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Review Article

Efficacy and safety of LHM for people with achalasia: a meta-analysis of randomized controlled trials

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Abstractl: Background: It is still not clear whether the laparoscopic Heller myotomy (LHM), botulinum toxin (BTX) or the pneumatic dilation (PD) is the most appropriate treatment approach to achalasia. Therefore, this meta-analysis study was conducted to assess the safety and effectiveness of these methods in the management of achalasia. Methods: Meta-analysis of randomized controlled trials was performed through searching a comprehensive list of electronic databases to compare the safety and effectiveness between these approaches in the treatment of achalasia. Calculations were made of effect sizes of efficacy and safety outcomes: response rate, recurrence rate, and complication rate, the effect sizes were then pooled through randomized- or fixed-effects model. Results: Sixteen RCTs involving 1,196 participants were included. There was no significant difference between BTX and PD treatment in short-term response rate [risk ratio (RR)=0.90, 95% credible interval (CI): 0.82-1.00, P=0.05], while the short-term response rate was higher in the LHM group than that in the PD group (RR=1.21, 95% CI: 1.05-1.38, P=0.008). The long-term response rate was significantly higher in the LHM group than that in the PD group (RR=1.27, 95% CI: 1.06-1.52, P=0.009), the long-term response rate of the PD group was superior to BTX in treating achalasia (RR=0.52, 95% CI: 0.29-0.90, P=0.02). The complication rate of achalasia in the BTX group was significantly lower than that in the PD group (RR=0.20, 95% CI: 0.07-0.58, P=0.003), but the recurrence rate was significantly higher in the BTX group than that in the PD group (RR=2.15, 95% CI: 1.19-3.88, P=0.01). Conclusion: The current meta-analysis demonstrates that LHM is the more effectiveness method for the treatment of achalasia.

Keywords: Achalasia, pneumatic dilation, laparoscopic Heller myotomy, botulinum toxin, meta-analysis

Introduction

Achalasia of cardia is an esophageal dyskinesia disease that may be caused by genetic factors, viral infection or autoimmunity, resulting in an imbalance of immune inflammation, decrease or absent inhibitory ganglionic cells in the myenteric plexus of the lower esophageal sphincter (LES). This results in impaired laxity of the LES after swallowing, resulting in esophageal sphincter dysfunction [1-4]. The most common symptoms of achalasia include recurrent regurgitation, dysphagia, chest pain, and aspiration. The degenerated myenteric plexus neurons cannot restore their function; therefore, aims to eliminate the outflow resistance caused by the non-relaxing LES. These possible therapeutic methods include surgical myotomy, drug therapy, and endoscopic treatment (botulinum toxin injection or pneumatic dilation) [5-7].

Peroral endoscopic myotomy (POEM) is a new method for the management of achalasia that combines the surgical element of controlled myotomy with the reduction of physiological damage from endoscopic technique demonstrated promising results, but only a few prospective studies support their conclusion [8-12]. Current standard for the treatment of achalasia cardia includes forceful PD and LHM with (or without) an anti-reflux procedure [13, 14]. However, several randomized controlled trials of the three most commonly accepted approaches (pneumatic dilatation, laparoscopic Heller's myotomy, and botulinum toxin injection) demonstrated conflicting results. Previous studies comparing the response rate of these therapeutic methods in the treatment of achalasia, and there were at most five RCTs be included [15-17]. Thus, the present meta-analysis was implemented to evaluate efficacy and safety outcomes (response rate, recurrence

Table 1. Main Characteristics of 16 studies included in the meta-analysis

Author	Year	Country	Case			Mean Age (y)			Sex (% male)			Outcomes*	Follow-up (M)	Jadad Score
			BTX	PD	LHM	BTX	PD	LHM	BTX	PD	LHM			
Bansal	2003	USA	16	18		49.8	51.8		43.8	66.7		1, 2, 3, 4	12	4
Boeckxstaens	2011	European		95	106		46.4	45.5		63.2	53.8	2, 4	24	3
Borges	2014	Borges		48	44		52.8	45.8		52	36.4	1, 2, 4	24	3
Cai	2003	China	62	56		NA	NA		NA	NA		1, 4	6	4
Csendes	1981	Chile		18	20		38	42		33.3	45	2, 4	48	3
Csendes	1989	Chile		39	42		40.2	42.7		41	47.6	2, 4	48	3
Ghoshal	2001	India	7	10		42.4	34.3		71.4	50		1, 3	6	3
Hamdy	2015	Egypt		25	25		30.8	32		25	47	1, 2, 3, 4	24	3
Mikaeli	2001	USA	20	20		59.8	50.1		45	52.6		1, 2, 3	12	5
Moonen	2015	European		96	105		46.4	45.7		64	53	2	60	4
Muehldorfer	1999	Germany	12	12		49	47		58.3	58.3		1, 4	6	3
Novais	2010	Brazil		47	47		52.3	46.5		53	38	1, 4	3	3
Persson	2015	Sweden		28	25		46	43		43	44	2, 4	48	5
Vaezi	1999	USA	24	24		57	56		58.3	70.8		1, 2, 3, 4	12	4
Liu	2005	China	24	24		35.2	36.2		41.7	45.8		1, 2	12	5
Zhu	2009	China	29	28		36.7	38.2		44.8	42.9		1, 2, 3	24	4

*Outcomes: 1, short-term response rate; 2, long-term response rate; 3, recurrence rate; 4, complication rate. Abbreviations: PD=pneumatic dilation, LHM=laparoscopic Heller myotomy, BTX=botulinum toxin, NA=not available.

rate, and complication rate) of these methods in the management of achalasia.

Methods

Literature search

A search of PubMed, EMBASE, Cochrane Library, and WanFang databases up to July 15, 2018 was conducted using a mix of the following keywords: achalasia, pneumatic/balloon dilation, laparoscopic Heller myotomy, botulinum toxin. All the relevant studies were reviewed respectively by two investigators. Eligible studies were selected based on the inclusion criteria as bellow and eligible trials were then selected on the basis of inclusion criteria as below.

Inclusion and exclusion criteria

Published randomized controlled trials researches are going to be involved in the current studies on reaching the criteria as follows: i) only RCTs were included; ii) a comparison of PD and BTX (or LHM) in the management of achalasia cardia; iii) the study reported at least one of the desirable outcomes mentioned below. Conference abstract, reviews, editorials, experimental research in animal models, and comments were excluded. When replicated research was published, merely the research having huge specimen size was involved.

Data extraction and quality assessment

Data extraction independently by two authors from all eligible studies: first author, publication year, country, sex ratio of subjects, age and type in the management of achalasia (BTX, PD, or LHM) (**Table 1**). The overall quality of the studies was used to assess by the Jadad scale [18]. High-quality studies have a score of ≥ 3 and low-quality studies ≤ 2 based on Kjaergard et al.'s recommendation [19]. Differences were resolved through discussion and consulting a senior reviewer, if necessary.

Statistical analysis

The strength of association was calculated by risk ratios (RRs) with 95% confidence interval (CI), comparing these therapeutic methods in the treatment of achalasia. Use of the Q-test and I^2 statistics was made for quantifying statistical heterogeneity. The use of random-effect framework was made once the heterogeneity was significant ($P<0.05$) [20]; or else, the fixed effects framework was utilized [21]. The sensitivity analysis performed by sequentially excluding any individual data one by one, with an objective of examining the impact of each individual data set or summarized findings. The funnel plot was made for estimating the possibility of publication bias by assessing the asymmetry. All analyses were conducted by using Review Manager Software (Rev Man 5.3).

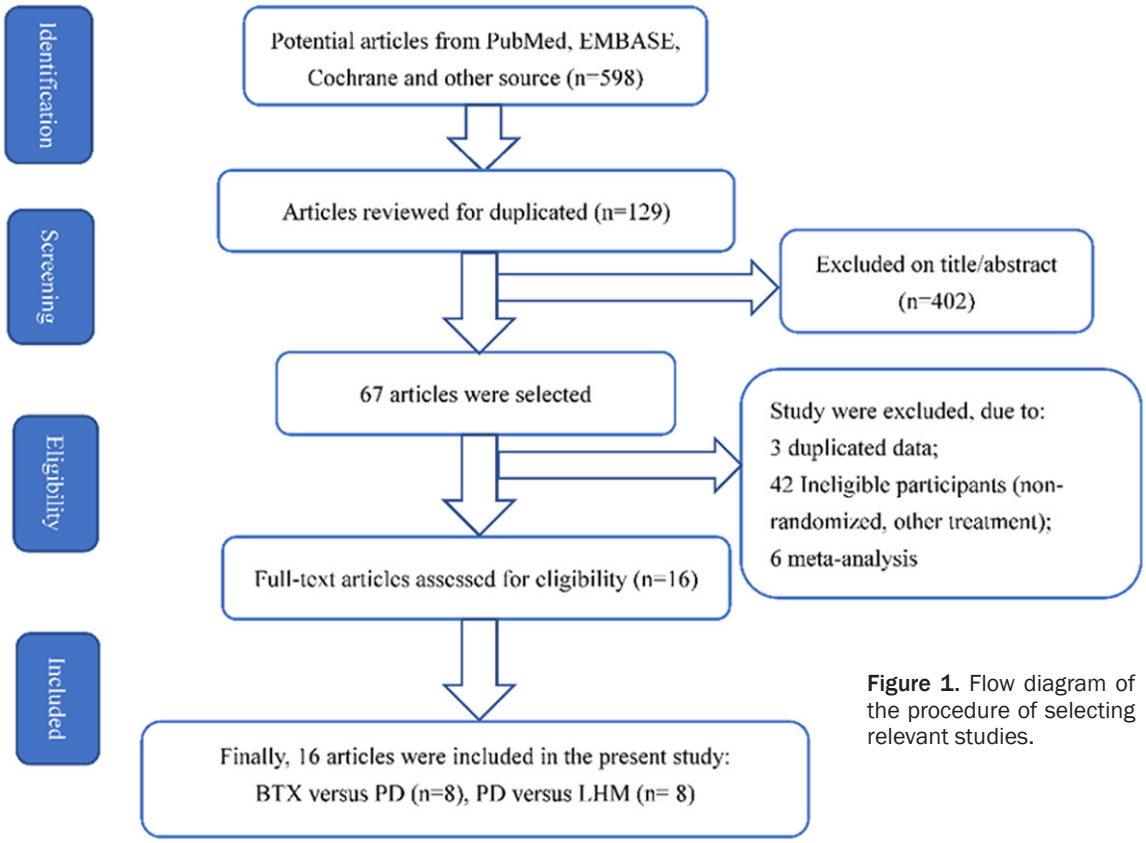

Figure 1. Flow diagram of the procedure of selecting relevant studies.

Results

Selection of eligible studies

The selection mechanism of entitled research works is displayed in **Figure 1**. A total of 598 considerably significant research works were primarily attained from PubMed, EBMASE, Cochrane Library, and WanFang databases. After removing duplicate articles, we assessed the titles and abstracts of these articles based on the inclusion and exclusion criteria, with a total of 67 studies remaining. Then the full-text was read and the ineligible studies were excluded, 16 randomized controlled trials involving 1,187 participants were included [6, 7, 22-35]. The characteristics of each study are shown in the **Table 1**.

Meta-analysis of BTX and PD in the treatment of achalasia

Short-term response rate: A total of 386 participants included in the eight studies were assessed for the outcome of the short-term response rate, with 145 response cases identified in the BTX group (74.4%) and 158 in the PD group (82.3%). Therefore, the short-term response rate was slightly lower in BTX than that in PD, but there was no significant difference between BTX and PD in the treatment of achalasia (RR=0.90, 95% CI: 0.82-1.00, P=0.05). The fixed-effect model was used, as there was moderate significant heterogeneity was detected in the two studies (I^2=38%, P=0.12) (**Figure 2**).

Long-term response rate: The long-term response rate analysis included 5 relevant studies with a total of 220 patients. Comparing BTX and PD, 28 (25.2%) and 54 (49.5%) cases of response were observed in the two groups, respectively, and the two groups was detected statistically significant (RR=0.52, 95% CI: 0.29-0.90, P=0.02). The random-effect model was selected, as there was moderate heterogeneity was detected in the two studies (I^2=51%, P=0.09) (**Figure 3**).

Recurrence rate: A total of 189 participants included in 5 studies were evaluated. Following comparison, 60 (65.2%) and 31 (32.0%) cases of recurrence were observed in the two groups, respectively, and the recurrence rate was sig-

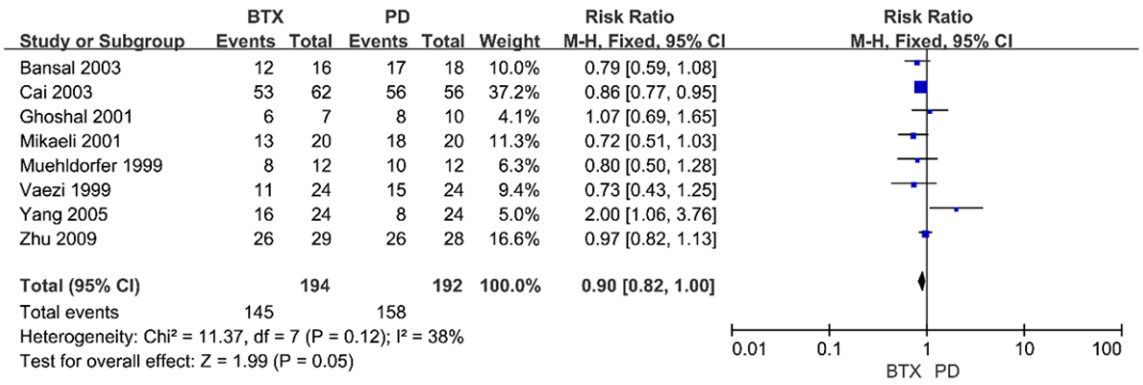

Figure 2. Meta-analysis of short-term response rate to BTX versus PD in the treatment of achalasia. BTX=botulinum toxin, PD=pneumatic dilation, CI=confidence interval.

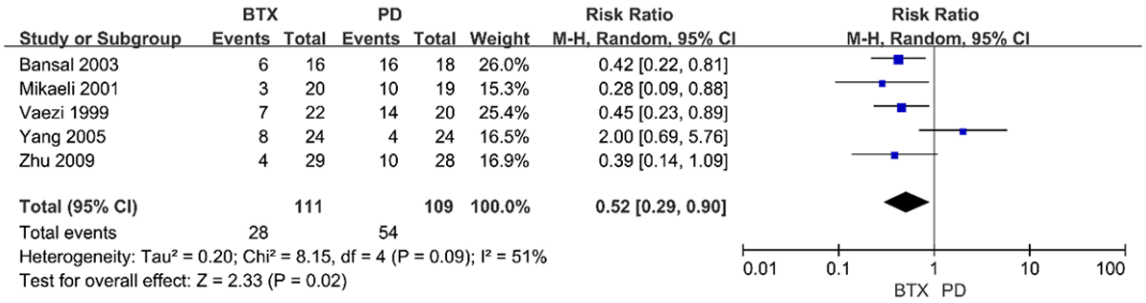

Figure 3. Meta-analysis of long-term response rate to BTX versus PD in the treatment of achalasia. BTX=botulinum toxin, PD=pneumatic dilation, CI=confidence interval.

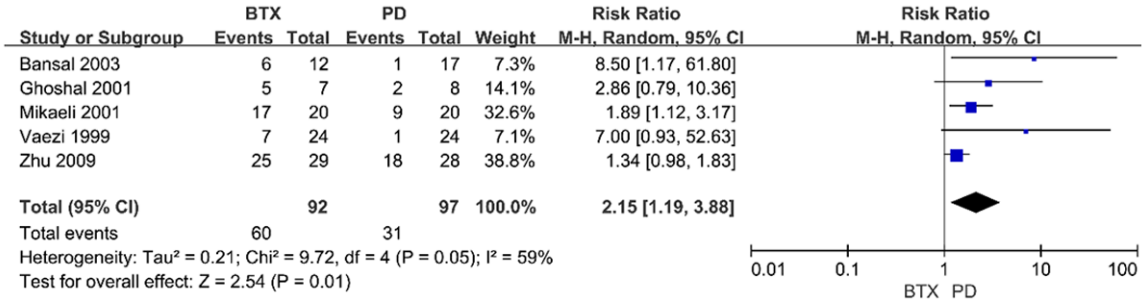

Figure 4. Meta-analysis of recurrence rate to BTX versus PD in the treatment of achalasia. BTX=botulinum toxin, PD=pneumatic dilation, CI=confidence interval.

nificantly higher in the BTX group than that in the PD group (RR=2.15, 95% CI: 1.19-3.88, P=0.01). Significant heterogeneity was observed in the two groups, so the random-effect model was selected (I^2=59%, P=0.05) (**Figure 4**).

Complication rate: This result included four-studies and 224 patients. The total numbers of events were 2 in the BTX group (1.8%) and 16 in the PD group (14.6%). The complication rate of achalasia in the BTX group was significantly lower than that in the PD group (RR=0.20, 95% CI: 0.07-0.58, P=0.003). The fixed-effect model was used, as there was no significant heterogeneity was detected in the two studies (I^2=0%, P=0.003) (**Figure 5**).

Meta-analysis of PD and LHM in the treatment of achalasia

Short-term response rate: A total of 236 participants included in the three studies were assessed for the outcome of the short-term

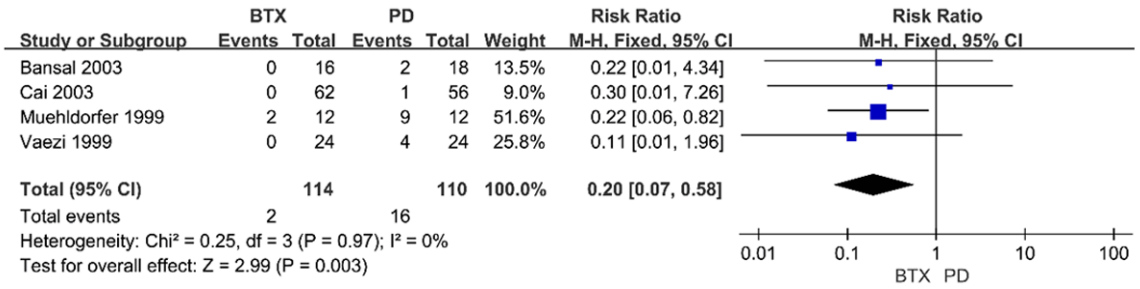

Figure 5. Meta-analysis of complication rate to BTX versus PD in the treatment of achalasia. BTX=botulinum toxin, PD=pneumatic dilation, CI=confidence interval.

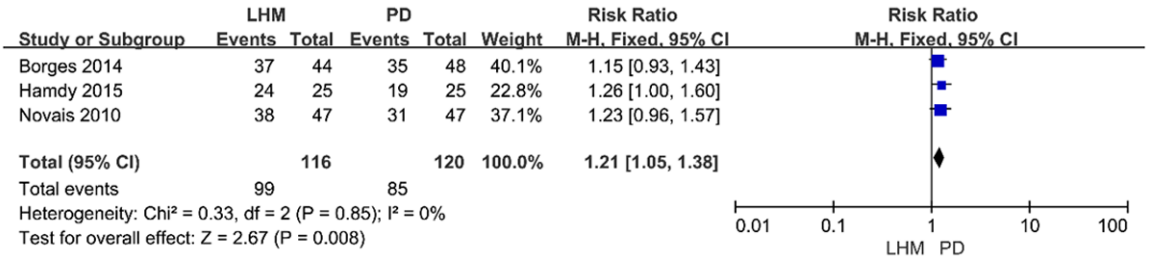

Figure 6. Meta-analysis of short-term response rate to PD versus LHM in the treatment of achalasia. PD=pneumatic dilation, LHM=laparoscopic Heller myotomy, CI=confidence interval.

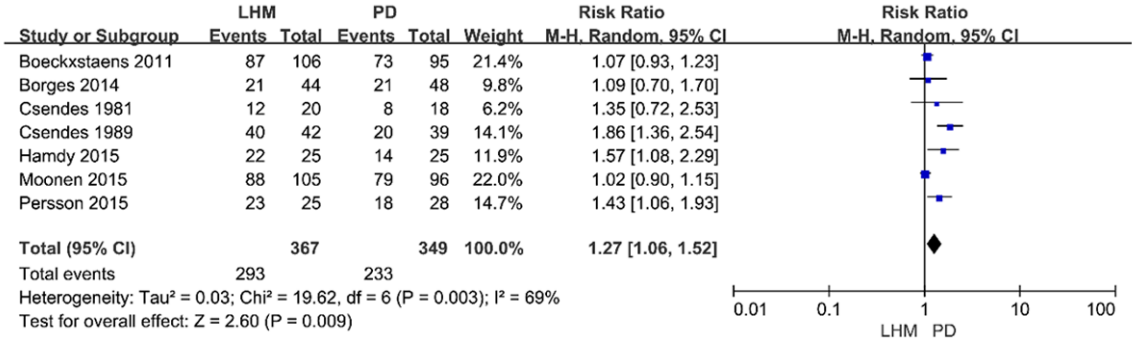

Figure 7. Meta-analysis of long-term response rate to PD versus LHM in the treatment of achalasia. PD=pneumatic dilation, LHM=laparoscopic Heller myotomy, CI=confidence interval.

response rate, with 85 response cases identified in the PD group (70.8%) and 99 in the LHM group (85.3%). Therefore, the short-term response rate was significantly higher in LHM than that in PD (RR=1.21, 95% CI: 1.05-1.38, P=0.008). The fixed-effect model was used, as there was no significant heterogeneity was observed in the two studies (I^2=0%, P=0.85) (**Figure 6**).

Long-term response rate: A total of 716 patients included in 7 relevant studies were evaluated the long-term response rate. Comparing LHM and PD, 293 (79.8%) and 233 (66.8%) cases of response were observed in the two groups, respectively, and the two groups was detected statistically significant (RR=1.27, 95% CI: 1.06-1.52, P=0.009). Significant heterogeneity was observed in the two studies, so the random-effect model was selected (I^2=69%, P=0.003) (**Figure 7**).

Complication rate: Seven studies and 609 participants were included regarding the postoperative complication rate. The total events were 16 in the LHM group (5.2%) and 15 in the PD group (5.0%). There was no significant difference between the two groups (RR=1.02,

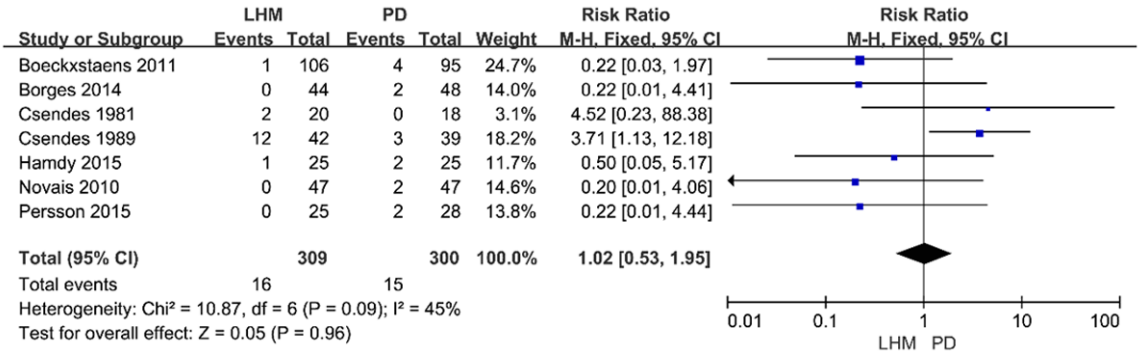

Figure 8. Meta-analysis of complication rate to PD versus LHM in the treatment of achalasia. PD=pneumatic dilation, LHM=laparoscopic Heller myotomy, CI=confidence interval.

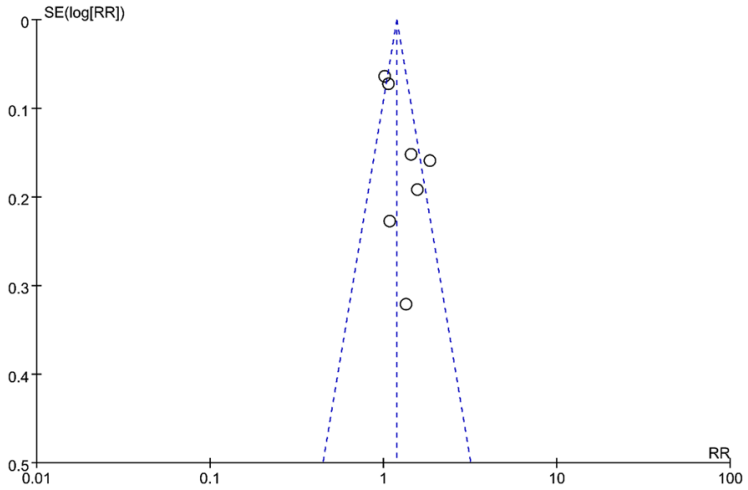

Figure 9. Inverted funnel plots analysis for PD versus LHM in the treatment of achalasia. PD=pneumatic dilation, LHM=laparoscopic Heller myotomy

95% CI: 0.53-1.95, P=0.96). Moderate-heterogeneity was detected in the two studies; therefore, the random-effect model was used. (I^2=45%, P=0.09) (**Figure 8**).

Sensitivity analysis and publication bias

Sensitivity analysis was performed by sequentially excluding any individual researches individually, with an objective of examining the impact of every single research work on summarized findings. Consequently, as revealed by the findings of the sensitivity analysis, our findings exhibited statistical robustness and credibility (data not shown). The shape of the funnel plot appeared symmetrical, suggesting that there was no obvious publication bias (**Figure 9**).

Discussion

Although the etiology of esophageal achalasia is scarcely understood, there is common consensus on its treatment, directed to reducing lower esophageal sphincter (LES) pressure in order to obtain symptoms relief, improve the esophageal emptying and prevent the development of megaesophagus [2, 4, 36]. Although PD, LHM, and BTX are the main approaches of treatment, the best treatment approaches is still controversial. These treatments have a variable risk of symptomatic recurrence, perforation, and other complication (urinary retention, subcutaneous emphysema, vagal nerve injury, and atrial fibrillation) [37]. Therefore, the best treatment method for short- and long-term symptom relief must be determined with sufficient consideration of complications.

A previous meta-analysis by Leyden et al. compared six months remission rate with twelve months remission rate, and the result demonstrated that PD is superior to BTX in treating patients with achalasia [15]. This study did not include long-term follow-up and recurrence rates. The other systematic review by Wang et al. compared several treatment approaches for patients with achalasia of cardia and included a small meta-analysis of LHM vs. PD [38]. Another meta-analysis by Baniya et al. com-

pared the results of PD and LHM in the treatment of cardiac achalasia, and the result showed that PD was as effective as LHM in the long-term relief of cardiac achalasia symptoms [16]. However, the results of these studies must be interpreted with caution, as these studies typically use variable of success rate and subjective definitions. To the best of our knowledge, this is the first attempt to perform a high-quality meta-analysis to assess the effectiveness and safety of these methods in the management of achalasia.

Botulinum toxin injection (BTX) treatment is less expensive, almost risk-free, and easy to administer. BTX in treating patients with achalasia has a very high safety profile, and even minor adverse-event with heartburn (or chest pain) have been observed in less than 10% of treated patients [39]. In a RCT comparing Heller myotomy to BTX, the results in both groups were comparable at six months, but the surgical patients improved more in the symptom scores. Only 87.5% of LHM versus 34% of BTX participants were asymptomatic during a two year follow-up [40]. Similarly, several randomized trials and a meta-analysis comparing BTX with PD consistently demonstrated that a higher cumulative response rate at one year after treatment [7, 15, 23, 26]. Our study suggests that the response rate was greater at both short-term (lower than six months) and long-term (greater than six months) for PD compared to those for BTX. Further analysis demonstrated that there was significant difference between the PD group and the BTX group in complication rate and recurrence rate.

In 2013, Borges et al. conducted a prospective randomized clinical study to assess the clinical response and the variables related to good results in ninety-two participants with achalasia in both treatments (PD or LHM with partial fundoplication). After 3 months of treatment, 84% of patients in the LHM group and 73% of patients with PD had a favorable result (P= 0.19). After 2 years of follow-up, 60% of patients in the LHM group and 54% of patients with PD group were symptom free, and there was no significant difference between LHM and PD in treating with achalasia, and they concluded that LHM was as equally effective as PD in the treatment of achalasia up to 2 years of follow-up [22]. However, several randomized clinical trials comparing LHM and PD showed better results of symptom control, dysphagia, and (gastroesophageal reflux disease) GERD respectively, after LHM in the treatment of achalasia [24, 25, 41]. For symptom remission, LHM was not superior to PD in the treatment of cardiac achalasia in one meta-analysis [42]. The present study suggests that response rate was greater at both short-term and long-term for LHM compared to those for PD. Further analysis did not reveal any significant difference between PD group and LHM group in complication rate. The present meta-analysis demonstrated that good clinical efficacy combined with low morbidity has established endoscopic myotomy as a safe, definitive, and effective alternative in the treatment of cardiac achalasia.

The present study has some limitations. First, there were variations in treatment protocols amongst the studies; therefore, a certain degree of heterogeneity may exit. Second, not all the studies were double-blinded; thus, subjective variables may have been be significantly affected by the enthusiasm surrounding any new treatment in the absence of double-blinding. Third, the study is that both the number of studies and the number of participants randomized to either treatment were small.

Conclusion

The present meta-analysis demonstrated that LHM may be more effectiveness method in the both short- and long-term for the treatment of patients with achalasia. Future large, blinded RCTs should evaluate whether laparoscopic myotomy combined with different fundoplication therapies comparable treatment protocols and outcome assessment criteria are needed.

Disclosure of conflict of interest

None.

Abbreviations

PD, pneumatic dilation; LHM, laparoscopic Heller myotomy; BTX, botulinum toxin; RCT, randomized controlled trial; RR, risk ratio; CI, credible interval; POEM, Peroral endoscopic myotomy; LES, lower esophageal sphincter; GERD, gastroesophageal reflux disease.

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