Butyrate: effect of oral administration in patients with mild hypertension

Published: 16-09-2020
Last updated: 09-04-2024

The primary objective of this study is to assess the effect of oral butyrate on blood pressure. Secondary objectives are to assess the effect of oral butyrate on faecal and plasma SCFA levels, gut microbiome composition, diuresis, renin and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON49499

Source
ToetsingOnline

Brief title
BEAM study

Condition

- Vascular hypertensive disorders

Synonym
hypertension; high blood pressure

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Blood pressure, Hypertension, Microbiome, Short chain fatty acids

Outcome measures

Primary outcome

The primary outcome is average daytime systolic blood pressure as measured by 24-hour ambulatory blood pressure.

Secondary outcome

Secondary outcomes are other blood pressure measurements, including:

- Average diastolic daytime ambulatory blood pressure, average systolic and diastolic night-time blood pressure and average systolic and diastolic 24-hour ambulatory blood pressure;

- Office blood pressure (two-weekly);

- Home blood pressure measurement (weekly).

Other study parameters include:

- Faecal and plasma SCFA levels, including butyrate;

- Gut microbiome composition;

- Parameters of renal fluid and electrolyte balance regulation, including:

weight and total body fluid as measured with body impedance analysis (BIA);

plasma renin activity and aldosterone levels; sodium excretion in 24 hour urine;

- Baroreceptor activity and pulse wave velocity as measured with Nexfin.

- Dietary intake (mijn.voedingscentrum.nl/nl/eetmeter)

- Change in immunophenotype

Study description

Background summary

Hypertension is the leading modifiable risk factor for cardiovascular morbidity and mortality, and thereby the most important risk factor for preventable death worldwide.1 The pathogenesis of primary hypertension remains incompletely understood, but it is currently attributed to a complex interplay of genetic predisposition and lifestyle.2 Lifestyle factors including diet, salt intake, and obesity are known to be important for the pathogenesis of hypertension.3-5 A large population-based study in the UK demonstrated that combined lifestyle factors can modify blood pressure with 4- 5 mmHg.6

The gut microbiota composition is a reflection of life long exposure to dietary factors. Other important determinants of the gut microbiota are age, body mass index (BMI), diabetes, antibiotics use and inflammatory bowel diseases.7-10 In addition, several cross-sectional studies have shown differences in the composition of the gut microbiota between hypertensive and normotensive subjects, even after adjusting for important confounders. Higher abundance of Klebsiella spp. and Prevotella spp. has been associated with higher blood pressure, while higher abundance of Akkermansia spp. and Ruminococcacae spp. and Roseburia spp. have been associated with lower blood pressure.11,12

Short chain fatty acids (SCFAs) are key metabolites of the gut microbiome, and are produced by intestinal gut microbiota, including Akkermansia, Ruminococcacae and Roseburia spp., in fermentation processes of otherwise indigestible dietary fibers.13 SCFAs with highest faecal and plasma levels are acetate, propionate and butyrate. Animal studies have indicated a direct association between faecal SCFAs and blood pressure by showing that SCFAs receptors, including free fatty acid receptors (FFAR) 2 and 3 and Olfr78, are present in kidneys and blood vessels.14 It was suggested that through these receptors, butyrate has effects on the renin-angiotensin-aldosterone system (RAAS). In one study, intravenous administration of butyrate to spontaneous hypertensive rats lowered both blood pressure and renin and angiotensin II levels.15

In humans, evidence of a direct link between SCFAs and blood pressure is scarce. Nonetheless, we do know that high fibre intake through the Mediterranean diet prevents gut dysbiosis by inducing a rise in SCFAs.16 This diet has been related to reduction of cardiovascular events and lower blood pressure.17 In addition, butyrate has been administered to human subjects before in trials at the Amsterdam UMC (2014-084 and 2014-291), which showed

that butyrate was safe and was cardiometabolically active both in the intestine (alterations in faecal SCFA levels) as well as on insulin sensitivity.18,19 If faecal butyrate levels are indeed related to blood pressure, this could provide new perspectives on the pathophysiology and treatment of hypertension. Hence, in this study, we aim to investigate the effect of oral butyrate treatment on blood pressure in subjects with mild hypertension.

Study objective

The primary objective of this study is to assess the effect of oral butyrate on blood pressure.
Secondary objectives are to assess the effect of oral butyrate on faecal and plasma SCFA levels, gut microbiome composition, diuresis, renin and aldosterone levels, hemodynamic parameters such as baroreceptor sensitivity and pulse wave velocity, and immunophenotype. In addition, changes in body weight and body composition (bioimpedance analysis; BIA) as well as dietary intake will be monitored.

Study design

Randomized placebo-controlled double-blind trial (parallel design)

Intervention

The investigational products are sodium butyrate (Sensilab) and placebo. Patients will be randomised over the intervention and control group. In the intervention group, patients will receive 13 capsules of sodium butyrate twice daily (total 4 gram), a similar dosage as previously administered to humans subjects at Amsterdam UMC (2014-084 and 2014-291). In the control group, patients will receive 13 placebo capsules twice daily filled with sodium chloride in order to ensure that the administered dosage of sodium is equal between the intervention and control group (780 mg sodium per day), since sodium could potentially modify blood pressure levels.

Study burden and risks

There is no direct benefit for participants in this study. Patients need to make five visits to the AMC for the purpose of this study over the course of six to nine weeks. Risks associated with procedures in this study, which include collection of faecal, urine and blood samples, body composition measurement and several non-invasive blood pressure measurements, are considered low. The maximum amount of blood that will be drawn over three study visits is 82,5 ml per patient. Patients could experience side effects of the butyrate intervention, however, no side effects were reported in intervention studies with similar dosages.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9, D3-316
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9, D3-316
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age between 40 and 65 years
- For females: postmenopausal status
- Caucasian
- Mild hypertension (defined as systolic blood pressure range 140-159 mmHg and/or diastolic blood pressure range 90-100 mmHg) without antihypertensive medication OR use of 1 antihypertensive drug due to hypertension and willing to temporarily stop this medication
- Body mass index (BMI) lower than 27 kg/m2

Exclusion criteria

- Insufficient knowledge of the Dutch language
- Use of betablockers
- Known secondary causes of hypertension such as renal artery stenosis, adrenal or thyroid disease
- History of cardiovascular disease: angina pectoris, myocardial infarction, cerebrovascular accident, transient ischemic attack, peripheral artery disease, heart failure.
- History of diabetes mellitus
- Current smoking
- Antibiotics usage within three months before inclusion
- Having a severe disease of the digestive tract, such as celiac disease, Crohn*s disease, active ulcerative colitis or short bowel syndrome.
- Impaired renal function, defined as an estimated glomerular filtration rate (eGFR) lower than 60 ml/min/1,73m2 using the CKD-EPI formula within a period of two years before the screening visit. Participants without an available lab result on renal function will not be included.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-03-2021
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	16-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2020
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	NL73625.018.20