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Is Heller Myotomy Better than Balloon Dilation? A Meta-Analysis

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ABSTRACT

Background & Aim: Endoscopic balloon dilation (EBD) and laparoscopic Heller myotomy (LHM) are the most commonly performed treatment options for achalasia. Decision between these treatment options is difficult. The aim of this meta-analysis was to evaluate the efficacy of EBD compared to LHM.
Methods: The electronic databases PubMed, Embase and Cochrane Controlled Trials Registry were systematically searched for the period between January 1, 1976 and December 31, 2015. Meta-analysis was performed using the PICOS (problem, intervention, comparison, outcome, study design) format. Efficacy and safety of EBD were compared to LHM. Forest plot analyses were used to illustrate the success rate, perforation rate and post-procedural gastroesophageal reflux.
Results: Using the search strategy, eight studies met the selection criteria and were included in the meta-analysis. The total number of patients included was 749 (360 in the EBD group and 389 in the LHM group). The success rate was lower in the EBD group than in the LHM group (OR=0.486; CI: 0.304-0.779; p=0.003). The rate of perforation did not differ significantly between the EBD and LHM group (RR= 0.635, CI: 0.340-1.186, p=0.154). The incidence of post-procedural symptomatic gastroesophageal reflux did not differ between the two treatment groups (RR=0.663, CI: 0.328-1.343, p=0.254).
Conclusion: Our data suggest that the efficacy of LHM is superior to that of EBD, while there is no difference in safety between the two treatment groups.

Key words: esophageal achalasia – endoscopic balloon dilation – laparoscopic Heller myotomy – success rate – meta-analysis

Abbreviations: EBD: endoscopic balloon dilation; GERD: gastro-esophageal reflux disease; LES: lower esophageal sphincter; LHM: laparoscopic Heller myotomy; OR: odds ratio; PICOS: Problem, Intervention, Comparison, Outcome, Study design; POEM: Per Oral Endoscopic Myotomy; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RR: risk ratio.

INTRODUCTION

Achalasia is an esophageal motility disorder characterised by aperistalsis of the esophageal body and impaired function of the lower esophageal sphincter (LES) [1, 2]. It is a rare condition, with an incidence rate of 1.63/100 000 and a prevalence of 10.82/100 000 in the North American population [3]. The first case of achalasia was reported in 1674 by Thomas Willis, who treated the patients by using a whalebone [4, 5]. The pathophysiology of the motor abnormalities is not well understood. Histologic studies have demonstrated chronic inflammatory infiltration of the myenteric plexus (Auerbach's). An initial injury results in myenteric plexus inflammation, which can lead to an autoimmune response [6]. As a result, esophageal aperistalsis develops with food retention in the lower esophagus, which causes the main symptoms. The typical symptoms of the patients with achalasia include dysphagia, regurgitation, weight loss, retrosternal chest pain and nocturnal coughing [7]. Therefore, treatment aims for achalasia include decreasing the pressure of the LES, ameliorating the esophageal emptying and preventing megaesophagus [5]. Pneumatic dilation and surgical myotomy are the most widely used treatment options for patients with achalasia.

Heller myotomy was first described in 1913 by Ernest Heller and has been used with only a few technical improvements. Laparoscopic management was added to the treatment options in 1991 [8]. Laparoscopic Heller myotomy (LHM) improves the symptoms of patients. The reported clinical success rate is 89% (range 76-100%) [9]. The most common post-myotomy complication is gastro-esophageal reflux disease (GERD).

Endoscopic balloon dilation (EBD) of the LES is the most effective non-surgical endoscopic treatment for achalasia [10]. Pneumatic dilation was the first attempt in the treatment of esophageal achalasia. The procedure tears the LES circular muscle fibers with an air-filled polyethylene balloon. Severe GERD is rare after pneumatic dilation. The most severe complication is perforation, which occurs in about 1-3% of the cases [5, 11], 50% of cases requiring surgery [12]. Over a 5-10 year period the balloon dilation is the most cost-effective treatment for achalasia [13]. Decision between these treatment options is difficult to make due to the lack of large randomized controlled trials. Our meta-analysis was conducted to find out whether there is a clinically significant difference in efficacy and safety between EBD and LHM when applied for the treatment of esophageal achalasia in adult patients. The latest meta-analysis on this topic (Schoenberg et al., 2013) [14] concluded that both the short and long-term efficacy of LHM is better. We used the PICOS (problem, intervention, comparison, outcome, study design) format for our study.

METHODS

Data sources

Electronic databases, including PubMed, Cochrane Controlled Trials Registry and EMBASE were searched for studies published between January 1, 1976 and December 31, 2015. To answer our clinical questions the PICOS approach was used, deciphered as P: achalasia, I: laparoscopic Heller myotomy, C: pneumatic dilation, O: remission, success, S: randomized and non-randomized, prospective and retrospective studies. The search strategy was achalasia AND Heller myotomy AND pneumatic dilation. We narrowed down the search focus to English language studies. The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Study selection and data extraction

In the meta-analysis we included all randomized, non-randomized, prospective and retrospective, original human, minimum 1-year-long-follow up studies on adult patients with primary achalasia reporting comparisons between EBD and LHM. An independent eligibility assessment was performed by each author, and disagreements were resolved by consensus. Duplicates, case reports, technical reports, reviews, editorials, abstracts were excluded. The following data were collected: type of study design, year of publication, number of patients, median/average patient age, gender distribution, post-procedural success rate, intra- and post-procedural perforation rate and post-procedural symptomatic gastroesophageal reflux. Treatment efficacy was defined by the success rate in percentage at 1 year after therapy. The investigators extracted the data from each publication independently and two investigators then validated these data. Disagreements were discussed and resolved by consensus.

Statistical analysis

Dichotomous outcome data from individual studies were extracted, from which risk ratios (RRs) or odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by meta-analysis, using the Mantel–Haenszel method [15]. The Comprehensive MetaAnalysis (Version3) statistical software was used for the calculations. Heterogeneity was tested by using the Cochrane's Q and the I^2 statistics. In the Q-statistics p-value less than 0.05 was regarded as significant heterogeneity. The I^2 shows the proportion of total variation contributed by between-study variability and an I^2 value higher than 50 suggests a considerable heterogeneity [16]. Homogeneous results utilized the fixed effects model (Peto method) for statistical analysis. The random effects model (DerSimonian–Laird method) was employed for heterogeneous results and the data were presented using a Forest plot [17].

RESULTS

Characteristics of the studies included

Using our search strategy, 176 publications were identified in the Embase, 142 were found in the PubMed database and 1 in the Cochrane Library. Finally, 8 studies met the selection criteria and were included in the quantitative synthesis of this meta-analysis (Fig. 1). Six randomized studies and two non-randomized studies were identified during our search.

In our meta-analysis, we compared the data of 749 achalasia patients from 8 trials who were treated with either EBD or LHM. The analysis included 360 patients in the balloon dilation group and 389 in the Heller myotomy group. One study (Borges et al.) [18] reported significant differences in the patients' ages between the two treatment groups, but in the other 7 studies no significant difference was found in this regard. The data published in 8 studies assessing the distribution of genders showed no difference between the two groups. Six of the 8 studies were single center trials while the remaining 2 were multi-centric. Table I shows the original data of the 8 studies included in our analysis.

Quality of the included studies

A Cochrane risk of bias assessment was applied to all studies. Risk of bias assessment included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data addressed and selective reporting. All trials were open, not blinded for participants and personnel. One study was blinded for outcome assessment while the remaining seven had high risk of performance and detection bias. Six studies were randomized and four reported allocation concealment. All of the included studies avoided selection bias. Six studies addressed incomplete outcome data and had low risk of attrition bias and the remaining two were unclear in this aspect (Supplementary Table I).

Funnel plot asymmetry was used to detect publication bias. Asymmetry was not confirmed regarding success rate, while it was detected in cases of reflux and perforation (Suppl. Figs. 1-3).

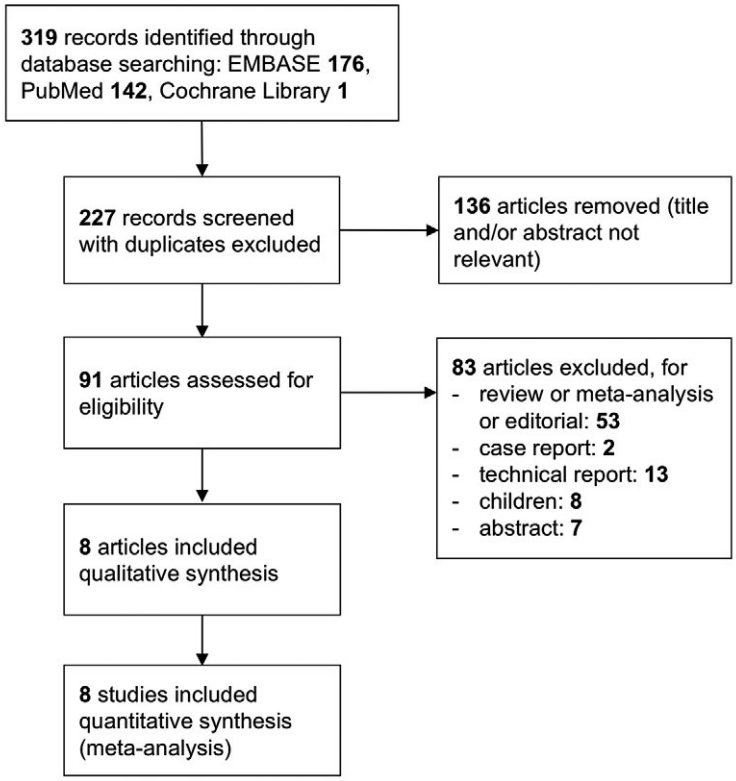

Fig. 1. Organogram of article search in the PubMed, EMBASE and Cochrane databases.

Meta-analysis of short-term efficacy and safety

Success rate

Perioperative symptom assessment was similar in two studies, Moonen et al. [19] and Boeckxstaens et al. [20]: the primary outcome of these studies was therapeutic success (a reduction in the Eckardt score to ≤3). Two other studies [21, 22] also used Eckardt score to evaluate the therapeutic success. Clinical remission was reported when the patient was totally asymptomatic or the Eckardt score decreased by at least 2 points and did not exceed 3 points in the study of Wang et al. [21]. Tabola et al. [22] applied symptom improvement rate by reduction of the Eckardt score and evaluated the frequency of reintervention. In the other 4 studies, symptom evaluation was based on various dysphagia scores. In the Hamdy et al. study

Table I. Original data collected from the eight articles.

	Type of therapy	Number of patients	Success rate 12 month (%)	Perforation rate (%)	Reflux rate (%)
Wang et al. 2015 [21]	Balloon dilation	21	81.0	0.0	19.0
	Heller myotomy	21	91.5	0.0	52.4
Moonen at al. 2015 [19]	Balloon dilation	96	90.0	5.0	12.0
	Heller myotomy	105	93.9	12.0	34.0
Tabola et al. 2013 [22]	Balloon dilation	21	81.0	4.8	No information
	Heller myotomy	38	92.1	5.2	
Borges et al. 2014 [18]	Balloon dilation	48	63.6	4.0	27.7
	Heller myotomy	44	69.0	0.0	4.7
Persson et al. 2015 [24]	Balloon dilation	28	79.0	7.14	No information
	Heller myotomy	25	96.0	0.0	
Hamdy et al. 2015 [23]	Balloon dilation	25	56.0	8.0	16.0
	Heller myotomy	25	96.0	4.0	28.0
Boeckxstaens et al. 2011 [20]	Balloon dilation	95	90.0	4.0	15.0
	Heller myotomy	106	93.0	12.0	23.0
Kostic et al. 2007 [25]	Balloon dilation	26	76.9 % (not failure)	8.0	No information
	Heller myotomy	25	96	0.0	

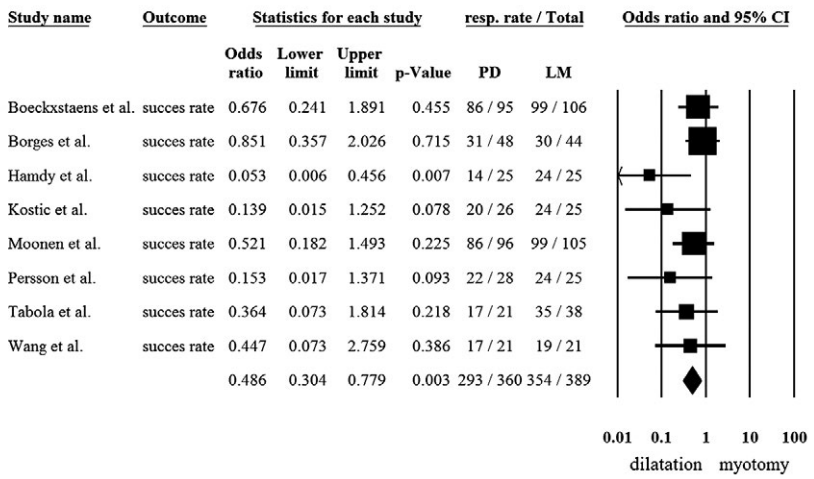

Fig. 2. Forest plot of success rate. The odds ratio (OR) and 95 % confidence interval (CI) was calculated and shows the success of dilation versus myotomy. PD: pneumatic dilation; LM: laparaoscopic myotomy.

[23], the primary outcome was the successful symptomatic improvement, which used Demeester's grading of dysphagia. In two other studies [24, 25], the primary end point was the cumulative number of treatment failures (incomplete symptom control, symptom relapse, serious complication, required re-intervention) and the dysphagia was assessed with the Watson dysphagia score. The major outcome of the study of Borges et al. [18] was the clinical improvement of the Vantrappen and Hellemans dysphagia score. Good responders mean excellent results (asymptomatic) or good results (dysphagia less than once a week, no weight loss or food regurgitation). All studies reported their success rate at 1-year of the follow up: the success rate was significantly lower in the EBD group than in the LHM group (OR: 0.486; CI: 0.304-0.779; p=0.003). Significant heterogeneity was observed among the included studies (Q=8.538 p=0.28; I^2=97.993), therefore, the random-effect model was used (Fig. 2).

Post-procedural symptomatic gastroesophageal reflux

In the Heller myotomy arm, all patients underwent an antireflux procedure, 4 studies reported anterior (Dor), 2 studies posterior (Toupet) fundoplication and 2 studies reported partial fundoplication without accurate description. Five studies reported the incidence of post-procedural symptomatic GERD, which was investigated by reflux symptom or DeMeester score at pH testing. The outcome showed no significant difference between EBD and LHM (RR=0.663, CI: 0.328-1.343, p=0.254) (Fig. 3). Since significant heterogeneity existed among the included studies, the random-effect model was used (Q=13.502, p=9.06, I^2=70.376).

Perforation

Perforation was the most severe complication of EBD or LHM. Seven studies reported acceptable data regarding the perioperative perforation rate. Our meta-analysis of perforation did not show any significant difference between perforation rates in the EBD and LHM groups (RR= 0.635, CI: 0.340-1.186, p=0.154) (Fig. 4). In this case, no significant heterogeneity could be detected between the studies, thus we used the fixed-effect model (Q=7.973, p=0.240, I^2=24.754).

DISCUSSION

Achalasia is a motility disorder of the esophagus characterized by degenerative changes of the myenteric plexus, which lead to a selective loss of inhibitory nerve endings [4]. The

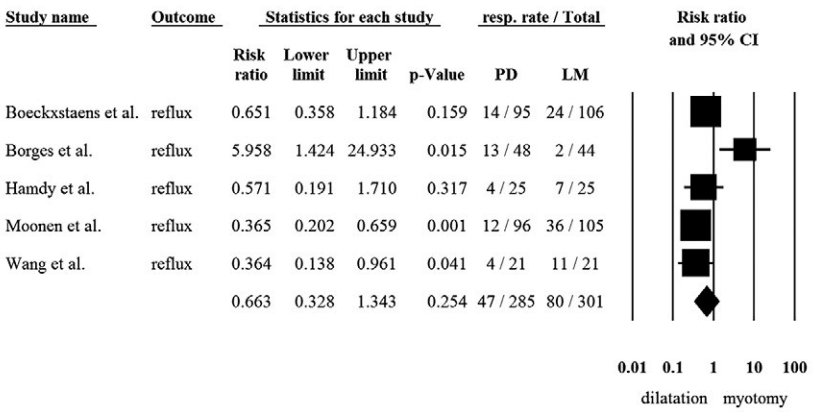

Fig. 3. Forest plot of risk ratio (RR) and CI for post-procedural reflux evaluation. PD: pneumatic dilation; LM: laparaoscopic myotomy.

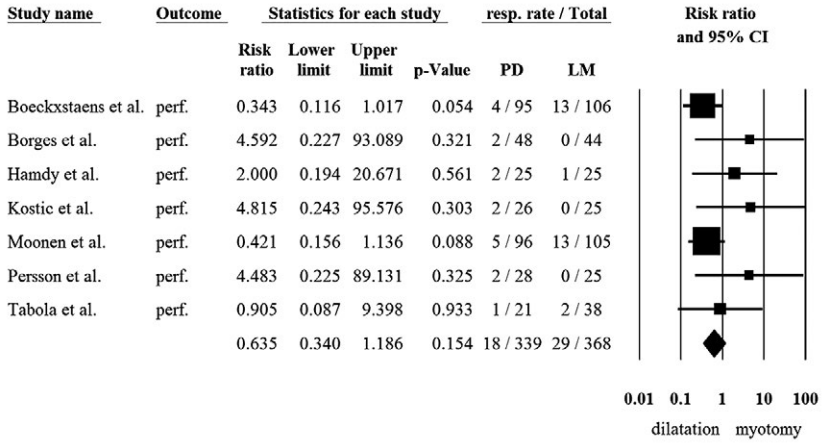

Fig. 4. Forest plot of risk ratio (RR) and CI for the perforation rate. PD: pneumatic dilation; LM: laparaoscopic myotomy; perf.: perforation.

goals of the treatment for achalasia are to decrease the pressure of the LES, ameliorate the esophageal emptying and prevent the occurence of megaesophagus [5]. Various therapeutic facilities are available. The most preferred therapeutic approaches are EBD and LHM, but a very promising new technique is the peroral endoscopic myotomy (POEM), a less invasive endoscopic treatment for esophageal achalasia [26]. While POEM seems to be a very promising technique, the availability of this endoscopic technique is still limited. On the other hand, EBD and LHM are both effectively and regularly used to treat achalasia. Decision between these treatment options is difficult.

Pneumatic dilation is a simple and safe procedure: the results of studies on the topic show that EBD is effective, with response rates ranging from 40% to 78% within 5 years and from 12% to 58% within 15 years [27, 28]. The major predictive factors for the failure of EBD treatment include young age (age < 40 years) [1, 29], male gender, dilation by using a 30-mm balloon, presence of pulmonary symptoms, failure of treatment after one or two dilation sessions [27, 30]. However, EBD is the most cost-effective treatment for achalasia for a period of 5 to 10 years after the procedures [13, 31]. The most serious complication is perforation, which occurred in about 1-3% of the cases [5, 11], and 50% of those patients required surgical intervention [12]. Other complications following pneumatic dilation are usually minor (mucosal tear, fever, bleeding, chest pain) [32].

When using LHM, an improvement of symptoms was recorded in 89% of patients (range 77–100%) after a systematic review of 39 uncontrolled studies on laparoscopic myotomy [9]. However, the success rates after 5 years decreased to 65-85%, possibly as a result of disease progression [33]. Gastro-esophageal reflux disease is a frequent complication following myotomy. The combination of myotomy with a partial fundoplication decreases, but does not completely eliminate the risk of GERD. Recently published guidelines from both gastroenterology and surgical societies recommend an antireflux procedure along with myotomy [10, 34]. A prospective randomized trial [35] evidenced a pathological GERD rate of 47.6 % in the group with Heller myotomy without antireflux procedure compared to a 9.1% in the group with Heller myotomy followed by anterior fundoplication.

Laparoscopic Heller myotomy with partial fundoplication is a very safe operation with a mortality rate of 0.1% [36]. The most common complication of LHM is perforation of esophagus or stomach with an average rate of 6.3% during the myotomy, which can be usually repaired without severe clinical consequences [37]. Recurrence of dysphagia usually develops within 12-18 months following LHM [38].

At present, EBD and LHM are the most effective treatment options for achalasia. When comparing the effect of LHM with EBD, most authors conclude that LHM is superior to pneumatic dilation with respect to clinical remission, relapse rate and safety. The latest meta-analysis [14] showed that myotomy has a higher short- and long-term efficacy. The goal of our research was to summarize the results of the treatment options for achalasia. The present meta-analysis involved 8 studies comparing EBD with LHM in 749 achalasia patients. The findings indicate that EBD and LHM are similar in terms of the incidence of perforation and post-procedural reflux disease, while regarding the success rate at 1-year follow up EBD evidences worse results compared to those of LHM.

Evaluation of the therapeutic success was variable in the analysed studies. In the studies by Boeckxstaens et al. [20], Moonen et al. [19], Wang et al. [21], Tabola et al. [22], the authors used the Eckardt score to assess the success rate, while Tabola et al. applied the symptom improvement rate by reduction of the Eckardt score and by evaluating the frequency of reintervention. In 4 other studies, symptom evaluation was based on various dysphagia scores. In the studies by Hamdy et al. [23] and Borges et al. [18] the primary outcome was the successful symptomatic improvement, which used the Demeester's or Vantrappen and Hellemans dysphagia score. In the studies by Persson et al. [24] and Kostic et al. [25] the primary end point was the cumulative number of treatment failures. Six of the eight studies included in the analysis found LHM more effective than EBD, while the remaining two studies showed similar results for both techniques within a follow-up period. The two studies [19, 20] which demonstrate that EBD and LHM are similar in effectiveness are large multicenter randomized trials involving many patients. The other six studies are small trials with a smaller sample size. We identified six randomized and two non-randomized studies. The two non-randomized studies [21, 22] found the same results as

the other four randomized small trials. We assume that the study type did not affect the results, but the number of patients and the duration of follow-up period may have influenced the outcomes.

Our meta-analysis has some limitations. Heterogeneity in the follow-up period and the various criteria of therapeutic success among different centres certainly represented the weak points of all included studies.

Previous studies also examined post-procedural complications. Our results showed that the perforation rate did not differ between the EBD and LHM groups. Wang et al. [21] did not observe perforation in either group, four studies demonstrated a lower perforation rate in the LHM group than in the EBD group, while other three studies showed lower perforation rate in the EBD group. Such contradictions are presumably due to the heterogeneity of centres and various expertise levels of the endoscopists and surgeons in different centers. Perforation is a significant complication, and therefore the procedure should be performed with care and by experienced endoscopists or surgeons. In our analysis, there was no significant difference between EBD and LHM regarding the evaluation of post-procedural GERD. Many previous studies found that GERD was more frequent in the LHM group than in the EBD group. Among the trials included in our meta-analysis, five studies reported symptomatic post-procedural GERD occurrence and four studies found that GERD developed more frequently in the LHM group. Our statistical analysis did not reveal significant differences, but we observed a trend for a higher occurrence rate of GERD after LHM than after EBD.

CONCLUSION

This meta-analysis suggests that the effectiveness of LHM is superior to EBD and a better success rate can be obtained after myotomy. There was no difference in the perforation rate and post-procedural GERD evaluation between the two treatment options. Further large, randomized, controlled trials are required to compare LHM and pneumatic dilation.

Conflicts of interest: No conflict to declare.

Authors' contributions: I.A., G.A., S.I., S.M., P.E., B.M., P.G., S.P., B.J., S.Á., C.J., S.K. designed the research, performed the research and collected the data. I.A. and F.N. analysed and interpreted the data. I.A. drafted the manuscript. H.P., G.A. and V.Á. revised the article and gave final approval.

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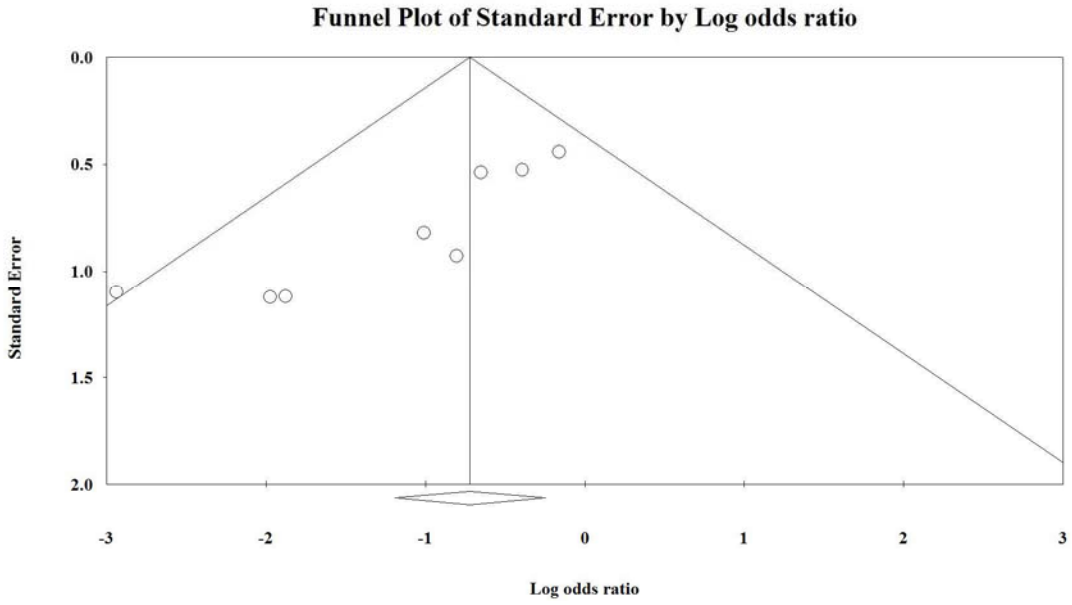
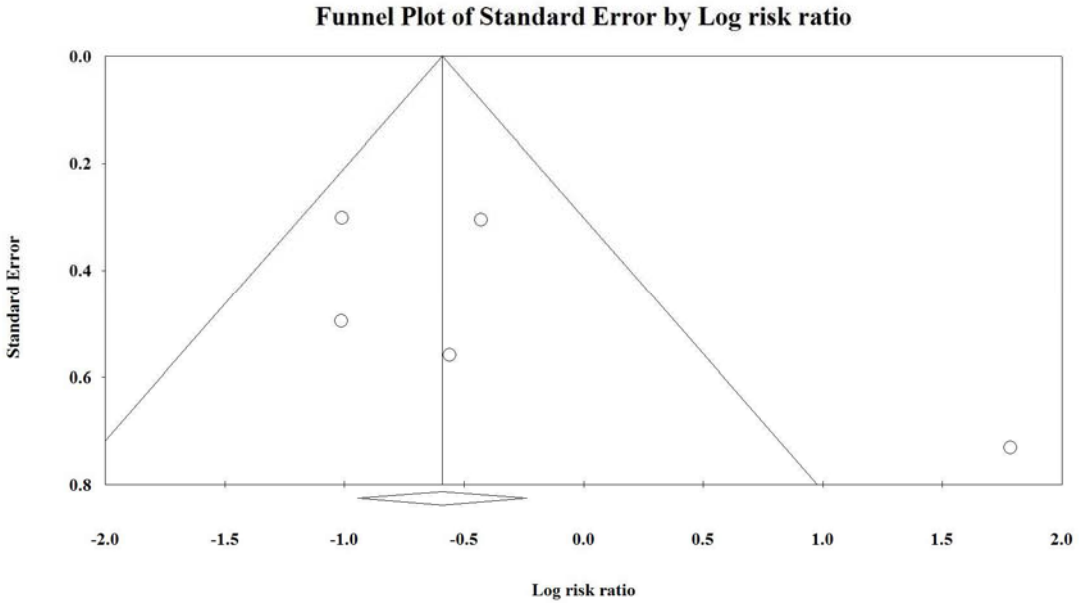
Supplementary Table I. Characteristics of studies included meta-analysis. Key: +: low risk of bias, –: high risk of bias, **?**: unclear risk of bias

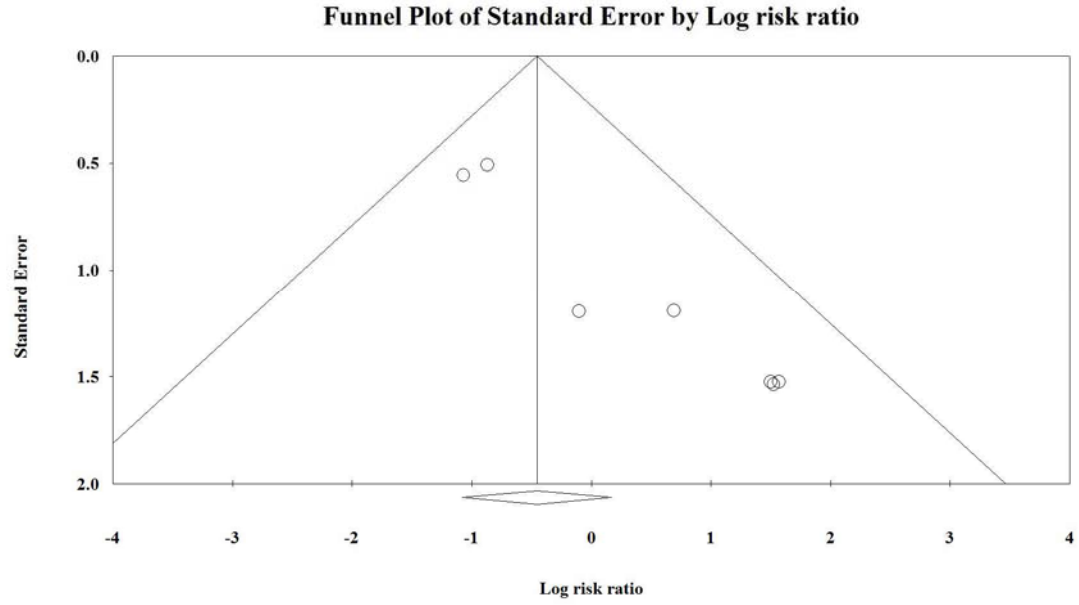
	Random sequence generation (selection bias)	Study design	Blinding of participants and personnel (performance bias)	Allocation concealment (selection bias)	Incomplete outcome data addressed (attrition bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)
Wang et al. 2015 (21)	Non-randomized	retrospective	–	–	?	–	+
Moonen at al. 2015 (19)	Randomized	prospective	–	+	+	–	+
Tabola et al. 2013 (22)	Non-randomized	prospective	–	–	+	–	+
Borges et al. 2014 (18)	Randomized	prospective	–	?	+	–	+
Persson et al. 2015 (24)	Randomized	prospective	–	+	+	+	+
Hamdy et al. 2015 (23)	Randomized	prospective	–	+	?	–	+
Boeckxstaens et al. 2011 (20)	Randomized	prospective	–	+	+	–	+
Kostic et al. 2007 (25)	Randomized	prospective	–	?	+	–	+



Supplementary Fig. 1.Funnel plot of studies evaluating success rate in balloon dilation and Heller myotomy groups. Visual inspection did not show asymmetry.



Supplementary Fig. 2. Funnel plot of studies evaluating post-procedural reflux in balloon dilation and Heller myotomy groups. Asymmetry is observed visually. In study by Borges et al. fell outside.



Supplementary Fig. 3. Funnel plot of studies evaluating perforation rate in balloon dilation and Heller myotomy groups. Asymmetry is observed visually.