Original Article

Heller's myotomy and pneumatic dilatation in the treatment of achalasia: a population-based case–control study assessing long-term quality of life

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SUMMARY. Long-term health-related quality-of-life (HRQL) outcomes have not been widely reported in the treatment of achalasia. The aims of this study were to examine long-term disease-specific and general HRQL in achalasia patients using a population-based case–control method, and to assess HRQL between treatment interventions. Manometrically diagnosed achalasia cases ($n = 120$) were identified and matched with controls ($n = 115$) using a population-based approach. Participants completed general (SF-12) and disease-specific (Achalasia Severity Questionnaire [ASQ]) HRQL questionnaires, as appropriate, in a structured interview. Mean composite scores for SF-12 (Mental Component Summary score [MCS-12] and Physical Component Summary score [PCS-12]) and ASQ were compared between cases and controls, or between intervention groups, using an independent t -test. Adjusted mean differences in HRQL scores were evaluated using a linear regression model. Achalasia cases were treated with a Heller's myotomy ($n = 43$), pneumatic dilatation ($n = 44$), or both modalities ($n = 33$). The median time from last treatment to HRQL assessment was 5.7 years (interquartile range 2.4–11.5). Comparing achalasia patients with controls, PCS-12 was significantly worse (40.9 vs. 44.2, $P = 0.01$), but MCS-12 was similar. However, both PCS-12 (39.9 vs. 44.2, $P = 0.03$) and MCS-12 (46.7 vs. 53.5, $P = 0.004$) were significantly impaired in those requiring dual treatment compared with controls. Overall however, there was no difference in adjusted HRQL between patients treated with Heller's myotomy, pneumatic dilatation or both treatment modalities. In summary, despite treatment achalasia patients have significantly worse long-term physical HRQL compared with population controls. No HRQL differences were observed between the treatment modalities to suggest a benefit of one treatment over another.

KEY WORDS: achalasia, quality of life.

INTRODUCTION

Achalasia is a relatively rare motility disorder of the esophagus of unknown etiology. Incidence varies

between 0.5 and 1.2 per 100 000 per year but recent evidence suggests that it appears to be rising.¹ The combination of early nonspecific symptoms, low incidence and a lack of endoscopic sensitivity can result in failure to diagnose achalasia for many years.¹ The physical, psychological, and social consequences of this disease process can therefore have a significant impact on a patient's quality of life.²

Pneumatic dilatation and Heller's myotomy are two recognized treatment options that involve disruption of the lower esophageal sphincter to improve esophageal emptying and relieve dysphagia. A multicenter randomized controlled trial (RCT) comparing pneumatic dilatation with laparoscopic Heller's myotomy demonstrated similar therapeutic success rates at 2 years (86% vs. 90% respectively, $P = 0.46$) with no significant difference in complication rates between the groups.³ Indeed, it has been

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reported in other series that up to 90% of achalasia patients can return to near normal swallowing with improved quality of life with these currently available treatments.^{3,4}

Health-related quality-of-life (HRQL) assessment is an important tool in the treatment of functional disorders where outcomes should be interpreted in terms of the overall health and well-being of the patient.⁵ In achalasia patients, studies reporting long-term HRQL are still quite limited, and to the best of the authors' knowledge, no other study has considered a population-based control group.⁶ A recent meta-analysis also suggests that laparoscopic Heller's myotomy may provide greater response rates compared with pneumatic dilatation up to 1 year after treatment {odds ratio (OR) 1.98 (95% confidence interval [CI] 1.14, 3.45)} but analysis of HRQL was not feasible.⁷ Therefore, the aims of this study were to assess long-term quality of life in a Northern Irish case-control study of achalasia patients compared with population-based controls, and assess HRQL between treatment interventions.

METHODS

Subject recruitment

A total of 304 patients with primary achalasia were identified from records of esophageal manometry (1989–2006) performed in the Gastrointestinal Physiology Unit, Royal Victoria Hospital, Belfast, Northern Ireland, United Kingdom. This was the regional center for esophageal manometry at that time, and it diagnosed all cases of primary achalasia in Northern Ireland. A nonpurposive sample of 202 cases was invited to participate in the study. A total of 102 patients were not contacted because the treating general practitioner did not consent ($n = 19$) or the recruitment period passed before the remaining cases were contacted ($n = 83$). In total, 151 cases were finally recruited (response rate: 74.8%). A total of 247 controls were frequency matched to achalasia cases ($n = 304$) within groups defined by age (<50, 50–69, ≥ 70) and sex using a population-based approach from general practitioner practices throughout Northern Ireland. Of these, 117 controls enrolled, corresponding to a response rate of 47.4%.

Two controls with incomplete questionnaires were excluded; therefore, the final number in this group was 115. Patients were excluded from the achalasia group if they did not undergo invasive treatment ($n = 22$) or were treated solely with Botulinum toxin injection ($n = 9$). Patients were included if Botulinum toxin injection was used as a bridge to more definitive intervention ($n = 23$). The final number of cases in the treated achalasia group was 120 (Fig. 1). This study was ethically approved by the Office

Fig. 1 Flow diagram demonstrating identification and recruitment of cases and controls (†Nonpurposive sampling for invitation. Not all cases were invited due to project time constraints. The $n = 102$ noninvited participants did not differ from invited participants in terms of age or sex).

for Research Ethics Committees Northern Ireland. Written informed consent was obtained, and all participants were given an information leaflet detailing the purpose and design of the study.

Quality-of-life assessment

All study subjects completed a structured interview consisting of validated general and disease-specific HRQL questionnaires. Mental and physical health was measured using version 2 of the UK 12-item Short Form Health Survey (SF-12).⁸ SF-12 is a validated and widely used HRQL questionnaire that has previously been used in achalasia patients.⁹ It consists of ten 5-point items and two 3-point items as measured on a Likert scale. Two composite scores, the Physical Component Summary score (PCS-12) and the Mental Component Summary score (MCS-12), were calculated using scoring algorithms designed to achieve standardization to a mean of 50 and a standard deviation (SD) of 10 in the 1998 general US population.¹⁰ Higher scores represent better well-being.

The achalasia disease-specific HRQL questionnaire (Achalasia Severity Questionnaire [ASQ]) developed by Urbach *et al.* was also administered.¹¹ This is a 10-item measure that samples food tolerance, dysphagia-related behavior modifications, pain, heartburn, distress, lifestyle limitation, and satisfaction. A summary raw score is calculated based on the sum of response scores for each item and then recalibrated to create an inter-level scale ranging from 0 to 100, with higher values representing greater disease severity, i.e. lower well-being.

Table 1 Descriptive characteristics of achalasia cases and matched controls

Characteristics	Controls <i>n</i> = 115	Achalasia cases <i>n</i> = 120	<i>P</i> -value
Age at interview, years (mean, SD)	55.9 (15.8)	54.4 (15.9)	0.47
Age at diagnosis, years (mean, SD)	—	44.7 (16.2)	—
Age at diagnosis, years (<i>n</i> , %)			
<30	—	25 (20.8)	—
30 ≤ 40	—	26 (21.7)	—
40 ≤ 50	—	20 (16.7)	—
50 ≤ 60	—	22 (18.3)	—
60 ≤ 70	—	21 (17.5)	—
≥70	—	6(5.0)	—
Sex (<i>n</i> , %)			
Male	60 (52.2)	63 (52.5)	0.96
Female	55 (47.8)	57 (47.5)	
Previous medical history (<i>n</i> , %)			
Ischaemic heart disease	7 (6.1)	6 (5.0)	0.72
Diabetes mellitus	3 (2.6)	3 (2.5)	0.96
Hypertension	17 (14.8)	20 (16.7)	0.69
Hypercholesterolemia	11 (9.6)	10 (8.3)	0.74
Asthma/COPD	4 (3.5)	5 (4.2)	0.78
Gastritis/peptic ulcer	8 (7.0)	12 (10.0)	0.40
Autoimmune/connective tissue disorders	1 (0.9)	1 (0.8)	0.98
Family history of achalasia (<i>n</i> , %)	0 (0.0)	4 (3.3)	0.05
Number of years in education (mean, SD)	12.8 (3.1)	12.6 (3.4)	0.57
Occupation class (<i>n</i> , %) [†]			
High	44 (38.3)	34 (28.3)	—
Medium	32 (27.8)	37 (30.8)	0.37
Low	34 (29.6)	40 (33.3)	—
Not classified	5 (4.4)	9 (7.5)	—

[†]Occupation class coded according to National Statistics Socio-Economic Classification (NS-SEC) as described in Experimental procedures. COPD, chronic obstructive pulmonary disorder; SD, standard deviation.

Assessment of other clinical and demographic factors

Information on past medical history, family history, medications, and previous intervention were recorded along with demographic data that included age, sex, number of years in education, and occupational class. This latter variable was coded according to National Statistics Socio-Economic Classification as used by the Office for National Statistics (High: Professional, employer, or manager occupations; Medium: Intermediate or junior nonmanual occupations; Low: skilled, semiskilled, or unskilled manual occupations; Not classified: students or not employed).¹²

Statistical analysis

Statistical analysis comparing continuous or categorical variables between achalasia cases and controls was conducted using an independent *t*-test or chi-squared test, respectively. Stratified analyses were performed to compare HRQL between cases and controls, and within cases, according to treatment types (Heller's myotomy, pneumatic dilatation, or both) using an independent *t*-test. Further subgroup analysis was also undertaken comparing HRQL between laparoscopic Heller's myotomy, controls, and pneumatic dilatation. In addition, adjusted mean differences in HRQL scores and associated 95% CIs were calculated using a linear regression model for non-matched analyses. To quantify the clinical significance

of statistically significant observations effect size was calculated using Cohen's *d* test statistic; an effect size of <0.30 is regarded as small, 0.3–0.80 as moderate and >0.80 as large.¹³ All statistical analysis was performed using Stata Version 13.1 (StataCorp, College Station, TX, USA).

RESULTS

Subjects

Baseline demographics and descriptive characteristics are summarized in Table 1, confirming no difference between achalasia cases and controls in terms of age, sex, comorbidities, number of years in education, and occupational class.

The median time from diagnosis to interview in all 120 achalasia patients was 7.1 years (interquartile range [IQR] 3.3–13.8), whereas the median time since last treatment was 5.7 years (IQR 2.4–11.5). A total of 43 patients were treated with Heller's myotomy (laparoscopic *n* = 21), 44 with pneumatic dilatation and 33 with both modalities. The corresponding number of patients who received Botulinum toxin injection as a bridge to definitive treatment in each of these groups was 8, 8, and 7 respectively. Patients treated exclusively with Heller's myotomy were younger than those treated exclusively with pneumatic dilatation (45.7 [SD 14.1] vs. 62.8 [SD 15.1]

years, $P < 0.001$) but there was no discrepancy in sex or comorbidity between these groups (Table S1).

The mean number of dilatations performed in the 75.3% ($n = 58$ of 77) of patients treated with pneumatic dilatation for whom these data were available was 1.9 (SD 1.9, range 1–10). Three (3.9%) patients in the pneumatic dilatation group had a perforation; only one needed operative intervention. A total of 76 patients were treated with Heller's myotomy with or without pneumatic dilatation. Detailed information on the timing of additional endoscopic intervention, if required, was available for 84.2% ($n = 64$ of 76) of cases treated with a Heller's myotomy. Analysis of this subgroup confirmed that 23.4% of all patients treated with a Heller's myotomy ($n = 15$ of 64) required additional endoscopic intervention after primary surgery for treatment failure, whereas 9.4% ($n = 6$ of 64) had pneumatic dilatation prior to surgical intervention.

Quality of life in achalasia cases versus controls

The mean disease-specific quality-of-life (ASQ) score for all patients was 41.0 (SD 19.1). PCS-12 and MCS-12 scores derived from the SF-12 questionnaire for achalasia patients compared with controls are summarized in Table 2. Overall, achalasia patients had significantly worse physical (40.9 vs. 44.2, $P = 0.01$) but not mental (51.6 vs. 53.5, $P = 0.24$) HRQL scores compared with population controls. This corresponds to an effect size of moderate clinical significance (Cohen's $d = 0.33$) for treated achalasia patients compared with controls. There was a trend toward worse adjusted physical HRQL in the individual Heller's myotomy and pneumatic dilatation groups compared with population-based controls ($P = 0.06$ and 0.08, respectively), but there was no difference in mental HRQL between these groups and controls. However, patients requiring both treatment modalities had significantly worse mental and physical HRQL of moderate clinical significance (Cohen's d 0.44 and 0.55, respectively, for the univariate observation) in both the adjusted and unadjusted analyses (Table 2).

Quality of life in achalasia cases by treatment type

Disease-specific HRQL (ASQ), PCS-12, and MCS-12 scores comparing different treatment interventions are summarized in Table 3. There were no statistically significant differences in HRQL outcomes between cases treated exclusively with Heller's myotomy or pneumatic dilatation after adjustment for age, sex, and time since treatment. Similar findings were observed comparing Heller's myotomy with patients requiring both treatment modalities across all HRQL measures. Finally, the time since last treatment was shorter for cases who underwent laparoscopic Heller's myotomy compared with pneumatic dilatation (2.2 vs. 7.3 years, $P = 0.005$). After adjusting for follow-up time, age,

Table 2 SF-12 HRQL measures comparing all achalasia patients, or achalasia patients defined by treatment intervention, with a population-based control group

HRQL measure	Controls ($n = 115$)		All cases ($n = 120$)		Heller's myotomy ($n = 43$)		Pneumatic dilatation ($n = 44$)		Both treatments ($n = 33$)	
	Score	P -value	Score	P -value	Score	P -value	Score	P -value	Score	P -value
PCS-12 (SD)	44.2 (9.8)		40.9 (10.0)	0.01	43.6 (8.4)	0.72	39.1 (11.2)	0.01	39.9 (9.7)	0.03
Adjusted difference in means (95% CI) [†]	—		N/A	N/A	-3.1 (-6.3, 0.1)	0.06	-2.9 (-6.1, 0.3)	0.08	-4.7 (-8.2, -1.3)	0.008
MCS-12 (SD)	53.5 (11.4)		51.6 (12.4)	0.24	51.8 (13.1)	0.43	55.1 (10.0)	0.40	46.7 (13.2)	0.004
Adjusted difference in means (95% CI) [†]	—		N/A	N/A	-1.0 (-5.3, 3.4)	0.67	1.0 (-2.9, 4.9)	0.62	-6.5 (-11.1, -2.0)	0.005

[†]Adjusted for age and sex. Bold represents significant results. CI, confidence interval; HRQL, health-related quality of life; MCS-12, Mental Component Summary score; N/A, not applicable; PCS-12, Physical Component Summary score; SD, standard deviation; SF-12, Short Form Health Survey.

Table 3 SF-12 and disease-specific HRQL measures comparing outcomes between patients undergoing Heller's myotomy (reference value) and pneumatic dilatation or both Heller's myotomy and pneumatic dilatation

HRQL measure	Heller's myotomy (n = 43)	Pneumatic dilatation (n = 44)		Both treatments (n = 33)	
	Score	Score	P-value	Score	P-value
PCS-1 (SD)	43.6 (8.4)	39.1 (11.2)	0.04	39.9 (9.7)	0.08
Adjusted difference in means (95% CI)†	—	0.8 (−3.7, 5.4)	0.72	−0.7 (−2.8, 1.5)	0.54
MCS-12 (SD)	51.8 (13.1)	55.1 (10.0)	0.18	46.7 (13.2)	0.10
Adjusted difference in means (95% CI)†	—	3.4 (−2.9, 9.8)	0.29	−2.4 (−5.8, 1.0)	0.16
ASQ (SD)	37.8 (21.0)	40.5 (16.5)	0.50	45.9 (19.3)	0.09
Adjusted difference in means (95% CI)†	—	6.4 (−3.2, 16.1)	0.19	3.3 (−1.3, 8.0)	0.16

†Adjusted for age, sex, and time since treatment. Bold represents significant results. ASQ, Achalasia Severity Score; CI, confidence interval; HRQL, health-related quality of life; MCS-12, Mental Component Summary score; PCS-12, Physical Component Summary score; SD, standard deviation; SF-12, Short Form Health Survey.

Table 4 SF-12 and disease-specific HRQL measures comparing outcomes between patients undergoing laparoscopic Heller's myotomy with controls and pneumatic dilatation

HRQL measure	Laparoscopic Heller's myotomy (n = 21)	Controls (n = 115)		Pneumatic dilatation (n = 44)	
	Score	Score	P-value	Score	P-value
PCS-12 (SD)	45.8 (6.4)	44.2 (9.8)	0.47	39.1 (11.2)	0.01
Adjusted difference in means (95% CI)	—	−1.2 (−5.4, 3.0)†	0.59	−0.7 (−6.2, 4.7)‡	0.79
MCS-12 (SD)	51.3 (13.2)	53.5 (11.4)	0.44	55.1 (10.0)	0.20
Adjusted difference in means (95% CI)	—	−1.0 (−6.7, 4.6)†	0.73	2.4 (−5.0, 9.9)‡	0.52
ASQ (SD)	33.5 (19.1)	—	—	40.5 (16.5)	0.13
Adjusted difference in means (95% CI)	—	—	—	9.5 (−1.8, 20.7)‡	0.10

†Adjusted for age and sex. Bold represents significant results. ‡Adjusted for age, sex, and time since treatment. ASQ, Achalasia Severity Score; CI, confidence interval; HRQL, health-related quality of life; MCS-12, Mental Component Summary score; PCS-12, Physical Component Summary score; SD, standard deviation; SF-12, Short Form Health Survey.

and sex, there were no significant differences in HRQL outcomes comparing the laparoscopic Heller's myotomy subgroup with population-based controls or the pneumatic dilatation subgroup (Table 4).

DISCUSSION

Results from our case-control study indicate that achalasia patients have poorer physical HRQL than population-based controls. Conversely, mental HRQL was preserved compared with population-based controls. Importantly, no difference in general or disease-specific HRQL was observed between patients treated with Heller's myotomy or pneumatic dilatation when outcomes were adjusted for age, sex, and time from treatment.

This is the first case-control study utilizing a population-based approach to compare long-term general HRQL between achalasia patients and controls. Frankhuisen *et al.* previously reported a case-control study of 131 achalasia patients treated in three affiliated units, but this was not population based.⁶ Median follow up was 4.6 years, and a decrease in HRQL was observed in achalasia patients, which were equivalent to noninstitutionalized patients who suffered a stroke or coronary heart disease.⁶ This current study, with 5.7 years of follow up further demonstrates

the ongoing burden of achalasia, despite intervention, with significantly reduced physical HRQL compared with population-based controls. Interestingly however, mental HRQL was preserved compared with the control group, suggesting that the majority of patients had learned to cope with their illness despite the ongoing physical implications.

In the present study, 23% of patients required additional endoscopic intervention after primary Heller's myotomy. This reintervention rate is consistent with other published literature. Long-term follow-up series clearly demonstrate that 18–21% of patients require reintervention after Heller's myotomy in the form of pneumatic dilatation, re-do myotomy, Botulinum toxin injection or even esophagectomy.^{14–17} In this study, patients requiring dual modality treatment had significantly lower mental and physical HRQL scores compared with controls, whereas those requiring single modality treatment only had impaired physical HRQL. This finding supports the concept that successful outcomes, with respect to the control population baseline, are difficult to achieve in the problematic group of patients who remain symptomatic after initial intervention. On balance, however, the actual clinical significance of this finding for achalasia patients is limited as there was no difference in HRQL between patients treated with single versus dual modality treatment.

Long-term follow-up of the European Achalasia Trial continues to show no difference in therapeutic success rates (defined as an Eckardt score of ≤ 3) at 5 years (81% for laparoscopic Heller's myotomy versus 80% for pneumatic dilatation, $P = 0.58$).¹⁸ This current study, assessing the long-term impact of these treatments with respect to HRQL, has also not been able to clearly demonstrate a benefit in the Heller's myotomy group compared with the pneumatic dilatation group, once age and follow-up differences were accounted for. Interestingly, there was no difference in physical HRQL between the laparoscopic Heller's myotomy subgroup and controls. However, it is inappropriate to speculate that laparoscopic Heller's myotomy may be a superior treatment modality on the basis of this observation as it is not adequately powered and no differences in HRQL were observed between this subgroup and the pneumatic dilatation subgroup after adjusting for the bias associated with shorter follow up.

Our study has a number of strengths compared with prior reports in this field. To date, six studies consider HRQL as an outcome measure when different achalasia treatment interventions are compared with each other^{3,7,19–21} or treated achalasia patients are compared with a control group.⁶ The limitations of these studies include short follow up (≤ 2 years),^{3,20,21} relatively small sample size^{19–21} or failure to include a disease-specific HRQL measure.^{19,20} Although the overall numbers included in this study are relatively small for a population-based design and there is potential selection bias in our recruitment, achalasia remains an uncommon condition, our numbers are comparable with the largest reported studies, and long-term outcomes have been considered. We also used a disease-specific HRQL questionnaire (ASQ), which samples important factors such as chest pain, heartburn, dysphagia, and food tolerance. Harnish *et al.* have demonstrated this to correspond well with symptom scores from the validated Eckardt score within an RCT of achalasia treatments.²²

The observational study design reflects real-world treatment of patients, although it could be argued that having no standardized protocol for treatment interventions is a limitation and treatment selection bias cannot be excluded. Due to the retrospective nature of this study, no information was available on the number of complications associated with surgical intervention or whether Heller's myotomy patients underwent a simultaneous antireflux procedure. Similarly, we have not been able to assess the impact of de-novo reflux symptoms and their impact on HRQL between the treatment groups. However, the ASQ does consider reflux symptoms in its global assessment, and there were no differences between the treatment groups. The timeframe of our study also reflects the inclusion of cases within the 'learning curve' for laparoscopic Heller's myotomy. However, although the inclusion of

open Heller's myotomy cases may reduce the external validity of any comparisons, the HRQL benefits associated with a laparoscopic technique are likely to be most pertinent in the early follow-up period. Objective measures, such as postprocedural esophageal emptying time, were also not routinely available; therefore, no functional comparisons can be made between the treatment groups. Finally, high-resolution manometry was not routinely available for patients in this study, and it is now recognized that patients with type III (spastic) achalasia, males, and those younger than 45 years are less likely to respond to pneumatic dilatation.^{17,23,24} Although these latter patients were not disproportionately represented in the dilatation group of this study, future prospective studies defining treatment by these manometric and demographic variables would be welcomed.

In summary, this study confirms that despite treatment, achalasia patients have significantly worse long-term physical HRQL compared with population controls. Overall however, no HRQL differences were observed between the treatment modalities, and based on these results, one treatment modality cannot presently be recommended in favor of the other.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Table S1. Descriptive characteristics of achalasia cases by treatment group.