2BEGIN

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

Summary

ID

NL-OMON57531

Source
Onderzoeksportaal

Brief title
2BEGIN

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Joint disorders

Synonym
Haemophilia; Synovial Hypertrophy; Hemophilic arthropathy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Novo Nordisk

Intervention

- No intervention

Explanation

N.a.

Outcome measures

Primary outcome

As no gold standard to identify active subclinical proliferation is available, “change in synovial proliferation over time” will be used as surrogate endpoint, with change expected in joints with active synovial proliferation compared to no change in inactive synovial proliferation. This is measured by ultrasound assessment according HEAD-US protocol and by quantifying maximal synovial thickness in millimetres. Possible outcomes are: no change (baseline HEAD-US score and thickness = 12-week follow-up HEAD-US score and thickness) or changed (baseline HEAD-US score and/or thickness < or > 12-week follow-up HEAD-US score and/or thickness). Fully recovered synovial proliferation will also be categorized as changed. The diagnostic accuracy will be derived comparing ‘change in synovial proliferation’ with the ‘presumed’ definition at baseline (active or inactive).

Secondary outcome

Baseline participant characteristics (age, baseline treatment, joint bleeding history) and joint characteristics (extent of arthropathy (Pettersson score on X-rays)) will be extracted from medical files.   Our clinical and ultrasound definition of active synovial proliferation: synovial proliferation on ultrasound (HEAD-US synovium score >0) and the presence of at least one of the following criteria: HJHS swelling >0 at baseline
Warmth palpation absent/present at baseline
Synovial hyperaemia JADE Synovial Hyperaemia >0 at baseline
Newly detected synovial proliferation (no history of synovial proliferation based on ultrasound assessments and medical records of the last 3 years); Yes/No The MRI-based definition and our hypothesized elastography-definition: Hemosiderin on MRI: IPSG 2.0 score Hemosiderin Deposit > 0 at baseline Elastography: elasticity of synovium in KiloPascal (kPa)

Study description

Background summary

There is cumulating evidence for the presence of non-observed or subclinical joint bleeding in patients with haemophilia. Active subclinical synovial proliferation is a marker for subclinical joint bleeding. Early detection of active subclinical synovial proliferation would allow early intervention in order to prevent deterioration of joint health. Inactive (fibrotic) subclinical proliferation is unrelated to current subclinical bleeding and does not require treatment. A

diagnostic test to differentiate active from inactive subclinical proliferation is still lacking. Patients with subclinical (=non-observed) signs of synovial proliferation in knee(s), ankle(s) and/or elbow(s) will be invited to participate in this study to further characterize the synovial proliferation status (active or inactive) by means of physical examination, MRI, ultrasound and elastography. Synovial proliferation status will be monitored for a maximum period of 12 weeks, during which participants will also receive standard-of-care treatment, i.e. administration of optimized coagulation factor replacement therapy and prescription of the NSAID celecoxib (optional).

Study objective

The primary objective of this study is to evaluate the diagnostic accuracy of physical examination and ultrasound to identify active synovial proliferation in haemophilia patients with subclinical synovial proliferation.

The secondary objectives are:

- To evaluate the diagnostic accuracy of the presence of synovial hemosiderin, as measured by MRI, to identify active synovial proliferation in haemophilia patients with subclinical synovial proliferation.
- To evaluate the diagnostic accuracy of synovial elastography to identify active synovial proliferation in haemophilia patients with subclinical synovial proliferation.
- To evaluate the association between synovial proliferation type (active/inactive), participant characteristics (age, baseline treatment, joint bleeding history) and joint characteristics (extent of arthropathy).

Study design

Study design: A prospective observational monocenter study.

Study population: Male participants ≥ 12 years of age, with severe haemophilia A or B treated with prophylaxis, who were diagnosed with subclinical synovial proliferation in ≥1 joint (ankle, knee and/or elbow) by means of ultrasound imaging during routine screening at the outpatient clinic of the Van Creveldkliniek, UMC Utrecht, the Netherlands.

Study procedures: Physical examination, ultrasound, MRI, synovial elastography and follow-up of the joints of interest, i.e. ankle(s), knee(s) and/or elbow(s) that show signs of subclinical synovial proliferation during routine screening at the outpatient clinic.

Intervention

NA

Study burden and risks

Patients are eligible for inclusion in this study when subclinical synovial proliferation is diagnosed during routine health-care visit (screening-visit). When diagnosed, standard-of-

care treatment will be given for all patients, this includes follow-up after 6 and/or 12 weeks depending on whether the synovial proliferation is fully recovered after 6 weeks. Due to logistical issues and consideration time to give consent for participants, MRI and elastography cannot be performed during screening visit. Therefore, patients need to visit the study site 1 time extra for study purposes only to undergo non-invasive diagnostic examination for approximately 1-2 hours. There are no known risks or side-effects of MRI and elastography. All other visits and treatments are standard-of-care and do not increase any burden nor risks for participants of the study.

Contacts

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Trial sites

Trial sites in the Netherlands

Universitair Medisch Centrum Utrecht
Target size: 51

Listed location countries

Netherlands

Eligibility criteria

Age

Adolescents (16-17 years)
Adolescents (12-15 years)
Adults (18-64 years)

Inclusion criteria

- Gender: male.
- Patients with severe haemophilia A or B (<1% FVIII/IX activity).
- Treated with registered prophylaxis medication including coagulation factors and non-factor replacement therapy.
- Age ≥ 12 years.
- Subclinical synovial proliferation in ≥1 joint (ankle, knee and/or elbow), defined as the presence of hypertrophic synovium, score >0 according to the HEAD-US protocol, as confirmed during routine ultrasound screening.
- Able to give written informed consent.

Exclusion criteria

- A major bleed (joint bleed resulting in clearly reduced range of motion, severe pain and swelling, requiring treatment with more than one infusion of clotting factor concentrate) ≤ 3 months or a minor bleed (resulting in a slightly reduced range of motion, moderate pain and swelling which resolved after a single infusion of clotting factor concentrate) ≤ 1 month prior to inclusion in the joint of interest.
- On demand therapy.
- Joints with prosthesis or arthrodesis will not be included for physical examination and ultrasound analysis. However, participants may still be included in the study with their other joints.
- Confirmed inflammatory joint diseases such as rheumatoid arthritis or psoriatic arthritis.
- Contra-indication for treatment with NSAIDs, (allergy, severe liver failure, renal failure (GFR <30ml/min), congestive heart failure (NYHA II-IV), peripheral arterial disease and/or cerebrovascular disease.)
- Contraindications for MRI (e.g., claustrophobia, metal, or electronic implants that are incompatible with MRI).

Study design

Design

Study phase: N/A

Study type:	Observational invasive
Intervention model:	Single
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2025
Enrollment:	51
Duration:	3 months (per patient)
Type:	Anticipated

Medical products/devices used

Product type:	N.a.

IPD sharing statement

Plan to share IPD: Undecided

Plan description
N.a.

Ethics review

Approved WMO

Date:	14-05-2025
Application type:	First submission
Review commission:	METC NedMec

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
ClinicalTrials.gov	NCT06809972
Research portal	NL-009166