Methylprednisolon Pulse Therapy vs Methylprednisolon Pulse Therapy combined with Radiotherapy for Moderately Severe and Active Graves* Orbitopathy

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In this study, we want to demonstrate that MPP is no less effective than MPP plus XRT.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Ocular structural change, deposit and degeneration NEC
Study type	Interventional

Summary

ID

NL-OMON47457

Source
ToetsingOnline

Brief title
PULSERAT

Condition

- Ocular structural change, deposit and degeneration NEC

Synonym
Graves' Orbitopathy; Swelling behind the eyes from Graves' disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Graves' Orbitopathy, Prednisolone, Radiotherapy

Outcome measures

Primary outcome

1. Change in vertical lid aperture * 2mm

2. Change in NOSPECS grade 2 with 2 degrees (e.g. 2c to 2a)

3. Change in proptosis * 2 mm

4. Change in (any) duction * 8 degrees

5. Change in Gorman score * 1 level

6. Change in CAS * 2 points

Endpoints are defined as:

Improvement: change of * 2 parameters in at least one eye, without deterioration of any parameter in the contralateral eye

Deterioration: deterioration in * 2 parameters in one or both eyes or development of new onset DON

Unchanged: no changes or change in any of the parameters smaller than defined above

Secondary outcome

1. Change of Goldmann field of BSV at 6 and 12 months

2. Change of GO-QOL at 6 and 12 months

Study description

Background summary

Graves* disease (GD) is an autoimmune disorder that may affect the thyroid gland (Graves* thyroid disease), the orbit (Graves* orbitopathy, GO) and the pretibial skin (Graves* dermopathy). The incidence of GO in the USA and in Denmark is calculated around 40:100.000 in women and 8:100.000 in men (1,2). In Europe, 1% of the women between 35-60 years are supposed to suffer from GD and half of them from GO (3).

Symptoms vary from eyelid retraction and eyelid swelling to protrusion of the eyes, eye motility restriction with diplopia, corneal ulceration and visual impairment resulting from optic nerve compression. Untreated, 3-5% of the patients become blind as a result of the latter two manifestations (4). Moreover, GO may cause severe facial cosmetic deformities.

GO is caused by an autoimmune mediated inflammation and swelling of the orbital muscles, followed by an increase of the orbital fat (5). The initial active phase of the disease is characterized by an increase of the severity of the symptoms. Even without treatment, this active phase sooner or later (after months to years) is followed by a burnt out phase in which the disease has become quiescent, but in which symptoms as proptosis or motility restriction may persist (6). In mild cases, a wait and see policy can be justified and persisting complaints like eyelid retraction can be surgically dealt with in the quiesent stage.

Consensus exists as how to treat patients with active and more severe or vision threatening GO (7). They are treated with intravenously administered high dose methylprednisolon (i.v. MPP) (8). Aim of this intervention is to reduce or erase symptoms of disease activity such as soft tissue swelling, prevent progression, reduce the need of successive surgery and allow surgery, if necessary, in an earlier stage of the disease (9). Several RCT*s have shown, that MPP is effective in 60 to 80%, but certainly not in all patients with GO (8,9).

Other studies demonstrated that the combination of external beam irradiation (XRT) and prednisone treatment might be more effective than each of them alone (11,12). Even low doses XRT have shown to be effective and side effects are limited (13). XRT is thought to inactivate the orbital fibroblast, which play a key role in the etiology of GO (14). XRT may sustain the improvement initiated by prednisone (15). XRT, however, implies 12 visits to the department of radiotherapy plus extra costs.

The combination of prednison and XRT has been studied in patients receiving

oral corticosteroids (11,12), but not yet in patients receiving MP. As MPP offers significant benefits over oral steroid therapy (more effective, less side-effects), it is at present the treament of choice. There is, however, a worldwide tendency to prescribe XRT together with MPP, although its advantages have not been demonstrated yet.

Study objective

In this study, we want to demonstrate that MPP is no less effective than MPP plus XRT.

Study design

Non-blinded parallel group intervention study

Intervention

One group receives both iv CS and XRT, the other only iv CS

Study burden and risks

In 1-2% of patients receiving radiotherapy mild retinopathy can occur.
There is a theoretical chance of cancer formation due to the radiotherapy, but the chance is very slim due to the small area receiving a small amount of radiotherapy

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

1. Active Graves' Orbitopathy (GO):
- onset less than 12 months, and
- CAS * 3 out of 7 or 4 out of 10
2. Moderately severe GO:
- NOSPECS grade 2b or c, and/or
- Severe proptosis (in women * 20mm and in men * 22 mm), and/or
- Motility restriction defined as a duction < 30 degrees in either abduction, adduction, elevation or depression, and/or
- Gorman/Bahn score of C (Gorman/Bahn score: A.no diplopia; B. intermittent; C. inconstant; D: constant)
3. Clinically and biochemically euthyroidism for at least 6 weeks

Exclusion criteria

1. Unable or unwilling to provide informed consent
2. Age <35 years or >75
3. Diabetes mellitus
4. Mild GO
5. Presence of dysthyroid optic neuropathy (DON)
6. Previous orbital surgery or radiotherapy for GO.
7. Corticosteroid or immunotherapy (on average > 20mg daily) for GO within previous 3 months
8. Pre-existent strabismus
9. Patients with amblyopia or with functional monocular vision making it impossible to measure diplopia and/or strabismus
10. Patients with pre existent glaucoma with severe visual field defects
11. Pregnancy

12. Unfit for corticosteroid therapy as decided by endocrinologist
13. Abnormal liver function (factor 2 above normal values)

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	130
Type:	Anticipated

Ethics review

Approved WMO Date:	13-04-2018
Application type:	First submission
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	NL60905.018.17