Title

Anterior Dor or Posterior Toupet with Heller Myotomy for Achalasia Cardia. A Systematic Review and Meta-analysis

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Running head

Dor or Toupet with Heller Myotomy

Abstract

Background and Aims:

Partial fundoplication is commonly performed in conjunction with Heller Myotomy (HL). It is however controversial whether anterior Dor or posterior Toupet partial fundoplication is the anti-reflux procedure of choice. The aim was to perform a systematic review and meta-analysis of studies comparing these two procedures.

Material and Methods:

A search of PubMed, Cochrane database, Medline, Embase, Science Citation Index, Google scholar and current contents for English language articles comparing Dor and Toupet fundoplication following HM between 1991 and 2018 was performed. The outcome variables analyzed included operating time, length of hospital stay (LOHS), overall complication rate, quality of life (QOL), postoperative reflux, residual postoperative dysphagia, treatment failure and reoperations. The meta-analysis was prepared in accordance with the PRISMA-P statement.

Results:

Seven studies totaling 486 patients (Dor = 245, Toupet = 241) were analyzed. LOHS was significantly shorter for Toupet repair compared to Dor procedure (WMD 0.73, 95% CI: 0.47 to 0.99; P <0.0001). Furthermore, patients after Toupet experienced significantly better QOL than those after Dor (WMD 1.68, 95% CI: 0.68 to 2.73, P < 0.001). All other variables showed comparable effects for these two procedures.

Conclusion:

Our systematic review and meta-analysis revealed that Toupet fundoplication is superior to Dor in terms of LOHS and QOL following HM. For other variables such as postoperative reflux, postoperative dysphagia, complication rates and treatment failure, both Dor and Toupet fundoplication produced effective and equivalent results.

Introduction:

Achalasia is a primary esophageal motor disorder of unknown etiology characterized manometrically by insufficient relaxation of the lower esophageal sphincter (LES) and loss of esophageal peristalsis. This abnormality in esophageal motility is due to loss of ganglion cells in its musculature resulting in dysphagia for both solids and liquids and loss of weight as a consequence. The surgical treatment i.e. Heller cardiomyotomy (HM), to re-establish the patient's ability to eat and drink, remains the gold standard [1,2]. Heller, on its own leads to gastroesophageal reflux (GER), which ranges from 31-100% in the literature. Therefore, it is always performed in conjunction with an antireflux procedure. However, the "ideal antireflux procedure" after HM is still controversial [2,1]. It has been well established that total fundoplication such as Nissen is contraindicated as it can cause total dysphagia and therefore a partial wrap either posterior 270^{o} Toupet or anterior 180^{o} Dor is generally recommended [3]. There are proponents and opponents of both types of partial fundoplication. Some authors have suggested that a potential disadvantage of the posterior approach is an angulation of the gastroesophageal junction, which may cause bolus obstruction and disruption of the periesophageal ligament and its attachments leading to reflux [4]. However, others are of the opinion that Toupet may keep the [5-7]edges of the myotomy separated therefore preventing stricturing of the myotomy scar and also provide better antireflux control [8,9]. Advocates of the Dor argue that this procedure preserves the periesophageal ligament and attachments, thereby decreasing the risk of reflux, it is less complex to perform and covers the exposed mucosa, which is an advantage in case of either inadvertent micro or macro perforation [10,11].

Over the years there are have been a number of studies comparing Dor and Toupet as an antireflux procedure following HM. Our aim was to conduct a meta-analysis and systematic review of all these comparative studies to determine the clinical outcomes, safety, effectiveness and side effects of these two procedures [12,13,4,14,6,15,16]

Material and Methods:

Literature Search Strategy, Study Selection, and Data Collection

All comparative studies (RCTs and non RCTs) were identified by conducting a comprehensive search of electronic databases, PubMed, Medline, Embase, Science Citation Index, Current Contents, and the Cochrane Central Register of Controlled Trials published between January 1991 and May 2018 using medical subject headings (MESH); ‘’Dor fundoplication’’, ‘’Toupet fundoplication’’, ‘’Heller myotomy’’, ‘’achalasia cardia’’, ‘‘comparative study,’’ ‘‘prospective studies,’’ ‘‘randomized/randomised controlled trial,’’ ‘‘random allocation,’’ ‘’clinical trial,’’ and ‘‘Human’’. Language restriction was applied to English. We further searched the bibliographies of all the included primary studies and existing reviews by hand for additional citations. Data extraction, critical appraisal, and quality assessment of the identified studies was carried out by 2 authors (MSS and MAM). The authors were not blinded to the source of the document or authorship(s) for the purpose of data extraction. Standardized data extraction forms were used by authors to independently and blindly summarize all the data available in the studies [17]. The data that were obtained was entered directly into Excel tables. Double data entry method was used to avoid errors in data extraction. The data were compared and discrepancies were addressed with discussion until consensus was achieved. The analysis was prepared in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement [18]. Random effects model using the inverse variance method was used for analysis of all the outcome variables.

Eligibility Criteria:

Two reviewers (MSS and MAM) individually considered the abstracts of the identified articles for eligibility. Appropriateness was determined by these independent reviewers and by discussion in case of inconsistency. The comparative trials must have reported on at least 1 clinically relevant outcome pertaining to the intraoperative and postoperative period. Outcomes assessed were those considered to exert influence over practical aspects of surgical practice and patient management. All studies reporting on outcomes of this nature were considered and final analyses were run on outcome variables where numbers were

sufficient to allow statistical analysis.

Inclusion Criteria:

(1) Type of study: All comparative (RCTs and Non RCTs) studies published in full peer-reviewed journals between January 1991 and May 2018 were included for analysis.

(2) Language: Language restriction was applied to English.

(3) Type of intervention: Two different partial fundoplications following elective laparoscopic HM, namely Dor and Toupet were being assessed for the differences in short and long-term surgical outcomes.

(4) Type of participants: Adult (>18 years) patients were the target population for this meta-analysis.

Exclusion Criteria:

(1) Duplicated studies, unpublished studies, and abstracts presented at national and international meetings presenting the preliminary data were excluded from our analysis.

Types of Outcome Measures Analyzed:

The outcome variables analyzed included (1) operating time; (2) length of hospital stay (LOHS); (3) overall complication rate; (4) reoperations; (5) postoperative GER; (6) residual postoperative dysphagia; (7) treatment failure and (8) quality of life (QOL). Treatment failure was defined as any endoscopic or surgical intervention needed to treat residual symptomatic dysphagia.

Methodological Quality:

The methodological quality of the identified RCTs was assessed using Jadad Scoring system [19]. Each study was allocated a score from 0 to 5, 0 being the lowest quality and 5 being the highest quality based on reporting of randomization, blinding, and withdrawals reported during the study period. The quality of non-randomized studies were assessed using Newcastle Ottawa Scale where each study is rated from poor to good quality [20].

Statistical Analysis:

Meta-analysis was conducted using odds ratio (OR) for binary outcome variable and weighted mean difference (WMD) for continuous outcome variable. To pool continuous data, mean and standard deviation of each study is required. However, some of the published clinical trials did not report the mean and standard deviation, but rather reported the size of the trial, the median, and interquartile range. Using these available statistics, estimates of the mean and standard deviation were obtained using formulas proposed by Hozo et al [21]. For the individual studies the between-study heterogeneity was assessed using Cochran's Q statistic that follows the χ^2 – distribution and the I^2 statistic, with $I^2 = 25\%$ indicating low, $I^2 > 50\%$ indicating moderate and $I^2 > 75\%$ indicating high level of heterogeneity introduced by Higgins and Thompson [22,23]. Random effects model using the inverse variance weighting method was used for all studies to obtain the pooled estimate of OR and WMD. The standardized effect size Z score is used to assess the significance of the difference between the Dor and Toupet groups based on the P value. Statistical significance was set at $\alpha = 0.05$ to represent the point estimate and 95% confidence interval for the population effect sizes of individual studies as well as the pooled estimate and 95% confidence interval of the common effect size. Funnel plots were used to explore the publication bias for all variables. All computations and graphs for the meta-analyses were produced using the statistical package "metafor" in R [24].

Results:

Included Studies:

The initial literature search yielded 350 articles. After removing 265 non-relevant studies, 85 articles were evaluated through full-text review. This yielded 8 articles with 1 of them being a duplicate [9]. Finally, 3 RCTs [13,4,12] and 4 non RCTs [14-16,6] were selected for this meta-analysis (Fig 1). There was almost perfect agreement (κ=0.99) between the two authors (MSS and MAM) regarding inclusion of these studies.

Methodological Quality:

The RCTs selected demonstrated moderate methodological quality based on Jadad score [19] with an average score of 3 (out of five), with a range of 2 to 4 (Table 1). The non RCTs were all of fair quality based on Newcastle Ottawa score [20].

Heterogeneity:

Significant heterogeneity with I^2 index of 50% or more was present for length of hospital stay, postoperative GER and residual dysphagia. As statistically significant heterogeneity was evident for more than half of outcome variables, random effects model was used to combine the data.

Publication Bias:

Funnel plots belonging to LOHS and residual postoperative dysphagia demonstrates asymmetry indicating publication bias. Funnel plots belonging to all other variables failed to demonstrate any publication bias. However, the number of studies included in some of these funnel plots may be too few to accurately detect such a bias.

Clinical Outcomes:

Seven comparative studies [14,13,12,6,15,16,4] totaling 486 patients (Dor = 245; Toupet = 241) were analyzed. The details of the study are summarized (Table 1).

Two variables favored Toupet fundoplication compared to Dor procedure. A statistically significant shorter LOHS by 18 hours was noted for Toupet compared to Dor based on 4 out of 7 studies [16,14,13,12] (WMD 0.73, 95% CI 0.47 to 0.99, P <0.0001) (Fig 2) and QOL was found to be significantly better for Toupet compared to Dor based on 2 studies [13,12] (WMD 1.68, 95% CI: 0.68 to 2.73, P < 0.001) (Fig 3). Comparable effects were noted for other variables when comparing Dor and Toupet fundoplication. These included, operative time, with mean difference of 5 minutes, based on 5 studies [13,4,12,15,14] (WMD -5.11, 95% CI 19.45 to 9.24, P =0.49) (Fig 4); complication rates, 2.3% for Dor vs 3.5% for Toupet, based on 6 studies [14,16,15,13,4,12] (OR 0.62, 95% CI 0.18 to 2.14, P = 0.45) (Fig 5); reoperation

based on 7 studies [13,4,12,16,14,15,6] (OR 1.93, 95% CI 0.54 to 6.85, P=0.31) (Fig 6); postoperative GER, 20.8% for Dor vs 28.2% for Toupet based on 7 studies [4,14,6,12,15,13,16] (OR 0.75, 95% CI 0.28 to 2.03; P = 0.57) (Fig 7); residual postoperative dysphagia was based on 7 studies, in which dysphagia score was provided by 3 studies [13,12,16] (WMD 0.49, 95% CI -0.54 to 1.52, P =0.35) (Fig 8) and 4 other studies provided with the number of patients suffering from significant dysphagia [14,15,6,4] (OR 0.87, 95% CI 0.34 to 2.20; P =0.77) (Fig 9); treatment failure, 8.5% for Dor vs 9.1% for Toupet based on 7 studies [6,16,15,14,12,13,4] (OR 0.99, 95% CI 0.43 to 2.27, P=0.98) (Fig 10).

Discussion:

HM remains the gold standard in young and surgically suitable patients [1,2] due to its low morbidity, long term symptom relief and good QOL [4,12,25]. It is still contentious whether Toupet or Dor fundoplication [2,1] following HM is the better one. We therefore undertook this systematic review and meta-analysis of all the published studies comparing these two partial fundoplications post HM to determine their clinical outcomes, safety, effectiveness and complication profile.

The main aim of HM is to relieve dysphagia while minimizing GER in order to prevent treatment failure. All the studied have defined or considered treatment failure as persistent or recurrent dysphagia. Studies considered in this meta-analysis have used various methods to assess dysphagia which includes achalasia score [26], subjective dysphagia score [27,28] and timed barium swallow. The first comparative study by Richardson et al [6] reported a significant difference in postoperative dysphagia between the groups; 20% Dor vs 66% Toupet, however, it was a questionnaire based study and included even minor dysphagia. If one only considers significant dysphagia post fundoplication as a parameter of success, the only study to report any significant difference between the two groups is the one by Wright et al [16] (17% for Dor vs 5% in Toupet).

Approximately 1 in 10, 8.5% in Dor and 9.1% in the Toupet group experienced treatment failure during the follow up period. The small differences in dysphagia rates may not be due to

fundoplication itself but rather due to difference in the myotomy length, which varied from 4 - 6 cms on the esophageal side and 1.5 - 4 cms on gastric side. This argument is further supported by the fact that almost all significant dysphagia resolved with either endoscopic dilatation (70% of the study population) or surgical extention of myotomy (30%)[9]. The varied results in individual studies and the overall result of the meta-analysis disputes the claim by the proponents of Dor fundoplication that a fuller wrap such as Toupet will lead to increased incidence of dysphagia.

Majority of the studies have utilized 24 hour pH study for assessing GER but some have made use of heartburn grading system [29] or health related QOL assessment scale [28], but all the studies have provided data on the number of patients affected by severe GER. Patients undergoing Toupet, with more fuller wrap, interestingly showed a trend towards experiencing higher rates of GER in the first ever comparative study by Richardson et al [6] (20% Dor vs 33% Toupet) but since then the studies have shown a different picture altogether.

Rawling et al in the first RCT comparing Dor vs Toupet after HM [4] reported 41.7% of Dor patients to be affected by GER compared to 21% in Toupet, while Kiudelis et al [14] reported a similar result (35% Dor vs 11% Toupet). Torres-Villalobos et al [12] the latest RCT to be published showed initially at 6 months a significant difference between the groups (7% Dor vs 34% Toupet) but at 24 months there was no statistical difference (10.5% Dor vs 31.5% Toupet). So the question remains, what is the clinical relevance of the differences in GER rates for these two procedures in terms of further treatment? The answer is none because no difference in intake of proton pump inhibitors or H_2 blockers or antacids has been reported between the two groups in any of these studies.

The difference in LOHS favores Toupet compared to Dor fundoplication and is significantly shorter by almost 1 day. The reason for this discrepancy is difficult to establish based on published data. While all of the studies have reported on surgical complications, very few have detailed non-surgical complications [30,16]. Given the fact that surgical complications showed a trend supporting Dor, it could be possible that non-surgical complications may have

played a role in increased LOHS in the Dor group. An early discharge also has a positive effect on pressure on hospital beds and is a marker of efficiency and has multitude of effects such as saving medical direct, non-medical direct, and indirect costs compared to conventional inpatient care, freeing beds for other elective operative procedures, early integration of patients back into their community and reestablishing workforce, etc [31]. In countries, where patients depend of private insurers for covering their hospital costs, it saves patient individual premiums and allows insurers to provide the public with a better range of options at a cheaper rate.

Quality of life (QOL) index is an important evaluator of success of an operation. However, several different QOL instruments are used in various studies, limiting the interpretation and comparison of results. They include the original Gastroesophageal reflux disease Health Related Quality of Life (GERD HRQL) scoring system [32] and the its modified version [33]. Some simply state that the QOL was better following HM. The limitation of these scoring systems is that, they mainly looks at quality of life related to GER when in fact ongoing or recurrent dysphagia is also another significant QOL indicator following HM and this element needs to be assessed as well. Disease-specific QOL instruments may aid differentiation of patients experiencing treatment failure from those being cured and from the healthy controls in future studies.

Conclusions:

Our systematic review and meta-analysis revealed that except for significantly shorter LOHS and better QOL associated with Toupet fundoplication compared to its Dor counterpart, both types of particle fundoplication produces effective and equivalent results in terms of postoperative reflux, dysphagia, complication rate and treatment failure following HM. Armed with this knowledge, one can confidently suggest that the choice of antireflux procedure following HM for achalasia therefore needs to be left at the surgeon's discretion. One hopes that in the future, a multicenter RCT addressing these issues with a reasonable powered study with predetermined pre- and postoperative measurable variables along with QOL measures will provide an insight into pros and cons of these two partial fundoplications.

Furthermore, a long-term longitudinal assessment over a 5 and 10 year will be needed to differentiate the success and failure rate of these procedures.

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