Int J Clin Exp Med 2017;10(8):11703-11709
www.ijcem.com /ISSN:1940-5901/IJCEM0055439

Original Article

A comparative meta-analysis on curative effects of thymectomy and sternotomy in treating the myasthenia gravis

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Received April 14, 2017; Accepted May 31, 2017; Epub August 15, 2017; Published August 30, 2017

Abstract: Objective: To assess the therapeutic efficacy of thymectomy as a treatment for myasthenia gravis (MG) by meta-analyses. Methods: Through the retrieval of related literature in Chinese National Knowledge Infrastructure database (CNKI), Wan Fang database, CiNii, NCBI, EBSCO, Web of Science and so on, the data, which concerned with thymectomy for myasthenia gravis and published from 2010 to 2016, were obtained. The meta-analysis of operating time, drainage time, hemorrhage volume and therapeutic efficacy were carried out by RevMan5.2 statistical software. Results: Seventeen foreign literature, were included in this study, with 642 cases of the video-assisted thoracic surgery (VATS) group and 603 cases of the sternotomy group. The analysis revealed that the hemorrhage volume of VATS thymectomy group was markedly less than conventional group (RR=6.25, P=0.01), while the drainage time was longer than that of conventional group (RR=1.26, P=0.12). No significant difference of MG improvement rate was found between both groups (RR=1.00, P=0.16). Conclusion: VATS thymectomy is a safe and reliable treatment for myasthenia gravis and it shares the same prostecdtive efficacy with conventional thymectomy. Combined with thoracoscopic surgery, the hemorrhage volume can be decreased and the hospital stay can be shortened in thymectomy.

Keywords: Myasthenia gravis, thymectomy, meta-analysis, video-assisted thoracic surgery

Introduction

Myasthenia gravis is an autoimmune disease involving neuromuscular junction. Its incidence rate is 1/2000. Currently, the pathogenesis of MG is uncertain, and there is no radical cure. It is usually treated with medicinal treatment, immunosuppressive agents and cholinesterase inhibitors [1, 2]. And performing a surgery is one of the main approaches. In conventional thymectomy, sternotomy is adopted as the primary method, for it can provide better visual field and remove anterior mediastinal fats more thoroughly. However, this method, with various postoperative complications, is prone to sternal infection [3]. With the application of video-assisted thoracic surgery (VATS) in recent years, thymectomy has achieved a great improvement. But the safety and prostecdtive efficacy of thymectomy are still strongly debated. In recent literature, many scholars conducted studies on the treatment of MG by different thymectomies, with different amount of cases and focuses. In this study, comparison of the curative efficacy of two treatments for MG was made by carrying out meta-analyses, and the data were generated as a basis for clinical reference.

Materials and methods

Inclusion and exclusion criteria

Inclusion criteria: English literature about comparative analyses of thymectomy for myasthenia gravis; literature contains clear inclusion criteria, grouping method, study cases, etc.; the initial data should be complete with specific number of cases, the mean and standard deviation of continuous variables.

Exclusion criteria: Incomplete literature; literature with uncertain study cases or cases involv-

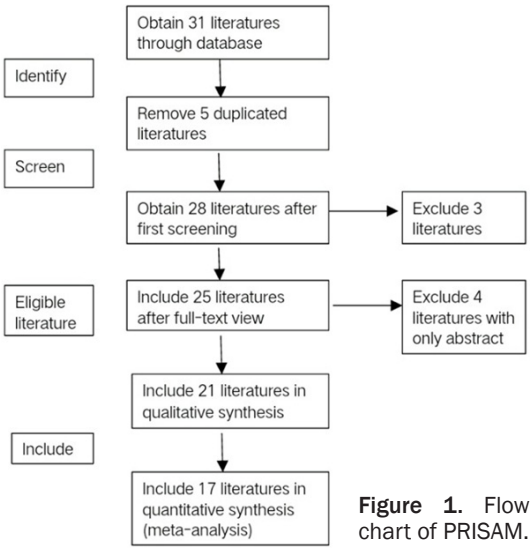

Figure 1. Flow chart of PRISAM.

ing robot surgery. Among a number of articles with different research emphases, published by the same research group, only the closest one could be included.

Strategy of literature retrieval

Through the retrieval of CNKI, Wan Fang database, CiNii, NCBI, EBSCO, Web of Science and so on, the literature on thymectomy for myasthenia gravis, which was published from 2010 to 2016, could be obtained. The literature language was restricted to English, and the search terms covered myasthenia gravis, myasthenia, thymectomy and video-assisted thoracic surgery. By retrieving the reference documentation of relevant literature and adding search words, 31 comparative articles were initially screened and 19 of them met our inclusion criteria after further review in the full text.

Data collection and quality evaluationof literature

According to the inclusion and exclusion criteria, literature retrieval was completed by two reviewers. Having read the enrolled literature carefully, the clinical outcomes, such as operating time, hospital stay, therapeutic efficacy, drainage time, were obtained. It was discussed when the data were discordant. The quality of literature was valued by Jadad score. The full scores were 5 and more than 3 points indicated that the quality of article was comparatively higher. MINORS score also used to evaluate the quality of literature.

Sensitivity analysis

The sensitivity analysis was performed by means of fixed-effect and random-effect model. If the results of two methods were consistent, it meant the reliability was good. In the included literatures, the treatment could be regarded as failure when patients dropped out during the treatment and then sensitivity analysis was performed to these data. Except for that, through the evaluation of literature quality, the literatures with low quality were screened and then conducted the two statistical analyses.

Statistical analysis

Adopted Microsoft Excel to establish databases, and analyzed the data with RevMan5.2 statistical software. Random effect model was used for data analysis and dichotomous data were used to calculate relative risk (RR). Results were presented at 95% confidence interval. $P<0.05$ was considered statistically significant. Funnel plot was adopted to analyze the deflection of literature. Heterogeneity of enrolled literature was tested and assessed by using the I^2 test. No heterogeneity: 0-25%; mild heterogeneity: 25-50%; moderate heterogeneity: 50-75%; high heterogeneity: 75-100%.

Results

Eligibility situation of literature

Literature retrieval started with the investigation of titles and abstracts. 31 comparative literatures were initially screened and 17 of them were finally included in this study after further review in full text. There were 3 articles about randomized control trials, and the Jadad scores of them were all above 3 points. The differences among these articles were not statistically significant. The other 14 articles studied non-randomized control trials, and the MINORS scores were 20.3 points. The **Figure 1** is the flow chart of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Essential information about enrolled literature was given in **Table 1**.

Meta-analyses

Patients performed with VATS thymectomy needed longer drainage time. But intraoperative hemorrhage volume was clearly decreased

Table 1. Essential information about included literature

Author	Time	Literature	Jadad score	MINORS score	Outcome measures	Thoracoscopic approach	Amount of cases	
							VATS group	Sternotomy group
Lee CY	2011	[4]	4.1	19.8	TE, HV, HS, DT, DV	RL	55	59
Chen Z	2014	[5]	4.2	19.6	HAR1, T cells, Alexine C3, HV	RL	54	73
Liu CW	2013	[6]	3.9	21.6	TE, HV, P, DAE	BIL	62	53
Jaretzki A 3rd	2000	[7]	4.2	21.3	TE, DT, HV	RL	10	10
He ZC	2013	[8]	3.9	22.7	TE, HV, DT	RL	15	18
Muhammad M	2014	[9]	4.6	20.4	TE, HV	RL	13	8
Manlulu A	2005	[10]	4.7	21.6	HAR2, T cells, HV, TE	RL	38	38
Lin MW	2010	[11]	4.1	18.9	TE, HV, P, RR, OT, Course, Mortality	RL	38	22
Chang PC	2005	[12]	4.2	18.6	Complication, HS, HV, OT, VAS	RL	15	16
Huang CS	2011	[13]	4.2	17.3	TE, OT, DT, HS, HV	RL	33	66
Lee HS	2015	[14]	4.6	22.5	HV, OT	BIL	55	59
Stang A	2010	[15]	4.3	16.3	TE			
Leuzzi G	2014	[16]	3.5	24.6	TE, HV, HS	RL	22	155
Nam TS	2011	[17]	3.5	22.3	TE, PF, IA, HV	BIL	20	46
Chu XY	2011	[18]	3.5	21.0	TE, OT, HD, Complication	RL	199	44
Choi KH	2014	[19]	3.9	21.3	TE, VCR, PR	RL	36	12
Ando T	2015	[20]	4.2	20.6	TE	RL	45	10

Note: TE, therapeutic efficacy; HV, hemorrhage volume; HS, hospital stay; HAR1, hospital admission rate of ICU; HAR2, postoperative hospital admission rate; DT, drainage time; DV, drainage volume; P, prognosis; DAE, dosage of anticholinergic enzyme; RR, retention rate of ICU; OT, operating time; VAS, visual analogue score; PF, pulmonary function; IA, immunosuppressive agents; HD, hormone dosage; VCR, vital capacity ratio; PR, postoperative recurrence; RL, right lateral; BIL, bilateral.

Table 2. Meta-analyses of included literature

Research index	Amount of cases	Test of heterogeneity, I^2, P	Summary statistic (95% CI)	*P* value
MG improvement rate	16	32, 0.18	1.38 (0.85, 2.13)	0.16
Hemorrhage volume	11	73, 0.00	-87 (-116, -59)	0.01
Drainage time	5	0, 0.76	0.26 (0.02, 0.42)	0.12
Hospital stay	6	42, 0.16	-1.7 (-3, -0.4)	0.01

and the hospital stay was shortened. The complete remission rate and improvement rate of MG were increased. Information was detailed in **Table 2**.

Comparison of intraoperative hemorrhage volume

In the eligibility literature, 6 of them studied the index of hemorrhage volume. The result of meta-analysis was shown in **Figure 2**, I^2=73, and the analysis was conducted with a random effect model, RR=6.25, P=0.01. The intraoperative hemorrhage volume of VATS thymectomy group was apparently less than that of conventional group.

Comparison of drainage time

In the included literature, 5 of them studied the index of drainage time. The result of meta-analysis was shown in **Figure 3**, I^2=0, and the analysis was conducted with a random effect model, RR=1.26, P=0.12. The drainage time of VATS thymectomy group was longer than that of conventional group.

Comparison of hospital stay

In included literature, 6 of them studied the index of hospital stay. The result of meta-analysis was shown in **Figure 4**, I^2=42, and the analysis was conducted with a random effect model, RR=1.00, P=0.01. The length of hospital stay of VATS thymectomy group was evidently shorter than that of conventional group.

Comparison of therapeutic efficacy

Therapeutic efficacy was basically included in all included literature. The result of meta-analysis was shown in **Figure 5**, and it was analyzed with a random effect model, RR=1.00, P=0.16. There was no obvious difference in MG improvement rate among patients of two groups.

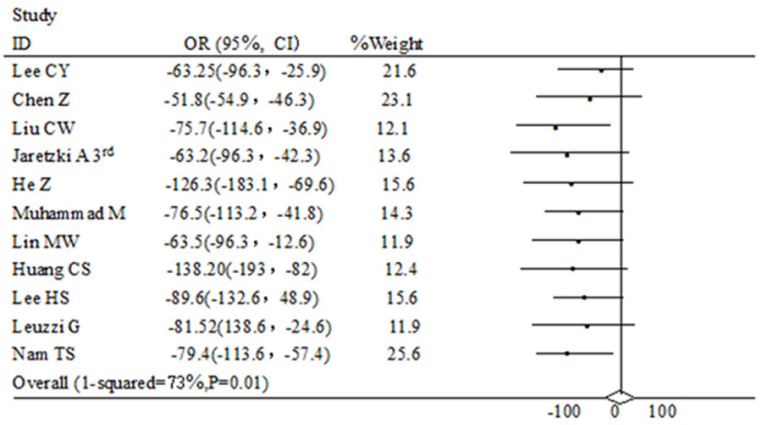

Figure 2. The meta-analysis of intraoperative hemorrhage volume.

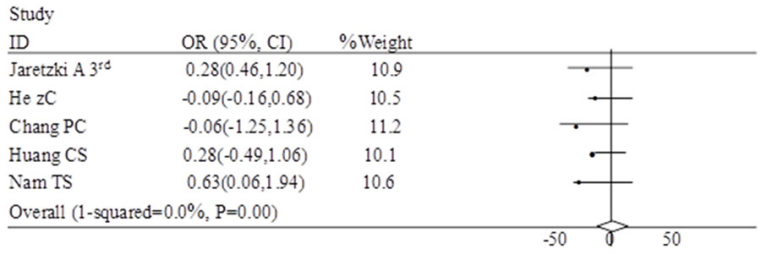

Figure 3. The meta-analysis of drainage time.

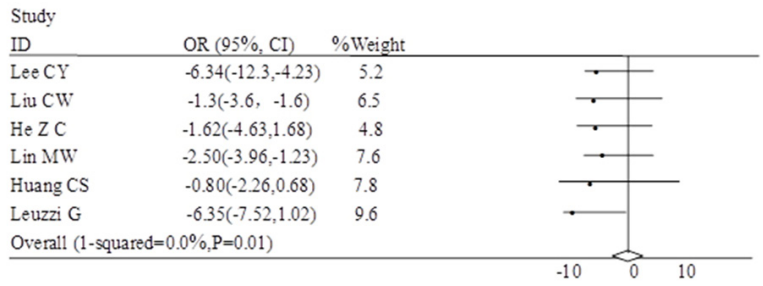

Figure 4. The meta-analysis of hospital stay.

Deflection analysis

Therapeutic efficacy was taken as an example to analyze literature deflection. The funnel plot was created to measure the publication bias. The result showed a good symmetry, indicating that there was no obvious publication bias (t=0.65, P=0.2000, **Figure 6**).

Discussion

Meta-analysis is one kindof quantitative assessments that requires evidence of certain levels. This study can offer evidences for supporting clinical treatment. The 17 included literature in this study came from five countries involving 1,296 study cases. Conducting meta-analyses can be conducive for making an objective and all-round evaluation of the therapeutic efficacy of different surgeries for MG.

Analysis of therapeutic efficacy of thymectomy

Therapeutic efficacy of conventional thymectomy for MG is apparent. Generally, its effective remission rate is 70-80%. Compared with conventional surgery, therapeutic efficacy of VATS thymectomy has no noticeable advantage. Some scholars thought VATS thymectomy had a better efficacy, while others held the opposite opinion. As for the therapeutic efficacy of thymectomy for MG at home and abroad, the reports differed slightly and the majority of studies confirmed that thymectomy can prevent further development of MG. It was reported in foreign literature that, for ocular type MG, whether to carry out surgery or not had no much differences. However, most of the studies indicated that surgery treatment should be positively applied because of the higher improvement rate on patients after surgery. In this study, it was found, through the meta-analysis, that VATS thymectomy could achieve the same therapeutic efficacy as conventional surgery.

Effect of different thymectomies on operating time, drainage time, intraoperative hemorrhage volume, etc

As the result shown, the operating time of VATS thymectomy was longer than that of conventional surgery. That is because in the implementation of thoracoscope, the observation of indirect operations through 2D image requires high technology. During the operation, it also acquires to place different positions and select

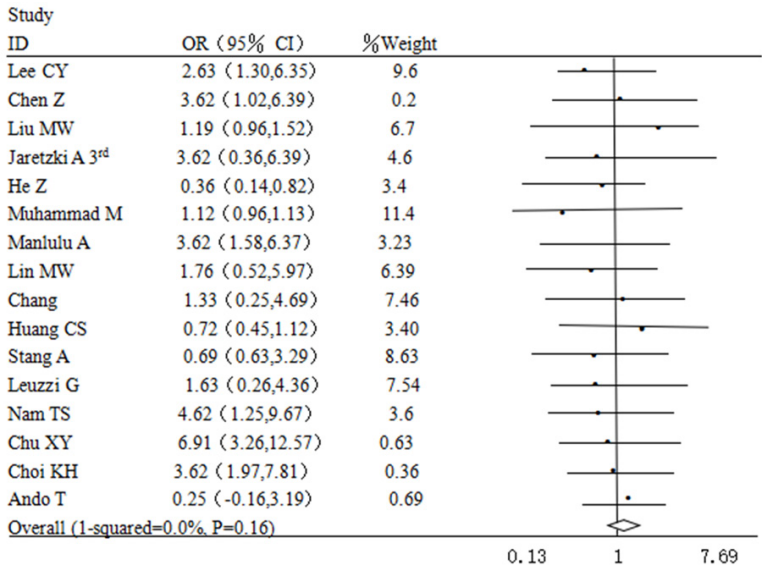

Figure 5. The meta-analysis of MG improvement rate.

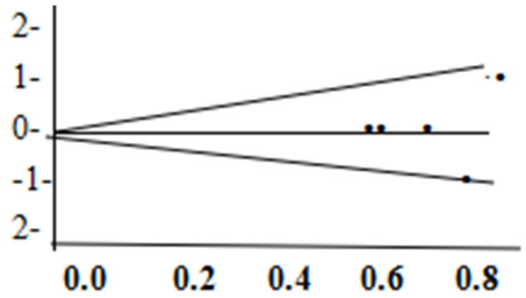

Figure 6. Deflection analysis.

proper operation incisions. The meta-analysis showed that operating time VATS group was longer and there was no statistical difference when it was compared with the conventional one.

As for the drainage time of intrathoracic drain tube, it is generally believed that the drainage time of VAST group is slightly longer than that of sternotomy group. In this study, meta-analyses were done with a random effect model. And it was found that the drainage time of the VATS thymectomy group was longer than that of the conventional group (I^2=0, RR=1.26, P= 0.12). That is maybe because VATS thymectomy needs to enter the pleural cavity, which requires adequate drainage and lung recruitment after operation. Only when drainage and lung recruitment reach certain outcomes, can the drainage tube to be removed. Besides, if situations like intraoperative pleura adhesion, or persistent air leak after operation and pleural damage during isolation happen, the drainage time would be further prolonged. There is no need to open the pleura in conventional thymectomy, so the leak tightness can be ensured. The drainage tube can be removed once the drainage of seepage is decreasing.

To analyze the effect of different surgical methods on intraoperative hemorrhage volume and hospital stay, minimally invasive techniques is adopted in VATS thymectomy, which can effectively reduce the occurrence of infection, shorten postoperative hospital stay and cut down intraoperative hemorrhage volume. Its slight impact on patients' respiratory function can reduce the incidence of postoperative pulmonary complications. At the same time, the decrease of surgical trauma, to a degree, can diminish the irritation to patients and shorten the hospital stay. In other meta-analyses, the intraoperative hemorrhage volume and hospital stay were important eligible indexes and both indicators were observed in this study. The meta-analysis, conducted with a random effect model, showed that the intraoperative hemorrhage volume of VAST thymectomy group was apparently less than conventional group (RR=1.00, P=0.01). The hospital stay of the VAST thymectomy group was evidently shorter than conventional group. The reason is that VAST thymectomy is a minimally invasive surgery with small wounds and thus can shorten the hospital stay and reduce the hemorrhage volume.

Limitations of the study

There were some limitations in this study. It was reported that patients of different ages would receive different therapeutic efficacy after thymectomy. And the different approaches of surgery varied greatly in complications. However, this study didn't analyze the indexes of patients' age, doctors' technical level, course of disease, intraoperative complication and so on, which

might affect the curative efficacy of thymectomy.

In conclusion, the current evidence suggests that the efficacy of VATS thymectomy is favorable for myasthenia gravis. It has greater advantages in reducing intraoperative hemorrhage volume and shortening hospital stay. And it shares the same prostecdtive efficacy with conventional thymectomy and possesses the promotion value.

Acknowledgements

This paper is supported by the Immune-Regulation Mechanism of Nux Vomica on Experimental Autoimmune Myasthenia Gravis Rats (2011ZA033) and Clinical Study on the Treatmentof Spleen Qi Deficiency Type of Myasthenia Gravis with Yiqibuyuantang (2012-ZB050).

Disclosure of conflict of interest

None.

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