ANTIBIOTIC EXPOSURE AT THE INFECTION SITE IN PERIPROSTHETIC JOINT INFECTIONS

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Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON20480

Bron
Nationaal Trial Register

Verkorte titel
ASTERICS

Aandoening

Orthopedic infections

Ondersteuning

Primaire sponsor: Erasmus MC
Overige ondersteuning: Erasmus MC

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

To develop a pharmacokinetic (PK) model for the relationship between dosage, blood concentration and infection site concentration, estimating covariates to determine differences in antibiotic concentrations in synovial fluid, synovial tissue and bone between different types of antibiotics and knee versus hip.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: Prosthetic joint infections (PJI, periprosthetic infection) is a serious complication of joint replacement surgery, leading to prosthesis failure. The standard treatment of PJI consists of a two-stage arthroplasty exchange, which includes a six-weeks course of orally and intravenously administered antimicrobial therapy. In practice, antibiotic regimens and the therapeutic efficacy are optimized by measuring concentrations in plasma. However, through this method it remains unclear whether effective concentrations of the antibiotics have reached the site of PJI, although adequate target site concentrations are important to achieve effective eradication of the micro-organism causing the PJI. Furthermore, antibiotic concentrations vary depending on individual patient characteristics such as body mass, renal function and bowel absorption. Additionally, the comparison of studies on the penetration of surgical prophylactic antibiotics in bone and joint tissue indicates a large variation in the antibiotic concentrations at the target site in extremities, making antibiotic dosage recommendations supported by limited evidence. Despite these insights, knowledge is lacking regarding the target site concentrations of the antibiotics, administered as part of the two-stage arthroplasty exchange, with respect to the dosage and plasma concentrations. The overall aim of this proposed study is to gain insight into the target attainment of the administered antibiotics during the two-stage arthroplasty exchange, in order to determine the efficacy in relation to the minimal inhibitory concentration (MIC) of the pathogen causing the infection. Additionally, by comparing the target site concentrations of orally and intravenously (IV) administered antibiotics we can determine whether a need exists per patient for both oral and IV administration of antibiotics, or if one route of administration is sufficient enough.

Objective: To develop a pharmacokinetic (PK) model for the relationship between dosage, blood concentration and infection site concentration, estimating covariates to determine differences in antibiotic concentrations in synovial fluid, synovial tissue and bone between different types of antibiotics and knee versus hip.

Study design: Cross-sectional observational study

Study population: Patients who underwent total hip arthroplasty (THA) or total knee arthroplasty (TKA) and suffering from PJIs for which they will be treated by the two-stage arthroplasty exchange. We will investigate the following 6 antibiotic strategies: vancomycin (IV), flucloxacillin (IV and oral), cefuroxime (IV), clindamycin (oral) and co-trimoxazole (oral).

Intervention: This is not an interventional study. Study participants will be treated according

to standard of care. During the study, we will measure antibiotic concentrations at the site of PJI in the matrices synovial fluid, synovial tissue and bone tissue of the affected joint.

Main study parameters/endpoints: PK/PD indices are calculated. The treatment drug Minimal Inhibitory Concentration (MIC) for the isolated pathogen and the free (unbound) drug exposure value are used to calculate pharmacodynamic indices. Epidemiological cut-off value (ECOFF) and MIC data for the expected bacteria will be used.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This study is relevant since effective concentrations of the applied antibiotics at the site PJI are of importance for not only the optimization of the treatment efficacy, but also to decrease the incidence of unnecessary antibiotic-related adverse events. Patients have to undergo study related procedures which are minimally invasive; risks and burdens associated with participation are minimized by combining them with procedures for standard care, as much as possible. Therefore, only undergoing venous blood sampling and joint punctures for collecting synovial fluid outside of the surgeries can be considered invasive and a burden for the patient. To reduce the extend of the burden on the patients these joint punctures will be combined with the periodic hospital visitations of the patients after prosthesis extraction; if not possible additional hospital visits will be necessary and unavoidable. Adverse events of joint punctures may include pain, bleeding, bruising and joint swelling; however, these events are rare making joint punctures a well-tolerated procedure. The individual patients participating in this study have no direct benefits. The possible risks associated with the study are outweighed by its benefits for the study population.

Doel van het onderzoek

The overall aim of this proposed study is to gain insight into the target attainment of the administered antibiotics during the two-stage arthroplasty exchange, in order to determine the efficacy in relation to the minimal inhibitory concentration (MIC) of the pathogen causing the infection. Additionally, by comparing the target site concentrations of orally and intravenously (IV) administered antibiotics we can determine whether a need exists per patient for both oral and IV administration of antibiotics, or if one route of administration is sufficient enough.

Onderzoeksopzet

Sampling for measurements will be performed at 4 time points during 6 weeks. Prior to the start of the prosthesis extraction surgery, IV antibiotics (flucloxacillin, cefuroxime or vancomycin) will be administered; 15-30 minutes after administration samples of blood, synovial fluid and tissue and bone will be collected. This will be repeated 90-120 minutes after administration of the antibiotics. Along with the sampling, the following information will be documented: time of antibiotic administration, time of sampling and whether or not a tourniquet is used during the surgery.

To determine the differences in the efficacy of the oral and IV antibiotic regimens applied during the two-stage exchange, samples will be obtained at the end of the IV administration (after two weeks of treatment) and oral administration (after 4 weeks of treatment) of the

antibiotics.

After two weeks of IV antibiotic therapy venous blood and synovial fluid will be drawn; the fluid will be obtained through a joint puncture of the joint capsule. In case of a treatment method without an antibiotic free interval after the oral therapy, synovial fluid, synovial tissue and bone along with venous blood will be collected during the surgical intervention to re-implant the prosthesis, which follows directly after antibiotic treatment. When an antibiotic free interval is applied, only synovial fluid (through joint punctures from the joint capsule) and blood samples will be collected, after completing the six-weeks antibiotic treatment. All sampling will be performed by an orthopaedic surgeon.

Standard statistical methods are used to calculate means, medians, ranges, and SDs., Comparisons between groups are made using the Student's t test, a P <0.05 is considered statistically significant. The t-test is used to determine whether the (population) average deviates from the optimum PK/PD targets, namely 100% ƒT>MIC, ƒAUC/MIC >400 and ƒAUC/MIC>27 (primary endpoints).

Secondary study parameter(s)
Univariate analysis for association with microbiological response between-group comparisons of PK/PD parameters (T>MIC <100% vs. 100%; T>4xMIC <100% vs. 100%; AUC/MIC < 400 vs. ≥400; AUC/MIC < 27 vs. ≥27) and both infection recurrence/success percentage scores are tested using one-way analysis of variance (ANOVA). The significance level is defined as $p<0.05$.

Multivariate analyses by means of logistic regression in R are performed to determine the independent association of PK/PD parameters with the clinical outcome of interest while adjusting for confounding variables.

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Age ≥ 18 years.
- Written informed consent has been obtained from the patient
- Suffering from periprosthetic (hip or knee) joint infections and therefore treated with one of the following antibiotics as part of the two-stage arthroplasty exchange:
o IV: vancomycin, flucloxacillin or cefuroxime
o Oral: flucloxacillin, clindamycin or co-trimoxazole
- Patients undergoing a two-stage implant exchange of hip or knee with or without antibiotic free interval prior to re-implantation.
- Able and willing to undergo joint punctures and venous blood sampling during and, in case of an antibiotic free interval, at the end of the six-weeks antibiotic treatment.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Unable to draw samples for study purposes.
- Language barriers.
- The use of the target antibiotics at the start of study participation (and therefore at the start of the antibiotic treatment as part of the two-stage arthroplasty exchange).
- The use of drugs interacting with the target antibiotics.

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	06-10-2020
Aantal proefpersonen:	120
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Ja

Ethische beoordeling

Positief advies

Datum:	27-04-2021
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL9461
Ander register	METC Erasmus MC : MEC-2020-0279

Resultaten