

Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: long-term symptomatic follow-up of a prospective randomized controlled trial

Kristy Kummerow Broman^{1,2} · Sharon E. Phillips¹ · Adil Faqih¹ · Joan Kaiser¹ · Richard A. Pierce¹ · Benjamin K. Poulouse¹ · William O. Richards³ · Kenneth W. Sharp¹ · Michael D. Holzman¹

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Abstract

Background Our prior randomized controlled trial of Heller myotomy alone versus Heller plus Dor fundoplication for achalasia from 2000 to 2004 demonstrated comparable postoperative resolution of dysphagia but less gastroesophageal reflux after Heller plus Dor. Patient-reported outcomes are needed to determine whether the findings are sustained long-term.

Methods We actively engaged participants from the prior randomized cohort, making up to six contact attempts per person using telephone, mail, and electronic messaging. We collected patient-reported measures of dysphagia and gastroesophageal reflux using the Dysphagia Score and the Gastroesophageal Reflux Disease-Health-Related Quality of Life (GERD-HRQL) instrument. Patient-reported re-interventions for dysphagia were verified by obtaining longitudinal medical records.

Results Among living participants, 27/41 (66%) were contacted and all completed the follow-up study at a mean of 11.8 years postoperatively. Median Dysphagia Scores and GERD-HRQL scores were slightly worse for Heller

than Heller plus Dor but were not statistically different (6 vs 3, $p = 0.08$ for dysphagia, 15 vs 13, $p = 0.25$ for reflux). Five patients in the Heller group and 6 in Heller plus Dor underwent re-intervention for dysphagia with most occurring more than five years postoperatively. One patient in each group underwent redo Heller myotomy and subsequent esophagectomy. Nearly all patients (96%) would undergo operation again.

Conclusions Long-term patient-reported outcomes after Heller alone and Heller plus Dor for achalasia are comparable, providing support for either procedure.

Keywords Achalasia · Heller myotomy · Dor fundoplication · Per-oral endoscopic myotomy (POEM) · Dysphagia · Gastroesophageal reflux

Achalasia, or impaired esophageal sphincter relaxation resulting in dysphagia, is treated surgically by performance of Heller esophagomyotomy, in which the constricting muscle fibers of the lower esophagus and upper stomach are divided [1]. A potential side effect of this procedure is gastroesophageal reflux [1, 2]. Our group previously demonstrated in a randomized controlled trial from 2000 to 2004 that combining Heller myotomy with anterior (Dor) fundoplication decreased postoperative pathologic gastroesophageal reflux while being equally effective in reducing subjective dysphagia at 6 months follow-up [3]. A reduction in gastroesophageal reflux after myotomy with fundoplication was subsequently demonstrated in a meta-analysis combining multiple retrospective and prospective cohort studies [1]. As a result, laparoscopic esophagomyotomy with partial fundoplication has become the mainstay of surgical treatment for achalasia [4–6].

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✉ Kristy Kummerow Broman
kristy.l.kummerow@vanderbilt.edu

¹ Department of Surgery, Vanderbilt University Medical Center, 1161 Medical Center Drive, D-5203 Medical Center North, Nashville, TN 37232, USA

² Geriatric Research, Education, and Clinical Center, Tennessee Valley Healthcare System, Veterans Affairs Medical Center, Nashville, TN, USA

³ Department of Surgery, University of South Alabama Health System, Mobile, AL, USA

Existing comparisons of Heller myotomy alone versus Heller myotomy with Dor fundoplication are limited in two ways. First, most were performed in non-randomized cohorts, increasing risk of selection bias in choice of operation. Second, the majority are limited to 5 or fewer years of follow-up, with very few examining outcomes more than 10 years after the operation [1]. Given that the majority of patients still experience some dysphagia even after operative intervention, long-term outcomes are needed to inform operative choice and advise patients [7]. To address this knowledge gap, we performed long-term follow-up of participants in our original randomized cohort to better inform whether anterior fundoplication should be performed routinely with esophagomyotomy as treatment for achalasia.

Materials and methods

Design overview

We conducted long-term follow-up of the previously assembled randomized cohort, comparing subjective dysphagia, re-intervention for dysphagia, and gastroesophageal reflux for the participants with achalasia who underwent Heller myotomy alone and those who underwent Heller myotomy plus anterior (Dor) fundoplication. We used a cross-sectional survey to obtain patient-reported measures of dysphagia and gastroesophageal reflux using validated measures, making up to six attempts to contact and actively engage each participant using telephone, mail, and electronic messaging. We also obtained longitudinal electronic medical record documentation of post-operative re-interventions for dysphagia.

Study population

The study population was defined as individuals who participated in our prior randomized controlled trial at Vanderbilt University Medical Center (VUMC) from 2000 to 2004 comparing Heller versus Heller plus Dor. Details of participant selection and recruitment, operative technique, and short-term outcomes have been described previously [3]. For the current study, we included all participants who were alive at the time of contact and consented to participate.

Outcomes

Dysphagia was measured using the Dysphagia Score, which is composed of patient-reported dysphagia frequency and severity scores for a total score ranging from 0 to 10 with higher scores indicating more frequent and/or

severe symptoms [3]. The Dysphagia Score was developed for the purpose of the original RCT and has been used to measure dysphagia in multiple subsequent cohorts of patients treated surgically for achalasia [8–10]. Gastroesophageal reflux was measured using the Gastroesophageal Reflux Disease-Health-Related Quality of Life (GERD-HRQL) instrument [11]. The GERD-HRQL is a brief, GER-specific symptom scale that correlates with objective assessments of GERD [11–13]. Total scores range from 0 to 50 with higher scores indicating more frequent and/or severe symptoms.

Re-intervention for recurrent dysphagia was measured by longitudinal ascertainment of procedural notes from electronic medical records. Participants were asked whether they underwent any subsequent procedures related to their swallowing (including operations and endoscopic interventions) after their initial operation for achalasia. Records were obtained and abstracted from VUMC and any other facility at which the patient reported receiving care. Re-intervention for dysphagia was defined as any operative or endoscopic procedure performed after the initial achalasia operation in which dysphagia was documented as the clinical indication on the procedural note or associated clinical documentation. Both diagnostic and therapeutic procedures were included to capture all instances in which recurrent or refractory symptoms necessitated additional intervention. We also determined time to first re-intervention to inform the necessary follow-up duration to adequately capture outcomes.

Survey development and administration

The survey tool consisted of all items comprising the Dysphagia Score and GERD-HRQL as well as items querying postoperative interventions. Additionally, we ascertained participants' current diet regimens, change in weight from the original operation, and any current medications for gastroesophageal reflux. The survey was administered using Vanderbilt REDCap (Research Electronic Data Capture), a HIPAA compliant tool for building and managing secure online surveys [14]. Participants were recruited using three modalities: electronic message using VUMC's online patient portal, telephone, and mail. The electronic message directed participants to the online survey web address. A single individual (KKB) administered the telephone surveys using the electronic survey as a guide. Participants who responded by mail completed paper versions of the survey. Participant recruitment occurred over a 2 years period (2014–2016) given barriers to locating many individuals whose contact information was out of date. We made up to six attempts to reach each individual at any contact number or address listed in their medical record and conducted online searches of publicly

available data to obtain updated contact information for participants when feasible.

Statistical analysis

Median Dysphagia Scores and GERD-HRQL scores were compared for the two groups (Heller and Heller plus Dor) using Wilcoxon rank-sum tests. We calculated the proportion of contacted participants that underwent re-intervention for dysphagia. We also performed a cumulative incidence analysis of time to re-intervention for recurrent dysphagia and compared the two groups using a log-rank test.

Sample size estimation and power analysis

The sample size was confined to the size of the original study. We estimated that 75% of original RCT participants would participate in this follow-up study ($N = 30$), which would enable detection of a two point difference in mean Dysphagia Scores and three point difference in mean GERD-HRQL scores with a type I error rate of 0.05 and power of 0.80.

Ethical considerations

The study was approved by Vanderbilt University Institutional Review Board. Verbal consent was obtained for participants contacted by telephone. Consent was implied by participation in the written or electronic survey.

Results

Of the original cohort of 43 patients, we confirmed two deaths. Both patient deaths were due to non-gastrointestinal metastatic cancer. Among presumed living participants, 27/41 (66%) were successfully contacted and all completed the follow-up study at a mean of 11.8 years postoperatively (Fig. 1). Contacted participants were 59% female with a mean age of 59 ± 14 years at the time of follow-up. There were no differences in demographic characteristics or preoperative lower esophageal sphincter pressures between the Heller and Heller plus Dor groups (Table 1). There were also no differences between participants who were and were not contacted with respect to age, gender, race, or vital status. Individually identifiable preoperative Dysphagia Scores were no longer available for comparison between the groups.

The median Dysphagia Score among contacted participants was 4 [Interquartile Range (IQR) 2–7 on a scale of 0–10 with 10 signifying greatest disease severity], which was worse than the immediate postoperative baseline of 0

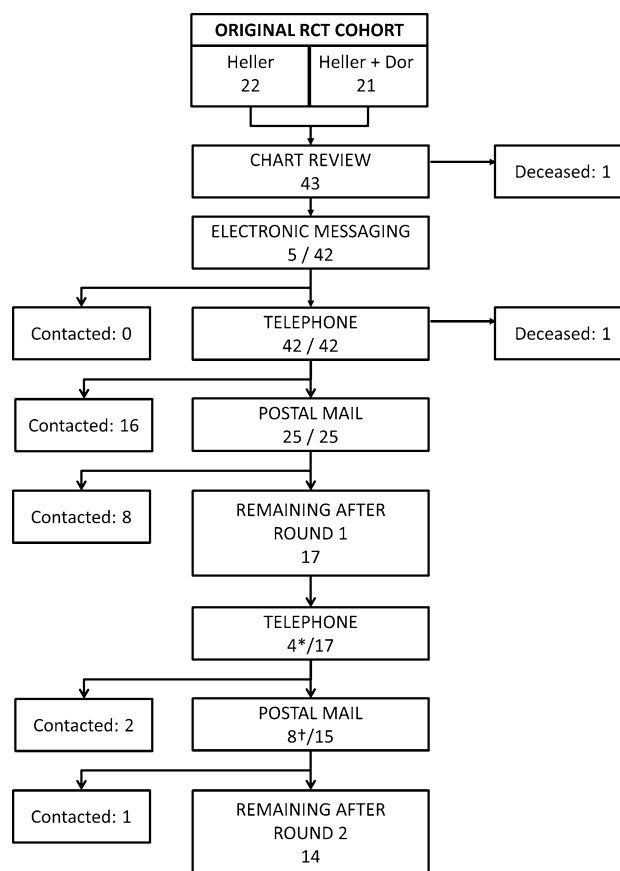


Fig. 1 Cohort flow. Multi-modal process used to contact participants in prior randomized controlled trial for participation in follow-up study. *In second round, phone contact attempted for participants with live numbers or new numbers located by public record search. † In second round, postal mail contact attempted for participants whose prior mail was not returned to sender or for whom new addresses were located by public record search

in both groups, reported previously [3]. At long-term follow-up, median Dysphagia Scores did not differ between Heller and Heller plus Dor [6 (IQR 4–8) vs 3 (IQR 0–5), $p = 0.08$] (Table 2). Sixty-three percent of participants reported that they had symptoms of gastroesophageal reflux with no difference between Heller and Heller plus Dor (69 vs 57%, $p = 0.52$). The median GERD-HRQL score was 14 (IQR 5–17 on a scale of 0–50 with higher scores indicating more symptomatic disease) and was comparable for Heller and Heller plus Dor [15 (IQR 11–19) vs 12.5 (IQR 5–15), $p = 0.25$] (Table 2).

Five patients in the Heller group and 6 in the Heller plus Dor group underwent re-intervention for recurrent dysphagia ($p = 0.82$) with most initial re-interventions occurring more than 5 years postoperatively (Fig. 2). There was no difference in time to re-intervention between Heller and Heller plus Dor ($p = 0.37$). One patient in each group underwent redo Heller myotomy and subsequent esophagectomy, both for refractory dysphagia. The 11

Table 1 Characteristics of participants in long-term follow-up study after Heller myotomy alone or Heller myotomy with Dor fundoplication for achalasia

Patient characteristic	Heller alone <i>N</i> = 13	Heller + Dor <i>N</i> = 14	<i>p</i> value
Age at follow-up, years, mean ± SD	56 ± 14	59 ± 13	0.57
Gender, <i>N</i> (%)			
Male	5 (38)	6 (43)	0.82
Female	8 (62)	8 (57)	
Race, <i>N</i> (%)			
Caucasian	8 (57)	8 (62)	0.86
African American	2 (14)	1 (8)	
Unknown	4 (23)	4 (31)	
Follow-up time, years, mean ± SD	11.8 ± 0.9	11.8 ± 1.3	0.89
Preoperative LES pressure, mean ± SD	33 ± 13	31 ± 12	0.61

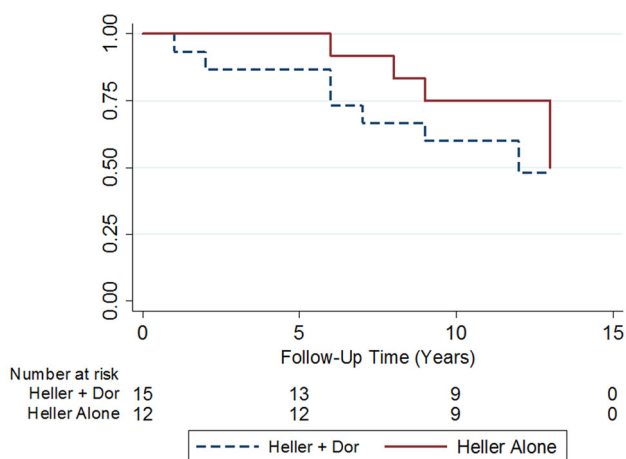
LES Lower Esophageal Sphincter pressure based on manometry

Table 2 Long-term outcomes after Heller myotomy alone or Heller myotomy with Dor fundoplication in a randomized cohort with achalasia

Outcome	Heller alone (HA) <i>N</i> = 13	Heller + Dor (HD) <i>N</i> = 14	<i>p</i> -value
Dysphagia score ^a , median (interquartile range)	6 (4–8)	3 (0–5)	0.08
GERD score ^b , median (interquartile range)	15 (11–19)	12.5 (5–15)	0.25
Intervention for recurrent dysphagia, <i>N</i> (%)	5 (38)	6 (43)	0.82
Redo Heller myotomy	1 (8)	1 (7)	0.96
Esophagectomy	1 (8)	1 (7)	0.96
Esophagogastroduodenoscopy	5 (38)	6 (42)	0.82

^aDysphagia scores can range from 0 to 10 with higher scores demonstrating more severe/frequent symptoms

^bGERD-HRQL scores can range from 0 to 50 with higher scores demonstrating more severe/frequent symptoms

**Fig. 2** Cumulative incidence plot demonstrating time from initial operation for achalasia to endoscopic or operative intervention for recurrent dysphagia. Comparison of time to re-intervention for Heller versus Heller plus Dor, *p* = 0.37

patients who underwent re-intervention had a total of 4 operations (2 in Heller, 2 in Heller plus Dor) and 42 EGDs (18 in Heller, 24 in Heller plus Dor), including 25

endoscopic dilations and 2 botox injections. Patients who underwent re-intervention had median of 2.5 EGDs each (range 1–13 per patient).

The majority of participants at long-term follow-up did not eat a regular diet. Fifty-nine percent (16/27) reported difficulty eating solids, liquids, or both, with no difference between Heller and Heller plus Dor (30% Heller alone vs 50% Heller plus Dor, *p* = 0.31). Seventy-four percent reported taking medication for gastroesophageal reflux on a regular basis, with no difference between Heller and Heller plus Dor (77 Heller alone vs 71% Heller plus Dor, *p* = 0.33). The majority of participants (26/27) stated that if placed in the same situation again, they still would have undergone the initial operation.

Discussion

In this long-term follow-up of a randomized cohort, there were no statistically significant differences between patient-reported measures of dysphagia or gastroesophageal reflux symptoms at a mean of 11.8 years

postoperatively for patients with achalasia who underwent Heller myotomy alone versus Heller myotomy plus Dor fundoplication. Forty-one percent of participants underwent re-intervention for recurrent dysphagia, with most re-interventions occurring later than 5 years postoperatively and no difference by operation type. Most re-interventions were endoscopic, although one patient in each group underwent redo Heller myotomy followed ultimately by esophagectomy. The majority of patients post-treatment of achalasia still required dietary modifications and anti-reflux medications.

To our knowledge this is the only report of long-term outcomes from a cohort of achalasia patients who were randomized to Heller alone or Heller plus Dor fundoplication. Follow-up of this specific cohort is essential because randomization mitigates potential bias in selection of patients for the two procedures, a key limitation of other studies. Among existing long-term follow-up studies of achalasia patients who underwent Heller alone and/or Heller with fundoplication, the majority did not compare outcomes of Heller alone versus Heller plus Dor, primarily because there was dominant use of a single procedure type [8, 15–24]. Of the three non-randomized studies that directly compared postoperative dysphagia for Heller alone versus Heller plus Dor, two found no difference, while one found decreased frequency and severity of dysphagia after Heller plus Dor [9, 10, 25]. The data from our randomized cohort demonstrate that while most patients do have dysphagia to some degree on long-term follow-up, there is no statistically significant difference in dysphagia frequency or severity long-term between Heller and Heller plus Dor.

In terms of re-interventions for dysphagia, seven percent of patients in this study underwent a subsequent operation. This is consistent with other follow-up studies which report re-operation rates of 2–10% (including redo myotomy and esophagectomy) [8, 10, 17–19, 21, 23]. When including endoscopic interventions, our finding that 41% underwent an intervention for recurrent dysphagia is slightly higher than other reported cohorts (7–25%) and is likely due to inclusion of diagnostic endoscopy and the longer follow-up time with the majority of first re-interventions having been performed more than 5 years after the initial operation [8–10, 19, 21].

While nearly half of the Heller alone group had pathologic reflux at 3–5 months postoperatively, on long-term follow-up, the majority of patients reported symptoms of gastroesophageal reflux and were on acid suppression therapy regardless of procedure type. This finding lends support to two prior non-randomized comparisons of Heller and Heller plus Dor which also found no difference in subjective gastroesophageal reflux on long-term follow-up, while opposing the findings of a third non-randomized study which showed that subjective reflux was decreased

by Heller plus Dor relative to Heller alone [9, 10, 25]. Despite the high prevalence of subjective GER symptoms in this study, they were generally well tolerated with use of histamine receptor blockers and proton pump inhibitors based on patients' low median GERD-HRQL scores. [12, 13, 26].

Gastroesophageal reflux was measured differently in the aforementioned studies, some using 24 h impedance-pH monitoring and others using subjective questionnaires. We believed that a subjective, patient-oriented measure was appropriate and more feasible for this long-term outcome assessment, acknowledging that this differs from how reflux was measured in the initial RCT. The selected instrument, GERD-HRQL, has been found to correlate with esophageal acid exposure and esophagitis grade in patients without achalasia. [12, 13] However, studies in patients with achalasia have shown no correlation between GERD symptoms and esophageal pH studies, possibly due to patients' difficulty differentiating between food regurgitation from obstruction and true acid refluxate [26].

In considering the value of fundoplication with Heller myotomy for prevention of gastroesophageal reflux, it is important to note that use of partial fundoplication as an anti-reflux procedure for patients with normal motility and medically refractory GERD is controversial. Some studies have demonstrated partial fundoplication to be less effective in treating reflux than total 360° fundoplication while resulting in similar long-term dysphagia, even in cohorts with abnormal esophageal motility [27, 28]. Other prospective and randomized studies and a meta-analysis suggested equivalency of partial and total fundoplication in treating gastroesophageal reflux; however, in the United States, the majority of surgeons still favor total over partial fundoplication [29–32]. Despite potential benefits of total fundoplication to better mitigate GER after Heller myotomy, total fundoplication is contraindicated in achalasia based on the finding of unacceptably high rates of recurrent dysphagia after Nissen (360°) relative to Dor fundoplication with Heller myotomy in a randomized controlled trial [32].

The need for partial fundoplication with myotomy has been increasingly challenged as interest in endoluminal myotomy increases. Per-Oral Endoscopic Myotomy (POEM) was developed in 2010 and accomplishes esophageal myotomy from within the esophageal lumen via a mucosal incision and submucosal tunnel. Notably, POEM does not include an anti-reflux procedure [33]. In a systematic review and meta-analysis of 29 studies that examined outcomes of POEM, there were five non-randomized studies that compared POEM with laparoscopic Heller myotomy, finding equivalent resolution of dysphagia albeit with a very short mean follow-up period (6 months) [34]. In a more recent report of 500 POEM

cases, 57% of which had more than 1 year of follow-up and 12% of which had 3 or more years of follow-up, dysphagia scores and LES pressures remained low [35]. Given our finding that most recurrent dysphagia occurs more than 5 years after the index procedure, more time will be needed to compare outcomes of POEM and laparoscopic Heller myotomy with respect to dysphagia.

The long-term impact of POEM on GER symptoms is also not well delineated. The aforementioned prospective, single-arm series of 500 POEM patients found symptomatic gastroesophageal reflux in 19% at 1+ years and 21% at 3+ years [35]. Of the few studies comparing POEM to laparoscopic Heller myotomy, three measured postoperative gastroesophageal reflux, finding no difference in postoperative GER measured by 24 h pH impedance monitoring in one case, the GERDQ questionnaire in another, and PPI use in the third [36–39]. Until long-term outcomes are available, the GER-related outcomes data from our RCT of Heller alone versus Heller plus Dor may be the best available evidence of the functional equivalency in patient-reported outcomes of myotomy with and without fundoplication.

Limitations

This study is limited in its small sample size, which was constrained by the sample size of the original RCT and further constrained by difficulty contacting individuals due to outdated contact information. We initially estimated that 75% of the original cohort ($N = 30$) would participate in the follow-up study and assumed normal distribution of outcomes data, which provided the basis for our power calculation. With the actual participation rate of 66% ($N = 27$), the study was powered to detect slightly larger differences of 2.3 points in Dysphagia Scores (scale range 0–10) and 4.6 points in GERD-HRQL Scores (scale range 0–50) between Heller and Heller plus Dor. While the participants in the follow-up study were balanced with respect to demographic characteristics, we were unable to assess whether they were balanced with respect to preoperative Dysphagia Scores given unavailability of individually identifiable data from the original study. Additionally, there is wide heterogeneity in the measurement of dysphagia and gastroesophageal reflux which hinders comparisons between study findings. We were able to use the same symptom scale for dysphagia in the original RCT and this follow-up. However, we were unable to perform objective assessments of pathologic gastroesophageal reflux as was done previously due to participant refusal to undergo esophageal pH testing again. We believe that use of patient-reported symptom scales is more feasible, replicable, and more appropriate for long-term follow-

up in a delivery system that highly values patient-reported outcomes.

Conclusions

This study provides the only existing long-term follow-up of a randomized cohort comparing Heller alone versus Heller plus Dor for achalasia. Early results from this study cohort demonstrated comparable dysphagia but decreased gastroesophageal reflux when Dor fundoplication is performed with Heller myotomy. The present study found that when measured by patient report greater than 10 years from the initial operation, there is no difference in symptoms of dysphagia or gastroesophageal reflux for Heller myotomy with or without Dor fundoplication. Further, these findings reinforce that despite initial clinical improvement, the majority of patients ultimately have some persistent or recurrent symptomatology, albeit less severe than at the time of their primary diagnosis. Still, even a decade after their initial operation, 96% would undergo Heller myotomy with or without Dor fundoplication again.

Compliance with ethical standards

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