Primary or secondary wound healing of the Pin Sites After Removal of the External Fixator: Study Protocol for a Prospective, Randomized Controlled Mono-center Trial

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Study protocol

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Abstract

Background: Temporary fixation with an external fixator is used for numerous indications in orthopedic trauma surgery. It is unclear whether primary wound healing or the secondary open wound healing after removal of the external fixator should be advocated for the pin site. This study compares primary wound closure with secondary wound healing for the pin sites. The primary aim is to compare the infections rates of the pin site. Secondary aim is to compare time to wound healing and esthetic outcome. The hypothesis was that primary wound closure does not lead to more infections than secondary wound healing. Methods: This is a prospective, randomized, controlled and blinded monocenter study based on a non-inferiority design. To obtain an equal patient population and groups, all pin entry sites of the patients are treated alternately at the time of removal of the external fixator with primary wound closure and secondary wound healing. Patients are randomized whether the proximal pin entry site is treated with wound closure or by secondary open wound healing, from which the further sequence develops. The pre- and postoperative protocol is standardized for all pin entry sites. A photo documentation of the pin entry sites takes place 2 and 52 weeks postoperatively during the routine clinically follow-up visits. Further controls take place after 6, 12 and 26 weeks after the removal. The primary outcome was to demonstrate the non-inferiority of primary wound closure compared to secondary wound healing in terms of postoperative wound infections according to center of disease control (CDC). The secondary outcomes are time to complete wound healing (days) and esthetical outcome (Subjective preference of patients and Vancouver scar scale). Discussion: This study aims in answering how to deal with the pin site after removal of the external fixator. To date, no routine and generally accepted protocol exists for the management of pin sites after removal of the external fixator. This prospective, randomized, blinded monocenter trial will answer if primary wound closure or secondary wound healing should be advocated after removal of the external fixator.

Background

In orthopedic trauma surgery, the use of temporary external fixators is common [6,8,11]. Pin entry site infections are frequently seen complications with infection rates up to 7.4% [2, 3,16, 18]. These infections can cause pain and discomfort to the patient and can lead to osteomyelitis. It is unclear whether primary wound closure or secondary open wound healing after removal of the external fixator should be the standard of care for pin sites to achieve a lower infection rate and better esthetic outcome [1, 4, 6]. Despite it being one of the basic procedures in orthopedic trauma, the wide variety in management of the pin site is underlined in a recent international survey [6]. To date no routine and generally accepted protocol exists for the management of pin sites after removal of the external fixator [6]. The primary aim of this prospective, randomized, blinded monocenter trial is to evaluate if primary wound closure or secondary wound healing is advocated after removal of the external fixator. The hypothesis was that primary wound closure does have a similar infection rate compared to open wound healing according to the CDC definitions [12].

The secondary aim is to investigate the time to complete wound healing, and the aesthetic outcome.

Methods And Design

Study design:

This prospective, randomized, controlled and blinded monocenter study based on a non-inferiority study design is enrolled in a Level 1 Trauma Centre in Central Switzerland. A total of 234 pin sites (+/- 70 patients) will be included. Ethical approvement of this study was obtained from the Swiss Ethics board with the project-ID 2018-01316.

Patient population:

All patients treated with a temporary external fixator are screened for eligibility. The in- and exclusion criteria are shown in figure 1. All pin sites except the pin sites at the calcaneus, due to the low mobilizability of the skin and thus a lack of tension-free wound closure, will be included. After both, written and oral informed consent, patients are included.

Inclusion and Exclusion criteria:

The population includes all patients who completed the 18^{th} year of life and were treated with an external fixator in our hospital. Patients with immunodeficiency or patients who cannot follow up on structural reasons are excluded. Patients with a lack of knowledge of German or a lack of consent to study participation are also excluded. The in- and exclusion criteria are listed in figure 1.

Randomization process:

To obtain an equal patient population or groups regarding to preexisting conditions, health status and trauma condition, all pin sites of the patients are treated at the time of removal of the external fixator alternately with a primary wound closure and by secondary wound healing. If a patient has consented to the study, the patient will be allocated to group A or group B by using a computerized randomization. Patients assigned in group A, the proximal pin site will be closed by a single-button suturing according to the Allgoewer-Technique. In patients of group B, the proximal pin site is treated by secondary open wound healing.

Intervention:

The pre- and postoperative protocol is standardized for all pin sites, including preoperative antibiotic prophylaxis with a single preoperative dose of cefazolin 2g intravenously 30-60 minutes prior to surgery. The pin sites assigned to the intervention group will be treated according to our current standard protocol, which implies that they will be closed by single button technique. The control group is simultaneously subjected to secondary wound healing without wound closure.

Postoperativ management:

No routine postoperative antibiotics are given. Patients with an open fracture will be treated according to the local protocol. Patients with a Gustillo grade 1 or 2 open fracture are treated with Cefazoline 2g i.v. TID for 24 hours. Patients with open fractures classified Gustillo 3 receive Amoxicillin/Clavulanic-Acid 2.2g i.v. TID for 72 hours [17].

The postoperative pin site care includes the daily inspection of pin entry sites, disinfection with Betadine ©, followed by a dry gauze dressing by the nursing staff during inpatient stay. In the further course this is done either by an outpatient wound care, the family doctor, or in case of good compliance the patient.

A photo documentation of the pin sites is made 2 and 52 weeks postoperatively. All patients are clinically controlled at 2, 6, 12, 26, and 52 weeks during regular follow-up visits. The chosen therapy for the examining doctor is blinded at the 6 weeks and 52 weeks controls. A flowchart is shown in figure 2 and a study schedule in figure 3.

Statistical Methods:

For the primary study objective, it should be shown in a non-inferiority approach that the rate of postoperative wound infection (within 12 weeks of removal of the external fixator) is not significantly greater following simple wound closure of the pin entry sites than in open secondary wound healing. The non-inferiority limit for this proof is 10%. The primary study objective to be confirmed is achieved when the upper limit of the 95% confidence interval (2-sided) for the difference in infection rates (simple wound closure - open wound healing) does not exceed the non-inferiority limit of 10%. Similarly, wound infection rates will also be evaluated at the other assessment time points. Furthermore, also for the secondary parameters, the rates of wound healing and the rates of revision surgeries and antibiotic therapies, the proportions per treatment group and time point will be calculated in the same manner as for the primary parameter, and 95% confidence intervals will be presented for the difference in proportions between treatment groups. For the secondary parameters, a comparison to a non-inferiority limit is no longer in the main focus. The wound healing rate, for example, is more about being able to possibly deduce from the pattern of proportions an earlier onset of the healing process after simple wound closure. All other parameters will be evaluated purely descriptively.

Sample size and Determination:

70 patients, resulting in up to 234 pin entry points, are included in the study. For each patient, up to four individual wounds are treated alternately with simple wound closure or by open wound healing; the treatment of the proximal pin entry site per patient is determined by a randomization scheme (1: 1). For secondary wound healing, an infection rate of 5% is assumed (within 12 weeks postoperatively), as well as an infection rate of 5% for primary wound healing. Assuming that the infection probabilities of the individual wounds (even within the same patient) are independent, at least 156 evaluable wounds are needed to maintain a non-inferiority limit of 10% for the difference in infection rates with a power of 80%.

Inclusion of 70 patients is expected to achieve the required number of wounds (even if individual patients contribute less than four evaluable wounds). With a possible dropout rate of approximately 25% we will generously include 234 pin sites, which equates to a number of around 70 patients.

Based on retrospective analyses it is expected that about 50 patients are being treated with an external fixator annually at our hospital. Therefore, the inclusion period will be from Januar 2019 to the middle of 2020, with an estimated end of this trial one year later after the follow up will be completed.

Ethical approval:

The sponsor, the investigator and swiss ethics have approved the trial`s protocol version 2, dated 30.10.2018. This trial will be conducted according to the ethic - protocol and the current version of the World Medical Association declaration of Helsinki, the ICH GCP guidelines and the ISO 14155, performing the standard, applied to the local legal requirements.

Methods of minimizing bias:

To avoid an initial bias, all patients are treated identical. Therefore, and to obtain an equal patient population or groups regarding preexisting conditions, health status and trauma condition, all pin sites of the patients are treated at the time of removal of the external fixator alternately by means of primary wound closure and secondary open wound healing. Randomization only applies to the treatment of the proximal pin site: closed by Allgoewer single button technique or left open for a secondary open wound healing, while the rest of the pin sites are treated alternately. This minimizes bias. Included are all pin sites, except those that affect on the calcaneus, due to the low mobilizability of the skin and thus a lack of tension-free wound closure. Regarding the back of the hand and foot, a medially located pin site is considered to be the proximal pin site.

Discussion

To date, there remains a lack of evidence concerning optimal treatment for pin site care. [10,14,15]. The peri- and postoperative management of the pin sites shows a high variability [1,6]. It is still hard to find a uniform standard that describes how to deal with the pin sites (after applying and removal of the fixator extern). There is no consent in preventing pin site infections, what is reflected in the many hospitals which have different post-operative pin site care protocols [19]. In one of the most frequently cited publications about pin site care of a fixator extern, a literature review examines the infection rate in terms of pin design, surgical technique, cleaning solutions, frequency of pin-site cleaning, dressing types, showers and antibiotic prophylaxis [2, 3, 4, 5, 7]. Again, the treatment of the pin sites after removal of the fixator extern is not considered in detail to show method leads to a reduction of infections and wound healing disorders. n the authors department, after removal of the external fixator, the pin sites are routinely treated by primary wound closure. However, a recently published international survey, showed that the majority of surgeons treated the pin site by secondary wound healing [7]. In a review paper Kazmers et all discussed different influencing factors for infections of the pin site. Therefor it is unknown

whether the pin design, the surgical technique, different disinfection solutions, the frequency of pin site cleaning, the dressing type or the choice of antibiotics is important for pin site infections [5]. In order to address the postoperative management of the pin site, this prospective randomized controlled trial is designed. This trial will answer if the pin sites should be left open or can safely be closed after removal of the external fixator with respect to the occurrence of postoperative wound infection. This study has some limitations which should be acknowledged. Firstly, this is a single center study. Although this might make results less generalizable, single center studies tend to have more complete data and less loss-to-follow-up improving the quality of data. Secondly, although the study population size is sufficient for detecting differences in primary outcome, it is not large enough for in-depth subgroup analysis.

Trial Status

The institutional board has approved the study and patient enrollment has started on January 2019. In the first eight months with an acute trauma were temporary treated with an external fixation. Eleven patients were excluded. To date, no patient showed signs of pin site infections. Based on our power analysis enrollment, the last patient is expected mid-2020. Final follow-up will be finished one year later.

Abbreviations

©	- Copyright
CDC	- Center for Disease Control and Prevention
Dr.	- Doctor
e.g.	- Exempli gratia – For example
HIV	- Human immunodeficiency virus
ICH GCP Guidelines	- International Conference on Harmonisation – Good Clinical Practice
i.v.	- intra venouse
MD	- Medical Doctor
ISO	- International Organization for Standardization
Prof	- Professor
TID	- ter en die – Three times a day

Declarations

Availability of data and material

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The sponsor, the investigator and swiss ethics have approved the trial`s protocol version 2, dated 30.10.2018. This trial will be conducted according to the ethic - protocol and the current version of the World Medical Association declaration of Helsinki, the ICH GCP guidelines and the ISO 14155, performing the standard, applied to the local legal requirements. Informed consent will be obtained from all study participants as a requirement to participate in the study.

Consent for publication

All participants have given consent for publication the anonymous data by given written and spoken “informed consent” in context of the study inclusion.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

There are no financial and no non-financial competing interests by the authors.

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Authors' contributions

FR: Main investigator and main author of this study

FC: Investigator

BCL: Investigator and Co-Sponsor

SH: Investigator

DL: Head of statistics

RB: Chief of the Department Traumatology of the Cantonal Hospital Lucerne and main Supervisor

FJPB: Sponsor

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Figures

Inclusion criteria	Exclusion criteria
• completed 18th year of life	• patients with immunodeficiency (HIV / hepatitis infection, leukemia, steroid therapy, autoimmune therapy)
• treated with an external fixator	• patients who cannot follow up on structural reason (tourist, distance to hospital, etc.)
• signed informed consent for study participation	• insufficient German language skills
	• patients not capable of consenting

Figure 1

in- and exclusion criteria

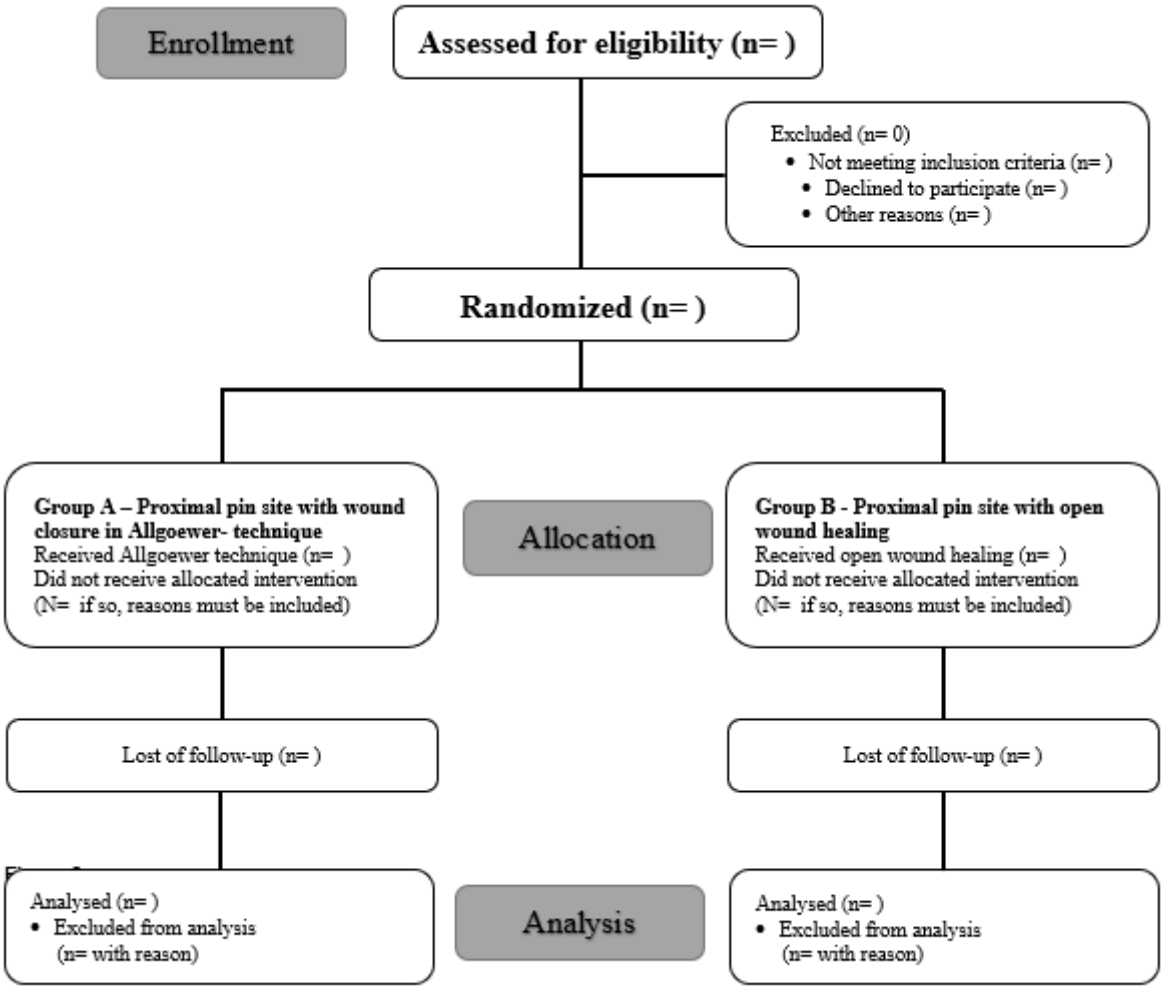

Figure 2

flowchart

Study Schedule	Inclusion	Removal of the external fixator	Follow up				
Week			2	6	12	26	52
Informed consent	□						
In-/Exclusion criteria	□						
Randomization	□						
Removal of the external fixator		□					
Questionnaire			□	□	□	□	□
Clinical examination			□	□	□	□	□
Foto documentation			□				□

Figure 3

study schedule

Supplementary Files

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