Creatine kinase, platelet aggregation, and bleeding risk in women with uterine leiomyomas

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Main study:We want to assess whether bleeding risk in women with uterine leiomyomas is associated with CK activity and attenuated platelet aggregation.Objective of pilot study:Firstly, to perform a feasibility pilot of CK/AK measurement in menstrual...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Platelet disorders
Study type	Observational invasive

Summary

ID

NL-OMON43648

Source
ToetsingOnline

Brief title
Creatine kinase and bleeding risk

Condition

- Platelet disorders
- Reproductive neoplasms female benign

Synonym
heavy menstrual bleeding, menorrhagia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: creatine kinase, platelet aggregation, uterine leiomyomas

Outcome measures

Primary outcome

The association between plasma CK activity, ADP-dependent platelet aggregation, and bleeding severity in women with uterine leiomyomas.

Pilot study parameters/endpoints:

Firstly, the feasibility and optimal strategy of CK and AK activity measurement menstrual and postpartum vaginal blood). Secondly, to assess the relation between vaginally lossed blood CK/AK activity, venous plasma CK/AK activity and bleeding severity. Thirdly, the concentration of DOAC and VKA in menstrual blood.

Secondary outcome

- To assess menstrual bleeding severity (Hb, amount of menstrual blood loss using the visual Pictorial Blood loss Assessment Chart (PBAC) score) in patients with uterine leiomyomas and controls in relation to CK .
- To assess whether measures of the volume of the neoplasms (the diameter of the largest fibroid and the number of fibroids) are related to CK, ADP-dependent platelet aggregation, and bleeding risk.
- Assessing whether the bleeding risk questionnaire score (see Appendix Bloedingen vragenlijst, in Dutch) is related to the presence and extent of the heavy menstrual blood loss, CK and ADP-induced platelet aggregation.
- Assessing CK activity, hemoglobuline and sodium concentration in menstrual

blood. This, to establish whether the CK activity in menstrual blood is high

and thus may locally attenuate ADP-induced platelet aggregation, and whether

the CK activity in menstrual blood is composed of CK derived from intravascular

blood (mainly the CKMM isotype) or CK derived from uterine smooth muscle tissue

(mainly the CKBB isotype).

Study description

Background summary

Excessive menstrual blood loss in the presence of uterine leiomyomas occurs frequently, but there is a lack of clinical studies that assess the potential causes of this excessive bleeding.
We hypothesize that relatively high plasma enzyme creatine kinase (CK) might increase bleeding risk. The enzyme is the main ADP scavenger in plasma, as it catalyses the reversible transfer of a phosphorylgroup from creatine phosphate (CrP) to ADP, creating ATP in the reaction:

CrP + ADP <-> Creatine + ATP

As ADP is central to platelet aggregation, high CK activity might lead to reduced ADP and thus inhibit platelet aggregation in a clopidogrel-like effect. ADP activates platelets in synergy with other platelet agonists such as collagen, epinephrine, and low concentrations of thrombin. The importance of ADP is evident from the bleeding risk in patients with so-called platelet storage pool disease, a condition with a reduced content of the platelet granules including ADP. Removal of ADP by CK, especially in the presence of CrP, is therefore likely to result in impaired platelet aggregation and thus an increased bleeding risk.
Plasma CK activities are particularly high in women of African ancestry as compared to European ancestry, additionally, a locally higher activity of CK is found in leiomyomas. Therefore, it is desirable to study the hypothesized greater bleeding risk associated with CK in these women with monthly heavy menstrual bleeding.

Rationale of pilot study:
We recently reported that increased activity of the ADP-consuming enzyme creatine kinase (CK) activity is associated with reduced platelet aggregation in healthy male volunteers. By inhibiting platelet aggregation CK could promote bleeding. The activity of CK and other ADP-consuming enzymes such as adenylate

kinase (AK) in menstrual blood and its effect on bleeding severity remains unclear. A high activity of ADP-consuming enzymes could be a contributing factor in heavy menstrual blood loss or postpartum haemorrhage. To our knowlegde, the measurement of CK and other ADP-consuming enzymes in menstrual or postpartum blood has not been studied previously. Prior to the main study, we will perform a feasibility pilot of CK/AK measurement in menstrual and postpartum vaginal blood, and compare the CK and AK activity in vaginal blood to venous plasma CK/AK activity, platelet aggregation and bleeding severity (also see the Appendix of the protocol).
Finally, as we are collecting menstrual blood, we would like to test whether we can measure DOAC (direct oral anticoagulant) and VKA (vitamin K antagonist) concentration in menstrual blood. In the further we might conduct a study on the effect of DOAC*s and VKA*s on menstrual bleeding.

Study objective

Main study:
We want to assess whether bleeding risk in women with uterine leiomyomas is associated with CK activity and attenuated platelet aggregation.

Objective of pilot study:
Firstly, to perform a feasibility pilot of CK/AK measurement in menstrual and postpartum vaginal blood. Secondly, to compare CK and AK activity in vaginal blood to venous plasma CK/AK activity, platelet aggregation and bleeding severity. Thirdly, the concentration of DOAC and VKA in menstrual blood.

Study design

Observational study

Study burden and risks

Participant will be ask to visit the Academic Medical Centre twice.
Venous blood will be drawn (50 mL) for platelet and coagulation test, and for CK estimations. Participants will be asked to collect menstrual blood once. Assessing the presence/absence of uterine leiomyomas will be done performing a transvaginal ultrasound once. During the ultrasound unexpected findings may occur, such as ovarian or uterine abnormalities; participants should be aware of, next to the identification of leiomyomas, the diagnostic character of this tests with its potential findings and consequences. When an unexpected finding does occur the gynaecologist will discuss this with the participant and initiate further care.
The risk and burden of these assessment are small. Assessing whether CK is associated with increased bleeding risk in these women might eventually lead to completely novel, conservative treatment options with CK inhibitors in women

with uterine leiomyomas.

With the pilot study, we aim to get more clarity in the assessment of CK and AK activity in vaginal blood loss. When the measurements are thought to be feasible and contributory, in a larger study the association between menstrual and postpartum blood CK and AK activity, platelet aggregation and bleeding severity can be further explored.

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

Main study:
20 premenopausal women aged 18-50 years, visiting the gynaecology outpatient clinic with

uterine leiomyomas and heavy menstrual bleeding, and women without leiomyomas and normal menstrual bleeding, forming the control group. ;Pilot study:
12 premenopausal female volunteers, 18-50 years:
a. 8 women with heavy menstrual blood loss;
- without treatment for the menstrual blood loss (n=2)
- with plasmin inhibitor treatment for the menstrual blood loss (n=2)
- with DOAC-induced heavy menstrual blood loss (n=2)
- with VKA-induced heavy menstrual blood loss (n=2);
b. 2 women normal menstrual blood loss;
c. 2 women postpartum.

Exclusion criteria

Main study:
Smoking, usage of NSAID, antiplatelet drugs and anticoagulants, hormone therapy or hormone supplements in 4 weeks prior to participation. Usage of CK-increasing drugs, such as statins, in the three months prior to participation. Glucose, lipid spectrum, thyroid, kidney or liver abnormalities, no history of secondary hypertension, (history of) cardiovascular disease including TIA and stroke; neuromuscular or endocrine disorders; vasculitis; HIV infection; malignancies; infectious hepatitis, bleeding disorders (other than heavy menstrual bleeding). ;Pilot study:
Usage of CK-increasing drugs, such as statins, in the three months prior to participation. Glucose, lipid spectrum, thyroid, kidney or liver abnormalities, neuromuscular or endocrine disorders; HIV infection; infectious hepatitis, bleeding disorders (other than heavy menstrual bleeding).

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-05-2016
Enrollment:	32
Type:	Actual

Ethics review

Approved WMO Date:	19-02-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL52254.018.15