Cerebrovascular reserve and white matter disease in patients with chronic anemia. (IMPROvE)

Published: 30-10-2018
Last updated: 12-04-2024

Primary Objective: The main goal of this project is to identify CVR predictors including CBF, age, sex and vascular stressors in anaemic and control patients using several MRI techniques. While anaemia is correlated with other cerebrovascular risk...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haematological disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON48763

Source
ToetsingOnline

Brief title
IMPROvE

Condition

- Haematological disorders NEC

Synonym
Sickle Cell Disease - Thalassemia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NIH

Intervention

Keyword: Anemia, Cerebrovascular Reserve, Improve, White Matter Disease

Outcome measures

Primary outcome

CBF measured by ASL; number and volume of silent cerebral infarcts (SCIs) on 3D fluid attenuated inverse recovery (FLAIR) and T2-weighted MRI scans; brain volume by T1 anatomical MPRAGE; CVR measured by ASL using ACZ.

Secondary outcome

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Study description

Background summary

Silent white matter strokes have been recognized as a major problem in sickle cell disease1,2. While the use of transcranial Doppler as a screening tool and appropriate chronic transfusion therapy have reduced the risk of symptomatic ischemic stroke in sickle cell disease (SCD) ten-fold in high risk patients, the prevalence of silent cerebral infarct (SCI) rises 1-2% per year with no plateau1. Sickle cell patients have a profound white matter volume loss and abnormal white matter diffusivity, even in the absence of silent strokes3-5. As a result, continuous neurovascular damage which has been related to impaired neuro-cognitive function continues to be a major contributor to unemployment, underemployment, and impaired quality of life in these patients2,6. Currently, no test is available to measure the risk for silent stroke in SCD patients. Our preliminary data suggests that SCIs are more common in SCD patients and occur in specific high-risk regions7.
SCIs are caused by a mismatch in oxygen supply and demand. Although the brain comprises only 2.5% of the body mass, it uses about 20% of the body*s oxygen at rest8. The brain cannot survive under anaerobic conditions, so cerebral oxygen delivery is tightly regulated. Over 98% of the oxygen that is delivered to the brain is transported by haemoglobin. In patients with SCD, the concentration of functional haemoglobin is chronically diminished and as a result, CBF is increased by vasodilation to maintain oxygen delivery9,10. However, this compensatory mechanism of cerebral vasodilation is limited. Blood vessels have a limited capacity to dilate11. The increase in CBF under metabolic stress,

relative to the baseline flow, is known as the cerebrovascular reserve (CVR). CVR is typically 40%-70% in healthy control subjects, but is much lower in subjects with SCD because of their already increased resting brain blood flow11. A decreased CVR does not directly cause damage, but it leaves the brain vulnerable to ischemic insults. This is because the brain*s increased oxygen extraction (under metabolic stress) can no longer compensate for decreased oxygen delivery or increased metabolic demand.

Many groups have estimated CVR by measuring the extent to which cerebral perfusion increases in response to vasodilation12-14. Vasodilatation can be caused by either inhalation of carbon dioxide (CO2)-mixed air or by administration of acetazolamide (ACZ)9. With CO2 inhalation there is an effect of hyperventilation on CBF15. However, ACZ induces maximal cerebral vasodilation without confounding effects of cardiovascular physiology16,17. Therefore, using ACZ, CVR can be measured most directly and accurately. In contrast to the CO2 inhalation, ACZ is independent of the patient's cooperation15,18. In addition, our group has experience using ACZ in SCD patients.

Sickle cell disease is not the only type of anaemia with white matter damage. Thalassemia is another group with a high prevalence of silent ischemic lesions19-21. Different studies showed white matter lesions in patients with intermediate thalassemia that were similar to the lesions found in SCD patients21,22. Pazgal et al. studied the presence of SCI in transfused beta thalassemia major patients23. They assumed that transfused patients would have less SCIs compared to patients with thalassemia intermedia. Unexpectedly, results showed multiple SCIs in 60.7% of the patients with transfused beta-thalassemia major. So, SCIs are observed in both nontransfused and transfused thalassemia patients. In patients with thalassemia, SCIs are most likely caused by thromboembolic events mostly as a consequence of splenectomy21. However, in contrast to the SCD patients, no blockage of the small vessels occur in patients with thalassemia.

Besides patients with SCD or thalassemia, white matter strokes also occur in more than 30% of all healthy individuals older than 65 years of age24 and are associated with significant neurocognitive dysfunction25, depression26, falling27, ischemic stroke28, and all-cause mortality28. However, these individuals do not have a hereditary hemoglobinopathy and do not experience chronic haemolysis. In contrast to these older healthy individuals, in anaemia patients, SCI occur in a younger age.

Our recent study (Cruise) has shown that CVR differs between healthy controls and SCD patients. However, it is not clear from that study whether these differences are sickle cell dependant or caused by anaemia (as in thalassemia). To better understand the aetiology of reduced CVR in SCD, studying a group of anaemic non-SCD patients (e.g. thalassemia patients) is required, in order to disentangle anaemia-related impairments and anaemia plus SCD related

impairments. In addition, a group of sickle cell patients will be included that have been selected for allogenic stem cell transplantation (SCT). By including this group a direct comparison of the impact of SCD on the hemodynamics of the cerebral perfusion can be obtained by comparing the parameters of the hemodynamics of the cerebral perfusion like CVR before and after successful SCT,

In order to understand the age depended CVR differences, inclusion of healthy subjects is needed. By measuring the regional CVR using a magnetic resonance imaging (MRI) technique called arterial spin labelling (ASL), we hypothesize to have an opportunity to optimize current therapies to prevent cerebral infarct. We will further investigate the CVR parameters such as perfusion, vasodilatation, vascular territories and wall shear stress (WSS) before and after vasodilatation The effect of interventions on CVR, will be investigated by including patients who undergo blood transfusion, hydroxyurea treatment or allogeneic SCT.

Study objective

Primary Objective:
The main goal of this project is to identify CVR predictors including CBF, age, sex and vascular stressors in anaemic and control patients using several MRI techniques. While anaemia is correlated with other cerebrovascular risk factors in the general population (hypertension, kidney disease, chronic inflammation, heart failure), we assume that anaemia, by decreasing CVR, creates an increased vulnerability to white matter damage in patients with SCD. Through the use of simple and exchange transfusions in selected patients with SCD and thalassemia, we will study the relative importance of haemoglobin S% and total haemoglobin level on regional CVR. We will identify other modifiable risk factors (iron overload, vascular inflammation) that may impair CVR. By comparing CVR and white matter damage across a broad spectrum of SCD and thalassemia syndromes, we will be able to separate the damaging effects of haemolytic anaemias in general from damage specific to sickle haemoglobin.

Secondary Objective(s):
1) Whether the regions of low CVR match the distribution of white matter damage
2) Whether changes in haemoglobin level or haemoglobin S% contribute to the global and regional CVR
3) Whether allogeneic SCT improves CBF, CVR and CMR02
4) Whether transfusion, the use of hydroxyurea or allogeneic SCT treatment improves CVR in the white matter regions at risk for stroke.
5) Whether allogeneic SCT improved neurocognitive functioning in patients with SCD.
6) Whether impaired CVR capacity is associated withbiomarkers of coagulation activation, neutrophil activation, endothelial damage or oxidative

stress.

Study design

Study will be performed at two large SCD Centres of Excellence, Children*s Hospital of Los Angeles in California, and the Academic Medical Centre of Amsterdam. The study is a multicentre observational study with intervention (MRI and the medicinal product). Depending upon inclusion, the project has a duration of four years. The control group and the nontransfused patients will undergo a single MRI-examination. Transfused patients and the patients who will start with hydroxyurea treatment will undergo two MRI examinations (before and after transfusion of hydroxyurea treatment). Sickle cell patients who will undergo an allogeneic SCT will have MRI imaging prior to and 6 and 12 months after the transplantation.

Study burden and risks

MRI is harmless, ACZ injection has proven to be safe and venapunction is routine in patients with anaemia. Parameters obtained by blood drawn in this study will be used clinically as well. Therefore, participation is considered to relate with low burden and minimal risks.

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

Inclusion criteria (patient groups)
• Sickle cell disease
• Thalassemia major, thalassemia intermedia, and HbH disease
• 18 Years of age or older
• Informed consent;Inclusion criteria control group
• Either AS or AA haemoglobin,
• 18 Years of age or older
• Informed consent

Exclusion criteria

Exclusion criteria (patient groups)
• Hospitalization in the past month for any reason
• Inability of the patient to provide informed consent
• Contraindications for MRI, such as claustrophobia or the presence of metal in the body
• Sickle cell crisis at the moment of participation up to one month prior to participation
• History of cerebral pathology that compromises measurements, such as cerebral palsy, brain tumour, meningitis, overt infarct
• Brain surgery performed in the last 3 months ;ACZ contraindications
• Severe liver, heart or renal dysfunction (clearance < 10 mL/min)
• Allergy to sulphonamide
• Pregnant or breastfeeding
• Use of phenytoin, procaine or acetylsacylic acid (*Ascal/aspirin*)
• Risk of hypokalaemia (use of diuretics, primary hyperaldosteronism)
• Addison*s Disease
• Severe asthma or emphysema ;Exclusion criteria (controls)
• Any known chronic illness that may compromise subject safety or data integrity. These include but are not limited to rheumatologic disorders, malignancy, severe asthma, chronic hepatic or renal insufficiency, and haemoglobinopathy or other chronic anaemia
• Vascular risk factors
• Hypercholesterolemia
• Contraindications for MRI, such as claustrophobia or the presence of metal in the body
• Contraindications for ACZ (listed in the exclusion criteria of patients)
• Developmental delay, stroke, seizure disorder, or neurological conditions other than simple migraine

• Inability to cooperate with MRI examinations
• Diabetes
• Uncontrolled hypertension or history of hypertension

Study design

Design

Study phase:	2
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):	22-01-2019
Enrollment:	140
Type:	Actual

Ethics review

Approved WMO Date:	30-10-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2020

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	NL66876.018.18