Peri-Operative PharmacokineTIc-guided dosing of CLOTting factor in Hemophilia

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON29652

Source
NTR

Brief title
OPTICLOT

Health condition

Hemophilia A, surgery, treatment, pharmacokinetic-guided, pharmacokinetics, costreduction; hemofilie A, operatie, behandeling, farmacokinetisch-gedoseerd, farmacokinetiek, kostenverlaging

Sponsors and support

Primary sponsor: Erasmus University Medical Center Rotterdam, Sophia Childrens Hospital
Source(s) of monetary or material Support: ZonMW research grant

Intervention

Outcome measures

Primary outcome

Total amount of infused FVIII concentrate (IU) per kilogram body weight during the peri-operative period per post-operative day (from 72 hours before surgery up to 14 days after surgery).

Secondary outcome

1. Peri-operative hemostasis as quantified by hemoglobin values pre- and postoperatively, blood loss and classification of blood loss as compared to expected blood loss in a hematologically healthy individual with that specific surgical procedure.

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

3. Length of hospitalization (days).

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

5. Economic evaluation.

Study description

Background summary

BACKGROUND

Hemophilia is a rare clotting disorder, caused by a deficiency of clotting factor VIII (FVIII; hemophilia A) or factor IX (FIX; hemophilia B). 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 90% 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 levels should be normalized for up to 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. In the current financial setting in our country, lowering of treatment costs in the individual patient may sustain the historically high level of quality of treatment in the Netherlands. In developing countries, cost-effective dosing may be of overriding importance to influence morbidity and to increase quality of life. Therefore we here propose a study to investigate the effects of peri-operative PK-guided dosing on

consumption of FVIII in hemophilia A patients.

STUDY OBJECTIVES:

To investigate whether peri-operative dosing using a population-based PK model in hemophilia patients leads to a significant reduction in clotting factor consumption in comparison to the standard dosing procedure, based primarily on body weight, with monitoring of FVIII plasma levels.

STUDY DESIGN:

A multi-center open-label randomized controlled trial, with stratified randomization with regard to type of surgery (low or medium risk surgery) and dosing strategy (continuous, bolus) in patients aged ≥12 years of age. Patients will be allocated to one of two treatment arms, either the intervention arm with dosing according to PK model or the standard treatment arm with dosing according to plasma FVIII levels. "OPTI-CLOT" is a superiority trial powered to detect a significant decrease in peri-operative FVIII concentrate consumption in the PK-guided intervention arm.

STUDY POPULATION:

Severe and moderate-severe hemophilia A patients will be included with FVIII plasma levels ≤ 5% of normal, ≥12 years of age, that are in need of elective, low or medium risk surgery under peri-operative replacement therapy with clotting factor VIII concentrates. Patients will be recruited from five Dutch Academic Hemophilia Treatment Centers. At least 60 hemophilia A patients will be needed to detect a difference of minimally 25% in consumption of FVIII clotting factor concentrate during the peri-operative period between treatment arms.

INTERVENTION/ PLANNING:

When an indication for elective low- or medium risk surgery is established, a PK profile based on Bayesian analysis will be constructed pre-operatively in all included patients, prior to stratified randomization. Patients will subsequently be randomized to one of two peri-operative treatment arms after stratification according to type of surgery (low-, medium risk) and dosing strategy preferred by the treating physician or Hemophilia Treatment Center (continuous, bolus). This will take place minimally one week and maximally ten weeks, before surgery. Randomization will take place as close to the intervention as is logistically possible.

In both treatment arms, (trough) target FVIII plasma values will be followed as set by the Dutch Hemophilia Consensus. In all peri-operative hemophilia patients, FVIII plasma levels will be monitored daily, as part of current standard clinical care.

A) TRIAL/INTERVENTION ARM: Dosing will be administered according to results obtained with a patient-specific PK model. This model will be established individually according to a pre-operative PK profile and using a population peri-operative PK model, developed earlier based on retrospective peri-operative FVIII concentrate infusions and subsequent FVIII plasma levels.
After providing the starting dose according to the model, in the intervention arm with dosing according to PK model, daily dosing adjustments will be made according to iterative PK-profiling using FVIII plasma levels.

B) TRIAL/STANDARD TREATMENT ARM:
Dosing will be set by the treating physician according to the standard dosing regimen consisting of a bolus followed by either continuous or bolus administration with target plasma FVIII values as described in the Dutch Hemophilia Consensus.

STUDY ENDPOINTS:

PRIMARY ENDPOINT:

Total amount of infused FVIII concentrate (IU) per kilogram body weight during the peri-operative period per post-operative day (from 72 hours before surgery up to 14 days after surgery).

SECONDARY ENDPOINTS:

1. Peri-operative hemostasis as quantified by hemoglobin values pre- and postoperatively, blood loss and classification of blood loss as compared to expected blood loss in a hematologically healthy individual with that specific surgical procedure.

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

3. Length of hospitalization (days).

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

5. Economic evaluation.

GENERAL RELEVANCE:

In an era of financial crises and cutbacks on health care budgets, standard PK-guided dosing in the prophylactic, on demand and peri-operative setting may contribute to more cost-effective treatment of hemophilia as excessive dosing without a clinical effect is avoided. Surgery in hemophilia is expensive as FVIII clotting factor replacement is targeted to normalize the FVIII plasma levels and therefore requires intensive replacement therapy during a period of 7-14 days. In the peri-operative period, a patient may consume up to 15% of his regular annual use.

The proposed study aims to investigate a novel peri-operative PK-guided dosing strategy, which is expected to reduce FVIII consumption and costs by minimally 25%. Moreover, the five participating hospitals will gain experience with PK-guided dosing as they participate in this trial, which will facilitate future implementation of this expectedly cost-reducing intervention.

Study objective

The proposed study aims to investigate a novel peri-operative PK-guided dosing strategy, which is expected to reduce FVIII consumption and costs by minimally 25%. Moreover, the five participating hospitals will gain experience with PK-guided dosing as they participate in this trial, which will facilitate future implementation of this expectedly cost-reducing intervention.

Study design

The primary endpoint: The total amount of infused FVIII concentrate (IU) per kilogram bodyweight will be assessed after the peri-operative period (from 72 hours before surgery up to 14 days after surgery).
During the peri-operative period peri-operative hemostasis will be quantified by the assessment of hemoglobin values pre- and postoperatively. FVIII plasma levels will be monitored daily during the peri-operative period. The effect of baseline VWF antigen, VWF propeptide values and blood type on FVIII clearance will be monitored after the peri-operative period. At the end of the study an economic evaluation will be performed from a health care perspective taking all health care costs into account.

Intervention

A multi-center open-label randomized controlled trial, with stratified randomization with regard to type of surgery (low or medium risk surgery) and dosing strategy (continuous,

bolus) in patients aged >=12 years of age. Patients will be allocated to one of two treatment arms, either the intervention arm with dosing according to pharmacokinetic (PK) model or the standard treatment arm with dosing according to plasma FVIII levels.

Contacts

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Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Severe and moderate hemophilia A (FVIII plasma level >= 5%).

- Elective and low or medium risk surgery as defined by surgical risk score (Koshy et al.)

- >= 12 years of age at inclusion date for the randomized controlled trial;

- Written informed consent, according to local law and regulations

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients with other congenital or acquired hemostatic abnormalities.

- Withdrawal of (parental) informed consent.

- Detectable FVIII inhibiting antibodies (>0.02 BU) at inclusion in study

- General medical conditions which may interfere with participation in the study.

- High-risk surgery

- Acute surgical interventions
Co-medication will be documented as this may influence the hemostatic system.

Due to the intention to treat analyses that will be applied, patients who develop infectious complications after surgery or patients who develop inhibitors post-operatively within 4-10 weeks of surgery will be included in the statistical analyses.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2013
Enrollment:	60
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	19-08-2013
Application type:	First submission

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
NTR-new	NL3955
NTR-old	NTR4121
Other	ABR / MEC Erasmus MC : 34911.07813 / 2013-243
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A