"OPTI-CLOT": Peri-OPerative pharmacokineTIc-guided dosing of CLOTting factor in hemophilia

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To investigate whether peri-operative dosing using a population-based pharmacokinetic model (non-linear mixed effect modelling) in hemophilia patients leads to a significant reduction in clotting factor consumption in comparison to the standard...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Blood and lymphatic system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON47823

Source
ToetsingOnline

Brief title
OPTI-CLOT

Condition

- Blood and lymphatic system disorders congenital

Synonym
abnormal clot formation, bleeding disorder

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: costreduction, hemophilia A, pharmacokinetic-guided, PK, surgery

Outcome measures

Primary outcome

Total amount of infused FVIII concentrate (IU) per kilogram body weight during peri-operative period per post-operative day (0-14 days after surgery).

Secondary outcome

1. Peri-operative hemostasis as quantified by hemoglobin values pre- and postoperative, blood loss and classification of expected blood loss during surgical procedure as documented by standardized form.

2. Achieved FVIII levels after FVIII infusion (IU ml-1)

3. Length of hospitalization (days).

4. Effect of baseline VWF antigen, propeptide values and blood type on FVIII clearance.

5. Economic evaluation.

Study description

Background summary

Hemophilia A is a rare clotting disorder, caused by a deficiency of clotting factor VIII. The costs of treatment of this disease weigh heavily on the Dutch national health care budget and are estimated at ¤128 million annually, of which more than ¤90 million consists of costs for clotting factor concentrates. Treatment includes prophylactic intravenous administration of the deficient clotting factor several times a week to prevent spontaneous bleedings. These infusions are aimed at raising clotting factor plasma concentration above the threshold of 1% of normal plasma levels. Surgery necessitates a more intensive regimen of clotting factor administration, as plasma clotting factor should be normalized for 7-14 days. To achieve this, continuous or bolus infusion of

clotting factor concentrate is necessary up to 14 days after surgery. In the peri-operative period, a patient may consume up to 15% of his regular annual use. There are large interindividual differences between patients in the pharmacokinetics (PK) of clotting factor concentrates. Previous studies in prophylactic dosing have demonstrated that FVIII consumption, and thus costs, can be significantly reduced by individualizing dosing based on the PK-profile of a specific patient. However, no studies have yet been performed that address PK-guided dosing in the peri-operative period. Although this does not directly have a positive effect for the patient in our country, lowering of treatment costs may in the long run be of influence on quality of treatment. In developing countries, cost-effective dosing may be of overriding importance to decrease morbidity and increase quality of life.

Study objective

To investigate whether peri-operative dosing using a population-based pharmacokinetic model (non-linear mixed effect modelling) in hemophilia patients leads to a significant reduction in clotting factor consumption in comparison to the standard dosing procedure.

Study design

Group * 12 years of age:

Multi-center open-label randomized controlled trial. Patients will be allocated to one of two treatment arms. "OPTI-CLOT" is a superiority trial powered to detect a significant decrease in peri-operative FVIII concentrate consumption in the PK-guided intervention arm. Stratification will take place according to low or medium risk surgery and dosing strategy (continuous, bolus,).

Implementation of Amendment 1:
Due to logistical reasons, the first patient per center other than from Erasmus MC will not be randomized but treated according to PK-guided dosing as a *training cohort* (n=7).

Implementation of amendment 4:
Group < 12 years of age (observational cohort); patients will not be randomized but treated according to the improved, with children's data enriched population PK model.
A trainings cohort is not necessary

Intervention

When an indication for elective low- or medium risk surgery is established, in all included patients, a PK-profile based on Bayesian analysis will be constructed pre-operatively prior to randomization, after obtaining informed

consent for the study.

Group * 12 years of age:

Patients will subsequently be randomized to one of two peri-operative treatment arms, one week before surgery. Randomization will take place into the following arms, after stratification according to low- or medium risk surgery and dosing strategy chosen by the treating physician (continuous, bolus):

(A) The intervention arm: dosing will be individualized according to a pre-operative PK-profile obtained using a population pharmacokinetic model, developed earlier based on retrospective peri-operative FVIII concentrate infusions and consequent FVIII plasma levels and iterative FVIII plasma level monitoring obtained locally, targeting for FVIII plasma trough levels stated in the Dutch Hemophilia Consensus (table 1).

(B) The standard treatment arm: pre-operative PK-profiling results will not be provided to the treating center, thus blinding the treating physician for PK-profiling results. Dosing will be set by the hematologist according to the standard dosing regimen, consisting of a bolus followed by either continuous or bolus administration with target values as set in the Dutch Hemophilia Consensus with adjustment according to daily FVIII plasma values and opinion of the treating hematologist.

More specifically, in this standard treatment arm, directly prior to surgery a FVIII bolus dose of 50 IU kg-1 will be administered. Subsequently, either a subsequent continuous maintenance dose is started, calculated by multiplying patient weight, estimated clearance (3-4 IU kg-1 hour-1) and initially a targeted steady state of 0.80 to 1.0 IU ml-1, following the Dutch Hemophilia Consensus, which describes daily post-operative FVIII target levels which decrease with per post-operative day, ór a dosing regimen based on daily bolus infusions targeting for minimal trough levels as stated by the Dutch Hemophilia Consensus. Subsequent dosing will be based on daily FVIII plasma values, and subsequent dosing will be adjusted according to doctor*s opinion based on a standard clearance of 3-4 IU kg-1 hour-1 and target values set by the Dutch Hemophilia Consensus .

Randomization will be stratified according to:
a. type of FVIII administration (continuous or bolus infusion)
b. type of surgery (low or medium risk).

Moreover, as described earlier, FVIII plasma levels will be monitored daily by the hematology laboratory on site in both groups according to standard clinical practice, already in place. However, in the intervention arm dose adjustments will be based on PK-profiling and communicated by the clinical pharmacologist directly to principle investigator and treating physician and in the standard treatment arm subsequent dosing will be based on FVIII plasma values and the

opinion of the treating hematologist.

Clinicians will be free in their choice of the brand of FVIII concentrate, and only commercially available product will be used. The product is generally patient-specific, with each participating centre having a limited number of products available. In the Netherlands, patients do not generally switch from FVIII concentrate product, as theoretically, there may be increased risk of sensitization and antibody formation. Pharmacovigilance will be covered by registration of batch-numbers by the trial-pharmacies and actual clotting factor use.

Group < 12 years of age (added in amendment 4):
These patients will not be randomized but treated according to the improved, with children's data enriched population PK model.

Study burden and risks

This study is an open-label randomized study aiming to optimize FVIII clotting factor concentrate replacement therapy, during the peri-operative period in elective surgical procedures in hemophilia A patients.
In this study we will compare whether administration of clotting factor can be improved by individual pre-operative and peri-operative PK-analysis, when compared to standard peri-operative clotting factor replacement therapy. PK-guided dosing theoretically will reduce the risk of under- and overtreatment of hemophilia patients and potentially may decrease consumption of clotting factor. Daily monitoring of FVIII plasma levels and subsequent adjustment of FVIII infusion according to protocol will verify FVIII plasma levels in both treatment arms, minimizing bleeding risk which is already not at all relevant in current practice as FVIII levels are corrected by clotting factor replacement therapy. Therefore this therapeutic study poses no additional risk to the patients.

Pre-operative PK profiling consists of a bolus infusion of FVIII concentrate (50IU kg-1) and extraction of three blood samples at (t=4 hours, t=24 hours and t=48 hours). At least three out of four of these punctures can be combined if necessary (by placement of an intravenous catheter). In addition, FVIII infusion may be combined with prophylactic FVIII infusion, avoiding an extra vena puncture and minimizing necessary FVIII infusion. Redundantly, the study population is accustomed to regular vena punctures due to prophylactic FVIII concentrate treatment, two to three times per week. Inclusion of children from 12 to 18 years of age is necessary as clearance of FVIII is especially unpredictable in children.

Note: Group < 12 years of age (observational cohort); these patients will not be randomized but treated according to the improved, with children's data

enriched population PK model.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 80
Rotterdam 3015 CN
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 80
Rotterdam 3015 CN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- Severe and moderate hemophilia A (FVIII plasma level *5%)
- Elective and low or medium risk surgery as defined by surgical risk score
- * 12 years of age at inclusion date for the randomized controlled trial
- <12 years of age at inclusion date for the PK-guided dosing observational children cohort

- Written informed consent.

Exclusion criteria

- Patients with other congenital or acquired hemostatic abnormalities.
- Withdrawal of (parental) informed consent.
- Detectable FVIII inhibiting antibodies (>0,2 BU) at inclusion in study.
- General medical conditions which may interfere with participation in the study.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-05-2014
Enrollment:	72
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aafact
Generic name:	Factor VIII
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Advate

Generic name:	Octocog alfa
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Helixate NexGen
Generic name:	Octocog alfa
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Kogenate
Generic name:	Octocog alfa
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Refacto
Generic name:	Octocog alfa
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-05-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-08-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-04-2014
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	01-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-000909-24-NL
CCMO	NL34911.078.13

Study results

Date completed:	16-04-2020
Actual enrolment:	66