more complications occurred in the RR group, mostly consisting of wound healing disorders. Previous studies have shown that the incidence of SSIs after syndesmotic screw removal was around 4%[Chapter I, this thesis]. We found SSI rates of 5%, and if patients without primary outcome were included this was even higher (8.2%). In addition, wound dehiscence was quite common (5/73).
We found that only 23% of patients randomized for ODR had their SS removed (within 12 months), in the scenario that patients were told that their screw could be removed at any time. If the results of this trial are implemented in guidelines, counselling of patients has the potential to further decrease the removal rate. As the results of this trial show, by not routinely removing SSs, many complications can be avoided.

Limitations

This study has several limitations. First of all, since this was a pragmatic trial without instructions for fixation and no post-operative CT scans, the quality of tibiofibular reduction could not be guaranteed or evaluated sufficiently. Secondly, a significant amount of patients who were eligible declined participation because of the randomization aspect, causing a potential selection bias. Moreover, the lost to-follow-up rate (22.8%) was higher than predicted, thereby decreasing the power of the study. Most patients resumed their daily lives between three and six months after fixation, and were therefore less motivated to come back to the hospital and/fill out the questionnaires at 12 months. Although baseline criteria of lost-to-follow-up patients were acquired, uncollected characteristics such as environment and social class may very well differ and be of influence on the outcome, causing a selection bias[25]. However, no significant differences were found in baseline criteria between patients lost-to-follow-up and included patients, loss-to-follow-up was equally distributed over randomization groups and the post-hoc power analysis showed sufficient remaining power (80%). Another limitation is that radiographic imaging at the 12-month time point was only acquired in a minority of patients, which leaves us uncertain about the status of the SS (broken/intact) at that time. To compare outcome between removed, broken and intact screws we have excluded patients with no confirmed status of the screw, leading to smaller groups and conclusions based on incomplete data. Finally, although we found a very low rate of complications in the ODR group, 12-month follow-up might not be sufficient. It is important to keep in mind that there might be long term complications of retaining the SS that we have

not encountered in this trial. Future studies should focus on the long term consequences of retaining the SS and identifying uncontested indications for removal.

CONCLUSIONS

On demand removal of the syndesmotic screw is non-inferior to routine removal in terms of functional outcome. Combined with the high complication rate of screw removal, this offers a strong argument to adopt on demand removal as standard practice of care after SS fixation.

ACKNOWLEDGEMENTS

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SUPPLEMENTAL MATERIAL

Table 1 Baseline characteristics of included and loss to follow up patients

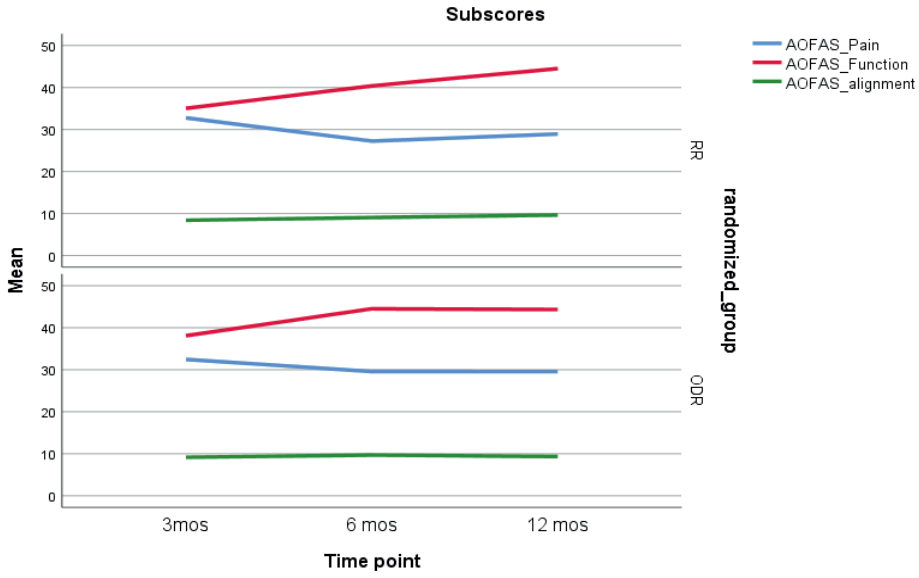
	Included (N = 152)	Lost to follow up (N = 45)	Sign.
Sex, men	90 (59.2%)	29 (64.4%)	0.648
Age, mean (SD)	46.9 (14.6)	43.1 (15.7)	0.132
- **<60 y/o**	- 120 (78.9%)	- 40 (88.9%)	0.200
- **>/=60 y/o**	- 32 (21.1%)	- 5 (11.1%)	
Weight, kg, mean (SD)	86.3 (16.4)	88.7 (20.9)	0.441
Missing	6	*4*	
BMI, mean (SD)	27.9 (5.1)	29.1 (6.9)	0.220
Missing	*8*	*6*	
Nicotine use	35 (24.6%)	14 (33.3%)	0.532
Missing	10	3	
Alcohol abuse (>2units/day)	14 (9.8%)	4 (9.8%)	0.866
Missing	9	4	
Illegal drug use	9 (6.3%)	4 (9.8%)	0.738
Missing	8	*4*	
Diabetes Mellitus	7 (4.6%)	3 (6.7%)	0.868
- **Type 1**	1	0	
- **Type 2**	6	3	
COPD	3 (2.0%)	4 (8.9%)	0.081
PAD	1 (0.7%)	0	1.000
Injury			
- **Weber B**	35 (23.2%)	12 (26.7%)	0.246
- **Weber C**	80 (53.0%)	20 (44.4%)	
- **Maisonneuve**	33 (21.9%)	9 (20.0%)	
- **Isolated synd.**	2 (1.3%)	3 (6.7%)	
- **Other**	1 (0.7%)	1 (2.2%)	
- **Missing**	1		
ASA classification			
- **I**	66 (44.3%)	22 (48.9%)	0.355
- **II**	74 (49.7%)	18 (40.0%)	
- **III**	9 (6.0%)	5 (11.1%)	
- **Missing**	3		
Duration surgery, min.	63.6 (37.0)	60.8 (27.2)	0.658
Missing	15	5	
Tourniquet use	39 (34.2%)	18 (48.3%)	0.168
Missing	38	8	
# Screw(s):			1.000
- **1**	101 (66.9%)	30 (68.2%)	
- **2**	50 (33.1%)	14 (31.8%)	
Screw diameter:			0.449
- **3.0 mm**	4 (2.6%)	2 (4.5%)	
- **3.5 mm**	138 (91.4%)	41 (93.2%)	
- **4.0 mm**	2 (1.3%)	1 (2.3%)	
- **4.5 mm**	7 (4.6%)	0	
Missing	1	1	

Cortices:			0.213
- **3**	119 (78.8%)	39 (88.6%)	
- **4**	32 (21.2%)	5 (11.4%)	
Missing	1	1	
Level, mm*	23.0 (8.3)	22.8 (9.6)	0.888
Missing	7	2	
Cast after surgery	135 (89.4%)	43 (97.7%)	0.156
Missing	1	1	
Full weight bearing	2 (1.3%)	0	1.000
Missing	1	1	

Table 2 Predictors of functional outcome

Variables	B	Lower Bound 95% CI	Upper Bound 95% CI	Sig.
(Constant)	101.938	91.9	111.9	.000
Sex	-10.137	-16.3	-3.9	.002
Duration of Surgery (min)	-.093	-.176	-.010	.029
Compl. fixation	-19.876	-27.7	-12.0	.000
Compl. intervention	-10.692	-20.9	-.528	.039

Figure 1 AOFAS sub-scores



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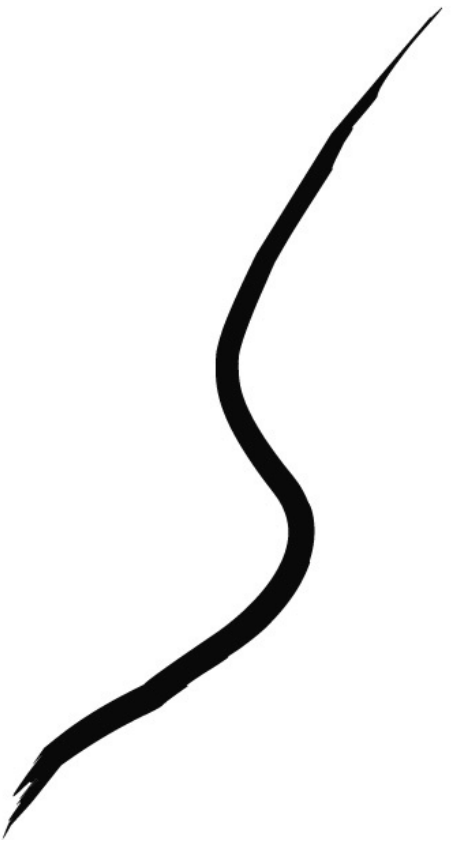

9

CLAIMS IN ORTHOPAEDIC FOOT/ANKLE SURGERY, HOW CAN THEY HELP TO IMPROVE QUALITY OF CARE? A RETROSPECTIVE CLAIM ANALYSIS

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ABSTRACT

BACKGROUND

Orthopedic foot/ankle surgery is a high risk specialty when it comes to malpractice claims. This study aims to evaluate the incidence, characteristics and outcome of claims in this area.

METHODS

This was a retrospective, 10-year claim analysis, with data from an anonymous database. Baseline claim/claimant characteristics were collected from all orthopedic foot/ankle related cases.

RESULTS

Of 460 claims in total, most were related to delay in/wrong diagnosis or to (complications of) elective surgical procedures. Whether a claims was settled was related to type of injury (fracture) and type of claim (diagnostic mistake). Median amount disbursed in settled claims was €12,549. Claim incidence did not increase over the years.

CONCLUSION

Missed fracture diagnosis and “failed”/disappointing results of elective surgical procedures were the most common causes for claims. Sufficient knowledge of missed (foot) fractures and clear communication/expectation management before elective procedures could help to improve quality of healthcare and patient satisfaction.

BACKGROUND

Recently, the fear of receiving a malpractice claim has increased and the consequences of that fear, such as overtreatment or depression/burnout among medical professionals, are not insignificant.[1,2] The number of claims and the life time chance of receiving a claim may have increased over the years.[3] Orthopedic surgery has been defined as a high-risk specialty when it comes to the probability of receiving a claim.[4,5] Within the orthopedic field, claims concerning the lower extremity seem to result in larger settlements then the upper extremity.[6,7] Moreover, the foot and ankle region accounts for a large number of claims.[8–10] However, research on causality and risk factors for claims in this area is limited. Most studies focusing on claims in orthopedic surgery have investigated spinal surgery, or elective procedures such as joint replacements.[11–14]

Identifying the most common reasons for claims in a specific field can lead to healthcare improvements to avoid patient damages and claims in the future. In the 90's, MediRisk, one of the 2 medical liability insurance companies in the Netherlands, analyzed national claim data and found that most claims in the emergency department were related to misdiagnosis or treatment of fractures and tendon injuries.[15] Following these results, new guidelines and a safety net were installed, comprising, among other things, a daily radiology meeting where every X-ray of the day was discussed with both radiologist and supervisor. A study on hand and wrist injury related malpractice claims evaluated the effect of that intervention and identified a mild decline in missed fractures.[16]

This study aims to evaluate 1. The incidence of claims related to orthopedic foot/ankle surgery, 2. The most common characteristics of claimants and claims, and 3. Consequences and outcome of claims, in order to identify opportunities to improve care of foot/ankle conditions.

METHODS

This is a retrospective, observational database study, investigating all claims related to foot/ankle injury within the scope of 10 years.

Key aspects of medical liability in the Netherlands

In the Netherlands, patients file a claim for compensation against the hospital and not at against the physician personally, as is common in some other countries. MediRisk, as a medical liability insurer for its member hospitals, handles the claims of these patients on behalf of the hospitals. The burden of proof for medical negligence, damages and causation lies with the patient. When medical negligence has been established, MediRisk will compensate all reasonably damages caused by the negligence. At present over 95% of all cases are settled outside of court.

Data collection

The data for this study was collected from the anonymous database of Medirisk. Medirisk is one of the 2 medical liability insurance companies in the Netherlands and represents around 50% of all non-academic hospitals in the country. The database is roughly classified for (among other things) concerned body part, cause, treating specialty, care process and consequences of claims, but also contains short descriptions of the individual claims (often in layman's terms). All claims filed between 1-1-2007 and 12-31-2018 classified as concerning the "foot", "ankle", "toes" or "lower leg", with the treating specialty being "surgery", "orthopedic surgery", "radiology" or "emergency medicine" were extracted. In addition to this, all claims with a description containing the words foot, ankle, toes or lower leg (and all medical and layman's synonyms for those words) in combination with all terms suggesting injury or surgery were acquired from the database. Claims which were filed after 2016 (due to proportion of claims still open), not concerning the foot or ankle, not concerning orthopedic/trauma surgery and claims concerning patients younger than 18 years old were excluded.

Table 1: Classification in types of claims

Type of claim	Definition
Diagnosis	all claims concerning a missed, delayed or wrong diagnosis
Communication	all claims concerning a lack of or the wrong information in communication with the patient
Treatment	all claims concerning inadequate treatment (excluding treatment through surgery or medicaments)
Surgery	all claims concerning the indication, technical aspects or results of a surgical treatment
Medication	All claims concerning withholding of or prescription of the wrong medication
Care	All claims concerning problems in the hospital, located on the ward and not related to medication

Outcome measures

Extracted variables were 1) baseline characteristics such as age, gender and type of injury/affliction of the claimant, 2) treatment characteristics such as treating physician and operative treatment and 3) claim characteristics such as the type of claim (Table 1), consequences of the claim (both reported by claimant and medical expert), how the claim was handled (settled, declined, amicable settlement, closed without conclusion, negligible without harm) and what the costs were. These were displayed using descriptive statistics, reporting continuous variables in mean and standard deviation when normally distributed, in median and interquartile range when not normally distributed and categorical variables in numbers and percentages. Variables were compared between in- and excluded cases and between settled and declined claims using a Mann-Whitney U test for the continuous outcome measures and a Chi-Square for categorical outcome measures. Claim incidence was calculated per year corrected for the number of insured hospitals each year by separately

depicting the constant group of hospitals (n = 42) and the number of hospitals that varied (n = 13).

Study population

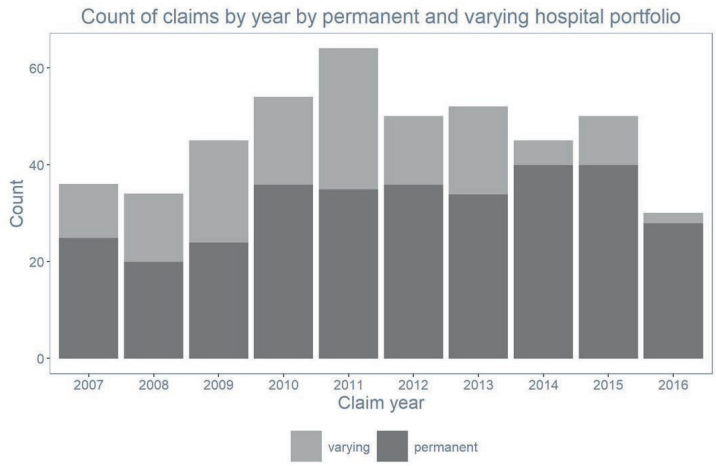
Out of the 909 claims that were extracted from the database, 449 were excluded because they were filed after 2016 (n=78), not concerning the foot or ankle (n=305), no orthopedic/trauma-surgical problem (n=15), the claimant was under 18 y/o (n=43), or because there was not enough information to classify the claim properly (n=8), leaving 460 for analysis. Excluded cases did not differ significantly from the included claims in age (47.1, SD 19.6 vs. 46.5 SD 15.9) or gender (218, 48.6% vs. 198, 43.0% males) of the claimant. There was a difference in location of the injury, which was significantly more in the lower leg for excluded cases, (193 vs 0, $p < .01$). The treating specialty was more often a general surgeon in excluded cases (246, 54.8% vs. 196, 42.6%) and excluded cases were more likely to be surgery related (242, 53.9% vs. 200, 43.5%) whereas included cases were more likely related to diagnosis. The status of excluded claims was more often still undecided (69, 15.4% vs. 23, 5.0%).

RESULTS

Claim incidence

The overall number of claims varied slightly per year, with the largest number of settled claims in 2014. Regarding only the constant group of insured hospitals, the peak in claim incidence was in 2014/2015 with a subsequent decline in 2016 (Figure 1).

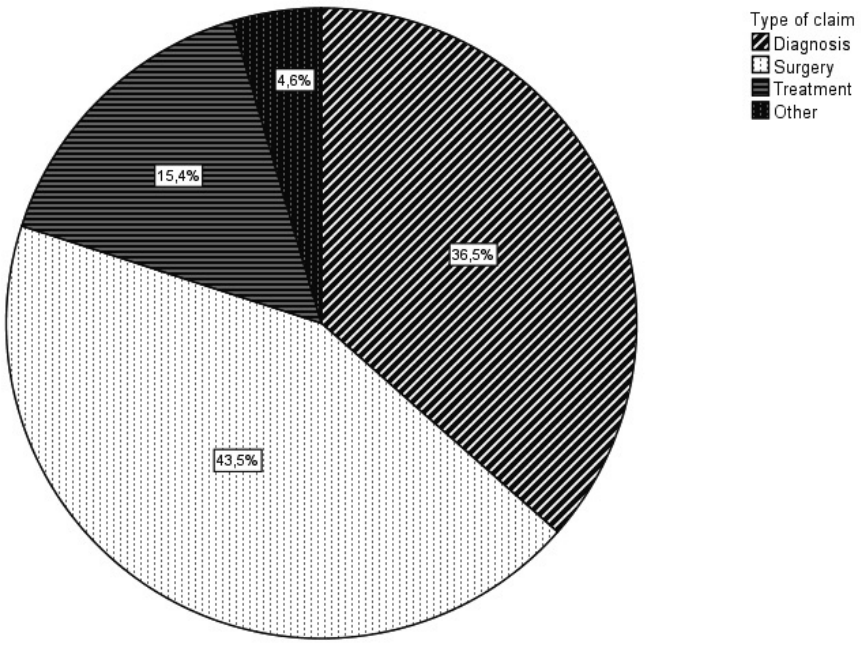
Figure 1.



Claim and claimant characteristics

Baseline characteristics of the claimant and the treatment he/she received are shown in Table 2. The claimant was 46.5 years old on average and female in 56.7%. The injury/affliction that was most frequently underlying the claim was a fracture and 80% of claims were related to either (the outcome/complications of) an operative procedure, or to a missed/wrong diagnosis (Figure 2).

Figure 2. Type of claim distribution



A subgroup analysis of only fracture related claims showed that these were mostly fractures of the ankle (111, 53.4%) or the foot (85, 40.9%) and the type of claim was diagnostic in 106 cases, 51.0%. Surgical claims and treatment related claims represented 23.6% (n = 49) and 22.1% (n = 46) respectively in fractures. A subgroup analysis of all surgical claims showed that these were related to an elective procedure in 112 (56.0%) of cases. The underlying injury/affliction was missing in 49 (24.5%), but of the remaining cases it was a fracture in 49 (32.5%) and a hallux valgus in 46 (30.4%) cases. A larger proportion of female claimants (128, 64%) was seen in this subgroup compared to the entire study population. When specifically looking at diagnostic claims, these concerned fractures in 106 (63.1%), followed by tendon injuries in 22 (13.1%). The location of the injury was the foot in 86 (51.2%), the ankle in 64 (38.1%) and the toes in 18 (10.7%). Age and gender did not differ from the rest of the study population.

Table 2: Baseline and surgical characteristics of claimants

Characteristics	N = 460
Age, mean, (SD)[a]	(15.9)
Gender, No of females (%)[b]	261 (56.7%)
Treating specialty	
Orthopedic surgeon	231 (50.2%)
(trauma) surgeon	196 (42.6%)
Radiologist	25 (5.2%)
ER	8 (1.7%)
Location of injury/affliction:	
Ankle (%)	189 (41.1%)
Foot (%)	192 (41.7%)
Toes (%)	79 (17.2%)
Type of injury/affliction:	
Fracture	208 (45.2%)
Toe deformities[c]	66 (14.3%)
Tendon/capsular damage	38 (8.3%)
Infection	22 (4.5%)
Luxation	4 (0.9%)
CRPS	4 (0.9%)
Other[d]	53 (11.5%)
Unknown[e]	65 (14.1%)
Type of surgery (N = 200)	
Acute	48 (24%)
Elective	112 (56%)
Unclear[e]	40 (20%)

a. in years, at time of the inflicted damage
b. 1 missing value
c. e.g. hallux valgus, hammer/claw toe, ingrown toenail
d. e.g. removal of foreign body, lipoma, neuroma, compartment syndrome, and other orthopedic pathology
e. unspecified underlying injury or procedure (e.g. complications after "foot surgery")

Abbreviations: N: number of patients, SD: standard deviation, ER: emergency room, CRPS: complex regional pain syndrome

Claim outcome and consequences

Out of 460 claims, 142 (30.9%) were settled/plaintiff verdict, 259 (56.3%) was declined/defense verdict and of the remainder; 36 (7.8%) came to an amicable settlement, 21 (4.6%) were closed without a conclusion and 2 (0.4%) were negligent without causing the claimant harm. Differences in baseline, surgical and claim characteristics between settled claims and declined claims are shown in Table 3.

Table 3: Baseline claim/claimant characteristics of settled and declined claims

Characteristics	Settled claims (N = 142)	Declined claims (N = 259)	p-value*
Age, mean, (SD)[a]	47.3 [35.4 – 58.6]	46.8 [32.9 – 58.6]	0.420
Gender[b]			0.636
Nr of males (%)	60 (42.3%)	117 (45.2%)	
Nr of females (%)	82 (57.7%)	141 (54.4%)	
Treating specialty			0.596
Orthopedic surgeon	68 (47.9%)	135 (52.1%)	
(trauma) surgeon	61 (43.0%)	109 (42.1%)	
Radiologist	9 (6.3%)	11 (4.2%)	
ER	4 (2.8%)	4 (1.5%)	
Location of injury/affliction:			0.201
Ankle (%)	64 (45.1%)	101 (39.0%)	
Foot (%)	60 (42.3%)	108 (41.7%)	
Toes (%)	18 (12.7%)	50 (19.3%)	
Type of injury/affliction:			0.024
Fracture	79 (55.6%)	103 (39.8%)	
Toe deformities[c]	13 (9.2%)	45 (17.4%)	
Tendon/capsular damage	11 (7.7%)	22 (8.5%)	
Infection	1 (0.7%)	18 (6.9%)	
Luxation	1 (0.7%)	2 (0.8%)	
CRPS	1 (0.7%)	3 (1.2%)	
Other[d]	13 (9.2%)	32 (12.4%)	
Unknown[e]	23 (16.2%)	34 (13.1%)	
Type of surgery (N = 200)			0.449
Acute	20 (29.4%)	24 (21.4%)	
Elective	34 (50.0%)	65 (58.0%)	
Unclear	14 (20.6%)	23 (20.5%)	
Type of claim:			0.033
- Surgery	68 (47.9%)	112 (43.2%)	
- Diagnosis	58 (40.8%)	85 (32.8%)	
- Treatment	13 (9.2%)	46 (17.8%)	
- Medication	3 (2.1%)	12 (4.6%)	
- Communication	0	4 (1.5%)	
- Care	0	0	

* determined by Mann-Whitney U for age and with a Chi Square test for all other, categorical variables
a. in years, at time of the inflicted damage
b. 1 missing value in "declined claims"
c. e.g. hallux valgus, hammer/claw toe, ingrown toenail
d. e.g. removal of foreign body, lipoma, neuroma, compartment syndrome, and other orthopedic pathology
e. unspecified underlying injury (e.g. complications after "foot surgery")

Abbreviations: N: number of patients, SD: standard deviation, ER: emergency room, CRPS: complex regional pain syndrome

The median amount in euros disbursed in settled claims was €12,549 with a maximum of €322,149, IQR: [€4264 – €36,145]. When analyzing the data per year, the year 2011 has the highest median disbursed amount (€23,566, IQR: €6,969 – €69,689). Amicable settlements were worth €2641 on average (IQR: €1391 – €7275). The most expensive claim of €325,000

concerned a 35 y/o male with a wrongly placed ankle prosthesis, which resulted in revision surgery and ultimately an amputation because of continuous pain. The second most expensive claim (€225,000) concerned a 45 y/o female with an intra-articular ankle fracture who did not receive a CT/MRI in the emergency department and initially received a cast instead of operative treatment, causing a delay in proper treatment and unresolved pain/limited function. The third most expensive claim (€190,000) concerned a Weber C ankle fracture in a 45 y/o male with limited functional outcome due to an operative procedure not performed according to protocol (ages and awarded amounts were rounded to guard privacy of claimant).

As shown in Table 4, the 3 most common patient-reported consequences were functional restriction, pain and revision surgery or readmission. When looking at the objective consequences (confirmed by a medical expert), the most common one is delay (in either treatment or diagnosis).

Table 4: Claim consequences as reported by claimant and verified by medical expert

Consequence	Claimant	Objective
Functional restriction	94 (20.4%)	19 (4.1%)
Pain	88 (19.1%)	13 (2.8%)
Revision or readmission	74 (16.1%)	29 (6.3%)
Delay	70 (15.2%)	39 (8.5%)
Disappointing results	15 (3.3%)	3 (0.7%)

Consequences of claims as reported by the claimant and the objective consequences as determined by the medical expert working on the case. Results are displayed as number and percentage of all included claims (N = 460)

DISCUSSION

Background and rationale

Events leading to filing a claim have a large impact on both the patient and the medical professionals involved.[1] Leaving patients unsatisfied goes directly against the fundamental motives of healthcare professionals to care for and cure patients. However, it is therefore especially important to evaluate the result of these good intentions. Analyzing claims gives us a unique chance to get a patient's perspective on the quality of healthcare. Something that is particularly useful in a high-risk specialty such as foot/ankle surgery, with a large variety of pathology/injuries and a high rate of postoperative complications.[17,18] This retrospective study therefore aimed to use foot/ankle surgery related claims to identify opportunities to improve care of foot/ankle conditions.

Claim incidence

The claim incidence did not seem to increase over the years. Although it is hard to draw conclusions because of the relatively small amount of claims per year in this subgroup, this

seems comparable to literature. Klemann et al. have previously shown an increase in number of claims until 2012 and a stabilization after that in an investigation of all claims in the Netherlands from 2007 – 2016.[19] A series of other studies could also not demonstrate an increase in the number of claims per year.[4,9] However, there are also a few European studies that did find an increase in claim incidence.[3,7]

Claimant characteristics

Considering the baseline characteristics of claimants, we found that claimants were on average young (46.5 y/o), female patients with a fracture. It has been previously reported that in general, elderly patients were less likely to file a claim.[20] In orthopedic surgery, this is supported by a Finnish study, linking all total hip and total knee replacements to the number of claims over a period of 5 years. They found that males and elderly patients were significantly less likely to file a claim, whereas increased comorbidity was positively associated with a claim.[21] However, a majority of male plaintiffs has also been described in a study looking at litigation after traumatic fractures.[22] Although we had no information about comorbidities, the claims in our cohort were mostly filed by young, female patients.

Claim characteristics

As for the reasons of filing a claim, in this cohort the claim was often related to a delay in/wrong diagnosis or to (complications of) an elective operative procedure. Both in general and in orthopedic surgery, multiple authors have previously suggested diagnostic mistakes as the most common cause for a claim.[9,23] Injuries of the foot often have a large impact on functional recovery and, within the extremities, the highest number of missed fractures,[24,25] which could also explain the high percentage of foot injuries in our cohort, especially in the subgroup analyses of diagnostic claims. Even though ankle injuries are much more common, the percentage of foot and ankle claims in our cohort was comparable. Many studies have stressed the large impact of foot injuries on functional outcome and quality of life.[26] The chance of filing a claim also seems to correlate to the patient reported outcome, as illustrated by Thornes et al. who found that patients pursuing compensation had significantly worse outcome scores, unrelated to objective outcome measures and whether they were operatively or conservatively treated for their calcaneal fracture.[27] Calder et al. confirmed this in their cohort of Lisfranc injuries and also identified delay in diagnosis and treatment as important independent predicting factors in filing a claim.[28]

The other major reason for filing a claim in this cohort, surgical errors or complaints about the outcome, have also been previously described.[10,29] Casali et al. also found that claims were most often related to a surgery and that the majority of those procedures were elective.[9] Other authors have mentioned a misbalance in expectations before surgery and the result that follows.[10,30] This could very well explain the fact that most surgical claims are related to an elective procedure, since in acute setting expectations might be lower.[31]

Claim outcome and consequences

Regarding the claim outcome, previous studies from the Netherlands have reported a settlement rate of 8 - 25% of claims.[32–34] This number was higher in our study (30.9%). An explanation might be that, in recent years, claims are more often filed by legal representatives. It is possible that through a selection process by these representatives, claims are only filed when there is a high probability of a settlement. This is supported by the mildly decreasing rate of declined claims over the past 10 years as Klemann et al. have shown in an investigation of all claims in the Netherlands from 2007 – 2016.[19]
In this cohort, settled claims were more often related to a fracture and to a missed/wrong diagnosis than declined claims. Bjørslev et al. previously analyzed claims after operative treatment of ankle fractures to identify iatrogenic risk factors for a settled/compensated claim. In contrast to our study, they found that most settled claims concerned a problem in the perioperative phase, most often incongruity of the ankle joint. However, they had a small cohort of 51 claims and did not analyze declined claims or foot injuries.[35] The average amount of €12,549 that was disbursed to patients in a plaintiff verdict was comparable to that of other studies from the Netherlands.[19,33,34] The patient-reported consequences (functional restriction, pain and revision surgery or readmission) are compatible with the earlier mentioned theory of a misbalance in expectations of surgery and the result that follows.[10,30] One can theorize that claims may have been prevented by sufficient expectation management and informing patient of the risks, especially since the common objective consequences are not the same as the patients reported ones.

Limitations

This study is subjected to a few limitations. First of all, the information supplied to the medical liability insurance company is from a patient perspective. Although it is checked and rated by medical professionals, the information extracted from the database is primarily “patient-reported”, making it subjective. Specific diagnoses were often not reported. Another possible limitation from this patient’s perspective is that it is not possible to directly link the highest awarded amounts to the biggest “mistakes”. Often, the awarded amount also depends on the consequences and circumstances of an individual claimant. However, to improve healthcare by identifying bottlenecks, the patient’s perspective on hospital procedures might even be more valuable than the objective events. Therefore, the patient’s perspective is at the same time a major strength of this study, since patient’s satisfaction plays a big part in quality of care.
The second limitation is that, because of the patient-reported data, this study could not give a specialist perspective. It might have been valuable to identify how many claims a certain medical professional receives and what the risk factors for receiving a claim are. However, this is out of scope of the current trial and has been previously studied.[9]
Finally, although it is important to compare results of this study with those of others, not all aspects can be compared between countries. Because of widely varying juridical claim procedures, information such as the rate of settled/declined claims and awarded amounts for

settled claims, cannot be compared. Therefore we were limited to a small number of previous cohorts from the Netherlands for these comparisons.

CONCLUSION

Despite the limitations, we feel that this study provides valuable information for the orthopedic/ trauma surgical community. Although claims have been previously studied in orthopedic fracture surgery, this study represents the largest cohort that focuses on foot/ankle surgery.[22,35] Given the high complication rate in this area of orthopedic surgery, it is important to identify pitfalls in (operative) care and communication, not only to prevent malpractice claims, but to improve the quality of care. In conclusion, the results of this study show that missed (foot) fractures and “failed”/disappointing results of elective operative procedures are the most common causes for claims. Although not all (alleged) medical errors can be avoided, some lessons can be learned from this conclusion. First of all, a high index of suspicion and adequate knowledge of the most commonly missed foot fractures could decrease the number of missed/wrong diagnoses in the acute setting and benefit timely and adequate treatment. Secondly, the importance of clear communication/expectation management before elective procedures is once more underlined.

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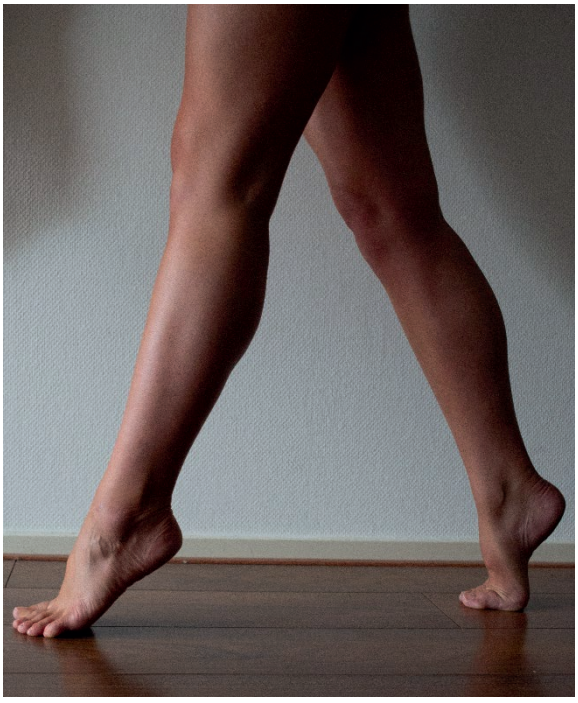

APPENDIX

THESIS SUMMARY

The articles in this thesis focus on the incidence and risk factors for developing a surgical site infection (SSI), on how to prevent SSIs and on the outcome of surgical procedures in trauma-related foot/ankle surgery. When it comes to outcome after procedures, the focus lies on patient reported outcome measures. In this section, the main findings are summarized and discussed per part, in order to make validated suggestions for future research and clinical use.

PART 1 INCIDENCE AND RISK FACTORS OF SURGICAL SITE INFECTIONS

In **Chapter 1** we investigated the incidence of infectious complications of syndesmotic screw removal in a systematic review, focusing specifically on planned screw removal. Removal of a syndesmotic screw is generally considered a small and short procedure, leading to assumptions of low complication rates. Results of the included studies showed percentages of SSI ranging from 0 to 9.2%, with a weighted average of 4%. comprising both superficial and deep infections. The largest proportion of these infections were superficial 3%, 95% CI: 2-5, compared to 2% deep infections (95% CI: 1-4). Predictors for infection could not be identified, since not many studies reported them. However, some studies described a benefit from prophylactic antibiotics. We concluded that the SSI rate after syndesmotic screw removal, as identified in this review, was comparable to that of other foot/ankle procedures. Although prophylactic antibiotics may be able to reduce this rate, the individual indication of syndesmotic screw removal should be carefully considered.

Chapter 2 delves deeper into the risk factors of developing a SSI, in a specific surgical approach used in calcaneal fractures, the sinus tarsi approach. In this prospective cohort study, all patients undergoing surgery for a calcaneal fracture using this approach were included and followed for at least one year. Out of 237 included fractures, 16 patients developed a SSI (6.8%), of which 9 (3.8%) were deep and 7 (3%) were superficial infections. The multivariate analysis pointed out that risk factors for SSI were: surgery within 1 week after the injury, an ASA classification of 2 or higher and more than 150 cc of blood loss during the procedure. Although not statistically significant, the results also indicated a higher risk of SSIs in smokers. To be able to identify true risk factors, many more patients are required, something that is hard to come by in this specific group of patients and in a procedure which is not performed in every hospital. Although the results may not be surprising, they can be used to identify “high-risk patients”. This subgroup of patients could potentially be referred to a specialized center and receive more information about potential risks of the procedure and a more intensive follow-up schedule.

In **Chapter 3** we investigated whether “seasonality” was a significant predictor for wound complications in trauma-related foot/ankle procedures. Additionally we were interested in other predicting factors which might explain a difference in complication rates between

seasons. We included all patients undergoing trauma-related procedures (e.g. fracture fixation, arthrodesis, implant removal) of the foot, ankle or lower leg between 2015 and 2019 at the Amsterdam UMC, loc. AMC. SSI rates were compared between procedures performed in summer (June, July or August) or in other seasons. In total, 43 (7.2%) wound complications occurred within 599 included procedures. Age, alcohol abuse, open fracture and no use of a tourniquet were independent predicting factors, but no difference in wound complications was found between summer and other seasons (4 (3.2%) vs 39 (8.2%)). We concluded that "seasonality" in wound complications does not exist in trauma-related foot/ankle surgery in the Netherlands. Possibly, this is a result of the temperate climate of this cohort, since larger temperature and precipitation differences may influence wound complications to a larger extent.

PART 2 PROPHYLACTIC ANTIBIOTICS TO PREVENT SURGICAL SITE INFECTION

Chapter 4 was a systematic review and meta-analysis in which we explored the difference in antibiotic concentrations in different parts of the extremity and while administering different dosages of cefazolin. We included 14 studies reporting on local cefazolin concentrations during orthopedic surgery in the shoulder, hip, knee or foot. From the 4 studies comparing different locations we were able to conclude that there were higher antibiotic concentrations in hip than in knee (mean difference: 4 ug/g, 95% CI 0.8–7). Moreover, articles comparing different doses of cefazolin reported higher bone concentrations after 2 grams than after 1 gram of prophylactic cefazolin, but pooling results did not lead to a statistically significant difference. We concluded that a dose of 1 gram of prophylactic cefazolin might not be sufficient in the most distal parts of the (lower) extremity and that future research should investigate whether a higher dose of cefazolin can lead to higher concentrations and fewer SSIs.

In **Chapter 5** we aimed to investigate the effect of 2 grams compared with 1 gram of prophylactic cefazolin on the incidence of SSIs in our own cohort of foot and ankle surgery patients. Of the 293 patients who received 1 gram, 19 (6.5%) had a SSI. In the 2 gram group (n=126) a SSI occurred in 6 patients (4.8%). Possible confounders of the effect of dosage on SSI were identified to be: alcohol, nicotine and illegal substance abuse, open fracture, tourniquet use, type of surgery, type of fixation, blood loss and type of wound dressing. Correcting for these possible confounders in a propensity score, the difference in SSIs between the 1 gram and 2 grams group was not statistically significant (OR, 0.770; P = .608). However, we did conclude that the difference may be clinically relevant given the considerable morbidity, mortality, and healthcare costs that SSIs entail.

Chapter 6 is the protocol for the WIFI-2 trial, a randomized controlled trial in which we aim to study the effectiveness of a single intravenous dose of 2g of cefazolin on SSIs after implant removal (IR) following fixation of foot, ankle and/or lower leg fractures. In this multicenter,

double-blind placebo controlled trial adult patients are being randomized to receive a single preoperative intravenous dose of either 2g of cefazolin or a placebo injection (NaCl) before IR. The primary outcome is the number of SSIs at 90 days after IR. Secondary, antibiotic concentrations are measured in a sub-section of patients to determine whether 2 grams of cefazolin is enough to penetrate the tissues in the most distal parts of the lower extremity. If the hypothesis that 2g of prophylactic cefazolin proves to be effective in preventing SSI is supported by the results of this study, this would have implications for current guidelines. Combined with the high infection rate of IR which has already been proved in previous studies, it would be sufficiently substantiated for guidelines to suggest protocolled use of prophylactic antibiotics in IR below the level of the knee.

PART 3 PATIENT REPORTED OUTCOME

In **Chapter 7** we used the prospectively collected data from the WIFI trial to study functional outcome after implant removal. All patients who filled out functional outcome questionnaires were included, coming to a total of 179 patients, who had undergone implant removal at least six months after fracture fixation below the level of the knee between 2014 and 2016. Primary outcome was the difference in functional status before and after implant removal, measured by the Lower Extremity Functional Scale (LEFS). With a median score of 60 before IR (IQR 45 to 72) and 66 after IR (IQR 51 to 76) on the LEFS, there was a statistically significant improvement in functional outcome ($p < 0$ .001). However, the minimal clinical important difference of the LEFS is 9 points, which was not reached. Therefore we concluded that in general, implant removal below the level of the knee does not result in a clinically relevant improvement of functional outcome.

Chapter 8 describes the results of the RODEO trial, a multicenter randomized controlled trial in which we aimed to investigate whether “on demand removal” (ODR) was non-inferior to routine removal (RR) of syndesmotic screws regarding functional outcome. Primary outcome was the Olerud-Molander Score (OMAS) at 12 months after placement of syndesmotic screw(s). There were 152 patients included in final analysis (73 patients in RR and 79 patients in ODR group), 59% male, mean age: 47 (SD 15). Median OMAS at 12 months after syndesmotic fixation was 85 (IQR: 60-95) for RR and 80 (IQR: 65-100) for ODR. The non-inferiority test indicated that the observed effect size was significantly within the equivalent bounds of -10 and 10 scale points (p= 0.000), meaning ODR was not inferior to RR. In the per-protocol analysis, ODR was also non-inferior to RR (p= 0.001). Moreover, there were significantly more complications after RR than in the ODR group. We therefore concluded that, although more research on long-term outcome of retaining the SS is necessary, on demand removal is preferred over routine removal and should be instated as standard practice of care.

In **Chapter 9** we describe a retrospective, 10-year claim analysis study, in which we aimed to evaluate the incidence, characteristics and outcome of claims in the foot/ankle area. Baseline claim/claimant characteristics were collected from an anonymous database, narrowing the search to all orthopedic foot/ankle related cases. Of 460 included claims in total, most were related to delay in/wrong diagnosis or to (complications of) elective surgical procedures. Whether a claims was settled was related to type of injury (fracture) and type of claim (diagnostic mistake). We concluded that fracture diagnosis and "failed"/disappointing results of elective surgical procedures were the most common patient reported causes for claims. Sufficient knowledge of missed (foot) fractures and clear communication/expectation management before elective procedures could help to improve quality of healthcare and patient satisfaction.

FUTURE PERSPECTIVES

The first part of this thesis has shown us that the incidence of surgical site infections (SSIs) in foot/ankle trauma-related surgery is high and that multiple patient-, injury- and surgical characteristics influence the chance of developing a SSI. Specifically, overall health (ASA classification), intoxications (smoking/alcohol), and open fracture, blood loss and tourniquet use were of importance. Although most of these risk factors were already known, they are not often consciously used in clinical practice. Future research should focus on developing a surgical site-specific prediction model, enabling foot/ankle surgeons to assign each patient to a "risk class". Interventions that have proved to be effective, but not necessarily cost-effective in preventing SSIs, could then be targeted specifically at "high-risk patients". Moreover, surgical indications could be even more critically evaluated in this high-risk group.

In part two of this thesis we discussed the use of prophylactic antibiotics in the prevention of SSIs. As previously mentioned in this thesis, SSIs are more common in the foot/ankle area, than in more proximal body parts. Chapter 4 confirmed that antibiotic tissue concentrations were also lower the further distally measured in the lower extremity. However, we could not confirm whether higher dosages of antibiotics would increase tissue concentrations. Although the results of chapter 5 did imply this, we could also not provide solid evidence on the clinical effect of a higher dose of antibiotics, resulting in lower SSI rates. Hopefully the results of the WIFI-2 trial will provide us with the sought after evidence of sufficiently high tissue concentrations with two grams of cefazolin and adequate infection prevention in implant removal. However, if the results are in line with the WIFI-1, and show no effect of prophylaxis on the SSI rate, this will results in a potentially even more interesting discussion. The target-site blood and tissue concentrations can be used to evaluate whether concentrations of antibiotics are sufficient to prevent bacterial growth in the first place. If that is the case, then overall effectiveness of prophylactic antibiotics in all trauma-related (foot/ankle) procedures should be reevaluated.

Part three discussed patient reported outcome measures (PROMs), which have recently justifiably become the most important outcome measures in orthopedic trauma surgery. However, chapter 7 very clearly demonstrated the importance of a clinical important difference, which is something that has not been established for all PROMs. With continuous outcomes and a score between 0 and 100, which many of these PROMs have, it is quite easy to achieve a statistically significant difference between 2 groups without the need for big groups. However, the clinical implications of this difference are still up for discussion. Future studies should focus on identifying a minimal clinical important difference for the most commonly used PROMs in foot/ankle surgery, like the Olerud-Molander Ankle Score (OMAS) and the American Orthopaedic Foot and Ankle Society Ankle Hindfoot Score (AOFAS).

The RODEO trial, featured in Chapter 8, has shown that on demand removal (ODR) of syndesmotic screws was not inferior to routine removal (RR), while RR resulted significantly

more complications. We therefore concluded that ODR should become standard practice of care. However, it is important to identify whether or not there are long term complications connected to retaining a syndesmotic screw, which is what future studies should focus on. What would be even more interesting, is to compare long term results of patients retaining a syndesmotic screw, to patients with absorbable screws or suture buttons. If it turns out that neither result in better outcomes than a retained screw, the “classic” syndesmotic screw would automatically prove to be the most cost-effective device for syndesmotic fixation.

Many more new research ideas have arisen over the years (and especially the last months) that this thesis was written. However, the most important perspective to keep in mind, is the patient’s perspective. Which is why I feel that patient reported outcome measures are the future, provided they are continuously improved and if necessary adapted to the individual.

NEDERLANDSE SAMENVATTING

De artikelen in dit proefschrift zijn met name gefocust op de incidentie en risicofactoren voor het ontstaan van postoperatieve wondinfecties (POWI), het voorkomen van POWI's en op de uitkomsten van chirurgische behandelingen van voet- en enkelfracturen. Qua uitkomsten ligt de nadruk op de zogenaamde patiënt-gerapporteerde uitkomstmaten. In dit gedeelte van het proefschrift worden de belangrijkste bevindingen per deel opgesomd en bediscussieert om zodoende gevalideerde suggesties voor toekomstig onderzoek en de klinische praktijk te kunnen doen.

DEEL 1 INCIDENTIE EN RISICOFACTOREN VOOR POSTOPERATIEVE WONDINFECTIES

In **hoofdstuk 1** hebben we door middel van een systematisch literatuuronderzoek de incidentie van wondcomplicaties na het electief (gepland) verwijderen van stelschroeven bij syndesmoseletsel in kaart gebracht. Deze procedure wordt gezien als een kleine, relatief korte ingreep, wat leidt tot de aanname dat het complicatierisico laag is. De resultaten van deze studie lieten echter POWI percentages van 0 tot 9,2% zien, met een gewogen gemiddelde van 4%. Het grootste gedeelte van deze infecties was oppervlakkig (3%, 95% CI: 2-5), vergeleken met 3% diepe infecties (95% CI: 1-4). Voorspellende factoren voor POWI konden niet geïdentificeerd worden aangezien slechts een aantal van de geïncludeerde studies dit rapporteerden. Sommige studies rapporteerden echter een voordeel van antibioticaprofylaxe. Wij concludeerden dat het POWI percentage, zoals geïdentificeerd in deze literatuurstudie, vergelijkbaar was met dat bij andere voet- en enkeloperaties. Hoewel antibioticaprofylaxe dit percentage mogelijk kan reduceren is het belangrijk om goed na te denken over de indicatie voor het verwijderen van stelschroeven.

Hoofdstuk 2 gaat dieper in op de risicofactoren voor het ontwikkelen van een POWI in een specifieke operatieve benadering die gebruikt wordt bij calcaneus (hielbeen) fracturen, de sinus tarsi benadering. In deze prospectieve cohortstudie zijn alle patiënten die een operatie ondergingen voor een calcaneus fractuur met deze benadering geïncludeerd en gevolgd voor tenminste een jaar. Van de 237 geïncludeerde fracturen, ontwikkelde 16 patiënten een POWI (6,8%), waarvan 9 (3,8%) een diepe en 7 (3%) een oppervlakkige infectie. De multivariabele analyse wees uit dat 'operatie binnen 1 week na trauma', 'ASA van 2 of hoger' en 'meer dan 150mL bloedverlies' onafhankelijke voorspellers waren voor een POWI. Hoewel dit niet statistisch significant was leek een POWI ook meer voor te komen bij rokers. Om alle daadwerkelijke risicofactoren te identificeren zijn veel grotere aantallen patiënten nodig, iets wat moeilijk te vinden is in deze specifieke patiëntengroep bij een operatietechniek die niet in elk ziekenhuis wordt toegepast. De resultaten van dit onderzoek zou gebruikt kunnen worden om hoog-risicopatiënten mee te identificeren. Deze subgroep van patiënten kan dan

verwezen worden naar een gespecialiseerd centrum, meer informatie ontvangen over potentiële risico's van de ingreep en intensiever gecontroleerd worden na de operatie.

In **hoofdstuk 3** beschrijven we een retrospectieve studie waarin we hebben onderzocht of het seizoen van operatie een voorspellende factor was voor het ontwikkelen van een wondcomplicatie na voet- en enkel ingrepen. Daarnaast waren we geïnteresseerd in andere voorspellende factoren die een mogelijk verschil in wondcomplicaties tussen seizoenen zouden kunnen verklaren. Alle patiënten die een trauma-gerelateerde ingreep van voet, enkel of onderbeen ondergingen tussen 2015 en 2019 in het Amsterdam UMC, loc. AMC, werden geïncludeerd. Complicatiepercentages werden vergeleken tussen ingrepen uitgevoerd in de zomer (juni, juli of augustus) en in andere seizoenen. In totaal zagen we 43 (7,2%) infectieuze complicaties binnen de 599 geïncludeerde ingrepen. Leeftijd, alcoholmisbruik, open fracturen en het niet gebruiken van bloedleegte tijdens de operatie waren onafhankelijke voorspellende facturen. Er werd echter geen verschil in wondcomplicaties gevonden tussen operaties in de zomer en in andere seizoenen (4 (3.2%) vs 39 (8.2%)). De conclusie was daarom dat het seizoen van operatie niet van invloed is op het aantal wondinfecties na trauma-gerelateerde voet-/enkelchirurgie in Nederland. Mogelijk is dit te verklaren door het gematigde klimaat in Nederland, aangezien grotere temperatuur- en neerslag-verschillen mogelijk meer invloed hebben op het ontstaan van een wondcomplicatie.

DEEL 2 ANTIBIOTICAPROFYLAXE ALS PREVENTIE VAN WONDINFECTIES

Hoofdstuk 4 beschrijft een systematisch literatuuronderzoek met een meta-analyse waarin we de verschillen in antibioticaconcentraties hebben vergeleken tussen verschillende gebieden in de ledematen en bij het toedienen van verschillende doseringen van cefazoline (antibioticum). We hebben daarbij 14 studies geïncludeerd die lokale cefazoline concentraties hebben gemeten gedurende orthopedische operaties van schouder, heup, knie of voet. Op basis van de 4 studies die verschillende lichaamsdelen vergeleken, konden we concluderen dat er hogere concentraties gemeten worden in de heup dan in de knie (mean difference: 4 ug/g, 95% CI 0.8–7). Artikelen die verschillende doseringen vergeleken lieten hogere botconcentraties zien na 2 gram dan na 1 gram profylactisch antibiotica, maar het samennemen resultaten van deze studies liet geen significant verschil zien. Onze conclusie was dat een dosis van 1 gram cefazoline wellicht niet genoeg is voor de meest distale gedeeltes van de onderste extremiteit en dat toekomstig onderzoek zich zou moeten richten op het effect van hogere doseringen op concentraties en het aantal POWI's.

In **hoofdstuk 5** hebben we onderzocht wat het effect van 2 gram vergeleken met 1 gram profylactisch cefazoline is op het aantal POWI's in ons eigen cohort van voet/enkel chirurgie patiënten. Van de 293 patiënten die 1 gram hebben gekregen ontwikkelde 19 (6,5%) een POWI. In de 2 gram groep (n=126) waren dit 6 patiënten (4.8%). Mogelijke confounders van het effect van dosering op POWI waren: alcohol, nicotine of drugs gebruik, een open fractuur,

bloedleegte, type operatie, type fixatie, bloedverlies en type wondbedekking na de operatie. Hiervoor gecorrigeerd, door middel van een propensity score, was het verschil tussen 1 gram en 2 gram niet statistisch significant (OR 0.770, p=0.608). Wij concludeerden echter dat het verschil mogelijk wel klinisch relevant was, aangezien POWI's een aanzienlijk morbiditeit, mortaliteit en gezondheidskosten met zich meebrengen.

Hoofdstuk 6 is het protocol voor de WIFI-2 studie, een gerandomiseerd onderzoek waarin we de (kosten-)effectiviteit van éénmalig 2 gram cefazoline op het aantal POWI's na het verwijderen van osteosynthesemateriaal (VOSM) uit voet, enkel en onderbeen onderzoeken. Patiënten worden in deze studie gerandomiseerd en krijgen ofwel 2 gram cefazoline ofwel een placebo via het infuus, vóór de operatie. Primaire uitkomst is het aantal POWI's op 90 dagen na de operatie. Tevens meten we lokale antibioticaconcentraties in een subgroep van patiënten om te kijken of 2 gram cefazoline voldoende is om het weefsel van voet/enkel te penetreren. Als onze hypothese dat 2 gram cefazoline effectief is klopt, dan heeft dit gevolgen voor de huidige richtlijn. In combinatie met de eerder bewezen hoge infectiepercentages na VOSM, zou het voldoende bewijs zijn voor richtlijnen om profylactisch antibiotica bij dit type operaties aan te bevelen.

DEEL 3 PATIËNT GERAPPORTEERDE UITKOMSTEN

In **hoofdstuk 7** hebben we de prospectief verzamelde gegevens van de WIFI studie gebruikt om functionele uitkomst na VOSM te onderzoeken. Alle 179 patiënten die een functionele uitkomst vragenlijst hadden ingevuld en een VOSM minstens zes maanden na fractuurfixatie hadden ondergaan tussen 2014 en 2016 werden geïncludeerd. Primaire uitkomst was het verschil in functionele uitkomst voor en na VOSM, gemeten door de Lower Extremity Functional Scale (LEFS). Met een gemiddelde score van 60 (IQR 45-72) vóór en 66 (IQR 51-76) na VOSM, was er een statistisch significante verbetering van functionele uitkomst (p<0,001). Het minimaal klinisch relevante verschil op de LEFS is echter 9 punten, wat niet behaald werd. Daarom concludeerden wij dat, over het algemeen, VOSM onder het niveau van de knie niet resulteert in een klinisch relevante verbetering van functionele uitkomst.

Hoofdstuk 8 beschrijft de RODEO studie, een multicenter gerandomiseerd onderzoek met als doel te onderzoeken of het "on demand" verwijderen (ODR) van stelschroeven vergelijkbaar is met het routinematig verwijderen (RR) van stelschroeven als het om functionele uitkomst gaat. De primaire uitkomstmaat was de Olerud-Molander Score (OMAS) gemeten op 12 maanden na het plaatsen van de stelschroef/ven. Er werden 152 patiënten geïncludeerd in de uiteindelijke analyse (73 in RR en 79 in ODR groep), waarvan 59% man was en de gemiddelde leeftijd 47 (sd 15) jaar. De Mediane OMAS op 12 maanden na fixatie was 85 (IQR: 60-95) voor RR en 80 (IQR: 65-100) voor de ODR groep. De "non-inferiority" test wees uit dat de effectgrootte binnen de marges van -10 en 10 lag (p=0.000), wat inhoudt dat ODR niet inferieur is aan RR. In de per-protocol analyse zat ook geen verschil tussen beide groepen.

Bovendien waren er significant meer complicaties na RR dan in de ODR groep. Wij concludeerden daarom dat, hoewel meer onderzoek naar lange termijn effecten van het behouden van de stelschroef noodzakelijk is, ODR de voorkeur heeft boven RR en moet worden geïmplementeerd als standaard zorg.

In **hoofdstuk 9** beschrijven we een retrospectief database onderzoek waarin we de incidentie, eigenschappen en uitkomsten van schadeclaims op het gebied van voet/enkel over een periode van 10 jaar hebben onderzocht. Baseline gegevens van de claim en de claim-eiser zijn verzameld uit een anonieme database, waarbij gericht is gezocht naar orthopedisch voet/enkel gerelateerde gevallen. Van alle 460 geïncludeerde claims waren de meeste gerelateerd aan een vertraagde of verkeerd gestelde diagnose of aan (complicaties van) een electieve ingreep. Of een claim toegekend werd, was gerelateerd aan het type letsel (fractuur) en het type claim (diagnostische fout). De conclusie was dat fractuur diagnose en “gefaalde”/teleurstellende resultaten van electieve operaties de meest voorkomende patiënt gerapporteerde oorzaken van claims waren. Voldoende kennis van vaak gemiste (voet)fracturen en heldere communicatie/verwachtingsmanagement voor electieve procedures zouden de kwaliteit van de zorg en patiënttevredenheid kunnen verbeteren

PHD PORTFOLIO

Name PhD student: Fay Sanders

PhD period: July 2017 – September 2020

Promotor: prof. dr. J.C. Goslings

Copromotor: dr. T. Schepers

PHD TRAINING

	Year	Workload (ECTS)
Courses		
AMC Graduate School, University of Amsterdam		
- The AMC World of Science	2017	0.7
- The NFU e-BROK	2018	1.5
- Practical Biostatistics (e-learning with exam)	2018	1.4
- Clinical Epidemiology: Randomized Clinical Trials	2018	0.6
- Scientific Writing in English for Publication	2018	1.5
- Project Management	2018	0.6
- Clinical Epidemiology: Systematic Reviews	2019	0.7
Seminars, workshops and master classes		
Weekly department research seminars	2017-2020	3.0
Journal Club (5 times a year)	2017-2020	3.0
BJS: How to Write a Clinical Paper Workshop 2018	2018	0.2
Jong AMC CV Building 2018	2019	0.2
Jong AMC, Geen bittere pil 31-10-2019	2019	0.2
ZonMw bijeenkomst Patiëntenінclusie	2019	0.3
Invited lectures		
Results WIFI trial at ZonMw congress Goed Gebruik Geneesmiddelen, subsession “Doen of Laten”	2018	0.5

Attended conferences

NVT Traumadagen, Amsterdam	2017-2019	3.0
ZonMw Congres Goed Gebruik Geneesmiddelen (GGG)	2018	0.5
NVvH Chirurgendagen, Veldhoven	2018/2019	3.0
Traumaplatform symposium/challenge	2018	1.0
37th Annual Meeting of the European Bone and Joint Infection Society (EBJIS), Helsinki	2018	2.0
Amsterdam Movement Sciences (AMS) PhD-day, Amsterdam	2018	1.0
Foot and Ankle Colloquium, Amsterdam	2019	0.5
Wetenschapsdag Heelkunde, Amsterdam	2019	0.5
38th Annual Meeting of the European Bone and Joint Infection Society (EBJIS), Antwerp	2019	1.0
Complicaties in de Traumachirurgie, Amsterdam	2019	0.5
Amsterdam Movement Sciences Annual Meeting (cancelled due to COVID-19)	*2020*	
21st European Congress of Trauma & Emergency Surgery (ECTES), Oslo (moved to 2021 due to COVID-19)	*2020*	
NVvH Chirurgendagen, Veldhoven (cancelled due to COVID-19)	*2020*	
NVT Traumadagen, Amsterdam (moved to 2021 due to COVID-19)	*2020*	

Oral presentations

Results of WIFI trial at GGG Congres and EBJIS 2018	2018	2.0
Protocol RODEO trial at Traumaplatform symposium	2018	1.0
Functional outcome of implant removal at Traumadagen 2018 and AMS PhD-day	2018	2.0
Claims in foot/ankle surgery at Wetenschapsdag	2019	1.0
Seasonality in wound complications at EBJIS 2019	2019	1.0
Results of EF3X trial at Traumadagen 2019	2019	1.0
Accepted but cancelled due to COVID-19: RODEO trial results at ECTES, Chirurgendagen 2020 and Traumadagen 2020 and benefits of 2g of cefazolin over 1g at ECTES		

Poster presentations

Systematic review on extremity tissue concentrations of prophylactic cefazolin at EBJIS 2018	2018	0.5
The benefit of 2g of cefazolin over 1g of cefazolin at EBJIS 2019	2019	0.5

TEACHING

	Year	Workload (ECTS)
Lecturing		
Teaching 1st year medical students about scientific writing in study groups 'wetenschappelijk verslag'	2018/2019	1.0
Teaching 3rd year medical students about the use of scientific literature to support clinical decisions making (evidence based medicine) in a study group 'PICO'	2018	0.5
Teaching a series of scientific writing study groups to a group of 1st year medical students	2019/2020	1.5
Supervising		
Bachelor students:	2018-2020	4.0
- Jess J. Peters		
- Robin Eelsing		
- Kevin C.S. Fransen		
- Mariem Abbou		
Master thesis students:	2017-2020	7.0
- Kaz L.J. van Schilt		
- Valentino Daqiq		
- Kimberly Spierings		
- Mirjam van 't Hul		
- Roos M.G. Kistemaker		
- Nigel S.V.L. Baboeram		
- Hafize Demirci		

PARAMETERS OF ESTEEM

	Year
Grants	
ZonMw, programma Goed Gebruik Geneesmiddelen, “Wound Infections Following Implant Removal (WIFI-2)”	2019
Awards and Prizes	
Best Paper Award, EBJIS 2018 for presentation of WIFI trial results	2018
2nd place in Best Abstract section of AMS PhD-day	2018

LIST OF PUBLICATIONS

THIS THESIS

Sanders FRK, Penning D, Backes M, Dingemans S, van Dieren S, Eskes AM, Goslings JC, Kloen P, Schep NWL, Spijkerman IJB, Schepers T. Wound infection following implant removal of foot, ankle, lower leg and patella; a randomized controlled trial investigating the (cost-)effectiveness of 2g of prophylactic cefazolin compared to placebo (WIFI-2 trial). *Submitted*

Sanders FRK[§], Birnie MFN[§], Dingemans SA, van den Bekerom MPJ, Parkkinen M, Roukema GR, van Veen RN, Vermeulen J, Winkelhagen J, RODEO collaborator group, Goslings JC, Schepers T. Functional outcome of routine versus on demand removal of the syndesmotic screw; a multicenter randomized clinical trial. *Submitted*

Sanders FRK, Birnie MFN, Penning D, Goslings JC, Schepers T. Surgical site infections following routine syndesmotic screw removal; a systematic review. *Accepted*

Sanders FRK, Wimmer-Boelhouwers P, Dijt OX, Kerkhoffs GMMJ, Schepers T. Claims in orthopaedic foot/ankle surgery, how can they help to improve quality of care? A retrospective claim analysis. *Eur J Orthop Surg Traumatol. 2020 Jul 26: online ahead of print*

Sanders FRK, Spierings KE, Nosewicz TL, Schepers T. Risk factors for surgical site infections with the Sinus Tarsi Approach in displaced intra-articular calcaneal fractures; a prospective cohort study with a minimum of one year follow-up. *Injury. 2020 Jul; 51(7):1676-1680.*

Sanders FRK, Van't Hul M, Kistemaker RMG, Schepers T. Seasonal effect on the incidence of post-operative wound complications after trauma-related surgery of the foot, ankle and lower leg. *Arch Orthop Trauma Surg. 2020 Mar 9: online ahead of print*

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Birnie MFN, Sanders FRK, Halm JA, Schepers T. Long-Term Follow-up of Functional and Radiographic Outcome After Revision Surgery for Fibula Malunion. *Foot Ankle Spec. 2020 Mar 16: online ahead of print*

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Kok END, Jansen EPM, Heeres BC, Kok NFM, Janssen T, van Werkhoven E, Sanders FRK, Ruers TJM, Nowee ME, Kuhlmann KFD. High versus low dose Stereotactic Body Radiation Therapy for hepatic metastases. *Clin Transl Radiat Oncol. 2019 Nov 27;20:45-50.*

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Concluderend, ik zou jullie voor geen goud willen inruilen! (geldt voor alle bovenstaanden)

CURRICULUM VITAE

Fay Sanders was born on the 26th of March 1991 in Baarn. She attended the Nieuwe Baarnsche School and Het Baarnsch Lyceum, two schools filled with potential fellow medical students. As daughter of two not so typically Gooische parents, she briefly tried to escape her somewhat preppy surroundings by joining a dance school instead of 'de hockey' at the age of 10. This turned out to be a decision she still enjoys to this day, as dancing is one of Fay's greatest passions.

After finishing high-school Fay studied Movement Sciences for a year. A study that well suited her interests in the human body, sports and physics. However, it also intensified the wish to become a doctor, and more specifically a trauma- or orthopedic surgeon. With this in mind she started studying medicine at the Vrije Universiteit in 2010.

Fay's scientific interest was piqued during a 3 month long scientific internship in Australia (Perth, WA, 2013), which was obviously carefully selected based on quality of the scientific research there and not at all on location. Conveniently, a month long trip along the East coast of Australia could be combined with that internship, where another (part-time) hobby was born: surfing. In the 2,5 years that followed this great experience, Fay finished her Masters with a final internship at the trauma surgery department of the VUmc (2016). To get acquainted with other aspects of surgery as well, she started working as a junior doctor at the Antoni van Leeuwenhoek cancer center. After 7 months of working there, the dream to become a surgeon was still strong as ever, and the opportunity to start a PhD project at the Trauma surgery of the Academic Medical Center presented itself.

During the past 3 years as a PhD student Fay mostly studied postoperative infections and functional outcome after lower extremity trauma-related surgery, which lead to the content of this thesis. Besides being partly responsible for the RODEO trial, she also secured a large ZonMw Grant to further study the influence of prophylactic antibiotics on infections after implant removal (WIFI-2 trial).

Besides research, Fay's additional hobbies include dancing, skiing, surfing and singing (in and outside of the shower). By this time next year she hopes to be in training to become a surgeon.

Amsterdam Movement Sciences

Amsterdam Movement Sciences conducts scientific research to optimize physical performance in health and disease based on a fundamental understanding of human movement in order to contribute to the fulfillment of a meaningful life.