Does Nifedipine 60 mg per day per os reduce the complaints of chronic chilblains?

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Research question: Does oral administration with regulated release of 60 mg nifedipine a day reduce the symptoms of patients as determined in 1st. line health care, provided there is a good tolerancy of the medication.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON34714

Source
ToetsingOnline

Brief title
NCCC

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
Chronic chilblains

Research involving
Human

Sponsors and support

Primary sponsor: Huisartspraktijk Souwer
Source(s) of monetary or material Support: ZonMw fonds alledaagse ziekten;projectnummer 4201.1006.

Intervention

Keyword: Chilblains, Nifedipine, RCT, Therapy

Outcome measures

Primary outcome

We consider the intervention effective if a reduction of the experienced complaints is found, displayed in a decline of the score "complaint" with at least 10 mm on the visual analogue scale concerned. "Complaint" is defined as Max (itch,pain): the Vas score for or itch or pain, depending on the highest score.

Secondary outcome

Secondary we register scores for impairment and the experienced side effects: headache and dizziness.

Study description

Background summary

Chilblained hands, toes and thighs form an acute and clinical picture labelled as perniones. Chronic perniones is a nasty and painful disorder often returning every winter and can cause considerable limitations in every day life (1,2). Little is known about nature and treatment. There is uncertainty about incidence and prevalence. Data of the Continual Morbidity Registration point to four new cases per GP per year, mostly women (3). Prevalence is probably significantly higher, also in our experience sofar.
There is limited evidence for three interventions: Vitamin D3, nifedipine and corticosteroïd cream (4).
We have already proven the unlikeliness of a positive effect of Vitamin D3 (5).
Indications for possible positve effects of nifedipine are described in only one publication with a randomized clinical trial of 10 participants and a open trial of 34 participants and therefore aren't very strong (6).
As patients with perniones do have a need for effective treatment to relieve them from their complaints and limitations (2), we are of the opinion that it is useful investigate the possible effectiveness of nifedipine in more detail.

References:
1. Souwer IH, Lagro-Janssen ALM. Perniones. Winterhanden, Wintertenen en *Winterdijen*. HuisartsWet
2004;47:594-6.
2. Souwer IH, Robins LJH, Lagro-Janssen ALM. Chilblains from the patient*s perspective. Eur J Gen
Pract. 2007;13:159-60.
3. Continue Morbiditeit Registratie Nijmegen: ongepubliceerde data.
4. Souwer IH, Lagro-Janssen ALM. De behandeling van perniones. Een literatuuronderzoek. Huisarts
Wet 2004;47:561-2.
5. Souwer IH, Lagro-Janssen ALM. Vitamin D3 is not effective in the treatment of chronic chilblains. Int
J Clin Pract 2009;63:282-6.
6. Rustin MHA, Newton JA, Smith NP, Dowd PM. Tjhe treatment of chillblains with nifedipine: the results of a pilotstudy, a double-blind pracebo-controlled randomized trial and al long term open trial. B J Derm 1989;120:167-275.

Study objective

Research question: Does oral administration with regulated release of 60 mg nifedipine a day reduce the symptoms of patients as determined in 1st. line health care, provided there is a good tolerancy of the medication.

Study design

Study design
This research has been set up as an RCT of the cross over type. A group of 50 perniones patients is randomised over two sub groups. After one week of baseline measurements withhout intervention, they are treated with nifedipine or a placebo for 6 weeks in turns, blindfold to the patient and researcher. The duration of the research is 13 weeks for each patient. The most important confounder, exposure to cold, is monitored by asking for the twenty-four hours data of "de Bilt" at the Royal Duch Meteorological Institute KNMI and specific questions at intake.

Informed consent
Participants are included in the study after informed consent only. All required information, written and oral, will be provided to the potential participant in the initial interview and is also incorporated in the diary that is kept up to date by the participant during the research.

Procedure and randomisation.
After application an intake interview takes place. The diagnosis is then confirmed by the researcher. It is checked whether the participant satisfies the inclusion criteria and should not be rejected on basis of the exclusion

criteria. After informed consent the lesions are documented by means of description and fotos. Additional information is gathered about the way of dressing, exposure to cold, housing conditions and working environment. Randomisation takes place over two regimes by means of *permuted block randomisation* with a block size of 10. Regime 1: 1 week no medication; 2 weeks placebo once a day and 4 weeks placebo twice a day followed by 2 weeks nifedipine 30 mg regulated release once a day and 4 weeks nifedipine 30 mg regulated release twice a day . Regime 2: 1 week no medication; 2 weeks nifedipine 30 mg regulated release once a day and 4 weeks nifedipine 30 mg regulated release twice a day followed by 2 weeks placebo once a day and 4 weeks placebo twice a day.

Measuring instrument
The measuring instrument is a diary kept up to date daily by the participant for the complete research period. Per day, experienced complaints of perniones (itch or pain), experienced limitations in daily life, experienced headache, experienced dizziness and experienced general indisposition are scored on a 100 mm visual analogue scale. For the complete research period of each individual patient the exposure to cold is registered by asking for the average day temperature as measured in "de Bilt" at the KNMI. There are 6 contact moments: intake (t1), end of week 1 (t2), end of week 3 (t3), end of week 7 (t4), end of week 9 (t5) and end of week 13 (t6). Control and correction on completeness of the diary and consistency of the therapy used is performed by counting forgotten tablets. During contols at t2-t6 bloodpresure and pulsrate are monitored. At t6 we will (after concent only) take a bloodsample for nifedipine level assesment.

Primary endpoint
We consider the intervention effective if a reduction of the experienced complaints is discovered, displayed in a decline of the score "complaint" with at least 10 mm on the visual analogue scale concerned. "Complaint" is defind as Max (itch,pain): the Vas score for itch or pain, depending on the highest score. Secondary we register scores for impairment and the experienced side effects, skin irritation, and symptoms of skin atrophy: purpurae, inclination to bleed and depigmentation.

Analysis.
A statistical analysis will be performed with a repeated measures mixed effects model. The effect of a possible change in temperature will be taken into account. An intention to treat analysis will take place. A check on the consistent use of the therapy will be done by counting forgotten tablets.

Power measurement
In previous research we found baseline VAS scores for complaint of 27.97 millimeter (SD 18.82mm) on average. We regard the intervention effective when

the VAS score has dropped by 10 millimeter or more. For the power measurement we took a paired T-test as a baseline. With one measurement per person for medication and placebo this is a considerable simplification of the real test. Repeated measurements allow less participants, which is more favourable. At alpha =0.05, beta=0.10 (power 90%) and an effect of 10mm VAS 38 patients are required to show a significant difference between the treatment with nifedipine and the placebo.

Numeric Results for One-Sample T-Test Null Hypothesis:
Mean0=Mean1 Alternative Hypothesis: Mean0<>Mean1
The standard deviation was assumed to be known.

Power N Alpha Beta Mean0 Mean1 Sigma
0.90583 38 0.05000 0.09417 27.97 17.97 18.82

Intervention

The intervention which is compared to the placebo consists of the oral administration 30mg nifedipine with regulated release once a day for two weeks and twice a day for four weeks.

Study burden and risks

After application an intake interview takes place. The diagnosis is then confirmed by the researcher. It is checked whether the participant answers to the inclusion criteria and should not be rejected on basis of the exclusion criteria. After informed consent the lesions are documented by means of description and fotos. Additional information is gathered about the way of dressing, exposure to cold, housing conditions and working environment. Randomisation takes place over two regimes by means of *permuted block randomisation* with a block size of 10. Regime 1: 1 week no medication; 2 weeks placebo once a day and 4 weeks placebo twice a day followed by 2 weeks nifedipine 30 mg regulated release once a day and 4 weeks nifedipine 30 mg regulated release twice a day . Regime 2: 1 week - no medication; 2 weeks nifedipine 30 mg regulated release once a day and 4 weeks nifedipine 30 mg regulated release twice a day followed by 2 weeks placebo once a day and 4 weeks placebo twice a day. The measuring instrument is a diary kept up to date daily by the participant for the complete research period. Experienced perniones complaints (itch or pain) and limitations in daily life are scored daily. For the complete research period of each individual patient the exposure to cold is registered by asking for the average day temperature as measured in "de Bilt" at the KNMI. There are 6 contact moments: intake (t1), end of week 1 (t2), end of week 3 (t3), end of week 7 (t4), end of week 9 (t5) and end of week 13 (t6). Control and correction on the completeness of the diary and the consistency of the therapy used is performed by counting the tablets that are left.

During controls at t2-t6 Blod pressure and pulsrate are monitored.

At t6 we will (after concent only) take a bloodsample for nifedipine level assesment.

We do not expect major side effects.

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

18 years or older; able to understand and follow instructions; Complaints of chronic pernio for at least 3 weeks at inclusion: itching or painful blue-red discolorated lesions at fingers and/or toes, other localisations at the feet or lateral side of the thighs ("the Kibes"). The lesions may be swollen and ulceration may be present but is not obligitory. Onset of complaints is in the

period November to Februari.

Exclusion criteria

Known inflamatory disease (RA, SLE etcetera); pregnancy; lactation; Use of Nifidipine or another calcium antagonis; hypotension (bloodpressure lower than 110/60, angina pectoris, recent myocardial infection (less than 1 month), heart failure, known liver or kidney failure, severe gastro-intentinal stricturation; use of rifampicine, fenytoin, cimetidine or ranitidine.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-11-2010
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nifedipine 30mg retard PCH
Generic name:	Nifedipine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-07-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-10-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 27062
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2009-016397-33-NL
CCMO	NL31484.091.10
OMON	NL-OMON27062