Anticoagulation bridging: the substitution of sintrom by heparin in the periprocedural period: the Brug study

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON37436

Source
ToetsingOnline

Brief title
the Brug study

Condition

- Other condition
- Embolism and thrombosis

Synonym
thromboembolism; blood cloth

Health condition

bloedingen

Research involving
Human

Sponsors and support

Primary sponsor: Philips Research
Source(s) of monetary or material Support: Philips Research

Intervention

Keyword: anticoagulants, bridging, coagulation cascade, periopererative

Outcome measures

Primary outcome

Primary: The perioperative measurement of various plasma proteins as well as the SNPs VKORC1 and CYP2C9 combined with the values of aPTT / INR and anti-FXa allows us to test the validity of our model for use in clinical practice. We want to have both the aPTT / anti-FXa and the INRs, measured once daily, from 3 days before surgery to 5 days after surgery. If aPTT / anti-FXa and INR of the patient are within the therapeutic framework during the study period, there is a good balance between bleeding risk and risk of thrombosis. We have the following reference values for the morning before the surgery: INR <1.5, aPTT 23-32 seconds.

Secondary outcome

Secondary: The data obtained from the patients can be used for further quantitative improvement of the model. The 30 days perioperative monitoring of the participants gives us an idea of the expected rate of bleeding and thromboembolic events during the bridging period in the MUMC + and will help us to determine the sample size of a possible future study.

Study description

Background summary

There are 400.000 persons in the Netherlands using vitamin K antagonist (VKA) daily to lower their risk at thrombus formation, both in venous and arterial thrombosis. Indications for VKA therapy are:
- Primary and secondary prevention of venous thrombosis
- Prevention of thrombus growth
- Prevention of thrombus formation in case of mechanical heart valves
- Prevention of thrombus formation as a result of atrial fibrillation
- Complementing the prevention of thromboemboli for patients with arterial pathologies

VKA limits the generation of fully active vitamin K dependent coagulation clotting factors, viz. coagulation factor II, VII, IX and X. This inhibitory effect offers protection against thrombus formation en thrombus growth, but is also responsible for the most important side effect of VKA, bleeding diathesis.

Approximately 10 % of the total population of VKA users has to undergo an invasive intervention on a yearly basis. In some of these interventions the patient is treated with bridging therapy. In case of perioperative (anti)coagulation management bridging is defined as being a temporary switch of approximately 7 to 11 days to short-acting anticoagulants such as low-molecular weight heparin (LMWH) or unfractionated heparin (UFH) during the period in which the VKA is discontinued. VKA is discontinued because of the bleeding risk it is associated with during invasive interventions. The purpose of the bridging therapy is to limit the period a patient is insufficiently anticoagulated to a minimum. One of the properties of VKA is that they have a long half-life time compared to heparin-like compounds. This results in a residual anticoagulant effect for a prolonged period of time after discontinuation of VKA. The day of the intervention the patient should have an INR, which is the measure of VKA efficacy, equal to its normal value of 1 in order to minimize the risk of bleeding as a result of the intervention. This means that the patient needs to stop taking VKA 3 to 5 days before the intervention. During these 3 to 5 days the patient is at elevated risk of thrombosis due to insufficient anticoagulation. Therefore the patient is treated with short-acting heparins, which can be stopped one day before the intervention. In the Netherlands acenocoumarol as VKA is mainly prescribed. Acenocoumarol has a half-life time of 8 to 14 hours.

There is widespread consensus in literature about VKA therapy not needed to be discontinued for small (surgical) interventions, such as dental procedures or small dermatological excision . The physician can decide to bridge the surgical patient with LMWH according to the CBO guidelines, when the patient has an increased bleeding risk around the intervention and a high risk of venous and/or arterial thrombosis . Patients with a low or moderate risk of thrombosis

can discontinue VKA treatment without bridging to LMWH perioperatively. different researchers report that patients treated according to this guideline have a risk between 0.0 % and 2.0 % at thrombosis and 0.5 % - 20 % to acquire a (major) bleeding.

There is not much scientific evidence available to justify the use of bridging therapy. There is lack of large, randomized studies because these studies are not feasible on ethical grounds. Currently there are only results available from one-armed, poorly executed observational studies of case series to measure the effect of the bridging in respect to bleedings and thromboses. Consequently, the difficult consideration between risk of bleeding or thrombosis can*t be supported by strong evidence. In 2008 the American College of Chest Physicians (ACCP) published a review of the until then published studies. Based upon this review they came to the nowadays generally accepted guidelines. These guidelines are also adopted by the CBO. The question whether a VKA patient has to be bridged perioperatively is answered by these guidelines by making an individual consideration of the risk of bleeding and thrombosis and subsequently use this to define the bridging strategy. Patient stratification of the thrombosis risk is based upon the indication for VKA therapy and comorbidity. This stratification is however not validated. The stratification of the bleeding risk is determined by using multiple conditions such as the planned intervention, age, INR value, medication use (for example NSAIDs) and comorbidity (for example diabetes mellitus, lever function, aneurysma). Unfortunately an algorithm is missing for a physician to calculate the bleeding risk of the planned intervention for this particular patient, inevitably resulting in misclassification. The lack of understanding the relationship between the used bridging strategy and perioperative bleeding and thrombosis forces us to search for alternatives, in order to develop an instrument that enhances the safety of VKA users that are bridged by using short-acting anticoagulants.

Philips researchers together with the Maastricht University have started a project to gain more insight in the molecular and biological processes that are taking place during bridging therapy, document biological variations associated with these processes and develop tests that support the physicians to prescribe a more individualized bridging therapy in order to lower the incidence of bridging-related thrombosis and bleeding. The first step of this project is to observe the bridging period of 30 patients that need to undergo a (small) intervention in the MUMC+ for 9 days by daily blood measurements (via venipuncture), starting 3 days before the intervention. In addition the patients are followed 3 days before until 30 days after the intervention documenting bleeding and/or thrombosis complications. The results of our computer model will be compared to the patient outcomes using this data. In addition the data will be used to investigate possible associations between bleeding and thrombosis risk and biological variation.

The computer model of the human coagulation system currently contains the

coagulation cascade and the pharmacokinetic and pharmacodynamic (PK/PD) of VKA and heparin-like compounds. The coagulation cascade contains the protein-protein interactions taking place after a disturbance of the hemostatic balance (for example after an injury of the vascular wall) and the formation of a fibrin network which is an important part of the formed thrombus. The computer model includes the intrinsic and extrinsic pathway of the coagulation cascade. The computer model is able to calculate the effect that VKA and heparin-like compounds have on the coagulation cascade. Besides this,it is possible with the model to simulate diverse test conditions, for example the INR/PT, aPTT and TGA.

The computer model is, as of yet, largely optimized (and validated) by means of laboratory measurements and plasma from healthy individuals. Using the here proposed study we would like to test the validity of the computer model in clinical practice and to improve the computer model. In the end, we will use the data from this study in combination with the improved model to design a larger randomized trial more efficiently in order to compare the functioning of our model compared to the common bridging guidelines in terms of postoperative thromboses and perioperative bleedings.

Study objective

We have set prior to the design and implementation of this research a primary and a secondary goal.
Primary goal:
Testing the validity of the computer model of the coagulation cascade and the related PK / PD model of VKA and heparin for use in clinical practice.
Secondary goal:
The computer model is now partially optimized with respect to the simulation of the TGA, INR and aPTT. Further optimization with respect to the clinical applicability of the model for bridging from VKA to low molecular weight heparin and a local adaptation to the blood tests used in MUMC+ is required.

The determination, using this computer model, of which patients, treated according to the standard bridging regimen, are at high or low risk of developing bleeding complications or thrombosis is explicitly not an objective of the present study. This study can be seen as a pilot study for a similar, larger study.

Study design

The present study is a mono-center validation study, performed in patients on chronic vitamin K antagonists who have to undergo minor surgery. This study was initiated to validate the computer model of the coagulation cascade, developed by Philips Research. Currently the model is constructed using information obtained from blood that was provided by the blood bank. We can reach further

alignment of the PK / PD models, currently based on literature study, if we would have blood of perioperatively bridged patients. In order to achieve our goals we will daily gather blood samples from the participant during and after the bridging period. Concentrations of various proteins related to the coagulation cascade will be measured in the blood. Relative simple measurements of blood proteins that are sensitive to changing concentrations of heparin and VKA are performed, as well as measurements of key blood proteins that influence the INR, aPTT/anti FXa and TGA and measurements of the INR, aPTT/anti FXa and TGA themselves. In addition, measurements of the SNPs related to the VKORC1 and CYP2C9 will be performed. VKORC1 is responsible for the production of enzymes that reduce oxidized vitamin K, making it available again for the full formation of clotting factors. CYP2C9 is an enzyme that contributes to the metabolism of VKA. These measurements may be included as variables in our model. Because we want to link patient outcomes to the outcomes of our model, we will follow participants for 30 days and document severe / not severe bleedings and thromboembolisms. In summary, we have access to the following information of all participants:

a) Blood samples from patients every day during the entire bridging period of 3 days before to 5 days after surgery.
o The plasma measurements: FII, FV, FVII, FVIII, FIX, FX, FXI, FXII, Fibrinogen, protC, prot, Protze, AT
o INR, aPTT, TGA, anti FXa
o Hb / Ht
o thrombocyte count
o Spare citraatplasma
b)The following measurements will be determined once using the blood samples of the first day.
o SNP of VKORC1 and CYP2C9
o Standard clinical renal function
o Standard clinical liver function
c)Follow-up until 30 days after the intervention regarding perioperative-related bleedings and thromboses via the electronic hospital documentation system.
d)The following patient characteristics, through the electronic hospital documentation system.
o Age
o Gender
o Length
o Weight
o Medication use: dosage, administration schedule and INR therapeutic target range
o Medical indication of planned intervention and expected bleeding risk (low, moderate, high)
o use of red blood cell (RBC) concentrate, thrombocyte concentrate and fresh frozen plasma (FFP)

Study burden and risks

The interventions necessary for our research do not conflict in any way with the treatment the patient has to undergo. The patient undergoes surgery at the time scheduled by the treating physician and all blood samples are taken as in patients who are not included in the research. The participants bridging regime is made according to the current CBO guidelines. Patients undergo 2 or 3 blood samples (venipunctures) in the context of bridging. The difference with the normal procedure is that 9 (6 to 7 extra) blood samples (venipunctures) are taken and per sample 23ml blood is taken instead of the usual 4.5 ml. The amount of extra blood is approximately 210 ml. When an INR is to be determined in the context of the treatment (2 to 3) the nurse will draw an additional amount of 4.5 ml blood and deliver the blood at the Trombosedienst Maastricht. A venipuncture can be experienced as annoying but gives little discomfort, except that the insertion site should be covered for some time with a bandage. The risk of a (severe) bleeding is present, especially since the patient is using anticoagulants. To avoid unnecessary burden, blood samples will be taken at home by a BIG registered nurse, who is competent to staunch bleeding or refer the patient to a general practitioner. The nurse makes appointments with the individual participant during business hours. With the obtained blood, the lab tests will be performed as described in the study design. To be able to follow the patient for any bleeding or thrombosis we use electronic patient records. Permission for use will be asked. The total duration of the study per participant is 9 days.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Chronic, more than 3 months VKA use
Acenocoumarol use
An invasive procedure is planned (scopy or small intervention)
The patient is bridged with heparin

Exclusion criteria

Renal failure (MDRD clearance < 30 ml/min/1.73m2)
Heparin induced thrombocytopenia (HIT)
Documented contra indication for heparin
Emergency procedures

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-06-2013

Enrollment:	36
Type:	Actual

Ethics review

Approved WMO Date:	16-01-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
CCMO	NL38436.068.11