The effectiveness of endolymphatic duct blockage versus endolymphatic sac decompression in patients with intractable Ménière*s disease

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This study assesses whether EDB surgery will result in a significant reduction in the number of patients without vertigo spells at 12 months follow up, compared to patients who undergo endolymphatic sac decompression.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Inner ear and VIIIth cranial nerve disorders
Study type	Interventional

Summary

ID

NL-OMON54168

Source
ToetsingOnline

Brief title
Endolymphatic duct blockage for Ménière's disease

Condition

- Inner ear and VIIIth cranial nerve disorders
- Nervous system, skull and spine therapeutic procedures

Synonym
Ménière's disease

Research involving
Human

Sponsors and support

Primary sponsor: HagaZiekenhuis
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Endolymphatic duct blockage, Endolymphatic sac decompression, Ménière's disease, Surgical intervention

Outcome measures

Primary outcome

The main study parameter is the number of patients free of vertigo attacks at

12 months after surgery. This parameter was chosen because vertigo is the most

invalidating symptom of MD.

Secondary outcome

We will determine if EDB has a beneficial effect on:

• Cumulative incidence of vertigo bouts

• Hearing

• Use of escape medication (including intratympanic injections)

• Co-interventions (ablative procedure)

• Complications of surgery

• FLS

• DHI

• THI

• SF-36

• EQ-5D

• CEA

• iPCQ

• iMCQ

• BIA

• Endolymphatic hydrops and perilymph signal intensity on MRI

• Physiotherapeutical outcomes: balance, gait, visual acuity

Study description

Background summary

- Ménière*s disease
Ménière*s disease (MD) is an incapacitating disease of recurrent vertigo attacks, accompanied by hearing loss, tinnitus and/or aural fullness. Between the attacks of vertigo intervals of days, weeks or even months may occur (Lopez 2015, Pullens 2013). The natural course of MD has been studied and it has been found that the attacks of vertigo become less severe and disappear after two years in 60% and after eight years in 80% of patients (Portmann 1980; Silverstein 1989, Perez 2008, Van Esch 2016). In the end phase of the disease patients without vertigo attacks may still suffer from lasting hearing loss and tinnitus and chronic instability caused by hypofunction of the labyrinth. Significant comorbidity is seen in patients with Ménière*s disease. The most important comorbidities that may also cause dizziness are anxiety disorders and BPPV (van Esch, 2016).

MD is an idiopathic disease associated with endolymphatic hydrops in the inner ear (Merchant, 2005). Visualization of the hydrops became possible with the introduction of delayed post-contrast high resolution MR imaging (Nakashima 2007; Naganawana, 2014; Baráth, 2014). Moreover, recent publications underline the relevance of the signal intensity of the perilymphatic fluid (Bernaerts 2019, Shi 2018, Steekelenburg 2020). This signal intensity is a surrogate marker for the permeability of the blood-perilymph barrier, and may therefore reflect acute inflammation or recent activity related to a vertigo attack.

Few articles have been published on the epidemiology of MD. Great variation exists in the published reports of the prevalence of MD, ranging from 34.5 cases per 100,000 population in Japan (Shojaku 2005) to 46 cases per 100,000 population in Sweden (Stahle 1978). In the United States of America, reported prevalence is much higher: Alexander (Alexander 2010) reports 190 patients per 100,000, Waldislavosky-Waserman (Wladislavosky-Waserman 1984) reports a prevalence of 218 per 100.000. The difference in prevalence might be due to the wide variations in definitions of MD.
In the Netherlands, a population of 60-100 per 100,000 patients is severely

impaired (defined as low quality of live) by the disease (Mateijsen, 2001). There seems to be a slight female preponderance, with up to 1.3 times more women affected than men. The disease is more common in adults in their fourth and fifth decade of life (Kotimaki 1999, Perez 2008, Van Esch 2016).

Currently, there is not specific guideline for the treatment of MD in the Netherlands. The guideline *Dizziness in Elderly* of the Dutch ENT Society (*Duizeligheid bij ouderen*, NVNKO, 2015) advises to refer the patients to a specialized ENT surgeon. The guidelines *Dizziness* of the Dutch General Practitioner Society (Bouma 2017) for general practitioners also advises to refer the patient to an ENT surgeon, but only in case of rapid progressive hearing loss or additional complaints such as instability, head ache of persisting tinnitus.
The treatment of MD both in primary and secondary care setting is focused on the reduction of the frequency and intensity of vertigo attacks. Current treatments have either proven to be ineffective (Betahistin;Adrion 2016), only have a temporary effect (intratympanic dexamethasone injections; McRackan 2014, or methylprednisolone; Patel 2016), or destroy the labyrinth function (intratympanic gentamicin, labyrinthectomy, selective neurectomy;Pullens 2013; Harner 2001, Sennaroglu 2001). Surgical destruction of the labyrinth reduces the episodes of attacks but causes loss of balance as well, due to one dysfunctional labyrinth. Moreover, permanent hearing loss is reported after this treatment.

- Endolymphatic sac surgery
Other surgical treatment techniques target the endolymphatic sac (ES). The advantage of these procedures is that they are non-destructive and do therefore not affect the cochlear and vestibular function, thereby preserving hearing and balance. These procedure involve decompression, shunting or drainage of the ES.

Endolymphatic sac decompression (ESD) consists of a mastoidectomy and, after identification of the endolymphatic sac, wide decompression of this structure (Sennaroglu, 2001). ESD has few surgical complications in comparison with the ablative surgery mentioned above. There is no consensus on the effect of decompression. Convert et al (Convert 2006) report improved quality of life after decompression in a case study of 90 subjects after a follow up period of 57.5 months on average.

Drainage or shunting of the endolymphatic sac (ESS) involves identification of the ES, followed by incision of the sac. A shunt is then placed, enabling drainage of the endolymph.
There are several studies that were directed to investigate the effectiveness of ESS (Bretlau 1989, Thomsen 1998, Brinson 2007). Bretlau and Thomsen compared ESS to a sham operation; no differences between the groups was observed. Brinson compared ESS to ESD performed on 88 and 108 patients, respectively. He

concluded that both procedures are effective

Multiple histological studies refute the rationale of endolymphatic sac surgery. Firstly, Chung et al (2011), performed a histopathological study 15 patients who had undergone ESS. If the endolymphatic sac does indeed have a function in resorption of the endolymph but does so inadequately, ESS and especially ESD would allow expansion of these structures and would therefore diminish hydrops. However, diffuse hydrops on temporal bone was seen in the cochlea, the saccule, the utricle, and the ampulla after ESD. The authors conclude that ESD does not relieve hydrops in patients with Ménière*s disease. In addition, if the ES was responsible for endolymph resorption, an increase of hydrops can be expected after amputation of the ES. However, Linthicum et al. (2011) reported a case in which removal of the ES did not lead to an increase of hydrops, as seen on temporal bone histopathology. In the assessed samples, Reissner*s membrane was attached to the spiral ligament in a normal way, without any evidence of hydrops in the cochlea. In conclusion, the role of the ES is not merely absorption of the endolymph and therefore, providing more space to allow dilatation is not the solution for the observed hydrops.

The success rates of these surgical interventions vary between 30-95% (Sennaroglu 2001; Huang 1991; Silverstein 1989, Durland 2005, Pullens 2013; Convert 2006). It should be noted that the natural course of MD is also favourable, and it cannot be determined to what extent this outcome is due to the surgical intervention. Moreover, the placebo effect may play a major role in the relief of complaints, as 70% of MD patients in all groups (all surgical interventions as well as the control groups) experienced some relief of complaints. This either implicates a beneficial effect of any surgical intervention or of any intervention, be it surgical or non-surgical. This was earlier suggested by Thomsen (Thomsen 1981).
Because the beneficial effect of any sort of endolymphatic sac surgery is not sufficiently proven, these procedures arenot performed in The Netherlands as standard treatment for MD. However, in many other countries decompression is performed as part of usual care.

- Endolymphatic duct blockage
Recently, a new surgical intervention has been studied by Saliba et al. (Saliba 2015). A paradigm shift for the pathofysiological model of MD underlies this new treatment. Until now it is believed that the disease is caused by a surplus of endolymph originating in the inner ear, caused by a disequilibrium in the production of endolymph in the inner ear and its resorption in the endolymphatic sac (Merchant, 2005, Semaan, 2010, Salt, 2010). However, Saliba et al. state that the organic substrate of the disease - the surplus of endolymph causing the hydrops - originates in the endolymphatic s

Study objective

This study assesses whether EDB surgery will result in a significant reduction

in the number of patients without vertigo spells at 12 months follow up, compared to patients who undergo endolymphatic sac decompression.

Study design

This is a prospective, multicentre, randomised, double blinded, parallelgroup trial. The study will take 4 years: 6 months of start up time, 2 years of inclusion, 1 year of follow up and 6 months to analyse the results.

Participating centres are: Haaglanden Medisch Centrum (Den Haag), HagaZiekenhuis (Den Haag), LUMC (Leiden), Apeldoorns Duizeligheidscentrum Gelre Ziekenhuizen, Beatrix Ziekenhuis (Gorinchem), Erasmus Medisch Centrum Rotterdam, Gelderse Vallei Wageningen, Isala (Zwolle), Maastricht UMC, Medisch Centrum Leeuwarden, Radboud UMC (Nijmegen), UMC Utrecht, Wilhelmina Ziekenhuis Assen

Intervention

- Surgical procedure in EDB group
First, a canal wall-up mastoidectomy is performed: the mastoid tegmen, sigmoid sinus, and sinodural angle are identified, and the posterior bony external ear canal wall is thinned. The posterior semi-circular canal (PSCC) and the dura mater of the posterior fossa are identified. Using the prominence of the horizontal semi-circular canal, Donaldson*s line is identified to approximate the position of the endolymphatic sac. The bone over the sac and the dura are thinned with diamond burrs. The sac is completely skeletonized. The infralabyrinthine dura is exposed because the main body of the sac and its lumen often lie within this area. The bone of the vestibular aqueduct operculum is dissected. The posterior fossa dura from the retrolabyrinthine bone medial to the sac around the endolymphatic duct is exposed in order to identify the duct in its superior and inferior part in continuity from the endolymphatic sac, and to create a place to insert the tips of the instrument to clip the duct. At this level, care must be taken not to traumatize the dura, which is often thin.

Finally, the dissected endolymphatic duct is blocked with an adequate titanium clip (Weck Horizon, size *micro* to *wide). The size and numbers of clips used will be determined intraoperatively. The titanium clips are applied by using a clip applier (Weck Horizon) and a McGee bending forceps (Aesculap). In the case of tearing of the dura leading to liquor leakage, this will be treated with tisseel, fascie and novacol. The cortex is not restored. The skin is closed in a regular way.

- Surgical procedure in sham group
The same surgical procedure is carried out in the sham group. After identification of the endolymphatic duct, a CT scan is performed to assess if

the endolymphatic duct was identified correctly. After ensuring the structure is indeed the duct, it is decompressed.

Study burden and risks

As for every surgery and general anesthesia, this intervention comes with risk. Firstly the risk of general anesthesia (mortality of 34 per 1 million patients).
The specific risks of this surgical procedure are:
- Injury to the facial nerve
- Injury to posterior semi-circular canal with loss of vestibular function
- Injury to the sigmoid sinus
- Hearing loss
- Leakage of cerebrospinal fluid (CSF), presenting after the operation
- Meningitis
- BPPV

These risk are related to the region where the intervention takes place. Because the operation procedure of Saliba was enhanced by Blom, we do expect lower rates of leaks of CSF and BPPV. Other complications that were mentioned above have not been seen. Overall, we do think these risks are proportional.

The additional visits and tests are concentrated in 4 visits over a period of a year. We do think this is not too much of a burden for the patient. Completing the daily questionnaire demands motivation, but we asked several patients for their opinion and they think it is feasible. Moreover, the relevant patient community supports the study.

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

- Definite unilateral MD according to diagnostic criteria of the Bárány Society (Lopez-Escamez, 2016)
- More than 3 patient reported attacks in the 6 months prior to inclusion and at least 1 attack in the 2 months prior to inclusion
- Age >= 18 years at the start of the trial
- Non responding to a sufficient extent to conservative medical treatment including at least two sessions of at least one intra-tympanic injection (IT) each with corticosteroids (dexamethasone, methylprednisolone, triamcinolonacetonide)
- Dutch health care insurance

Exclusion criteria

- Severe disability (e.g. neurological, orthopedic, cardiovascular) according to the investigator, pregnancy or serious concurrent illness that might interfere with surgery or follow-up.
- Active additional neuro-otologic disorders that may mimic MD (e.g. vestibular migraine (VM), recurrent vestibulopathy, phobic postural vertigo, vertebro-basilar TIAs, acoustic neuroma, congenital disorders, enlarged vestibular aquaduct (EVA)-like or genetic disorders (like DFNA9), cervicogenic dizziness), based on the complete clinical record.
- Previous ear surgery for MD (IT injection is not an exclusion criterion)
- Language difficulties
- Active otitis media (with or without effusion)
- Unable or unwilling to use DizzyQuest App
- Unable to undergo MRI (such as gadolinium allergy, claustrophobia, implanted non-MRI compatible device of material, BMI)

- Deafness of the contralateral ear

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-06-2021
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO

Date:	19-03-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	06-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	12-04-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	22-05-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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
Other	https://www.trialregister.nl/trial/9095. Registratie in ISRTCN met referentienummer 39224
CCMO	NL74967.058.20