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Effects of beetroot juice and folate supplementation on blood pressure

Submission date
15/08/2018

Recruitment status
No longer recruiting

Registration date
05/11/2018

Overall study status
Completed

Last Edited
17/01/2024

Condition category
Circulatory System

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
High blood pressure (hypertension) is closely associated with cardiovascular diseases (CVD) and contributes significantly to cardiovascular disease morbidity and mortality. The public health impact of hypertension in developing countries is even worse, due to a lack of, or ineffectively implemented nutritional guidelines or inadequate of health care systems. Nitrate and folate are compounds that can be obtained from the diet that have been shown to reduce hypertension. This study aims to look at the feasibility of using a nutritional intervention in hypertensive and pre-hypertensive Tanzanian adults, where nitrate and folate will be supplemented in their diet to determine if this affects their blood pressure.

Who can participate?
Men and women between the age of 50 and 70 which are non-smokers, drug-naive hypertensives with a body mass index in the range of 20 to 40 kg/m²

What does the study involve?
Participants will be randomly allocated into 3 groups - Group 1, Group 2, and Group 3.
Group 1 will be asked to consume daily a small bottle (70ml) of concentrated beetroot juice and folate capsules (5 mg/day) for 8 weeks. Group 2 will consume the beetroot juice and a placebo capsule for 8 weeks. Group 3 will be the control group and participants will be asked to consume a nitrate-depleted beetroot juice and a placebo capsule for 2 months.
Throughout the study, participants in all groups will be asked to record the time at which they drink the juice and take the supplements. They will also receive phone calls and complete various tests, including blood pressure and blood tests, along with questionnaires.

What are the possible benefits and risks of participating?
The possible benefits of taking part in this study include careful assessment of their cardiovascular risk and end organ damage, along with routine blood tests and assessment of hypertension. Participants will receive copies of their blood results and ECG readings for reference, and in the event of any abnormal results, these will be explained to the patient and the further recommended action and offered referral by the research team. Participants may also benefit from having hypertension diagnosed, as this will enable them to seek treatment for this.

There are also wider benefits to other individuals with hypertension in Tanzania, if these low cost nutritional based interventions are found to be useful.
This is low risk study. Participants will be asked to provide a blood sample (a routine procedure); however this may potentially involve brief discomfort to them. The risks to this procedure involve small bruising; however this is minimised by fully trained and experienced personnel undertaking these. Participants will undergo a number of minimally invasive tests that our team employs routinely in research studies and that participants regard as highly acceptable.
The amount of inorganic nitrate contained in the beetroot juice is approximately 300mg which is amount usually found in a portion of rocket or lettuce. Evidence suggest that there is no current risk for human health associated with nitrate intake below 2000mg/day.
Folate is water-soluble vitamin which is currently recommended for the prevention of neurological defects at birth and anaemia. The dose prescribed in the study is higher than current recommendations but within the safety limits of intake for folate prescribed to humans. Tablets with this dose are currently available on the market as a nutritional supplement.

Where is the study run from?
Trial study centre: Kilimanjaro Christian Clinical Research Institute (Tanzania)
Trial run from: Newcastle University (UK)

When is the study starting and how long is it expected to run for?
April 2018 to August 2018

Who is funding the study?
MRC Confidence in Concept (UK)

Who is the main contact?

Contact information

Type(s)
Scientific

Contact name
Dr Mario Siervo

Contact details
Human Nutrition Research Centre
Newcastle University
Newcastle upon Tyne, NE2 4HH
Newcastle upon Tyne
United Kingdom
NE2 4HH

Additional identifiers

Protocol serial number
NAE 1/18

Study information

Scientific Title
Effects of dietary nitrate and folate supplementation on blood pressure in hypertensive Tanzanians: a feasibility trial

Study objectives
We hypothesise that a combined folate and nitrate supplementation could lead to a greater nitric oxide generation and determine a greater effect on systolic BP compared to a control group or nitrate alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
FMS Ethics Committee, 09/04/2018, 1458/3377/2018
CRERC, 29/01/2018, 1105

Study design
Interventional three-arm parallel double-blind placebo controlled randomised clinical trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Hypertension

Interventions
The study is divided in four phases: selection of participants, screening, baseline/randomisation and intervention.
Participants will be randomised into 3 groups using an online platform (sealed-envelopes.com). A member of staff not involved in the study will be the custodian of the randomisation list and he /she will be responsible for the provision to the study participants of the nutritional interventions so as not to compromise the double-blinding of the trial.
Group 1 and Group 2 will be provided with a nutritional interventional, whereas Group 3 will be the control group.
Participants in Group 1 will be asked to consume a small bottle (70 ml) of concentrated beetroot juice (Beet it shots, James White LTD, UK), which is naturally enriched in inorganic nitrate (approximately 400 mg of inorganic nitrate). Participants will be asked to drink the beetroot juice in the morning and will be provided with a form to record the time of the consumption and if they experience any problems. Participants will be considered not compliant to the intervention if they miss 7 or more supplementation days. Participants will be asked not to change their habitual dietary habits, physical activity level and alcohol and caffeinated drinks consumption during the trial. Participants will be provided with the specific amount of beetroot juice to be consumed during the intervention period.
Participants in Group 1 will also be asked to take one folate capsule (5 mg folate) every morning after consumption of the beetroot juice, and will be provided with a form to record the time of consumption and if they experience any problems. Participants will be considered not compliant with the intervention if they miss seven or more supplementation days. Participants will be provided with the specific amount of capsules to be consumed during the intervention period.

Capsules will be dispensed in plastic containers showing the individual participant code, the number of capsules, expiry date, storage and prescription instructions.
Group 1 participants will be asked to complete this intervention for a period of 8 weeks.
Participants in Group 2 will be asked to consume the beetroot juice as above, and will be provided with folate-free placebo capsules to take daily. They will be asked to do so for a period of 8 weeks.
Participants in Group 3 will be the control group, and will therefore be provided with nitrate-depleted beetroot juicer (<1 mg per 70 ml) and/or folate-free placebo capsules to be consumed everyday in the morning for 2 months. Both placebos (beetroot juice and capsules) will have the same appearance, taste and colour as the active interventions. As in Group 1 and Group 2, participants in this group will receive a form to record the timing of consumption.
After 2 weeks, participants in all 3 groups will be contacted via telephone to assess the compliance to the intervention and discuss any problems that they may have had. Participants will be asked to return to the research centre after one month for a measurement of body weight, resting blood pressure, assessment of safety and compliance with the intervention, and collection of a blood sample. At the 1 month follow up they will complete a questionnaire about their experience of the study and their compliance. At the end of the visit they will receive another 1 month supply of the study treatment to complete the intervention. They will return to the research centre after 4 weeks for their last visit and the measurements conducted at baseline will be repeated in the same order. Participants will be recompensated for their time being involved with the study at each of the follow ups with an extra payment at the final follow up appointment if they have been compliant throughout.

Intervention Type
Supplement

Primary outcome(s)
Compliance to the intervention, assessed using self-developed standardised feedback questionnaires at the baseline, 30 days and 60 days (end of the study).

Key secondary outcome(s))
1. Changes in resting and 24 hour ambulatory blood pressure (BP):
1.1. Resting blood pressure assessed using an automated BP monitor at the baseline, after 1 month and at the end of the study
1.2. 24 hour ambulatory blood pressure assessed using a BP monitor with an inflatable cuff secured around the arm, which will regularly inflate and deflate over the 24 hour period
2. Changes in whole-body nitric oxide (NO) production, assessed using the Oral Nitrate Test (non-invasive stable isotope method) at the baseline and after 60 days (end of the study)
3. Blood nitrate concentration, assessed using the ONT method, with samples then being derivatised using the nitromesitylene method and the enrichment level of the tracer will be determined using gas chromatography/mass spectrometry at the baseline and after 60 days (end of the study)
4. Blood folate concentration, assessed using the ONT method, with samples then being derivatised using the nitromesitylene method and the enrichment level of the tracer will be determined using gas chromatography/mass spectrometry at the baseline and after 60 days (end of the study)
5. Validity of Berkeley Life Nitric Oxide Saliva Test Strips for the assessment of nitrite concentrations, assessed at the baseline and after 30 and 60 days

Completion date
07/08/2018

Eligibility

Key inclusion criteria
1. Aged 50-70 years old
2. Non-smokers
3. Drug naïve
4. Hypertension (stage 1, systolic blood pressure 130-170 mmHg)
5. BMI 18-40 kg/m²

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Senior

Lower age limit
50 years

Upper age limit
70 years

Sex
All

Total final enrolment
47

Key exclusion criteria
1. Current participation in other clinical investigations
2. Physical disabilities, trauma or surgery which limit mobility and affect participation to the trial
3. Vegetarianism
4. Aversion to beetroot consumption or inability to comply with the study diet
5. Substantial weight change in the last 3 months
6. Active cancer and any diagnosis of malignant cancer in the last 5 years
7. Chronic and acute metabolic and inflammatory conditions interfering with the study outcome (e.g. history of severe liver disease, inflammatory bowel diseases or rheumatoid arthritis)
8. Previous diagnosis of type 1 or type 2 diabetes treated with insulin
9. Taking any drugs that have an effect on nitric oxide production or insulin sensitivity, including oral corticosteroids, sildenafil, anti-hypertensive (beta-blockers, calcium antagonists, ace-inhibitors and angiotensin receptors inhibitors), diuretics, laxatives, anticoagulants, nitrate derived agents and anti-cholinergics
10. Taking hormonal therapies (oestrogens, thyroxine, progesterone, oral hypoglycaemic agents) if the dose has been started/changed in the previous 3 months
11. Taking statins and any other anti-dyslipidaemic agent if the dose has been started/changed in the previous 3 months
12. Taking psychiatric drugs (antidepressants, sedatives, antipsychotics) if the dose has been started/changed in the previous 3 months

13. History of severe anaemia (Hb < 8mg/dL) (risk for the participant and effects on the study outcomes).
14. Current diagnosis of severe infectious diseases (known HIV positive, malaria, hepatitis, yellow fever etc)
15. Major surgical operations interfering with the study outcomes

Date of first enrolment
01/03/2018

Date of final enrolment
31/05/2018

Locations

Countries of recruitment
United Kingdom

England

Tanzania

Study participating centre
Institute of Health and Society
Institute of Health & Society, Newcastle University
Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX, United Kingdom
Newcastle upon Tyne
United Kingdom
NE2 4AX

Study participating centre
Institute of Cellular Medicine
Institute of Cellular Medicine, Newcastle University, 4th Floor, William Leech Building, Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH
Newcastle upon Tyne
United Kingdom
NE2 4HH

Study participating centre
Institute of Neuroscience
Newcastle University, NE1 7RU, United Kingdom,
Newcastle upon Tyne
United Kingdom
NE1 7RU

Study participating centre
Kilimanjaro Christian Clinical Research Institute
KCRI
Box 2236, MOSHI-TANZANIA
Moshi
United Kingdom
251

Study participating centre
Northumbria Healthcare NHS Foundation Trust
Department of Medicine
North Tyneside General Hospital
Rake Lane
North Shields
United Kingdom
NE29 8NH

Sponsor information

Organisation
Institute of Cellular Medicine, Newcastle University

ROR
https://ror.org/01kj2bm70

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype

National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and analysed during the current study will be available upon request from Dr Mario Siervo (mario.siervo@ncl.ac.uk). Electronic datasets (Excel or SPSS files) will be available from 1st January 2020 for a period of 5 years. Data requests will be evaluated by the main investigators in the UK and Tanzania and data will be released if proposed use is within the scope and aims approved by the ethical committees approving the study in the UK and Tanzania. Written consent was obtained from all participants included in the study. Data will be provided in full anonymised form and recipients will be asked to destroy the dataset at the end of the agreed access period of use. Material transfer agreements will have to be formalised between institutions before transferring the datasets.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/09/2020	03/08/2020	Yes	No
Other publications	Design and baseline characteristics	15/10/2019	17/01/2024	Yes	No