ISRCTN94484747 https://doi.org/10.1186/ISRCTN94484747

The effect of organic nitrates on osteoporosis

Submission date
18/11/2005

Recruitment status
No longer recruiting

Registration date
18/11/2005

Overall study status
Completed

Last Edited
02/03/2011

Condition category
Musculoskeletal Diseases

[ ] Prospectively registered

[ ] Protocol

[ ] Statistical analysis plan

[X] Results

[ ] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT00252421

Protocol serial number
MCT-77376

Study information

Scientific Title
The effect of organic nitrates on osteoporosis: a randomised controlled trial

Study objectives

1. Women will report fewer headaches when they are randomised to intermittent nitroglycerin (NTG) ointment at 15 mg/day compared to intermittent oral isosorbide mononitrate (ISMO) at 20 mg/day
2. After two years, women randomised to intermittent nitrates will have a greater percent increase in lumbar spine bone mineral density (BMD) compared with women randomised to placebo

As of 06/03/2009 this record was updated to include a change to the sponsor address due to the Principal Investigator relocating to another hospital. The previous sponsor was St. Michael's Hospital, Toronto (Canada).

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. St. Michael's Hospital Research Ethics Board gave approval on the 3rd October 2005
2. Womens College Hospital Ethics Committee approved on the 29th May 2007 (after the trial was moved to this location - see hypothesis for more information on this)

Study design
Randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Pilot Study:
Group 1: Subjects will receive NTG ointment at 15 mg/day (one inch of 2% ointment applied to the upper arm) for one week and ISMO at 20 mg/day for one week. The order of treatments will be randomised. In between each treatment there will be a two week washout.
Group 2: Subjects will receive ISMO at 20 mg/day for one week and NTG ointment at 15 mg/day (one inch of 2% ointment applied to the upper arm) for one week. In between each treatment there will be a two week washout.

Subjects who report headaches during the wash out will be excluded from the second treatment phase and considered as drop outs in our analysis.

Main Study:
Subjects who are eligible and willing to participate in the main study will complete a standardised, validated, interviewer administered questionnaire designed to collect general demographics and evaluate factors that have been demonstrated in prospective observational studies to influence levels of bone turnover markers, BMD, and fracture risk. All subjects will be instructed to take the nitrate, identified in the pilot study to be the best tolerated, daily for one

week. Subjects who do not develop headaches during the nitrate run-in phase will enter the main trial. The first 3 months of the main trial consist of a calcium and vitamin D pre-treatment phase.

All subjects who return to the study centre at three months will undergo pQCT assessments, have blood and urine taken for measurement of bone turnover markers, and be randomly assigned to placebo or active treatment. Subjects will receive a 3 month supply of study medication, calcium, and vitamin D, and will receive standard verbal and written instructions on how to take the medication, calcium, and vitamin D. At 3 months post-randomisation, subjects will return to the study centre and provide blood and urine samples for bone turnover markers; unused calcium, vitamin D, and study medication will be collected and counted, and subjects will be given a nine month supply of study medication, calcium, and vitamin D. At 12 and 24 months post-randomisation, subjects will visit the study centre and provide blood and urine samples for bone turnover markers; the unused calcium, vitamin D and study medication will be counted (at the 12 month post-randomisation visit we will provide a 12 month supply of calcium, vitamin D and study medication) and we will obtain BMD and pQCT assessments.

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Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Nitrates

Primary outcome(s)
Pilot Study:
Mean headache score associated with each of intermittent NTG and ISMO use. Subjects will be given four seven day diaries, with a visual analogue scale (VAS) for each day of both treatment periods and the wash out period. Subjects will rate their headache upon awakening on a daily basis; our previous study demonstrated that subjects randomised to ISMO who developed headaches reported that the headache was most severe upon awakening and gradually subsided over the day. The VAS uses a 100 mm continuous horizontal line with the left pole labeled 'no headache' and the right pole labeled 'terrible headache'; subjects will be instructed to draw a vertical line intersecting the VAS indicating the severity of their morning headache. We will calculate the mean headache score with intermittent NTG and intermittent ISMO for each subject. Then we will calculate the mean headache score for all subjects when taking ISMO and when taking NTG. The nitrate that gives the lowest mean headache score will be used in our main study. Our earlier work indicates that the nitrate formulation associated with the most

severe headaches will result in the greatest number of drop outs. The VAS can detect subtle changes in subjective complaints (i.e. headache), has documented reliability, and has been used in several studies designed to study the effects of NTG ointment on headache in healthy women.

Main Study:
Change from baseline in BMD at the lumbar spine over 24 months among women randomised to treatment compared with women randomised to placebo. BMD will be measured (on the same machine in all subjects) at the lumbar spine (L1 to L4) using a Lunar DPX-L bone densitometer (Lunar Corporation, Madison WI). A single experienced technician, certified by the International Society of Clinical Densitometry (ISCD) and blinded to the treatment assignment, will perform all BMD measurements. The intraclass correlation coefficient for BMD measurements is 0.98. The PI will be blinded to treatment assignment and will report the BMD. BMD reporting is objective and based on standard ISCD criteria.

Key secondary outcome(s))

Main study:
1. Change from baseline in total hip BMD. This will provide information about the effects of nitrates on cortical and trabecular bone and ultimately on the ability of nitrates to prevent hip fractures.
2. Change from baseline in bone formation and bone resorption markers. Measuring markers of bone turnover will increase our understanding of the mechanisms by which intermittent nitrates increase BMD (i.e. a decrease in bone resorption and/or an increase in bone formation). We will measure bone turnover markers three months after initiating calcium and vitamin D because we expect a 10% decrease in markers with the use of supplements, and the maximal change in bone markers is typically observed at three months. Thus, we will be assessing any additional effects of intermittent nitrates on markers of bone turnover in women receiving calcium and vitamin D supplements. Urinary NTx will be measured on a second morning urine sample using a monoclonal antibody technique (Osteomark). The intra-assay variability is 7.6% and the inter-assay variability is 4.0%. Serum BSAP will be measured on a fasting serum sample using a monoclonal antibody technique (Metra Biosystems). The intra-assay variability is 5.8% and the inter-assay variability is 5.2%. To minimise variability, subjects will be given written and verbal instructions on how to collect the second morning urine sample; for each subject we will collect all the samples (baseline, three, 12 and 24 months post-randomisation) at the same time, and we will store the blood and urine at -70°C and analyze all the samples together in a single laboratory. We will compare measures of bone turnover markers at 3, 12, and 24 months after randomisation using a repeated measure of analysis of variance. By measuring markers at three months we will be able to directly compare these results to the findings in our earlier study. By measuring markers at 12 and 24 months we will be able to evaluate to a limited degree, the question of tachyphylaxis with nitrates. Recall that in our earlier study we found a decrease in markers of bone resorption and an increase in markers of bone formation after 90 days of treatment with intermittent ISMO. Measuring markers after one and two years of treatment will allow us to determine if there is still a marked decrease in bone resorption and increase in bone formation; no further changes in markers may indicate that the effects of nitrates on bone is transient.
3. Adverse events. Adverse events will be assessed using a standardized, validated interviewer administered questionnaire on a monthly basis by telephone. We will assess nitrate and non nitrate related adverse events. Documentation of adverse events is critical before proceeding to a larger, longer study of intermittent nitrates and fractures.
4. Bone Microarchitecture. Fracture risk is influenced by both the quantity of bone (assessed by BMD) and quality of bone. Features of bone quality include trabecular and cortical volumetric bone density, measures of bone geometry, and trabecular texture. We will measure trabecular

and cortical volumetric bone densities at the radius and tibia using an XCT2000 pQCT scanner at Hamilton Health Sciences. Transaxial images will also be processed to yield values of bone geometry and trabecular bone texture. Measurements of trabecular bone structure discriminate women with low BMD and fracture from women with low BMD but no fracture. As such, they may be particularly important when assessing the effect of a new treatment on fractures. The various measurements produced by pQCT will allow us to describe the effects of nitrates on the various compartments of bone.

Completion date
30/09/2010

Eligibility

Key inclusion criteria
The pilot and main study have identical inclusion and exclusion criteria.

Inclusion criteria:
1. Women aged 50 and older
2. Lumbar spine BMD (L1 to L4) T score between 0 and -2.0
3. Greater than or equal to 3 years post-menopausal

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Senior

Sex
Female

Key exclusion criteria
1. Prior low trauma hip or vertebral fracture; these subjects have OP and require treatment
2. Total hip or femoral neck T score of less than -2.0; these subjects either have OP and require treatment, or are at increased risk of developing OP over the course of the main study
3. Bone disorders other than osteopenia (e.g. hyperparathyroidism or Pagets disease); these subjects require treatment
4. Treatment within six months of study entry with androgen, calcitonin, oestrogen, progesterone, fluoride in a tablet form, raloxifene, tamoxifen, etidronate, prednisone or an equivalent at 5 mg/day for 12 months or greater, lithium or anticonvulsants. These agents can alter levels of bone turnover markers for up to six months.
5. Alendronate or risedronate use for at least four weeks, within the last three years. These agents may influence bone remodeling for up to three years.
6. Current treatment with nitrates
7. Systolic blood pressure of less than 100 mmHg or diastolic blood pressure greater than 110 mmHg at the baseline screening examination
8. Abnormal electrocardiogram (ECG) at the baseline screening examination
9. History of myocardial infarction, angina, valvular or congenital heart disease
10. Disabling conditions that may interfere with follow-up visits

11. Inability to give informed consent
12. Migraine headaches; nitrates can exacerbate migraines
13. Hypersensitivity to nitrates

Date of first enrolment
01/09/2005

Date of final enrolment
30/09/2010

Locations

Countries of recruitment
Canada

Study participating centre
76 Grenville St. 8th Floor
Toronto, Ontario
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Sponsor information

Organisation
Womens College Hospital (Canada)

ROR
https://ror.org/03cw63y62

Funder(s)

Funder type
Research organisation

Funder Name
Canadian Institutes of Health Research (CIHR) (Canada) - http://www.cihr-irsc.gc.ca (ref: MCT-77376)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	26/04/2006		Yes	No
Results article	results	23/02/2011		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes