The Clinical Relevance and Significance of New Diagnostic Options in patients with unexplained bleeding

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The primary objective of this study is to investigate the additive value of new diagnostic tests to categorize patients with currently unexplained bleeding in order to refine therapeutic interventions.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Observational invasive

Summary

ID

NL-OMON45968

Source
ToetsingOnline

Brief title
The CRESCENDO-study

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
bleeding disorder, unexplained bleeding tendency

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Fonds NutsOhra

Intervention

Keyword: Bleeding tendency, Coagulation disorder, Diagnostics, Hemostasis

Outcome measures

Primary outcome

To determine the association between the bleeding phenotype (based on medical history and / or bleeding score), new diagnostic tests and bleeding complications during a one year follow-up period.

Secondary outcome

The (number of) abnormalities identified or localised (platelet related, primary or secondary hemostasis, fibrinolysis) in the individual patients coagulation potential based on new diagnostic tools. These abnormalities can be:

o Abnormalities in ROTEM® pattern

o Abnormalities in thrombin generation pattern

o Abnormalities in clot lysis pattern

o Combined abnormalities in global hemostatic assays

o Abnormalities in platelet proteomics

o Abnormalities on electron microscopy

o Abnormalities on flowcytometry

o Abnormalities in megakaryocyte development

o Novel DNA mutations

o Secondary abnormalities in patients with low VWF-levels

o Secondary abnormalities in patients with heterozygous factor deficiencies

o Abnormalities in fibrinolytic activators or inhibitors

Evaluation of treatment advice during two years follow-up, by means of:

o Type of bleeding symptoms

o Frequency of bleeding symptoms

o Treatment advice given in patients with unexplained bleeding

o Treatment advice followed during (dental) surgical procedures or after trauma

o Management of bleeding: Local treatment, Antifibrinolytic agents or DDAVP, Transfusion of red blood cells (RBC), platelets, plasma, PCC or other factor concentrates, Surgical, endoscopic or radiologic interventions to control bleeding

o Thromboemolic complications within 30 days after treatment of bleeding

Most optimal timing of diagnostic evaluation in premenopausal women with unexplained bleeding based on the cyclic variation of hemostatic variables.

Study description

Background summary

Each year approximately 150 patients, both adults and children, are referred to the Erasmus University Medical Center and the Erasmus MC * Sophia Children*s Hospital due to an experienced subjective or objective bleeding tendency. Retrospective data analysis (unpublished) shows that, despite extensive history taking combined with routine laboratory tests, in approximately 60% of these patients a bleeding disorder cannot be confirmed. Of this group 25% is younger than 12 years of age. This is unfortunate as a diagnosis is of great significance with regard to preferred treatment in case of trauma, (dental) surgery or other situations requiring medical intervention. Currently, if a bleeding tendency is regarded significant and no bleeding disorder is diagnosed, general treatment guidelines are followed.

In this study, we intend to evaluate the role of novel diagnostic tools and tests in all patients with a currently unexplained bleeding tendency and the

effect of hormonal influences in women with bleeding symptoms. Novel diagnostic tools will include a validated and a novel international (pediatric) bleeding assessment tool. Novel diagnostic tests will include tests that assess the global hemostatic potential e.g. Thromboelastometry (ROTEM®) and Thrombin Generation Assay (TGA) as well as test that aims to quantify the fibrinolytic potential of the individual e.g. plasma clot lysis assay (CLA). In addition a third category of tests will be performed that aims to quantify and study the proteomic constellation of the platelet in order to identify potential platelet disorders. As hemostatic testing is currently a developing field, informed consent will be obtained for blood sample storage in order to perform novel techniques in the near future currently under development (e.g. whole exome sequencing, other platelet specific techniques).

Study objective

The primary objective of this study is to investigate the additive value of new diagnostic tests to categorize patients with currently unexplained bleeding in order to refine therapeutic interventions.

Study design

Prospective case-control study

Study burden and risks

Burden: After obtaining informed consent by the patient when aged >12 years of age and also by his parents when the or caregivers when the patient is <18 years of age, bleeding symptoms will be quantified by both a validated adult and pediatric bleeding assessment tool (BAT). Blood samples will obtained in combination with routine laboratory tests. A maximum of eight (eleven for evaluating the cyclic variation of hemostatic variables) (see appendix 5 * Blood sampling CRESCENDO study) extra tubes will be taken.

Risks: The risks associated with study participation are considered negligible and the extra burden is minimal. Patients participating in the study will receive the same routine diagnostic tests and treatment advice as patients not included in the study, according to current clinical practice guidelines. In the patients participating in the study, additional diagnostic tests will be performed in a small amount of extra blood extracted from the patient during blood sampling moments required for the standard diagnostic work up.

Benefits: In current practice, patients (and parents) experience a burden of uncertainty when a bleeding tendency cannot be specified and only general treatment can be recommended. We aim to increase knowledge with regard to the aetiology of the bleeding tendency in patients with currently unexplained bleeding by systematic documentation of the bleeding symptoms by bleeding

assessment tools and by performance of novel tests that investigate the global hemostatic potential or focus on a defect in part of the coagulation cascade which is not tested in routine laboratory testing. In the future this might allow for targeted therapy of bleeding complications and prevent patients from getting unnecessary treatment, avoidable medical intervention or (prolonged) hospitalization.

Contacts

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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

Patients of all ages;

Patients with a significant history of bleeding tendency according to physician opinion or abnormal bleeding score based on a BAT
o with no defined diagnosis after routine testing (see appendix 4 of the research protocol),
o with a heterozygous factor deficiency or low Von Willebrand Factor levels that do not correspond with the experienced bleeding tendency,
o with aberrant laboratory results not fitting a diagnosis;
Informed consent should be provided prior to any study specific procedure.

Exclusion criteria

Patients with a defined bleeding disorder after routine testing (see appendix 4 of the research protocol, except when they serve as controls for the trombocytopathy arm);
Patients under therapy with anticoagulants and / or antiplatelet and / or anti-inflammatory agents whom cannot stop their medication during the diagnostic work-up;
Patients with thrombocytopenia < 80 x 109/L (with exception to the patients with suspected or volunteers in the control group with a proven platelet disorder);
Patients with a bleeding tendency due to an acquired platelet function disorder (e.g. idiopathic thrombocytopenic purpura * ITP);
Patients with impaired liver function, eg a documented liver cirrhosis or signs of acute liver failure;
Women that are pregnant or up to three months postpartum;
Patients who are inable to give informed consent.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-07-2016

Enrollment:	330
Type:	Actual

Ethics review

Approved WMO Date:	21-06-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-01-2018
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

ID: 23281
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL55101.078.16
OMON	NL-OMON23281