Comparison of types different fundoplications used in combination with laparoscopic Heller’s cardiomyotomy for achalasia: A systematic review (Protocol)

Background: Achalasia is a rare primary motility disorder of the oesophagus characterised by an absence of oesophageal peristalsis and incomplete relaxation of a frequently hypertensive lower oesophageal sphincter (LOS) (Cotran 1999). The incidence of achalasia is about 1 in 100,000 people per year and the prevalence is about 10 per 100,000. (Sadowski 2010). The likely cause is myenteric inflammation with injury to and subsequent loss of ganglion cells and fibres of myenteric nerves (Goldblum 1996).

The patients usually present with one or more of the following symptoms: dysphagia to both solid and liquid diet (>90%), regurgitation of undigested food (76-91%), nocturnal cough (30%), aspiration (8%), chest pain (25-64%), heart burn (18-52%) and weight loss (35-91%) (Boeckxstaens 2014). The investigations done to confirm the diagnosis are: (1) Barium swallow which shows a smooth tapering of lower oesophagus (bird’s beak appearance), (2) Oesophageal manometry which shows reduced peristalsis of oesophagus with hypertensive, non-relaxing LOS and (3) OGD to rule out any tumour at GOJ (pseudo-achalasia) (Pandolfino 2015, Stefanidis 2012, Vaezi 2013).

The treatments available are:
(1) Pharmacotherapy- calcium channel blockers and long acting nitrates.
(2) Botox injections into the LOS
(3) Pneumatic dilatation of the LOS
(4) Peroral endoscopic myotomy (POEM)
(5) Laparoscopic Heller’s cardiomyotomy (LHC)

Pharmacotherapeutics agents have to be taken every day, have incomplete symptom control and lose their potency of time. Botox injection relieves symptoms in 85% of the patients but its effects last for 6-12 months (Pandolfino 2015, Stefanidis 2012, Vaezi 2013). Pneumatic dilatation is currently considered the most effective non-surgical treatment with a response rate reaching 93% (range 50-93) at 10 years with on-demand repeat dilations (Pandolfino 2015, Stefanidis 2012, Vaezi 2013). Treatment with single dilation is only effective in 13% of the patients. POEM is a new treatment and long term results are still uncertain. LHC
provides symptomatic improvement in 89% (range 77-100) (Compos 2009) of the patients on long term follow up. It has completely replaced open abdominal, thoracic or thoracoscopic approaches of Heller’s cardiomypotomy. Robotic Heller’s cardiomypotomy is a new technique but long term results are not available for this approach.

Description of the intervention
LHC is performed under general anaesthesia. Five small incisions (1-2 cm long) are use for ports on the upper abdomen to introduce a laparoscopic camera and instruments. The lower end of the oesophagus is dissected through the hiatus and mobilised into the abdomen. The muscles of the oesophagus, including the LOS, are divided at the gastro-oesophageal junction to expose the mucosa. The division of the muscles is carried proximally into the oesophagus for 4-5 cm and distally into the stomach for 2-3cm. Any hiatal defect is then apposed using interrupted non-absorbable sutures. The greater curvature of the stomach is then mobilised by dividing the short gastric vessels and a fundoplication is performed. If a Dor (anterior 180 degree) fundoplication is created, the fundus is sutured to each edge of the myotomy and to the right crus with non-absorbable sutures and overlies the anterior surface of the distal oesophagus including the myotomy defect. If a Toupet (posterior 270 degree) fundoplication is created, the mobilised fundus is pulled from left to right behind the oesophagus and is sutured to the edges of the myotomy wound on each side. It creates a wrap covering the posterior and lateral aspects of the oesophagus leaving the mucosa in the floor of the myotomy wound exposed. In Nissen’s (360 degree) fundoplication, the fundus is pulled from left to right behind the oesophagus and is sutured on to itself in front of the oesophagus, forming a complete wrap encircling the distal oesophagus.

How does the intervention work?
The division of the muscles (myotomy) of the hypertensive, non relaxing LOS relieves the symptoms of dysphagia but it also causes gastro-oesophageal reflux. To prevent the reflux symptoms, a fundoplication is added to LHC.

Why is it important to do this review?
SAGES guidelines for the surgical treatment of achalasia (Stefanidis 2012) and the ACG Clinical Guidelines on the diagnosis and management of achalasia (Vaezi 2013) recommends that a patient undergoing myotomy should have a fundoplication to prevent reflux, but there is no recommendation to suggest which fundoplication is best to combine with LHC for achalasia.
There has been one meta-analysis (Wei 2013) which compares outcomes of LHC with Dor fundoplication to LHC with other fundoplications or no fundoplications. Another systematic review (Mayo 2012) found that routine fundoplication following LHC reduces the incidence of pathological reflux. But neither of these studies have conclusively proved which fundoplication is the best procedure. Moreover, even though fundoplications are good at controlling the reflux symptoms following LHC, there is evidence that it also increases the risk of recurrent dysphagia, especially in patients treated with Nissen’s (360 degree) fundoplication (Rebecchi 2008).

**Objectives**
To compare the advantages and disadvantages of different types of anti-reflux procedures used in combination with LHC.

**Eligibility criteria**

**Type of study**
We will include randomised control trials (RCT) published as full text, abstract or unpublished data in any language.

**Types of participants**
We will include adults undergoing LHC for achalasia.

**Types of intervention**
We would include trials where one fundoplication procedure is compared against a different fundoplication in patients undergoing LHC for achalasia. We will also include trials where a fundoplication procedure combined with LHC is compared against LHC without any fundoplication.

**Outcomes**

**Primary outcomes:**
1) Pathological acid reflux- obtained from pH studies
2) LOS pressures- obtained from manometry
3) DeMeester score
4) Major complications (Dindo 2004, Clavein 2009)- perforation, pneumothorax, bleeding etc.
Secondary outcomes:
1) Dysphagia
2) Health related Quality of life scores
3) Length of hospital stay
4) Operating time

Search methods for identification of studies

Electronic searches
We will conduct a literature search to identify all published and unpublished RCTs in all languages. We will search the following databases:
1) the Cochrane Central Register of Controlled Trails (CENTRAL) (Appendix 1)
2) MEDLINE (Appendix 2)
3) EMBASE and (Appendix 3)
4) Science Citation Index.

Searching from other sources
We will cross check references of all the primary and review articles for additional studies.

Data collection and analysis

Selection of studies:
Two authors (SM and MWM) will independently screen the titles and abstracts for inclusion. Full text reports are retrieved for eligible / potentially eligible / unclear studies. The review authors will screen the full text and identify studies for inclusion and record the reasons for exclusion of ineligible studies. Any disagreement will be resolved through discussion or consulting a third person. The selection process will be recorded in a PRISMA flow diagram.

Data extraction and management:
The two review authors will collect the data on a standardised form. The data collected would include the following information:

(A) Characteristics of the studies-
   (i) methods: study design, duration, location, follow up period
   (ii) participants: age, gender, ASA (American Anaesthesiologist Association) status (ASA 2014)
(iii) interventions: types of intervention, person performing the intervention.
(iv) outcomes: primary and secondary outcomes, time outcome reported

(B) Assessment of risk of bias in the included studies-
(i) random sequence generation
(ii) allocation concealment
(iii) blinding of participants and personnel
(iv) blinding of outcome assessment
(v) incomplete outcome data
(vi) selective outcome reporting
(vii) other bias- funding source, conflict of interest of authors

Measurement of treatment effects:
We will analyse dichotomous data (pathological acid reflux, dysphagia and complications) as risk ratio (RR) and continuous data (LOS pressure, Quality of life scores, length of stay and operating time) as mean difference (MD) when they are reported in all the trials in the same units or as standardised mean difference (SMD) when they are reported in different scales in different trials. We will calculate the risk ratio (RaR) for outcome reporting of adverse events and hazard ratio (HR) for reporting time-to-event adverse outcomes. We will undertake meta-analyses only if there is enough similarity between the participants and intervention to make meaningful pooling. The unit of analysis would be individual participants undergoing LHC with an anti-reflux procedure for achalasia.

Dealing with missing data:
We will contact the authors of the trials to verify the characteristics of study and find out the missing outcome data. If we are unable to obtain this information from them, we will impute the mean from median and standard deviation from standard error, interquartile range or P values according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). If we are unable to calculate the standard deviation from standard error, interquartile range or P values, we will impute standard deviation as the highest standard deviation of all the trials included in the outcome. All these methods of imputation will decrease the weight of the study in the meta-analysis of MD.

Assessment of heterogeneity:
We will assess heterogeneity by $I^2$ statistics and if there is significant heterogeneity (greater than 50%- 60% according to Cochrane Handbook
for Systematic Reviews of Interventions; **Higgins** 2011), we will undertake pre-specified subgroup analysis.

**Data synthesis:**
We will use Review Manager 5 (**RevMan** 2012) to analyse the data and calculate the 95% confidence intervals for the treatment effect.

**“Summary of findings” table:**
We will create a “Summary of findings” table using the GRADEpro software of all the outcomes.

**Subgroup analysis and investigation of heterogeneity:**
We plan to carry out the following subgroup analysis:
1. different age groups
2. different genders
3. different ASA groups
4. different BMI
We will use all the primary analysis in the subgroup analysis using the Chi-square test.

**Sensitivity analysis:**
We will perform sensitivity analysis to assess the robustness of our conclusions which will include:
1. excluding trials with unclear or high risk of bias
2. excluding the trials where the mean and standard deviation have been imputed.

**Deviation from protocol:**
We will perform the systematic review according to this protocol and will report any deviations and the reasons behind it in the section “Differences between protocol and review” of the systematic review.

**References:**

**ASA 2014**

**Boeckxstaens 2014**
**Campos 2009**

**Clavien 2009**

**Cotran 1999**

**Dindo 2004**

**Goldblum 1996**

**Higgins 2011**

**Kumagai 2014**

**Mayo 2012**
Pandolfino 2015

Rawlings 2012

Rebecchi 2008

RevMan 2012

Sadowski 2010

Stefanidis 2012

Tomasko 2014

Torres-Villalobos 2015
from a randomized trial including high resolution manometry evaluation. Gastroenterology 2015; 148(4 Suppl. 1): S1138.
(Presented in DDW Conference 2015)

Vaezi 2013

Wei 2013

Zhu 2008

Appendices

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Esophagus] explode all trees
#2 (esophag* or oesophag*)
#3 MeSH descriptor: [Achalasia] explode all trees
#4 (esophag* or oesphag*) achalasia
#5 MeSH descriptor: [myenteric plexus] explode all trees
#6 esophageal motility disorder
#7 hypertensive esophageal sphincter
#8 {OR #1 - #7}
#9 MeSH descriptor: [Laparoscopy} explode all trees
#10 myotomy*
#11 cardiomyotomy*
#12 (esophag* or oesophag*) myotomy*
#13 laparoscop* myotomy*
#14 Heller* myotomy*
#15 Heller* cardiomyotomy*
#16 {OR #9 - #15}
#17 MeSH descriptor: [Fundoplication] explode all trees
#18 fundoplication*
Appendix 2. MEDLINE search strategy

1. exp Esophagus
2. (esophag$ or oesophag$).mp.
3. Esophageal Achalasia/
4. ((esophag* or oesophag*) adj2 achalasia) .tw.
5. Myenteric Plexus/ ab, in, pa, pp [Abnormalities, Injuries, Pathology, Physiopathology]
6. Esophageal Motility Disorders/ di, pp [Diagnosis, Physiopathology]
7. Esophageal Junction/ ab, ir, pp [Abnormality, Innervation, Physiopathology]
8. (hypertensive adj2 oesophageal adj2 sphincter).mp.
9. or/1-8
10. Laparoscopy/
11. ((esophag* or oesophag*) adj2 myotom*).mp.
12. (esophagomyotom* or oesophagomyotom*).mp.
13. (surg* adj2 myotom*).mp.
14. (Laparoscop* adj2 myotom*).mp.
15. cardiomyotom* .mp.
16. (Heller* adj2 myotom*).mp.
17. or/ 10-16
18. Fundoplication/
19. fundoplication$.mp.
20. (nissen or rossetti).mp.
21. (Toupet).mp.
Appendix 3. EMBASE search strategy

1. exp esophagus
2. (esophag$ or oesophag$).mp.
3. exp achalasia
5. (oesophageal adj3 achalasia).mp.
7. (hypertensive adj3 esophageal adj3 sphincter).mp.
8. (hypertensive adj3 oesophageal adj3 sphincter).mp.
9. or/ 1-8
10. myotomy/
11. cardiomyotomy/
12. myotomy$.mp
13. cardiomyotomy$.mp.
15. (Heller$ cardiomyotomy$).mp.
16. Heller’s myotomy/
17. Heller’s cardiomyotomy/
18. (esophago$ or oesophago$) myotomy/
Contribution of authors:
SM and KG have contributed in writing this protocol

Conflict of interest:
None declared
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