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Effects of vitamin C and inorganic nitrate on blood pressure and vascular health

Submission date
12/02/2014

Recruitment status
No longer recruiting

Registration date
26/02/2014

Overall study status
Completed

Last Edited
17/12/2020

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
Nitric oxide (NO) is the primary molecule for the control of vascular resistance and blood pressure in humans. We hypothesise that the NO-generating and antioxidant properties of inorganic nitrate and vitamin C respectively will have more effect on vascular function than each agent alone. These effects will be derived from the combined effects of ascorbic acid on the enzymatic and non-enzymatic NO pathways. The purpose of the study is to assess a number of combinations.

Who can participate?
Non-smoking healthy adults aged 18-40 years and aged 55-70 years, with a BMI between 20.0 - 29.9 kg/m2

What does the study involve?
Eligible participants will be invited to the research unit for their first visit. Prior to the visit, participants will also be invited to follow a diet with a standardised amount of nitrate and vitamin C for 2 days. Participants will arrive early in the morning (around 8 am) in fasting conditions (12 hours). Each participant will be invited to sign an informed consent before proceeding with the measurements.
Participants will be randomly allocated to one of the four interventions: inorganic nitrate + vitamin C, or inorganic nitrate + placebo (dummy), or vitamin C + placebo, or placebo + placebo. The visit will continue with anthropometric, body composition and resting BP measurements (systolic, diastolic, heart rate). A cannula will then be fitted in an ante-cubital vein and a portable BP device and a heart rate ECG monitor for the measurement of BP and heart rate will be fitted. A baseline blood sample (volume=20mL) will be collected and a 6-minute baseline recording time will be started for BP (1 measurement every 2 minutes) and HR recordings. Participants will be then invited to drink a solution containing potassium nitrate or vitamin C or both combined or placebo (nitrate free water). Recordings of HR will be measured continuously over the next 240 minutes. BP measurements will be automatically performed every 30 minutes during the same period. Blood samples will be collected at 30, 60, 90, 120, 180, 240 minutes. Measurements of vascular function will be performed after cannulation and at 120 minutes of intervention and at 240 minutes. After the collection of the last blood sample at 240 minutes, participants will be free to leave. Participants will be asked to maintain their habitual diet and physical activity level

during the wash out period (7 days) until they will come back for their second. They will again follow a standardised nitrate diet 2 days prior to the visit and arrive in fasting conditions at the research centre on the next day. The measurements performed at the first visit will be repeated and each participant will receive the second intervention.

What are the possible benefits and risks of participating?
The study will include a number of clinically relevant measurements which will be provided information on each participant's health. These measurements include: body mass index (BMI), waist circumference, resting blood pressure, heart rate and blood tests including nutrients and free radicals concentrations. There will not be additional direct benefits for the participants but their contribution to the project will be essential to advance scientific knowledge. All the laboratory procedures involved in this study are simple to perform and involve minimal risk to participants. Venous cannulation will be performed in the participant's forearm for blood sampling. This is a routine clinical procedure and it will be performed by a medically qualified member of the research team. Although there might be a risk for a small bruise, these will be minimised by the fact that personnel undertaking these is widely experienced. The amount of nitrate intake (12 mg/kg as sodium nitrate) to be used in this study is commonly observed in subjects with a high intake of vegetables (particularly leafy vegetables) and comparable to the nitrate intake that may be observed in vegetarian subjects. There is no established health risk associated with this level of inorganic nitrate intake supplementation.

Where is the study run from?
The Clinical Ageing Research Unit located on the Campus of Ageing and Vitality, Institute for Ageing and Health, Newcastle University, UK.

When is the study starting and how long is it expected to run for?
April 2014 to March 2015

Who is funding the study?
BNF Drummond Pump Priming Awards 2013

Who is the main contact?
Dr Mario Siervo

Contact information

Type(s)
Scientific

Contact name
Dr Mario Siervo

Contact details
Human Nutrition Research Centre
Institute for Ageing and Health
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Biomedical Research Building
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Newcastle upon Tyne
United Kingdom
NE4 5PL

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
Acute effects of dietary nitrate and vitamin C supplementation on blood pressure and endothelial function in young and older human subjects: a 2*2 factorial cross-over trial

Study objectives
The combination of the antioxidant vitamin ascorbic acid and inorganic nitrate (as a source of NO) may have an additive effect on vascular function. We hypothesise that this may be derived from the cumulative enrichment of the NO pool through
1. Reduction of NO degradation
2. Increased efficiency of the enzymatic eNOS pathway and
3. Enhanced non-enzymatic conversion of inorganic nitrate into NO.
The effect size of the interventions may be enhanced in subjects with greater endothelial dysfunction such as hypertension or type 2 diabetes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
East of Scotland Research Ethics Service (EoSRES) REC 2, ref: 14/ES/0059

Study design
Randomised placebo-controlled crossover trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet

Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Cardiovascular disease, endothelial function

Interventions
1. Inorganic nitrate + Vitamin C (12 mg sodium nitrate per kg body weight in in saline solution + 20 mg ascorbic acid per kg body weight in saline solution)
2. Inorganic nitrate + placebo (12 mg sodium nitrate per kg body weight in in saline solution + saline solution)
3. Vitamin C + placebo (20 mg ascorbic acid per kg body weight in saline solution; in saline solution)
4. Vitamin C placebo + Inorganic nitrate placebo (given as two separate saline solutions)

Intervention Type
Supplement

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Vitamin C, inorganic nitrate

Primary outcome measure
Systolic and diastolic BP: Screening, -5', -4', -3', -2', -1', 30', 60', 90', 120', 150', 180', 210', 240' (minutes from intervention)

Secondary outcome measures
Forearm blood flow (laser Doppler): -15, 120, 240 minutes from intervention
The biomarkers of oxidative stress (nitro-tyrosine) and NO production (nitrate, nitrite, cGMP): Screening, -1', 30', 60', 120', 180', 240' minutes from intervention.

Overall study start date
01/04/2014

Completion date
31/01/2016

Eligibility

Key inclusion criteria
Current inclusion criteria as of 02/12/2014:
Non-smoking healthy adults aged 18-40 years and aged 55-70 years, with a BMI between 20.0 - 29.9 kg/m2.

Previous inclusion criteria:
Non-smoking healthy adults aged 18-40 years, with a BMI between 20.0 - 29.9 kg/m2.

Participant type(s)

Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
70 Years

Sex
Both

Target number of participants
12 participants

Total final enrolment
10

Key exclusion criteria
1. Current participation in other research clinical studies
2. Vegetarianism (likely to have very high nitrate intake)
3. High physical activity level (may have BMI in obese range but low fat mass)
4. Weight change more than 3.0 kg in the last 2 months (important influence on systemic metabolism and vascular function).
5. Active cancer and any diagnosis of malignant cancer in the last 5 years (systemic effects on study outcomes).
6. Diagnosis of chronic and acute metabolic and inflammatory conditions interfering with the study outcome (systemic effects on study outcomes). For example flu, Chrohns Disease, rheumatoid arthritis.
7. Previous diagnosis of type 1 or type 2 diabetes treated with insulin and oral hypoglycaemic agents (modification of regulation of intermediate metabolism). Type 2 diabetic patients treated with diet only will be included in the study.
8. Weight loss medications (sibutramine, orlistat, rimonabant) and history of bariatric surgery (weight loss related changes in systemic metabolism).
9. Drugs: corticosteroids, sildenafil, aspirin, diuretics, beta-blockers, antacids, anticoagulants, nitrate-derived agents, anti-cholinergic, (all drugs may have either an effect on NO production or insulin sensitivity via different mechanisms).
Subjects on hormonal therapies (oestrogens, thyroxine, progesteron), anti-hypertensive (Ca++ channel blockers, ACE inhibitors), statins and any other antidyslipidaemic agent, and psychiatric drugs (antidepressants, sedatives, antipsychotics) will be excluded if dose has been started /changed in the previous three months. (make sure that these disorders are under strict control to avoid interference with the study outcomes).
10. Haematological disorders including severe anaemia (Hb< 10mg/dL) (risk for the participant and effects on the study outcomes).
11. Major surgical operations interfering with the study outcomes (systemic effects on study outcomes).
12. Alcohol intake >21 units/week for men and >14 units/week women
13. Blood donations in the previous 3 months.

Date of first enrolment
12/11/2014

Date of final enrolment
12/11/2015

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Newcastle University
Newcastle upon Tyne
United Kingdom
NE4 5PL

Sponsor information

Organisation
The Newcastle Upon Tyne Hospitals NHS Foundation Trust (UK)

Sponsor details
Level 6, Leazes Wing
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
England
United Kingdom
NE1 4LP

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
British Nutrition Foundation

Alternative Name(s)
BNF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
To be confirmed at a later date

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/03/2020	17/12/2020	Yes	No
HRA research summary			28/06/2023	No	No