

# Compensatory sweating after restricting or lowering the level of sympathectomy: a systematic review and meta-analysis

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**OBJECTIVE:** To compare compensatory sweating after lowering or restricting the level of sympathectomy.

**METHOD:** A systematic review and meta-analysis were conducted of all randomized controlled trials published in English that compared compensatory sweating after lowering or restricting the level of sympathectomy. The Cochrane collaboration tool was used to assess the risk of bias, and the Mantel-Haenszel odds ratio method was used for the meta-analysis.

**RESULTS:** A total of 11 randomized controlled trials were included, including a total of 1079 patients. Five of the randomized controlled trials studied restricting the level of sympathectomy, and the remaining six studied lowering the level of sympathectomy.

**CONCLUSIONS:** The compiled randomized controlled trial results published so far in the literature do not support the claims that lowering or restricting the level of sympathetic ablation results in less compensatory sweating.

**KEYWORDS:** Sympathectomy; Compensatory sweating; Meta-analysis.

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## INTRODUCTION

Endoscopic thoracic sympathectomy (ETS) is known to be a highly efficient method for treating palmar hyperhidrosis (PH). The success rate of ETS is greater than 95% in most series (1). However, controversy remains regarding the optimum level and extent of sympathectomy. The main source of the debate is the presence of compensatory sweating (CS), which substantially influences the quality of life after these operations (2). The pathophysiology of CS remains unknown. Chou and Lin reported that lowering the level of sympathectomy could reduce CS (3,4), and Licht and Yazbek suggested that lowering the level of sympathectomy could reduce severe CS (5,6). However, a thorough review of 246 articles has shown that the literature from 1999 to 2006 does not support this claim (7).

To date, there is only one systematic review and meta-analysis published in English examining compensatory sweating after the treatment of PH (8). The review only included studies in which sympathectomy was used to treat PH, and the papers included not only randomized controlled trials (RCTs) but also clinical trials because of the limited number of RCTs. ETS is used to treat not only PH but also facial blushing, facial hyperhidrosis, and axillary hyperhidrosis, among other conditions. Recently, several RCT studies on treating facial blushing and axillary hyperhidrosis have been published (9,10).

Therefore, we are the first group to conduct a meta-analysis of RCTs on ETS to assess whether lowering or restricting the level of sympathectomy can reduce compensatory sweating.

## METHODS

### Study selection

A systematic literature search with predefined search terms of "hyperhidrosis" or "facial blushing" and "sympathectomy" or "sympathicotomy" was conducted in MEDLINE (from 1960), EMBASE (all years), Cochrane Library (issue 2, 2013), and Web of Science (all years). The search was conducted in July 2013 and was limited to RCTs

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No potential conflict of interest was reported.

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**Table 1 - Description of the Included Studies.**

| Authors     | Year | Country   | Sympathectomy |      | Follow-up<br>(month) | n   |     | EG |           | CG |           |
|-------------|------|-----------|---------------|------|----------------------|-----|-----|----|-----------|----|-----------|
|             |      |           | EG            | CG   |                      | EG  | CG  | CS | Severe CS | CS | Severe CS |
| Baumgartner | 2011 | USA       | T3            | T2   | More than 12         | 60  | 61  | 37 | 1         | 43 | 1         |
| Inan        | 2008 | Turkey    | T2-4,T2-3     | T2-4 | 35.3 ± 15.6          | 60  | 20  | 13 | absence   | 3  | absence   |
| Ishy        | 2011 | Brazil    | T4-5          | T3-4 | 12                   | 20  | 20  | 15 | 1         | 20 | 1         |
| Katara      | 2007 | Singapore | T2            | T2-3 | 2-65                 | 25  | 25  | 20 | 0         | 20 | 0         |
| Li          | 2008 | China     | T3            | T2-4 | 1-12                 | 117 | 115 | 25 | 4         | 33 | 11        |
| Licht       | 2012 | Denmark   | T2            | T2-3 | More than 12         | 42  | 51  | 40 | 0         | 46 | 0         |
| Liu         | 2009 | China     | T4            | T3   | 17.8 ± 7.9           | 73  | 68  | 39 | 0         | 48 | 0         |
| Mahdy       | 2008 | Egypt     | T3-4,T4-5     | T2-3 | 13 ± 8               | 40  | 20  | 11 | 5         | 12 | 7         |
| Munia       | 2008 | Brazil    | T4-5          | T3-5 | 12                   | 33  | 31  | 14 | 0         | 29 | 0         |
| Yang        | 2007 | China     | T4            | T3   | 13.8 ± 6.2           | 85  | 78  | 38 | 0         | 55 | 0         |
| Yazbek      | 2009 | Brazil    | T3-4          | T2-3 | 20                   | 30  | 30  | 29 | 4         | 28 | 13        |

EG, Experiment group; CG, Control group.

published in English. All of the full texts or abstracts and their citations were scanned and reviewed.

**Inclusion criteria**

The inclusion criteria were RCTs comparing CS and severe CS after endoscopic thoracic sympathectomy.

**Exclusion criteria**

Studies were excluded from the analysis if they did not meet the inclusion criteria or if the corresponding author was not able to provide data from the published results. Abstracts of RCTs were excluded if the fundoplication circumference, surgical technique, methodological quality, and risk of bias could not be assessed.

**Data extraction**

The titles and abstracts of all retrieved records followed by the full text of the articles were examined independently by two authors (Cai SW and Zhang JH) according to the Quality of Reporting of Meta-analyses guidelines (11-13). The corresponding author for each included publication was contacted if information was missing or unclear. If no response was received within 1 month, we used the available data for the analyses.

**Risk of bias assessment**

The risk of bias was assessed for all of the articles using both Cochrane Collaboration’s tool for assessing the risk of bias (14) and the Jadad scoring system (15). Cochrane Collaboration’s tool evaluates random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other sources of bias. The Jadad scoring system assesses randomization, double blinding and withdrawals and dropouts, with a total score of 5. Any discrepancies were resolved by discussion among all of the authors.

**Statistical analysis**

Meta-analyses of the RCTs and observational studies were performed separately in all analyses using Review Manager 5.2. A separate meta-analysis was performed for bariatric surgery and non-bariatric surgery across both subgroups. In all analyses, the outcomes of surgical site infection were calculated as odds ratios (ORs) with 95% confidence intervals (CIs). For pooled estimates, the Mantel-Haenszel [chi]<sup>2</sup> method was used. Statistical heterogeneity

for the pooled ORs was calculated as I<sup>2</sup> with a Z-statistic test for the overall effect. A fixed effects model was applied for meta-analysis of the RCTs when I<sup>2</sup> <40%. A random effects model was used for meta-analysis of the observational studies irrespective of the I<sup>2</sup> value due to considerable clinical heterogeneity in the surgical procedures and study designs (16).

**RESULTS**

**Characteristics of the pooled RCTs**

A total of 2719 studies were searched; 11 studies fulfilled the inclusion criteria and were included in this study. The meta-analysis included 11 RCT studies with a total of 1079 patients (585 in the experimental groups and 519 in the control groups), and 25 patients were enrolled in both an experimental group and a control group because they had undergone unilateral T2 and T3 ablation followed by contralateral ablation at level T2 only. Five of the RCTs studied restricting the level of sympathectomy (17-21), and six studied lowering the level of sympathectomy (22-26) (Table 1). Two of the studies did not report the exact number of severe CS patients (19,20), and we obtained the unpublished results by e-mail. In both cases, the studies had no severe CS patients.

One study allocated patients into four groups; we designated group 3 in that study as the control group and the other three groups as experimental groups according to the operation location (18). One study divided patients into three groups; we renamed the R2-3 group as the control group and the other groups as experimental groups based on the level of operation (25). Table 2 presents the results of the risk of bias assessment for the included studies.

**Quality assessment**

In general, the overall methodological study quality was good (Table 2). Most studies applied randomization and concealed the patient allocation information. However, most studies were not double blinded because this design is difficult to accomplish in the perioperative period.

**Publication bias**

There were inadequate numbers of RCTs to assess publication bias. Funnel plots were drawn for each outcome. Based on the graphical examination, no asymmetry of the funnel plots was found; therefore, no publication bias was present (data not shown).



**Table 2 - Risk of Bias.**

| Author           | Cochrane Risk of Bias Criteria |                        |  |                                |                         |                     |                       | Jadad score |
|------------------|--------------------------------|------------------------|--|--------------------------------|-------------------------|---------------------|-----------------------|-------------|
|                  | Random sequence generation     | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other sources of bias |             |
| Baumgartner F.J. | Low                            | Unclear                | High                                   | High                           | Low                     | Low                 | Low                   | 2           |
| Inan K.          | Unclear                        | Unclear                | High                                   | High                           | Low                     | Low                 | Low                   | 2           |
| Ishy A           | Low                            | Unclear                | High                                   | High                           | Low                     | Low                 | Low                   | 2           |
| Katara A.N.      | Low                            | Low                    | High                                   | High                           | Low                     | Low                 | Low                   | 3           |
| Li X             | Low                            | Low                    | High                                   | High                           | Low                     | Low                 | Low                   | 3           |
| Licht PB         | Low                            | Low                    | Low                                    | Low                            | High                    | Low                 | Low                   | 4           |
| Liu YG           | Low                            | Unclear                | High                                   | High                           | Low                     | Low                 | Low                   | 2           |
| Mahdy T          | Low                            | Low                    | High                                   | High                           | Low                     | Low                 | Low                   | 3           |
| Munia MA         | Unclear                        | Unclear                | High                                   | High                           | Low                     | Low                 | Low                   | 2           |
| Yang J           | Low                            | Unclear                | High                                   | High                           | Low                     | Low                 | Low                   | 2           |
| Yazbek G         | Low                            | Unclear                | High                                   | High                           | Low                     | Low                 | Low                   | 2           |

The level of bias was determined as follows: "Low" indicates a low risk of bias; "Unclear" indicates an uncertain risk of bias; and "High" indicates a high risk of bias.

**Restricting or lowering the level of sympathectomy**

The test for heterogeneity showed that statistical heterogeneity was detected between the two groups in terms of CS after the operation ( $I^2 = 54\%$ ;  $p = 0.02$ ), and a random effects model was used. CS differed between the two groups (OR: 0.52; 95% CI: 0.32 to 0.84;  $p = 0.008$ ), as shown in Figure 1. The test for heterogeneity showed that statistical heterogeneity was not detected between the two groups regarding severe CS after the operation ( $I^2 = 0\%$ ;  $p = 0.76$ ), and a fixed effects model was used. Subgroup analysis revealed that the two groups were significantly different regarding severe CS after the operation (OR: 0.31; 95% CI: 0.16 to 0.61;  $p = 0.006$ ) (data not shown).

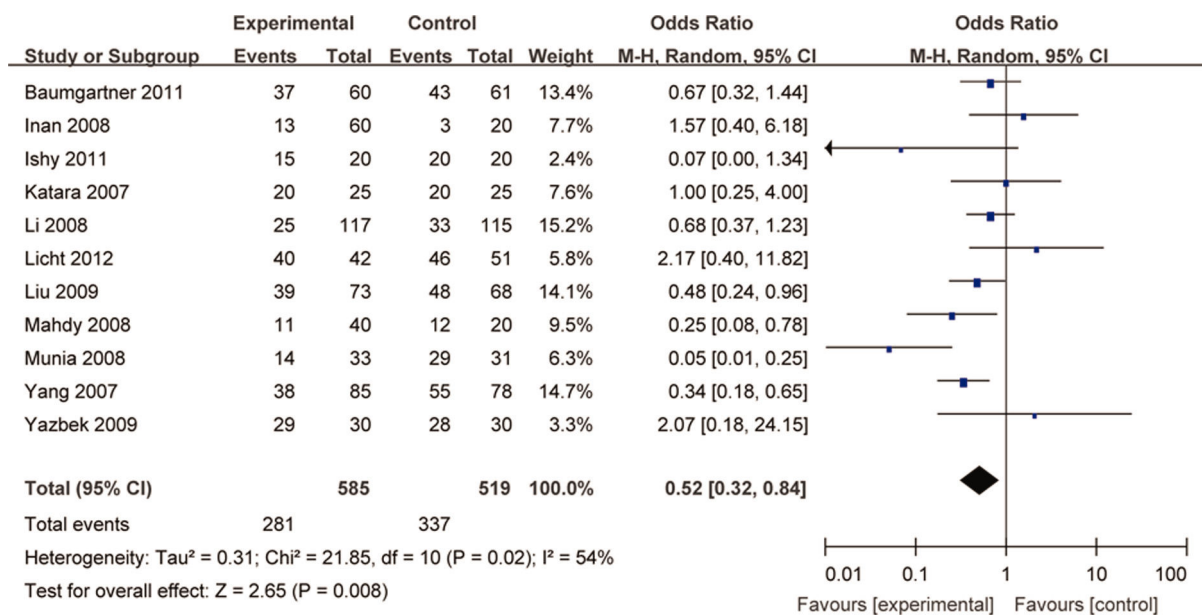
**Restricting the level of sympathectomy**

The test for heterogeneity showed that statistical heterogeneity was detected between the two groups in terms of CS after the operation ( $I^2 = 71\%$ ;  $p = 0.007$ ), and a random effects

model was used. CS did not differ between groups (OR: 0.66; 95% CI: 0.23 to 1.88;  $p = 0.44$ ), as shown in Figure 2. Subgroup analysis revealed that the two groups were not significantly different in terms of severe CS after the operation (OR: 0.33; 95% CI: 0.10 to 1.08;  $p = 0.007$ ) (data not shown).

**Lowering the level of sympathectomy**

Statistical heterogeneity was not detected between the two groups ( $I^2 = 15\%$ ,  $p = 0.32$ ), and a fixed effects model was used. Lowering the level of sympathectomy significantly reduced CS compared with that of the control group (OR: 0.43; 95% CI: 0.30 to 0.61;  $p < 0.00001$ ), as shown in Figure 3. Subgroup analysis revealed that lowering the level of sympathectomy significantly reduced the severe CS compared with the control group (OR: 0.30; 95% CI: 0.13 to 0.67;  $p = 0.004$ ), and statistical heterogeneity was not detected ( $I^2 = 0\%$ ;  $p = 0.61$ ) (data not shown).



**Figure 1 - CS after restricting or lowering the level of sympathectomy. CI, confidence interval; CS, compensatory sweating.**

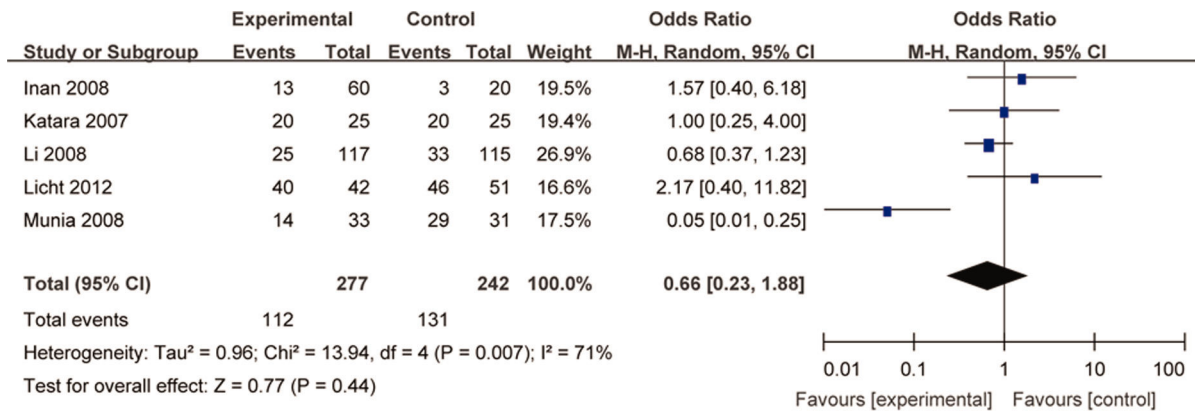


Figure 2 - CS after restricting the level of sympathectomy. CI, confidence interval; CS, compensatory sweating.

### Preserving the T2 level in the sympathectomy

Statistical heterogeneity was not detected between the two groups (I<sup>2</sup>=29%; p=0.23), and a fixed effects model was used. Preserving the T2 level during sympathectomy reduced CS compared with that of the control group (OR: 0.51; 95% CI: 0.36 to 0.73; p=0.0002), as shown in Figure 4. Subgroup analysis revealed that preserving T2 in the sympathectomy significantly reduced the severe CS compared with that of the control group (OR: 0.29; 95% CI: 0.14 to 0.58; p=0.0005), and statistical heterogeneity was not detected (I<sup>2</sup>=0%; p=0.61) (data not shown).

### DISCUSSION

The results of this meta-analysis show that restricting or lowering the level of sympathectomy can decrease CS after surgery. However, statistical heterogeneity was found. To explore the heterogeneity, we conducted subgroup analyses on restricting the level of sympathectomy and lowering the level of sympathectomy. The results indicated that the statistical heterogeneity mainly originated in the subgroup in which the level of sympathectomy was restricted.

Subgroup analysis indicated that lowering the level of sympathectomy can reduce CS and severe CS after surgery but that restricting the level of sympathectomy does not

reduce CS and severe CS. These findings differ from those of the meta-analysis conducted by Deng et al and published in 2009 (8). That meta-analysis demonstrated that single ganglia sympathectomy could reduce the total CS and severe CS compared with multiple ganglia blocking.

Our results showed that lowering the level of sympathectomy can reduce CS and severe CS after surgery, and this finding implies that the T2 ganglia may be very important for CS after ETS. The T2 ganglion is considered important for sympathetic innervation of the upper extremities. Some investigators have suggested that preservation of the T2 ganglion may decrease the severity of CS (3,27). Based on feedback mechanisms, Chou and his colleagues believe that T2 sympathectomy stops the main negative feedback sympathetic signals and that T2 sympathectomy therefore causes more severe CS than does T3 or T4 sympathectomy (3). To explore this phenomenon, we divided the data into two groups: an experimental group in which T2 was not reserved and a control group in which T2 was reserved. The meta-analysis results showed that preserving T2 increases CS.

We were unable to determine the optimal approach for sympathectomy. Multiple sympathectomy techniques have been described in the literature, including those in our analysis: T2-4, T2-3, T2, T3-5, T3-4, T3, T4-5 and T4. Excluding

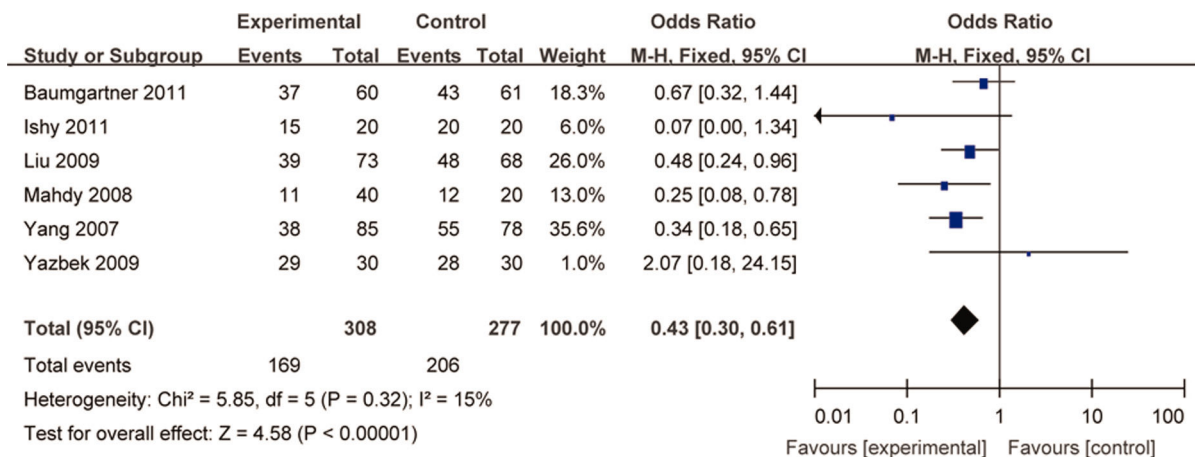


Figure 3 - CS after lowering the level of sympathectomy. CI, confidence interval; CS, compensatory sweating.

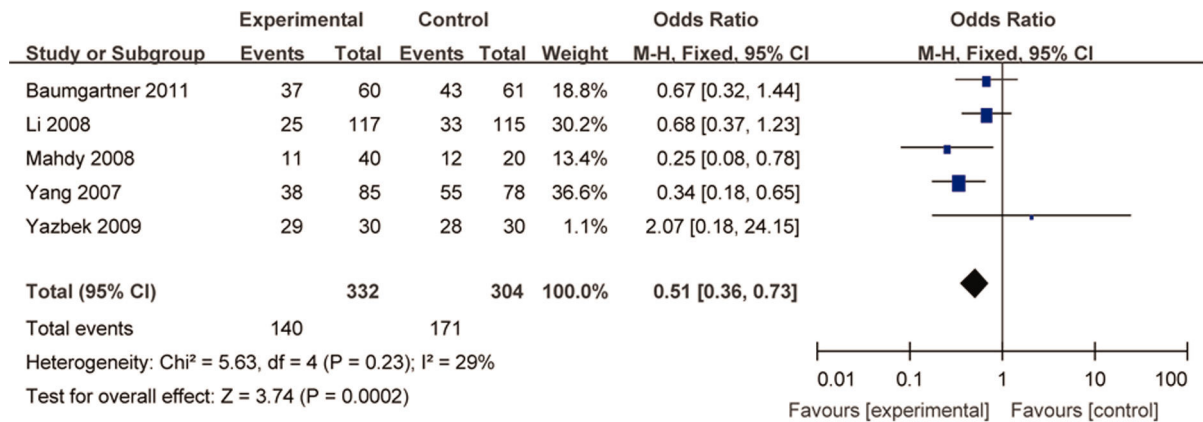


Figure 4 - CS after preserving T2 in sympathectomy. CI, confidence interval; CS, compensatory sweating.

T2-4, T2-3 and T2 sympathectomy based on our finding that the group in which T2 was preserved showed increased CS, only four studies analyzed T3-5, T3-4, T3, T4-5 and T4 sympathectomy. We were therefore unable to assess the superiority of T3-5, T3-4, T3, T4-5 and T4 sympathectomy.

This is the first systematic review and meta-analysis of RCTs investigating ETS to assess whether lowering or restricting the level of sympathectomy can reduce compensatory sweating. The methodological approach in this systematic review has its strengths and limitations. One strength is the inclusion of RCTs.

The limitations of this study are the inclusion of trials of low methodological and surgical quality and the presence of significant heterogeneity in the results. The Oxford Centre for Evidence Based Medicine guidelines show that although systematic reviews of RCTs are considered to be the highest level of evidence, this determination relies on the absence of significant methodological, clinical and statistical heterogeneity. If a systematic review/meta-analysis has significant heterogeneity, then the maximum recommended grade that can be allocated is the lowest level (D) (28). A lack of standardized definitions may be responsible for heterogeneity in the results. There are many nomenclature systems used to describe the exact level of cauterly or chain and ganglia clipping used in ETS procedures; this variety of systems complicates any attempt to compare the results of various studies. The degrees of CS are also analyzed according to many different criteria.

Another limitation is the low sample size. There are only 11 included studies, and the number of included studies was insufficient to perform some of the preplanned subgroup and meta-regression analyses.

In our study, the heterogeneity in the meta-analysis in terms of restricting the level of sympathectomy to reduce CS was significant. In other words, the results pertaining to restricting the level of sympathectomy to reduce CS are underpowered.

In summary, the compiled RCT results published so far in the literature do not support the claims that lowering or restricting the level of sympathetic ablation results in less CS.

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**AUTHOR CONTRIBUTIONS**

Cai SW<sup>#</sup> and Shen N<sup>#</sup> contributed equally to this work and should be considered co-first authors. Cai SW and Zhang JH conceived and designed the experiments. Shen N, Li DX, and Wei B performed the experiments. Cai SW and Li D analyzed the data. Shen N and Jun A contributed reagents/materials/analysis tools. Cai SW and Zhang JH wrote the paper. All of the authors read and approved the final version of the manuscript.

<sup>#</sup>These authors contributed equally to this work.

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