A prospective randomized multi-center study comparing endoscopic pneumodilation and per oral endoscopic myotomy (POEM) as treatment of idiopathic achalasia

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal stenosis and obstruction
Study type	Interventional

Summary

ID

NL-OMON53016

Source
ToetsingOnline

Brief title
POEM vs PD

Condition

- Gastrointestinal stenosis and obstruction

Synonym
dysfagie, idiopatic achalasie, sphincter into the esophagus

Research involving
Human

Sponsors and support

Primary sponsor: University Hospital Leuven
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: endoscopic myotomy, endoscopic pneumodilation, idiopathic achalasia

Outcome measures

Primary outcome

Therapeutic success

This study is designed to evaluate which of the two treatment modalities results in the highest success rate after 2 years. Thereafter, follow-up will continue and a similar analysis will be performed 5 years after treatment (and every 5 years thereafter) to determine the long-term outcome of both treatment arms.

As described in more detail later, symptoms will be evaluated using the Eckardt scoring system. Therapeutic success is defined as a reduction to an Eckardt score of 3 or less. This implies that only patients with an Eckardt score > 3 will be included in order to be able to detect a relevant drop in symptom score.

Two years after treatment, the number of patients with a successful symptom control will be determined for both groups of treatment. If symptoms recur within the first year of follow-up in patients randomized to pneumatic dilation, retreatment with pneumatic dilation is allowed. If retreatment however does not result in reduction of the symptom score below 4, the patient will be considered as a failure. In case of a failure, patients will be offered

the choice to undergo an alternative treatment (surgery, botox), and will be excluded from the study. Data collection will however be continued.
When patients successfully treated with pneumatic dilation develop recurrent symptoms during follow-up, retreatment is allowed. Again, treatment is started with a 35 mm balloon, and symptoms are evaluated 4 weeks later. In case the Eckardt score is still above 3, redilation with a 40 mm balloon will be performed. After this second series of pneumodilation, symptoms should be controlled for at least 2 year before a third and last session is allowed. If symptoms occur before this 2 year interval, the patient is considered as a failure. In total, only three dilation sessions will be allowed. If symptoms recur after the third series of dilations, this patient is considered as a failure.
If symptoms recur after POEM, the patient is considered as a failure and other treatment options are discussed with the patient.

Follow-up of failures
If treatment fails (pneumatic dilation or POEM), alternative treatment options are to be considered. The investigator/attending physician will judge (in consultation with the subject) which treatment modality should be used in case of alternative treatment. There are no obligatory alternative treatment modalities.
For all failures the follow-up visits should be scheduled with regard to the date of alternative treatment instead of to the date of initial treatment, starting with visit 3 (1 month after alternative treatment). All data should be

filled out in a new, blanc CRF.

Secondary outcome

Quality of life

The quality of life will be determined using a general QoL questionnaire, namely the SF36 questionnaire. In addition, a more disease specific questionnaire, i.e. the EORTC QLQ-OES24, the Reflux Disease Questionnair RDQ and the Achalasia DSQL questionnaire, will be filled out. These questionnaires will score the QoL at fixed time points during follow-up (3 months, yearly) and if possible before withdrawing from the study for patients who wish to stop their participation.

Complication rate (related to the procedure, GERD)

As discussed in detail in section 3.1. and 3.2, complications (perforation, bleeding, aspiration, infection, sepsis, *) occurring during or immediately following the procedure will be recorded. In addition, reflux symptoms will be scored using a disease-specific questionnaire (HRQL) and gastroesophageal reflux will be measured using 24h pHmetry / endoscopy (see table)

Need for retreatment

As described above, retreatment is allowed to some degree. The number of retreatment sessions after the initial therapy (pneumodilation) will be compared between the two groups. Retreatment is accepted in PD under restricted conditions (see above) whereas the need for retreatment is considered a failure in case of POEM.

Costs

Costs will be calculated for each procedure in each center separately.

Functional parameters (Lower esophageal sphincter pressure (LESP), esophageal emptying, distensibility)

To evaluate the impact on LES function, LES function will be assessed via manometry (LESP), timed barium esophagogram (emptying). Depending on the expertise, patients will undergo an endoFLIP (distensibility) study to assess distensibility. These data are of crucial importance to determine predictors of clinical outcome.

Study description

Background summary

Achalasia is a rare esophageal motor disorder with an annual incidence of 1 per 100 000 persons, clinically characterized by dysphagia, chest pain and regurgitation of undigested food. These symptoms result from esophageal aperistalsis combined with a defective relaxation of the lower esophageal sphincter (LES), leading to impaired propulsion of the bolus and stasis of food in the esophagus. Abundant evidence illustrates that degeneration and dysfunction of the intrinsic inhibitory innervation of the esophagus, with absence of nitric oxide releasing neurons is the underlying abnormality. The exact cause remains to be determined, although a genetic, auto-immune or an infectious origin of the neural damage has been suggested1.
The treatment of achalasia consists of reduction of LES pressure either by forceful endoscopic pneumatic dilatation (PD) or by surgical myotomy (laparoscopic Heller myotomy or LHM)7. Forceful endoscopic dilation of the LES can be accomplished with a balloon dilator designed to distend the LES to a diameter of 30-40 mm aimed at reducing LES pressure by disrupting the sphincteric muscle. The success rate of this technique varies widely between 60 and 85 %, strongly depending on the criteria used to define success and the length of follow-up. The other most commonly used treatment is surgical myotomy. With the introduction of the laparoscopic technique, the surgical approach has gained a lot of interest, especially since the morbidity has significantly improved and the results so far are excellent, ranging between 90-95 %. Until recently, it was unclear however which of these two treatments was superior and should be considered as treatment of choice. In a multicenter European randomized clinical trial, we therefore compared PD and LHM in a large cohort (n=201). This study revealed that both treatments were equally effective 2.

In 2010, Inoue et al. introduced a new minimal invasive technique, i.e. per oral endoscopic myotomy or POEM, as new treatment for achalasia6. In brief, a long submucosal tunnel is created, followed by endoscopic myotomy of the circular muscle bundles of the distal esophagus (8-10 cm) and cardia (2-3 cm). The advantage of this technique is that the muscle bundles are electively transsected and not stretched as with PD. On the other hand, in contrast to LHM, there is no need for a laparoscopic procedure. The results reported so far are excellent with relief of dysphagia in all patients (n=18) and relief of chest pain in 83% after a mean follow-up of 11 months 8. One drawback may be the absence of an anti-reflux procedure, leading to increased risk of gastro-esophageal reflux.
To date, POEM is embraced with great enthusiasm, however, before accepting this technique as new treatment of achalasia in clinical practice, it should be compared with the current treatment modalities. In Germany, a randomized trial will be preformed comparing POEM with LHM. In the present multicentre randomized trial, POEM will be compared with PD.

Study objective

This study is designed to evaluate which of the two treatment modalities results in the highest success rate after 2 years. Thereafter, follow-up will continue and a similar analysis will be performed 5 years after treatment (and every 5 years thereafter) to determine the long-term outcome of both treatment arms.
As described in more detail later, symptoms will be evaluated using the Eckardt scoring system. Therapeutic success is defined as a reduction to an Eckardt score of 3 or less. This implies that only patients with an Eckardt score > 3 will be included in order to be able to detect a relevant drop in symptom score.
Two years after treatment, the number of patients with a successful symptom control will be determined for both groups of treatment. If symptoms recur within the first year of follow-up in patients randomized to pneumatic dilation, retreatment with pneumatic dilation is allowed. If retreatment however does not result in reduction of the symptom score below 4, the patient will be considered as a failure. In case of a failure, patients will be offered the choice to undergo an alternative treatment (surgery, botox), and will be excluded from the study. Data collection will however be continued.
When patients successfully treated with pneumatic dilation develop recurrent symptoms during follow-up, retreatment is allowed. Again, treatment is started with a 35 mm balloon, and symptoms are evaluated 4 weeks later. In case the Eckardt score is still above 3, redilation with a 40 mm balloon will be performed. After this second series of pneumodilation, symptoms should be controlled for at least 2 year before a third and last session is allowed. If symptoms occur before this 2 year interval, the patient is considered as a failure. In total, only three dilation sessions will be allowed. If symptoms recur after the third
series of dilations, this patient is considered as a failure.

If symptoms recur after POEM, the patient is considered as a failure and other treatment options are discussed with the patient.

Study design

This study is a prospective randomized multi-center study, executed in fourteen different centers.
Treatment comparing endoscopic pneumodilation and POEM will be evaluate in the highest success rate after 2 years. THereafter follow-up will continue and a similair analysis will be performed 5 years after treatment an every 5 years thereafter to determine the long-term outcome of both treatments arms.
Therapeutic success is defined as reduction to an Eckardt score of 3 or less.

Intervention

POEM and PD

Study burden and risks

Side effects of Pneumodilatatie
Respiratory tract infections or pneumonia may be caused by the choke on food or drink. Risk is small (1 in 1000) because patients must be sober during treatment.
There may occur a crack in the esophagus or in the stomach during the inflation of the balloon (at 1 to 3 at 100). This will be checked by a radiography. De sphincter can be stretched (less than 10 in 100) so that the stomach can no longer close good enough. Reflux, this can be treated with medication.
Side effects of POEM
Respiratory infection or pneumonia (1 in 1000)
(1-6 in 100) there may be a crack or leak in the lining of the esophagus. As check there will be made on the day after surgery a radiography.
At (10 in 100), the probability exists that after the cutting of the sphincter muscle can not close the stomach this good enough anymore. As a result, The stomach contents from flowing back into the esophagus (reflux) This can be treated with medication.
Small chance that the submucosal tunnel can not be created. The POEM procedure can not be executed.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Between 18 and 75 year of age
- Manometric diagnosis of achalasia
- Eckardt score >3
- signed Informed consent

Exclusion criteria

- Severe cardio-pulmonary disease or other serious disease leading to unacceptable surgical risk.
- Previous treatment, except treatment with nitroderivatives, Ca++ channel blockers or sildenafil, or dilation with Savary bougies or balloons of 2 cm diameter or smaller
- Pseudo-achalasia
- Mega-esophageal (> 7 cm) and/or sigmoid-like esophagus
-Previous esophageal or gastric surgery (except for gastric perforation)
- Not capable to fill out questionnaires (e.g. due to language barrier)
- Not available for follow-up
- Esophageal diverticula in the distal esophagus
- Malignant or premalignant esophageal lesions

- Patients with liver cirrhosis and/or esophageal varices
- Pregnancy

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-10-2016
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	13-11-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL50896.078.15