

# **Master of Public Health Degree**

## **Faculty of Health Sciences**

### **University of Cape Town**

**TITLE:** PNEUMATIC BALLOON DILATATION  
VERSUS LAPAROSCOPIC HELLER'S  
MYOTOMY IN PATIENTS WITH IDIOPATHIC  
ACHALASIA

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**Abstract** - Pneumatic Balloon Dilatation versus Laparoscopic Heller's Myotomy in Idiopathic Achalasia.

## **Background**

Both laparoscopic Heller's myotomy (LHM) and pneumatic balloon dilatation (PBD) are widely used in the management of achalasia, but there is still no clarity as to which of these interventions is the best treatment for patients with the condition.

## **Methods**

Newly diagnosed achalasia patients were randomised into PBD or LHM. The severity of achalasia symptoms in all participants was documented using the Eckardt score, a clinical symptom score whose components are dysphagia, chest pain, regurgitation and weight loss. The Eckardt score ranges from 0 in those with no symptoms to 12 in patients with pronounced symptoms. The primary outcome, therapeutic success, was defined as a drop in the Eckardt score to  $\leq 3$  or subsequent need for alternative intervention. The secondary outcome was the complication rate, including mortality, in the two treatment arms.

## **Results**

A total of 26 patients were enrolled into the study, 13 patients on each treatment arm. The median follow up period was 49 months and baseline characteristics were similar in the two intervention groups. There were 3 failures in each treatment arm, resulting in equivalent therapeutic success rates of 77% (or 10/13) after 49 months of follow up. The p-value, obtained using the log-rank test, was not significant at 0.988. There were no deaths or balloon dilatation-related oesophageal perforation in this study. But there was one LHM-related oesophageal perforation which was repaired during the procedure. The patient subsequently developed an oesophageal leak which required open surgical repair. He did very well after the second procedure. There were 4 patients who had erosive oesophagitis, two on each treatment arm and one patient had minor wound sepsis post-LHM.

## **Conclusion**

In this study, the therapeutic success rate of PBD was similar to that of LHM after 49 months follow up. Both procedures were safe with no mortality and only one mucosal breach following LHM.

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## **Part A: study protocol**

The protocol was submitted to the Research Ethics Committee of the University of Cape Town and approval was granted on the 24<sup>th</sup> October 1999. Protocol approval number: REC REF: 283/99. A copy of the approval letter is included under Appendix 1

### **1. Background and literature review**

Achalasia is a rare primary oesophageal motility disorder characterized by absent peristalsis and impaired lower oesophageal sphincter (LOS) relaxation after swallowing (Vaezi, Pandolfino & Vela, 2013). The combination of absent peristalsis and failed LOS relaxation results in impaired oesophageal emptying or functional obstruction. The hold-up of undigested food in the oesophagus leads to the symptoms of achalasia. Common clinical manifestations of the disease include dysphagia for solids and liquids, chest pain, regurgitation, weight loss and heartburn. The characteristic feature on contrast imaging is oesophageal dilatation with a smooth distal stricture resembling a “bird’s beak”, from the non-relaxing LOS. The hallmarks of achalasia on manometry (gold standard investigation) are incomplete LOS relaxation and absent peristalsis. Endoscopy is useful for excluding anatomical lesions like neoplasia which may present with features similar to that of primary achalasia (pseudo-achalasia).

There is no cure for achalasia. Therapeutic options are limited to reducing the pressure gradient across the LOS, facilitating oesophageal emptying by gravity in the process. Pneumatic balloon dilatation (PBD) and Laparoscopic Heller’s myotomy (LHM) are the two most commonly used treatment options. During PBD, a non-

compliant polyethylene balloon is positioned across the LOS and gradually inflated until waist is flattened (forceful rupture of LOS muscle fibres) under fluoroscopic guidance. This is an outpatient procedure and the patient is discharged home after 4-6 hours of observation provided the procedure was uncomplicated. Patients can eat and return to normal activities the following day (Richter, 2011). More than one pneumatic dilatation is often needed for optimal results, either 'on demand' dilatations or scheduled graded pneumatic dilatations irrespective of symptoms (Richter & Boeckxstaens, 2011). Laparoscopic Heller's Myotomy is usually combined with partial fundoplication to reduce the frequency of post procedural gastro-oesophageal reflux disease. Using the laparoscopic approach, the anterior muscle fibres of the LOS, including the sling fibres of the gastric fundus are cut under direct vision. Following LHM, patients remain in hospital for 2-3 days and normal activity after about 2 weeks (Richter, 2011).

When compared to single pneumatic dilatation, LHM is superior in efficacy and durability (Spechler, 2011). However, there is paucity of good quality data confirming the superiority of LHM over graded pneumatic dilatation. In the European Achalasia Trial published in 2011, newly diagnosed achalasia patients were randomised into PBD and LHM (Boeckxstaens et al, 2011). Up to 3 dilatations were allowed and at 2 years the success rates were comparable in the 2 arms (86% and 90% respectively). The groups were also comparable with regards to lower oesophageal sphincter pressure (LOSP) measurements, oesophageal emptying and quality of life. In a meta-analysis comparing the two treatment modalities, the success rate at 5 years was 76% with LHM versus 62% with PBD. At 10 years, the data on LHM was even more impressive with 80% success versus 48% after PBD (Weber et al, 2012). Thus over the longer-term (>5-10 years), LHM remain the standard for primary achalasia.

But most of the long term data is old with marked methodological variability. The current question is whether advances in PBD technology and standardisation of dilatation protocols will result in better efficacy when compared with Heller's myotomy in the long term (5-10 years).

## **2. Study rationale**

Until recently, LHM has been the unquestionable standard of care procedure in achalasia. This perception was supported by the majority of available data at the time. But many of the old studies were retrospective with different endpoints. The European Achalasia Trial which showed that PBD is equivalent to LHM (at least up to 2 years) has changed perceptions in the treatment of achalasia. Pneumatic dilatation is not only convenient for the patient (outpatient procedure and can resume normal function the following day), but also more cost effective and accessible compared to LHM. In a resource setting like ours, it is important to know what to advise our patients. Waiting for a few months for a Heller's myotomy may be worthwhile if the results are indeed better and more durable. But if the 2 modalities are equivalent, then the advice may be tailored to the patient's wishes. The aim of our study is to compare the efficacy of PBD with that of LHM in a prospective randomised trial of newly diagnosed achalasia patients. Outcome will be documented by means of clinical outcome (achalasia dysphagia scores) as well as physiological studies.

### **3. Specific objectives**

1. Assessment of achalasia symptoms scores before and after intervention, as well as during subsequent follow up in the two arms
2. Documentation of intervention-related complications (perforation, morbidity/mortality) in the two arms
3. Exploration of parameters that might predict success with either interventions or risk of mortality/morbidity

### **4. Study Methods**

#### **4.1 Study design**

This was a prospective randomised clinical trial comparing PBD and LHM, two effective and commonly used interventions in achalasia patients. The diagnosis of idiopathic achalasia was based on a combination of compatible clinical presentation, oesophageal manometry, barium swallow and endoscopy. High resolution manometry was not available at the time of the study and so all patients were evaluated using conventional manometry. Manometric features used to make the diagnosis of achalasia were;

- Absence of oesophageal peristalsis
- Incomplete relaxation of the lower oesophageal sphincter after swallowing.

Subjects were then randomised into either PBD or LHM and the clinical symptom score measurements documented. Adverse events as well as the need for alternative treatment were documented. A maximum of two further dilatations were allowed in those on the PBD arm if symptoms recurred after the initial dilatation.

## 4.2 Study setting and population

Most of the patients enrolled came from the Groote Schuur Hospital (one of only two Western Province tertiary hospitals) drainage area. The rest were referred from the Eastern Cape Province of South Africa as well from Cape Town private hospital, Vincent Pallotti hospital.

### Inclusion criteria

- Newly diagnosed achalasia with compatible clinical, manometric, radiographic and endoscopic features
- No prior intervention

### Exclusion criteria

- Secondary achalasia
- Previous pneumatic dilatation or myotomy
- Pregnancy
- Severe medical comorbidity that made patients unsuitable for surgical intervention

### Baseline

- **Diagnostic investigations** – barium oesophagogram, manometry and oesophagogastroduodenoscopy
- **Demographics** – age, gender, weight loss, baseline weight, duration of symptoms and duration of follow up

- **Achalasia symptom assessment** –dysphagia for solids, semi-solids or liquids, chest pain, regurgitation and heartburn
- **PBD** – sedation, operator, balloon size, distention pressure and maximum pressure
- **LHM** –difficulties during the procedure, duration, operator, fundoplication and hospital stay
- **Complications** – mortality, perforation, sepsis, failed treatment and need for alternative therapy

## Definitions

### Failure

- Eckardt score of more than 3 (clinical symptom) –see table 1 in appendix, (Eckardt et al 2011). Up to 2 further dilatations allowed on PBD arm, before intervention deemed to have failed
- If a patient has alternative intervention
- Perforations on PBD treatment arm, but not on LHM arm

### Success

- Eckardt score of 3 or less

## 4.3 Study endpoints

- **Primary end point** – to compare efficacy of PBD with that of LHM by comparing clinical symptomatic scores (dysphagia scores)
- **Secondary end point** – compare mortality and morbidity rates in the 2 arms

## **5. Statistical analysis**

Categorical variables were compared with the use of the chi-square test. Continuous variables were summarised as means with 95% confidence intervals and compared using the student t-test. The log-rank tests on Kaplan-Meyer estimates were used to compare therapeutic success rates in the two treatment groups and the Cox-proportional-hazard models used in the estimation of hazard ratios associated with failure.

## **6. Ethical considerations**

The clinical trial was submitted to the University of Cape Town Research Ethics Committee and approval granted on the 24<sup>th</sup> of November 1999. Both treatment modalities were explained to participants and only those who consented were randomised. Subjects were made aware that they could withdraw from the study at any point and that such a decision would not affect their medical care in any way.

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## **Part B: literature review**

### **1. Introduction**

Achalasia is an oesophageal motility disorder characterized by absent peristalsis of the body of the oesophagus and impaired relaxation of the lower oesophageal sphincter (LOS). It is a rare disorder of unknown cause, affecting approximately 1 in 100,000 persons annually (Weber et al, 2012). Although the great majority of cases are sporadic, achalasia may also be part of recognised syndromes such as Allgrove syndrome (alacrima, achalasia and adrenocorticotrophic hormone deficiency), Down's syndrome or familial visceral neuropathy (Boeckxstaens, Zaninotto & Richter, 2013).

The oesophageal aperistalsis and impaired LOS relaxation in achalasia results from degeneration of neurons in the oesophageal wall (Spechler, 2011). On histology, the number of myenteric neurons (ganglion cells) is reduced and the remaining neurons are surrounded by inflammatory cells. The inflammatory degeneration predominantly affects the nitric oxide-producing inhibitory neurons that mediate smooth muscle relaxation. Cholinergic neurons that mediate smooth muscle contraction are relatively spared leading to unopposed cholinergic stimulation [Spechler, 2011; Boeckxstaens, Zaninotto & Richter, 2013]. The resulting loss of inhibitory innervation in the LOS is the cause of impaired LOS relaxation after swallowing. Loss of inhibitory innervation in the body results in aperistalsis.

Several mechanisms have been put forward to explain the aetiology of the inflammatory degeneration of myenteric neurons in achalasia. Various studies suggest that there may be more than one or two mechanisms involved in the pathogenesis of the disease. These include autoimmune, hereditary,

neurodegenerative and infectious mechanisms (Chuah et al, 2012). Current evidence favours an auto-immune neuronal damage triggered by an infectious agent (a virus such as herpes simplex virus 1 or measles virus) in genetically predisposed individuals [Richter & Boeckxstaens, 2011; Vaezi, 1999]. Immunohistochemical analysis findings of myenteric ganglia infiltration by activated cytotoxic lymphocytes as well as evidence of complement activation in resected specimens are consistent with the autoimmune hypothesis (Boeckxstaens, Zaninotto & Richter, 2013). In addition antibodies against myenteric neurones are found in achalasia patients, especially in those with HLA DQA1\*013 AND DQB1\*0603 alleles [Spechler, 2011; Boeckxstaens, Zaninotto & Richter, 2013].

## **2. Diagnosis of Achalasia**

### **2.1 Symptomatology**

Dysphagia for both solids and liquids with regurgitation of undigested food are the commonest clinical manifestations of achalasia, occurring in over 90% of cases.

Other symptoms of achalasia include chest pain (25% to 64%), heartburn (18% to 52%), weight loss (35% to 91%) and nocturnal cough (30%) (Moonen, 2014).

However, patients with malignant infiltration of the LOS (pseudo-achalasia) may present with similar symptoms, although the duration of symptoms is often shorter and weight loss usually much more pronounced than in idiopathic achalasia. Thus endoscopic and radiologic evaluation of all suspected achalasia patients is important to exclude pseudo-achalasia.

## 2.2 Manometry

Oesophageal manometry is the gold standard test for achalasia (Torresan, 2015). The main manometric features of achalasia are; absence of peristalsis (with or without increased intra-oesophageal pressure) and incomplete LOS relaxation after swallowing. An elevated resting LOS pressure is another manometric feature that is found in majority of achalasia patients, but this is not a diagnostic criteria. In most centres around the world, conventional oesophageal manometry has been replaced by high resolution manometry (HRM) which provides more detail about oesophageal function. Compared to conventional manometry, HRM is much more sensitive. However, the main innovation in HRM is the conversion of pressure data into a topographical plot (high resolution oesophageal pressure topography or HREPT) which has made it possible to classify achalasia into 3 subtypes with different treatment outcomes (Muller, 2015).

All achalasia manometric subtypes are associated with abnormal lower oesophageal sphincter relaxation, but they differ in their pattern of oesophageal body contraction and pressurization. Achalasia subtype 1 (classical achalasia) shows no significant pressurization within the oesophageal body on HREPT, while subtype 2 (achalasia with compression) shows pan-oesophageal pressurization (pressures > 30mmHg). Achalasia subtype 3 (spastic achalasia) is characterized by non-propulsive high-amplitude contractions in the body of the oesophagus (Torresan et al, 2015). There is ample evidence suggesting that HREPT achalasia sub-classification is useful in predicting response to therapy. Patients with subtype 3 have particularly poor response to PBD therapy and LHM is recommended for these patients. Subtypes 1 and 2 have an excellent response to both PBD and LHM (Rohof

et al, 2013). In summary, the introduction of HREPT has made diagnosing early disease easier and allows us to individualize therapy according to specific achalasia subtype.

### **2.3 Radiology and Endoscopy**

Both endoscopy and radiology may be completely normal in a genuine case of achalasia, especially in the early stages of the disease. Manometry is clearly more sensitive than these two investigations, with a sensitivity of approximately 90% (Moonen, 2014). But, as already stated above, endoscopy and barium swallow are useful in excluding pseudo-achalasia. The typical endoscopic feature of achalasia is a dilated oesophagus with food and saliva stasis as well as some resistance at the gastro-oesophageal junction. A barium swallow in achalasia often shows a dilated oesophageal body with an air-fluid level and a “bird beak” appearance at the LOS. Oesophageal emptying can be assessed by performing a timed barium swallow, in which the height of the barium column 5 minutes after ingestion of the barium is a measure for emptying (Moonen, 2014).

## **3. Management of Achalasia**

There is currently no treatment that can reverse the oesophageal muscular dysfunction that results from the neuronal damage in achalasia. Therapeutic options are directed at palliation of symptoms and prevention of disease complications like aspiration pneumonia. The oesophageal outlet obstruction in achalasia can be relieved by disruption of the oesophagogastric junction sphincter. Such intervention reduces the pressure gradient across the LOS, facilitating oesophageal emptying by gravity in the process. Disruption of the LOS can be accomplished by endoscopic

intra-sphincteric injection of botulinum toxin, endoscopic pneumatic balloon dilatation (PBD) or by Heller's myotomy. Although endoscopic injection of botulinum toxin is safe and effective in relieving dysphagia in over 80% of patients, the clinical benefit is short lived and is thus reserved for patients who are poor candidates for more durable interventions. Pneumatic balloon dilatation and Heller's myotomy (with or without an anti-reflux procedure) are considered the definitive treatment modalities for achalasia (Richter, 2012).

### **3.1 Heller's Myotomy**

Surgical myotomy for achalasia was performed for the first time by Ernest Heller in April 1913. The original Heller's procedure was an open anterior and posterior myotomy, dividing the muscle fibres down to the level of the mucosa. The results were spectacular and the procedure was soon the surgical treatment of choice for achalasia worldwide. However, it soon became clear that complete disruption of the LOS was associated with an unacceptably high incidence of severe gastro-oesophageal reflux disease whose symptoms may be as disabling as the condition being treated, especially when associated with peptic stricture. Over the years a number modifications were made to the original Heller's procedure. Such modifications include only performing anterior myotomy, limiting the gastric extension of the myotomy and the addition of an antireflux procedure to reduce the risk of gastro-oesophageal reflux (Boeckxstaens, Zaninotto & Richter, 2013). Limited gastric extension of the myotomy ensures that the LOS competency is not completely destroyed with the modified procedure. Open Heller's myotomy relieved dysphagia in over 80-90% of patients while the risk of gastroesophageal reflux disease was much reduced with the technique modifications already alluded to. Despite the impressive results with Heller's myotomy, the procedure was not

embraced by some patients and physicians who favoured the less efficacious single balloon dilatation which had a therapeutic success rate of around 60% at the time. Barriers to myotomy included high initial cost and protracted recovery period after open myotomy. In contrast, balloon dilatation is a day procedure with minimal inconvenience to the patient and is widely accessible in most centres. However, the advent of minimally invasive surgery has profoundly changed perceptions and attitudes towards surgical myotomy for achalasia. The minimally invasive approach is as effective as the open counterpart with the added advantage of a shorter hospital stay, less time absent from work and reduced overall morbidity. Instead of the 7-10 days of hospital care following open myotomy, patients are able to resume oral food intake and are up and about the day after minimally invasive surgery. They are at home within 2-3 days of the procedure. Laparoscopic Heller's myotomy (LHM) combined with partial fundoplication is currently the procedure of choice because of better therapeutic efficacy and lower morbidity compared to thoracoscopic Heller's myotomy (Boeckxstaens, Zaninotto & Richter, 2013).

### **3.2 Laparoscopic Heller's Myotomy**

When the minimally invasive surgical technique for achalasia was introduced in the early 1990s, a left thoracoscopic myotomy was the preferred approach. But it was soon evident that this technique was linked with poor gastroesophageal junction exposure and a high rate of post-procedure reflux disease (50-60% of cases) as no fundoplication was done (Patti & Fisichella, 2014). Laparoscopic Heller's myotomy on the other hand, allowed easy access to the gastroesophageal junction and an anti-reflux procedure is added to the myotomy. The current practice in most centres includes extending the myotomy 2-3 cm onto the proximal stomach to cut the gastric

sling fibres and adding a partial fundoplication (anterior Dor or posterior Toupet). A full fundoplication is associated with a high rate of persistent or recurrent dysphagia and thus a partial fundoplication is preferred. With reported effectiveness of between 90-95% over 5 years and 89 -90% over 10 years, it is not surprising that many consider LHM as the gold standard for the treatment of achalasia (Patti & Fisichella, 2014).

### **3.3 Pneumatic Balloon Dilatation**

Pneumatic balloon dilatation uses air pressure to forcefully tear the LOS muscle fibres. It is an outpatient procedure and the patient can go home after 4-6 hour observation in uncomplicated cases. Normal activity can be resumed the following day. The most serious complication of PBD is oesophageal perforation and occurs in up to 5% of patients (Yaghoobi, 2013). The majority of perforations occur during the initial dilatation. Although small perforations can be managed conservatively with antibiotics plus total parental nutrition (with or without stenting), large perforations with mediastinal soiling require surgical repair by thoracotomy (Vanuytsel et al, 2012). Less serious complications of PBD include chest pain, aspiration pneumonia, bleeding, transient fever, mucosal tear without perforation, haematoma as well as gastro-oesophageal reflux disease.

### **3.4 Laparoscopic Heller's Myotomy versus Pneumatic Balloon Dilatation**

The optimal initial therapy for newly diagnosed achalasia patients has been a subject for debate for many years. Ideally, the choice between two treatment modalities is based upon prospective, randomised controlled studies. Unfortunately the majority of the studies published in the treatment of this condition don't meet the quality criterion which makes it difficult to make sense of the data. A number of these studies were

underpowered to show a difference if such a difference existed. Since the majority of the studies were retrospective studies from single centres, the risk of confounding and bias in the data is significant. To compound matters, there was wide variation in the way the studies measured or reported the efficacy of the interventions and other endpoints. Changes in technology and dilatation protocols have also made it difficult to compare old studies with current ones. A Medline literature search for randomised controlled trials comparing LHM and PBD in newly diagnosed achalasia patients yielded 3 studies whose findings are summarized in table 1 below.

Table 1. Characteristics of the Randomised Control Trials (n=3)

Study	Patient group	Sample size (N)	LHM/PBD (n)	PBD Method	Median follow up (months)	Key Outcome
<b>Kostic et al, 2007</b>	Newly diagnosed achalasia, Single centre - Sweden	51	25/26	Graded Rigiflex 30, 35, 40mm	12	Treatment failure LHM vs PBD 1/25 vs 6/26 p-value=0.04 (PP) p-value=0.09 (ITT)
<b>Novais et al, 2010</b>	Newly diagnosed achalasia, Single centre Rio de Janeiro, Brazil	134	47/47	Graded Rigiflex 30, 35 women & 35, 40mm men	3	Therapeutic success LHM vs PBD 88.3% vs 73.8% in p-value = 0.08
<b>Boeckxstaens et al 2011</b>	Newly diagnosed achalasia, Multi-centre European study	201	106/95	Graded Rigiflex 30, 35, 40mm	43	Therapeutic success LHM vs PBD 93% vs 90% -1 <sup>st</sup> year 90% vs 86% -2 <sup>nd</sup> year p-value=0.46

The first randomised controlled clinical trial comparing LHM to PBD in newly diagnosed achalasia patients enrolled 51 participants, 26 had PBD and 25 had LHM with posterior partial fundoplication (Kostic et al, 2007). The primary endpoint was treatment failure - defined by one or more of the following;

- Incomplete symptom control or relapse requiring 3 additional interventions
- Serious complication requiring switch over to alternative intervention
- Clinician or patient requesting change to alternative intervention

After 12 months follow up, there were 6 treatment failures on the PBD group compared to only 1 in the LHM group. The difference reached statistical significance when the analysis was done using per protocol analysis (p-value = 0.04), but not in the intention to treat analysis (p-value = 0.09). One patient was lost to follow up and thus the differences between the PP and ITT analyses. The study was clearly underpowered and of course the 12 months follow up far too short.

The second randomised controlled clinical trial enrolled 94 patients, 47 on the LHM arm and 47 on the PBD arm (Novais & Lemme, 2010). Therapeutic success was assessed using the Vantrappen and Hellemans criteria, a tool for grading residual dysphagia after the intervention. The grades were;

- Excellent result : absence of dysphagia
- Good : occasional dysphagia, less than a week
- Fair : dysphagia less than a week
- Poor : dysphagia more than a week, associated with regurgitation and weight loss

Therapeutic success was considered when the patient had excellent or good symptom relief after intervention. Therapeutic success was observed in 88% of patients treated with LHM and 74% in those treated with PBD, but the difference did not reach statistical significance (p-value = 0.08). This study was also underpowered.

The last of the 3 randomised controlled trials is the European Achalasia Trial which is considered by many to be a landmark trial in the treatment of achalasia. It was not only well designed, but also multi-centred (14 study sites in 5 European countries) and more importantly adequately powered as well (Boeckxstaens, et al 2011). A total 201 patients were enrolled into either PBD (95 patients) or LHM (106) and therapeutic outcome was reported after a mean follow up of 43 months. Therapeutic success which was defined as a drop in the Eckardt score (sum of the symptom scores for dysphagia, regurgitation, chest pain and weight loss)  $\leq 3$ . Eckardt scores range from 0 in patients who are asymptomatic to 12 in those with pronounced symptoms. The scores are allocated as shown below;

- Dysphagia, regurgitation and chest pain - 0, absent; 1, occasional; 2, daily; and 3, with each meal
- Weight loss - 0, no weight loss; 1, <5 kg; 2, 5–10 kg; and 3, >10 kg

There was no significant difference in therapeutic outcome between the two groups in an intention to treat analysis at 2 years of follow up. Therapeutic success with PBD was 86% compared to 90% with LHM and the p-value was 0.46. The only blemish in this study is the exclusion of the patients who had oesophageal perforation before amendment of the protocol, because of the unexpected high initial perforation rate in the PBD arm.

In summary, the best current evidence suggests that LHM and PBD are equivalent in efficacy, at least up to 2 years. Some gastroenterology treatment guidelines have changed their recommendations in line with the new evidence. It is desirable though that the results are reproduced by other investigators in adequately powered randomised studies. An even more important question is how these modalities

compare long term as 2 years follow up is a very limited period in a patient with achalasia.

### **3.5 Per-Oral Endoscopic Myotomy**

Per-oral endoscopic myotomy (POEM) is the new kid on the block in the management of achalasia. The procedure was first described in 2009 and preliminary results suggest that it may be as effective as LHM without the need for a surgical incision. POEM involves using a flexible endoscope to create a submucosal tunnel to reach the LOS and then perform a selective anterior myotomy (dissecting only the circular muscle fibres and preserving the longitudinal muscle layer). The mucosal entry site which is in the middle of the oesophagus is closed with endoscopic clips at the end of the procedure. Reported therapeutic success rates range from 89% to 100% (Moonen & Boeckxstaens, 2014). However, it is still too early to tell whether POEM will replace LHM. But long term follow up results and head to head comparisons with established interventions data is awaited before we know the unique role POEM will play in the management of achalasia.

In conclusion, the well-designed European Achalasia Trial has put to rest the debate over the short term, PBD is equivalent to LHM in efficacy overt 1 and 2 years follow up. But there is still no clarity on the even more important question of how the two interventions compare 10-20 years down the line. Currently available data favours LHM. But the limitations of the available long term data make it imperative that research in this field is continued. The kid on the block, POE, will find its niche in due course.

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## **Part C: Journal ready manuscript for submission to the South**

### **African Medical Journal**

#### **Introduction**

Achalasia is a rare motility disorder characterized by absent oesophageal body peristalsis and impaired relaxation of the lower oesophageal sphincter (LOS). It results from progressive degeneration of neurons in the oesophageal wall which ultimately leads to impaired oesophageal emptying or functional obstruction (Vaezi, Pandolfino & Vela, 2013). There is hold-up of undigested food and secretions in the oesophagus as a result of the motility dysfunction. Clinically, patients present with dysphagia for solids and liquids, chest pain, regurgitation, weight loss and heartburn. Since achalasia is not curable, the goal of therapeutic intervention is palliation of symptoms which is achieved by reducing the degree of obstruction at the LOS. The two most widely used treatment options are pneumatic balloon dilatation (PBD) and laparoscopic Heller’s myotomy (LHM). These procedures are effective in disrupting the LOS, facilitating oesophageal emptying by gravity in the process (Moonen & Boeckxstaens, 2014). Both LHM and PBD have evolved over the last 10 years or so. The older compliant balloon dilators have been replaced by the newer noncompliant

Rigiflex (Boston Scientific) dilators. With regards to Heller's myotomy, the laparoscopic approach has replaced open myotomy leading to shorter hospital stay and early recovery (Stavropoulos, 2013).

The aim of this study was to compare these two widely used treatment modalities, PBD and LHM with fundoplication, in a randomised clinical trial.

## **Methods**

### **Study Design**

Patients were enrolled from September 1999 and April 2006 at Groote Schuur hospital (a major tertiary hospital in Cape Town) as well as Vincent Pallotti and University of Cape Town private hospitals. The study protocol was approved by the local institutional review board and written consent was obtained from each participant prior to enrolment. The study is a prospective, investigator-initiated randomised trial comparing PBD to LHM in patients with newly diagnosed primary achalasia. The main author was involved in the analysis of the study results, but the study was conceived and administered by the surgical arm of the gastrointestinal unit in the hospital.

### **Study Population**

Only newly diagnosed idiopathic achalasia patients were enrolled into this randomised controlled study. The diagnosis of idiopathic achalasia was based on a combination of compatible clinical presentation, oesophageal manometry, barium swallow and endoscopy. High resolution manometry was not available at the time of

the study and so all patients were evaluated using conventional manometry. Manometric features used to make the diagnosis of achalasia were;

- Absence of oesophageal peristalsis
- Incomplete relaxation of the lower oesophageal sphincter after swallowing.

Patients with secondary achalasia, those less than 18 years of age or had prior achalasia treatment and those with medical comorbidity rendering unfit for surgical intervention were excluded from the study. All patients had to give consent prior to enrolment to trial. Patients were randomised using computer generated numbers paired in ten and sealed in non-transparent envelopes. All enrolled participants underwent standard pre-treatment evaluation which included clinical symptom assessment, oesophageal manometry, barium oesophagogram and gastroduodenoscopy.

Clinical and demographic characteristics of patients were documented, including age, gender, duration of symptoms prior to diagnosis, current weight as well as estimated weight loss before treatment. The severity of dysphagia and related symptoms was evaluated using the achalasia symptom scores (the sum of the symptom scores for dysphagia, regurgitation, heartburn, and weight loss and chest pain). The widely used Eckardt score (sum symptom scores for dysphagia, regurgitation, chest pain and weight loss) was calculated from the achalasia scores. For each of the 3 symptoms (dysphagia, regurgitation and chest pain) in the Eckardt scale, 0 indicates no symptoms, 1 indicates occasional symptoms, 2 daily symptoms and 3 symptoms with each meal. With regards to weight loss, 0 indicated no weight loss, 1 weight loss less than 5 Kg, 2 weight loss between 5-10 Kg and 3 indicated

weigh loss of over 10 Kg. Thus the maximum Eckardt score was 12 and a score of 0 indicated complete relief of symptoms.

### **Interventions**

Pneumatic balloon dilatation was performed using a Rigiflex balloon (Microinvasive Inc., Belmont, Massachusetts, USA) dilator of 35 mm diameter which was introduced over guide wire and positioned across the LOS under fluoroscopic guidance. The balloon was inflated until the balloon “waist” disappeared (between 7-15 psi) and the pressure was maintained for up to 60 seconds. A second dilatation was performed after a one minute interval to confirm disappearance of the balloon waist. The procedure was done under conscious sedation in the endoscopy unit following a minimum of 8 hours fast. All patients were closely monitored after the procedure and were discharged only if they showed no features of oesophageal perforation on review by the attending clinician after the period of observation. A second balloon dilatation with a 40mm balloon was performed within a few weeks in patients who did not respond to the initial dilatation.

An anterior Heller’s cardiomyotomy was performed starting at the midpoint of the LOS and extending upward onto the oesophageal musculature for a distance of approximately 6 cm using a diathermy hook. The cardiomyotomy was extended onto the stomach for a distance of 0.5 cm. On table endoscopy was used to identify the oesophago-gastric junction. An antireflux procedure was performed routinely in patients with a hiatus hernia or those who had iatrogenic oesophageal perforation. There were only two surgeons involved in performing the surgical technique which was standardized.

## **Study Outcomes**

Therapeutic success, the primary outcome of the study, was defined as a reduction in the Eckardt score to  $\leq 3$  following intervention. The outcome was deemed to be a failure if the Eckardt score was  $>3$  at follow up or patient (or treating physician) subsequently opted for alternative treatment. Secondary outcomes included morbidity and mortality.

## **Follow up**

Patients were assessed during follow up visits at 1, 6, 12 months following intervention and thereafter yearly. The achalasia symptom scores (Eckardt scores) were documented as well as weight and reflux symptoms.

## **Statistical Analysis**

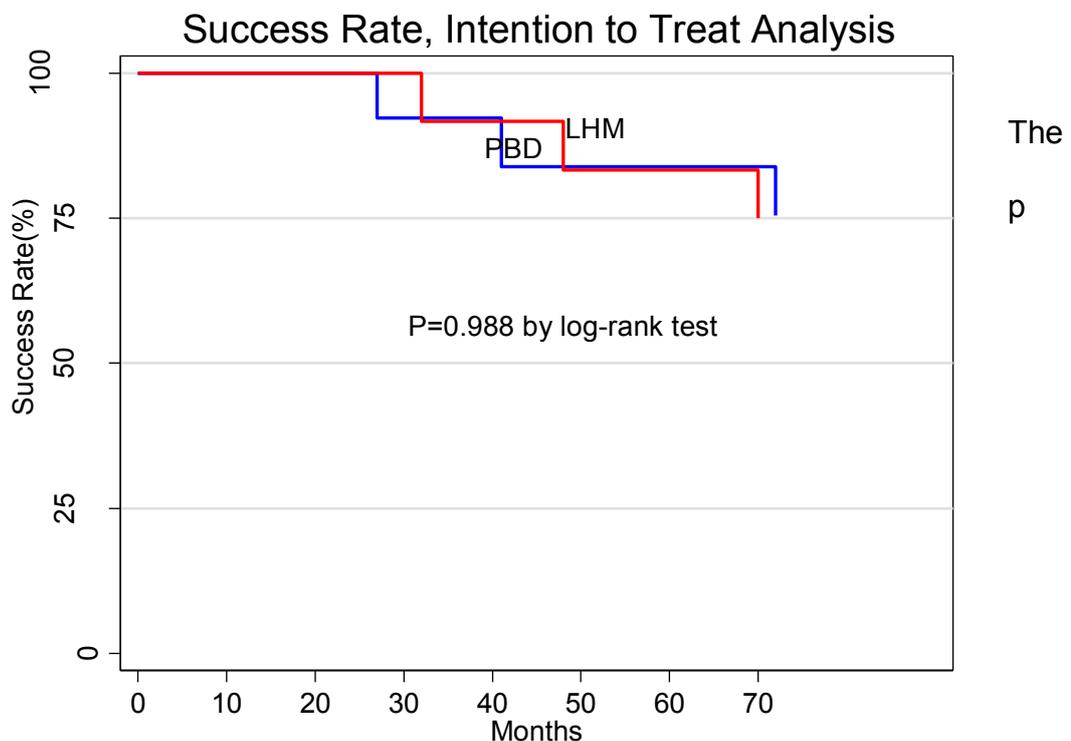
Categorical variables were compared with the use of the chi-square test. Continuous variables were presented as means for those variables that were normally distributed and compared using the student t-test. Variable that were not normally distributed were presented as medians and compared using the Wilcoxon rank-sum test. The log-rank test on Kaplan-Meier estimates was used to compare the success rates between the two treatment groups.

## **Results**

Twenty six patients, 13 on each arm, were enrolled in the study between September 1999 and December 2005. During the 6 year enrolment period, 37 other patients met

the enrolment criteria, but refused to be randomised and opted for one or the other procedure. Of the patients who did not consent for the trial, 22 opted for PBD while 15 wanted to have LHM. The median follow up duration of enrolled patients was 49 months whilst the interquartile range was 24 – 61months. Patients managed by LHM were slightly older than those managed by PBD (mean age 47 versus 42), although the difference did not reach statistical significance (p value 0.695). The two treatment groups otherwise had similar baseline characteristics.

There was no significant difference between LHM and PBD in the primary outcome which was therapeutic success, defined as reduction in Eckardt score to 3 or less. Three treatment failures were observed in each intervention arm (3/13) during the median 49 months observation period. Thus the success rate was 77% (or 10/13) in each treatment arm. The Kaplan-Meier survival curves in figure 1 below show the rate of therapeutic success following treatment with the two interventions and the lines are almost on top of each other!



**Figure 1.** Kaplan–Meier Curves for the Rate of Treatment Success. Kaplan–Meier survival curves show the rate of treatment success with PBD as compared with LHM

value obtained with the use of a log-rank test was 0.988, which is not statistically significant. An intention to treat analysis, which was identical to per protocol analysis, was performed. In the PBD group, all the three patients who failed treatment had initial dilatation using a 35 mm balloon followed by the larger 40mm balloon. Two of the 3 patients subsequently had LHM with good results, but the third patient maintained weight despite Eckardt score of 4. Two of those who failed LHM were successfully treated with PBD, while the third patient failed three balloon dilatations, but responded well to open revision myotomy.

With regards to secondary outcomes, there were no deaths during the 49 months follow up period. One of the 13 patients who had LHM had a mucosal tear which was repaired immediately. There were no perforations on the PBD arm of the study. The patient who had mucosal breach later developed an oesophageal leak requiring open repair on day 1 post LHM. Patient did well after the second procedure. A total of two patients had erosive oesophagitis, one on each arm. Both patients responded well to maintenance proton pump inhibition. One patient had minimal wound sepsis following myotomy which settled on topical therapy.

Cox's proportional hazard regression analysis was used to determine the potential impact of variables like gender, age, type of symptoms, duration of symptoms, LOSP, Eckardt score and BMI, but none of these variables were found to significantly affect therapeutic outcome.

## **Discussion**

In this study the therapeutic success rates (primary outcome), defined as reduction in Eckardt score to  $\leq 3$ , of the two interventions were similar after 49 months of follow up. But the 77% therapeutic success rate on each arm in this study was lower than the 86% and 90% reported in the European Achalasia Trial. The lower success

rates could be explained by the longer follow up in our study, 49 months versus 24 months. The complication rate (secondary outcome) with both interventions was low in our study, and was lower than in the European Achalasia Trial. However, patient numbers in our study were much lower compared to those in the European Achalasia Trial (Boeckxstaens, et al 2011). Two randomised controlled studies published in 2007 and 2010 showed no significant differences between these two interventions in intention to treat analyses, but both studies were underpowered (Novais & Lemme, 2010; Kostic et al, 2007). Another randomized controlled trial comparing open myotomy and pneumatic dilatation published in 1989 found that myotomy was superior to pneumatic dilatation (Csendes et al, 1981). As already alluded to above, it is difficult to compare results of studies done 30 years ago with current studies because the pneumatic dilator systems available today are technically superior to those available then. The definition of failure of pneumatic dilatation has also changed over the years. Before, PBD was deemed to have failed if the patient was symptomatic after a single dilatation. Currently, it is generally accepted that adequate pneumatic dilatation involves at least two PBD sessions before considering an alternative therapy.

In a meta-analysis that reviewed 36 achalasia studies involving a total of 4733 patients (1522 LHM and 3211 PBD) that had at least 5 years of follow up data, LHM was found to be superior with 76% therapeutic success rate after 5 years compared to 62% after PBD (Weber et al, 2012). The superiority of LHM was more pronounced with the 10 year follow up data with an 80% therapeutic success rate versus 48% after PBD. Unfortunately, the impressive numbers (close to 5000 patients) cannot compensate for the variable quality and heterogeneity of the individual studies. The

authors of the paper did highlight the absence of randomised controlled trials as a limitation of the meta-analysis. In the Cleveland Clinic study cohort of close to 200 patients, LHM and PBD had comparable success rates after 4 years of follow up. But at 5-8 years, myotomy was superior to dilatation although the patient numbers were much smaller at that stage (Vela et al, 2006). Thus, although currently available long term data favours LHM, the scarcity of good quality data warrants that we keep an open mind until good quality long term data becomes available.

Other factors found to influence outcome in achalasia, besides the type of treatment received, include the age, gender and manometric sub-type as determined by high resolution manometry (Boeckxstaens, Zaninotto & Richter, 2014). Patients over the age of 40 years do well on pneumatic balloon dilatation and this finding is consistent for both male and female patients (Boeckxstaens, Zaninotto & Richter, 2014).

Younger patients, especially young males, have a poor outcome following PBD.

These patients have a favourable outcome with LHM. Another consistent finding is the poor outcome in patients with achalasia types 1 and 3 after PBD. In the European Achalasia Trial, the success rates were 56% and 29% respectively, after PBD. Achalasia type 2 patients on the other had a success rate of 96% after PBD. In our patient cohort, none of the 3 factors were found to be predictors of clinical outcome when evaluated using a Cox proportional-hazards regression analysis.

Other factors evaluated as potential predictors of outcome were the lower oesophageal sphincter pressure, body mass index, Eckardt score, degree of weight loss and duration of symptoms, but none of them were associated with clinical outcome. A factor that was not evaluated in our study because of insufficient data is the diameter of the oesophagus which has been reported to be predictive of outcome

in some studies (Vela, 2006). The small sample size in our data (13 patients in each arm) is the likely reason why none of the variables evaluated were predictive of clinical outcome in our data set.

The strengths of our study include the randomised controlled design as well as the clearly outlined clinical outcome. We also used a frequently used achalasia clinical evaluation tool, the Eckardt score which made comparing our results with other published data easier. Demonstrating therapeutic equivalence after 49 months of follow up (versus the 24 months in the European Achalasia Trial) is also a strength of this study. The major limitation was the small sample size. The majority of the participants in the study had a strong preference for one procedure over the other and in the end only a few of the eligible participants were randomised. The data which includes the randomised as well as the non-randomised patients will be published at a later stage. The absence of post-intervention oesophageal manometry and timed barium swallow data is another limitation in this study. Lastly, the lack of HRM achalasia subtyping data in this study is another limitation. Despite the limitations outlined above, it is reassuring that both interventions were associated with only minimal morbidity and no mortality.

In conclusion, our study showed that both PBD and LHM were effective in alleviating the dysphagia in patients with primary achalasia. There was no statistically significant difference in the therapeutic success rates between these two interventions after 49 months follow up.

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## Appendix

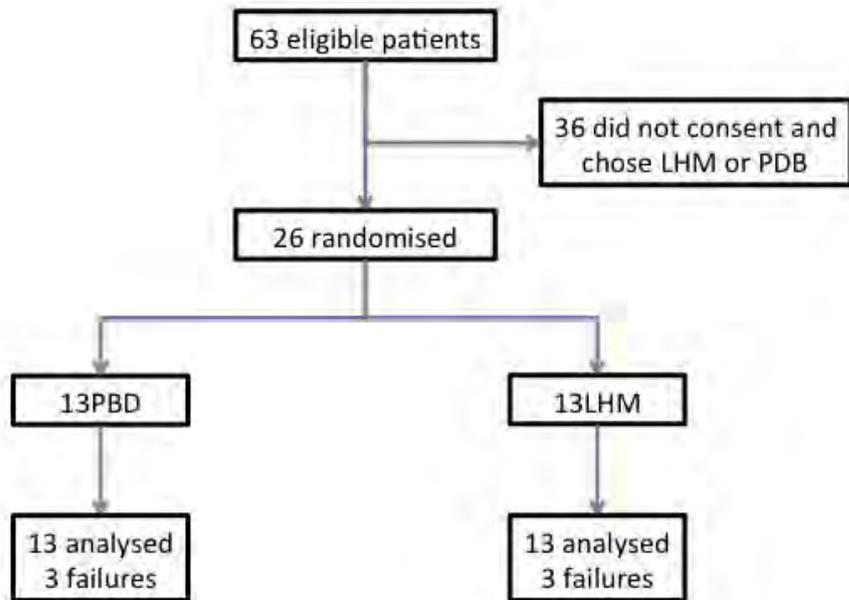
### 1. Table 1. Baseline Characteristics

Table 1. Baseline Characteristics of the Patients.				
Characteristic	Total N=26	LHM N=13	PBD N=13	P Value
Age –years Mean	44.23	46.69	41.77	0.356
Sex Male female	13 13	7 6	6 7	0.500
Weight –Kg Mean 95%CI	60.24	60.50	60.00	0.837
Body Mass Index Mean	21.23	20.88	21.57	0.605
Eckardt score Median IQR Range	7.5 6-8 4-11	7 6-8 4-10	8 7-8 5-11	0.380
Lower Oesophageal Sphincter Pressure- mmHg	34.7	35.9	33.5	0.908
Follow up time-months Median IQR	49 24-61	44 26-56	51 24-58	0.700

### 2. Table 2. Pre and `post Eckardt scores in the treatment arms

	Baseline Eckardt score	Post-treatment Eckardt score
LHM (median)	7	0
PBD (median)	8	0
Failures (median)	7	4

2. Figure 1. Enrolment, Randomisation and Follow up



3. Table 3: Clinical scoring system for achalasia (Eckardt score)

Value	Dysphagia	Regurgitation	Retrosternal pain	Weight loss
0	Never	Never	Never	0 kg
1	Occasionally	Occasionally	Occasionally	0–5 kg
2	Daily	Daily	Daily	5–10 kg
3	With every meal	With every meal	With every meal	>10 kg

## 4. Ethics Let

## UNIVERSITY OF CAPE TOWN



*Research Ethics Committee*  
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26 November 1999

REC REF: 283/99

Prof P Boraman  
 Surgery

Dear Prof Boraman

**PROSPECTIVE RANDOMISED TRIAL OF PNEUMATIC BALLOON  
 DILATION VERSUS LAPAROSCOPIC HELLERS MYOTOMY FOR  
 ACHLASIA**

Thank you for your application submitted to the Research Ethics Committee on  
 01 October 1999.

I have pleasure in informing you that the above study has been **formally approved** by  
 the Research Ethics Committee on 24 November 1999.

Included is a list of Research Ethics Committee Members who have formally approved  
 your protocol.

Please quote the above Reference number in all correspondence.

Yours sincerely,

**PROFESSOR TOLE**  
**CHAIR: RESEARCH ETHICS COMMITTEE**

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