Title:

Effect of Myofunctional Therapy on Children with Obstructive Sleep Apnea: A Meta-Analysis

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Keywords: obstructive sleep apnea, systematic review, myofunctional therapy

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Abstract
Objective: To systematically review the current literature for articles describing the effect of myofunctional therapy on pediatric obstructive sleep apnea (OSA) and to perform a meta-analysis on the sleep study data.

Methods: Three authors (A.B., K.K. and M.C.) independently searched from inception through April 20, 2020 in PubMed/MEDLINE, Scopus, Embase, Google Scholar and The Cochrane Library. Mean difference (MD), standard deviations and 95% confidence intervals were combined in the meta-analysis for apnea-hypopnea index (AHI), mean oxygen saturations, and lowest oxygen saturations (nadir O2).

Results: 10 studies with 241 patients met study criteria and were further analyzed. The AHI reduced from 4.32 (5.2) to 2.48 (4.0) events/hr, a 43% reduction. Random effects modeling demonstrated a mean difference in AHI of -1.54 (95% CI -2.24,-0.85)/hr, z-score is 4.36 (p<0.0001). Mean oxygen saturation increased by 0.37 (95% CI 0.06,0.69) percent, z-score is 2.32 (p=0.02). There was no significant increase in nadir O2.

Conclusions: Despite heterogeneity in exercises, myofunctional therapy decreased AHI by 43% in children, and increased mean oxygen saturations in children with mild to moderate OSA and can serve as an adjunct OSA treatment.

Keywords: Obstructive sleep apnea; Sleep apnea syndromes; Systematic review; Meta-Analysis; Myofunctional Therapy

Credit Author statement: AB-Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing - original draft; KK- Data curation, Methodology,
INTRODUCTION:
Obstructive sleep apnea (OSA) can affect 1-6% of children\(^1\). OSA is characterized by repeated episodes of upper airway obstruction during sleep\(^2\). Untreated OSA can lead to adverse cardiovascular, neurocognitive outcomes and lower quality of life\(^3,4\).
Pathophysiology of pediatric OSA differs significantly from adult OSA\(^5\). Children with OSA report narrower maxilla, mandibular retrognathia, longer lower facial height, caudal placement of hyoid bone, larger adenoids, tonsils and soft palate\(^6,7\). Facial growth in pediatric OSA is influenced by route of breathing. Mouth breathing induces morphological skeletal changes in the maxilla and mandible which is at least partially reversible after treatment\(^8,9\). In children, the primary cause of OSA is thought to be hypertrophy of upper airway lymphoadenoid tissue\(^10\). This is not seen in adults. Consequently, adenotonsillectomy is regarded as the first line of treatment for pediatric OSA\(^11\). However, there is a high prevalence of residual OSA despite adenotonsillectomy\(^12\). Causes for residual OSA may be due to (1) abnormal craniofacial anatomy, (2) increased tissue deposition/infiltration or (3) due to increased airway collapsibility. Decreasing airway collapsibility by strengthening airway muscles has been utilized in myofunctional therapy (MT) \(^13,14\). A meta-analysis of myofunctional therapy demonstrated reduction in severity of OSA in adults and children\(^15\). However, this meta analysis included only 2 pediatric studies\(^14,16\). Another recent meta analysis concluded that there is a high level of heterogeneity of myofunctional therapy interventions and high risk of bias due to low quality evidence\(^17\). Due to intrinsic differences in the
pathophysiology of OSA between adults and children, it is important to look at the pediatric data separately.

Myofunctional therapy was first described in 1918, to increase mandibular growth and improve nasal breathing\textsuperscript{18}. In 1999, it was proposed as a new therapy for management of OSA\textsuperscript{13}. The premise of this therapy is built on isotonic and isometric exercises that promote the sensitivity, proprioception, mobility, coordination and strength of orofacial structures\textsuperscript{19}. MT include different types of soft palate, tongue and facial muscle exercises. These exercises are performed daily and lead to strengthening of the tongue and orofacial muscles thereby realigning to the correct intraoral position. It is relatively easy to teach and has very few complications. However, it relies on patient co-operation and adherence for optimal benefit. Recently, some studies have used a passive MT through an intra-oral device instead of an active exercise structure and is expected to have improved compliance. However, no study has evaluated the effect of active and passive MT separately on OSA in children.

The objective of this study is to systematically review the literature for articles evaluating active and passive MT as treatment for OSA in children and to perform a meta-analysis on the available polysomnographic data.

**METHODS:**

The **inclusion criteria** for this study were as follows (with the PICOS acronym):

- **Patients:** any child (<18 years) with OSA
- **Intervention:** myofunctional therapy, active or passive
- **Comparison:** pre- and postintervention sleep study data
- **Outcomes:** apnea-hypopnea index (AHI), mean oxygen saturation, nadir oxygen saturation (LSAT), prevalence of mouth breathing (determined by study PI)
- **Study Design:** case series, case-control, cohort, and/or randomized controlled trials

Studies were included if outcome data was reported before and after myofunctional therapy was implemented. Post intervention study should have been conducted at the conclusion of myofunctional therapy.

**Information source:**

Databases include the Ovid Medline, Embase, Cumulative Index to Nursing and Allied Health, Cochrane Library, Scopus searched from inception through May 1st, 2020.

**Search strategy:**

- Terms related to obstructive sleep apnea, obesity hypoventilation, snoring, sleep disordered breathing, or upper airway resistance/obstruction were searched, and combined with terms for myofunctional therapy, myotherapy, myology, myofacial, myofascial. Additionally, facial anatomical terms (lip, tongue, facial muscles) and speech therapy or exercises were also searched.
- Refined for children 0-18 years old in addition to text word searching for keywords related to children.

The detailed search strategy has been outlined for Ovid Medline in supplemental data.

**Data extraction:**
Search strategy was discussed by all 3 participants at the onset of the study. Once search study was finalized, librarian KK ran the search and provide all the references to both reviewers in an Endnote file.

Both reviewers (AB and MC) independently screened the titles, abstracts and relevant full text articles and finalized the articles to be included, containing primary outcome (AHI).

AB extracted data and entered it in Review manager 5.3 for each of the outcomes. MC checked the extracted data.

Data included:

1. Study design and methodology (prospective, retrospective, case control, randomized controlled trial)

2. Participant demographics and baseline characteristics including age, gender, prior history of adenotonsillectomy, orthodontic treatment

3. Intervention: Data was collected on the nature of the intervention, including, whether it was active or passive in nature.

4. Outcomes: mean (SD) AHI, mean oxygen saturations, nadir oxygen saturations prior to myofunctional therapy as well as post intervention. Number of patients with mouth breathing (determined by study PI) before and after mouth breathing.

Data items:
If a study reported outcomes for obstructive AHI and overall AHI, we selected obstructive AHI, as this number includes only the obstructive component derived from the sleep study.

Secondary outcome included mouth breathing. Although mouth breathing should be assessed by polysomnogram, several studies have measured mouth breathing indirectly by using Iowa Oral Performance Instrument (IOPI) to evaluate tongue endurance and muscle strength.

Any disagreement between individual judgments was resolved by a discussion between AB and MC. Final inclusion was decided by MC.

Missing data (unreported or clarifications) was handled by contacting the first author via email. A second email was sent in 2 weeks if no response was received. If no response was received after the second email, then a third email was sent to the last author. If no response was received, then that particular study was excluded from the analysis for the missing outcome.

**Data synthesis:**

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were utilized for this review as much as possible. Data was synthesized using Review Manager 5.3 software. The data collected for meta-analysis included means, standard deviations, mean differences, standardized mean differences and 95% confidence intervals [95% CI]. To
determine the standardized mean differences’ magnitudes of effect, we used the guidelines outlined by Cohen: 0.2, a small effect, 0.5 a medium effect and 0.8 a large effect\textsuperscript{21}.

**Statistical analysis:**

Means and standard deviations were calculated before and after myofunctional therapy for AHI, mean oxygen saturations and nadir oxygen saturations. Studies providing raw patient data without means and standard deviations were manually calculated or the respective authors were contacted for the data. The null hypothesis for this study is that there is no difference in outcome data before and after myofunctional therapy. For the meta-analysis, the program: Review Manager (RevMan) [Computer program] Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used. A random-effects model was used throughout the meta-analysis. The means, standard deviations, and 95% confidence intervals (CI) were calculated by REVMAN. $I^2$ statistic was used for determining the inconsistency (inconsistency levels: low = 25%, moderate = 50% and high = 75%).\textsuperscript{22} The Cochran Q statistic was used for determining heterogeneity, with a $P \leq 0.1$ being considered as significant heterogeneity.\textsuperscript{23} If inconsistency and/or heterogeneity were identified, then a sensitivity analysis was performed by individually removing one study at a time.

Forest plots were created after extracting pre and post myofunctional therapy data for each of the primary outcomes. Mean difference and effect estimate were combined using random effects meta-analysis for AHI, mean oxygen saturations
and nadir oxygen saturations pre and post MT. Odds ratios were combined using a random effects meta-analysis for mouth breathing. Effect estimate was reported for all 4 outcomes.

A funnel plot to assess for risk of publication bias was performed if at least 10 studies report a specific variable (as recommended by Cochrane collaboration).

RESULTS:

A total of 598 were screened for relevance and 470 were excluded as they did not meet study criteria. After identification of 128 potentially relevant studies, they were downloaded, and abstracts were reviewed. Ten studies met criteria and were selected for this review\textsuperscript{14,16,24-31}. We were unable to obtain outcome measures from one of these studies, despite contacting the authors. This study was removed from our quantitative analysis\textsuperscript{14}. Figure 1 summarizes the flow for study selection. One study was a case report\textsuperscript{24}, 2 studies were retrospective case series\textsuperscript{14,28}, 3 studies were prospective case series\textsuperscript{25,29,31}, 1 study was a prospective case control\textsuperscript{26} and 3 studies were randomized controlled trials\textsuperscript{16,27,30}. None of the randomized controlled trials were blinded and none gave details on randomization.

Table 1 depicts details of the selected studies. 3 studies used passive myofunctional therapy\textsuperscript{25,26,29}, 6 studies used active myofunctional therapy while 1 study had 3 arms, dividing the cohort into passive, active myofunctional therapy and control groups\textsuperscript{27}. 285 children were included in this review, of which 241 received myofunctional therapy and the remaining were 44 children were
controls\textsuperscript{26,28,30}. If the same authors published more than two articles, they were contacted to ask whether data from any of the recruited children in one study overlapped with another study or not\textsuperscript{16,28}. One of the articles, did not provide outcome measures on the children who received myofunctional therapy. The authors were contacted and data was obtained\textsuperscript{28}. Five authors were contacted for secondary outcome measures and data was obtained from four of the authors\textsuperscript{16,25,29,31}. We were unable to obtain data from one of the articles so excluded the study from quantitative analysis\textsuperscript{14}. All studies were performed on children who had residual OSA after adenoidectomy, tonsillectomy or adenotonsillectomy except 3 studies which included children with OSA without adenotonsillar hypertrophy\textsuperscript{26,27,29} and 1 study which did not report previous history of surgery\textsuperscript{30}.

**Compliance:**

Six studies did not report compliance for myofunctional therapy\textsuperscript{14,16,24,25,29}. Lee\textsuperscript{28} reported that only 9, out of the 35 patients referred to myofunctional therapy, (25.7\%) pursued it. Chuang\textsuperscript{26} reported 80\% compliance. Von Lukowicz\textsuperscript{31} reported 100\% compliance for 1 week intense therapy. Huang\textsuperscript{27} reported that 10 of 23 children (43.4\%) had good compliance with active myofunctional therapy while 50 of 56 (89\%) children had good compliance with passive myofunctional therapy. Huang\textsuperscript{27} reported data only on the 50 children who reported good compliance.

**Comorbidities:**
While 2 studies specifically mentioned that the included children were non-syndromic, the rest of the studies did not report this comorbidity\(^{14,29}\). 1 study was performed entirely on children with Down syndrome\(^{31}\). BMI was reported in 3 studies\(^{25-27}\) and was within normal range. One study reported that the children were normal weight\(^{28}\). Villa reported mean BMI centile of 81.85 (29.94)\(^{16}\) and in another study reported prevalence of obesity to be 2\%\(^{30}\). The rest of the 4 studies did not report data on weight. Chuang reported data on prematurity, while the rest of the studies did not report this data\(^{25}\).

**Polysomnogram:**

Three studies utilized home sleep study\(^{24,29,31}\), while the rest of the 6 studies were performed in-laboratory. 4 studies reported using AASM criteria for scoring studies\(^{14,16,30,31}\), while the rest of the studies did not report the criteria they utilized.

**AHI**

After myofunctional therapy, AHI decreased by 1.54 events/hr (95% CI -2.24,-0.85), \(Z\) score of 4.36 (\(p<0.0001\)) (**Figure 2a**). Both the \(I^2\) (72\%) and \(Q\) statistics (\(p=0.0003\)) suggested significant heterogeneity. Studies were individually excluded to identify the source. Exclusion of studies by Alexander\(^{24}\), active myofunctional therapy subgroup of Huang\(^{27}\) and Lee\(^{28}\), resulted in no heterogeneity in the remaining 160 children with \(I^2\) of 0\% and \(Q\) statistic value of 0.48. The mean decrease in AHI for the remaining studies was 2.22 events/hr (95% CI -2.87,-1.57) (\(Z=6.69\), \(P<0.00001\)). This has been shown in Figure 2b. After excluding study by
von Lukowicz, which performed 1 week intense myofunctional therapy in children with Down syndrome, there was a sustained decrease in AHI by 2.26 events/hr (95% CI -2.92, -1.59)\textsuperscript{31} (z=4.34, p<0.00001). After excluding all the studies performing home sleep studies, there was a decrease in AHI by 2.35 events/hr (95% CI -3.26,-1.44) in 133 children\textsuperscript{24,29,31} (z=4.41, p<0.0001).

Next, we analyzed change in AHI in children with residual OSA. 72 children were included in the study\textsuperscript{16,24,25,28,31}. There was a significant decrease in AHI by 1.61 events/hr (95% CI -2.70,-0.53), z=2.91, p=0.004). There was significant heterogeneity with I\textsuperscript{2}=79% and Q statistic value of 0.0009. We also analyzed change in AHI in 122 children with OSA without adenotonsillar hypertrophy\textsuperscript{26,27,29}. There was a significant decrease in AHI by 1.58 events/hr (95% CI -2.73,-0.44), z=2.71, p=0.007). There was significant heterogeneity (I\textsuperscript{2}=70%, Q statistic=0.02).

**Mean saturations**

After myofunctional therapy, there was a significant increase in mean oxygen saturations 0.37 percent (95% CI 0.06,0.69), z score 2.32 (p=0.02) (Figure 3a). There was significant heterogeneity, I\textsuperscript{2} (57%) and Q statistics (p-0.02). After removing study by Villa\textsuperscript{30}, there was no heterogeneity (I\textsuperscript{2}=0%, Q statistic value of 0.53) and the remaining 178 children still had an increase of 0.2 percent (95% CI 0.00, 0.39)% (z=1.99,p=0.05). This has been shown in Figure 3b.

**Nadir Saturations**
After myofunctional therapy, there was no significant increase in nadir oxygen saturations with significant heterogeneity ($I^2=87\%$, $Q$ statistics of $p<0.0001$) (Figure 4). This was sustained, even after removing studies\textsuperscript{29,30} to reduce heterogeneity.

**Mouth breathing**

Three studies reported mouth breathing. Two studies reported mouth breathing based on a myofunctional therapist evaluation\textsuperscript{16,30}. One of those two studies reported using a separate myofunctional therapist for evaluations to avoid observer bias\textsuperscript{30}. Another study reported mouth breathing using an oral scoop\textsuperscript{28}. In our review, children who received MT had a decreased odds ratio of persistent mouth breathing, OR 0.03 (95% CI 0.01,0.10). There was no heterogeneity with $I^2=0\%$ and $Q$ statistics ($p=0.49$) (Figure 5).

**Passive myofunctional therapy**

We separately analyzed the subgroup who received passive myofunctional therapy\textsuperscript{25-27,29}. After passive myofunctional therapy, AHI decreased by 2.14 events/hr (95% CI -2.87, -1.4), $Z$ score of 5.69 ($p<0.00001$) (Figure 6) in 128 children. Both the $I^2$ (4\%) and $Q$ statistics ($p=0.37$) suggested no significant heterogeneity. In contrast, 66 children who received active myofunctional therapy, had a decrease in AHI by 1.04 events/hr (95% CI -1.98,-0.09), z score of 2.15 ($p=0.03$). There was significant heterogeneity, $I^2=80\%$ and $Q$ statistics ($p=0.0004$). Exclusion of 2 studies, showed low heterogeneity, $I^2=37\%$ and $Q$ statistics ($p=0.21$).
and showed a decrease of AHI by 1.87 events/hr (95% CI -2.98,-0.75) in 41 children\textsuperscript{24,27}.

There was no significant increase in mean oxygen saturations in the subgroup who received passive myofunctional therapy.

**DISCUSSION:**

Our systematic review and meta-analysis of ten studies is the first to report the effect of MT in children with OSA. Myofunctional therapy, active and passive, decreased AHI and increased mean oxygen saturations in children with mild to moderate OSA. Myofunctional therapy decreased odds ratio of persistent mouth breathing in children with mild to moderate OSA.

Our study showed a small yet significant decrease in AHI after myofunctional therapy, even after removing studies causing heterogeneity, study on syndromic children as well as study utilizing home sleep studies. This decrease is lower compared to adult literature\textsuperscript{15}. This is an interesting observation, since there is a wide variation in the type of myofunctional exercises and duration of therapy. Reported compliance for active myofunctional therapy was lower than passive myofunctional therapy. Active exercises involved soft palate, tongue, labial seal and lip tone exercises. Passive myofunctional therapy included an oral device for advancing mandible with bead mounted on lower frame for the tip of the tongue to roll on. Frequency of therapy ranged from 20 min/day to three 45 min sessions per day. Duration of therapy ranged from 1 week to 50 months. One of the studies
had an active and passive myofunctional therapy arm compared to a control arm\textsuperscript{27}. The study did not find a significant difference in AHI in the active myofunctional therapy group, however, there was a high rate of drop out in the active myofunctional therapy group. Our study found a small yet significant decrease in AHI in children with residual OSA as well as children with OSA without adenotonsillar hypertrophy.

Our study showed a small but significant increase in mean oxygen saturations in the children who received myofunctional therapy. There was no significant difference in nadir oxygen saturations. This is different compared to adult literature. While it may be argued that myofunctional therapy does not result in a drastic difference in polysomnographic parameters, it should also be remembered that there is a significant difference in the sleep and respiratory physiology of children and adults\textsuperscript{32}. The small difference in mean saturations holds promise and needs further investigation.

Our study reports significant improvement in mouth breathing after myofunctional therapy. Mouth breathing is fairly common in children with OSA and has been shown to be persistent despite adenotonsillectomy. Mouth breathing can lead to changes in proprioception, posture and loss of usage of nose. There is a growing body of literature which states that nasal breathing is of critical developmental importance for normal oropharyngeal development. Myofunctional treatments encourage normal orofacial muscle tone associated with normal nasal
breathing through daily exercise involving orofacial muscles and stimulation of sensory pathways.

While polysomnographic data is important to determine improvement in OSA, few studies have evaluated other outcome measures. Due to inconsistency in reporting other outcome measures, we were unable to include them in our study. Cephalometric films\textsuperscript{26,27}, Iowa Oral Performance Instrument (IOPI)\textsuperscript{30} and quality of life assessed with OSA-18\textsuperscript{26} have been utilized by various studies. Night time symptoms like snoring and daytime symptoms like sleepiness or hyperactivity have not been consistently studied. There is a need to assess these symptoms to ascertain the clinical effectiveness of myofunctional therapy in children with OSA.

**Limitations**

Our study is the first to focus on the effect of myofunctional therapy in children with OSA. However, there were a few limitations. There were only 3 randomized controlled studies. However, due to the nature of the therapy, these studies had a high risk of bias. Risk of bias was due to paucity of random sequence generation, allocation concealment and blinding. Data on co-interventions has not been consistently reported so there is a risk for unclear bias. Another limitation is that there was no long term follow up of studies. Thus, it is difficult to infer whether the difference in AHI, mean oxygen saturations or mouth breathing were sustained or not. The heterogeneity of the frequency, duration and type of myofunctional exercises is another limitation. Moreover, most of the studies did not report compliance of the prescribed myofunctional therapy. Finally, there is a lack of
studies focusing on effect of myofunctional therapy on night/daytime symptoms and quality of life\textsuperscript{26}.

**Conclusion**

Despite heterogeneity in exercises, myofunctional therapy can decrease AHI and increase mean oxygen saturations in children with mild to moderate residual OSA as well as children without adenotonsillar hypertrophy and serve as an adjunct treatment. Future studies should focus on ascertaining the sustainability of the effects of myofunctional therapy and interpreting a dose response relationship.
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CONFLICT OF INTEREST: None

Disclaimer:
The views expressed in this manuscript are those of the author(s) and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.
REFERENCE:

18. Rogers AP. Exercises for the development of muscles of face with view to increasing their functional activity. *Dental Cosmos LX.* 1918;59(857):e76.
Figure 1: PRISMA 2009 Flow Diagram Effect of Myofunctional Therapy on Children with Obstructive Sleep Apnea: A Meta-Analysis

Figure 2a: Forest plot of Effect of myofunctional therapy on AHI in children

Figure 2b: Forest plot of Effect of myofunctional therapy on AHI in children (removing studies for heterogeneity)

Figure 3a: Forest plot of Effect of myofunctional therapy on mean oxygen saturations in children

Figure 3b: Forest plot of Effect of myofunctional therapy on mean oxygen saturations in children (removing studies for heterogeneity)

Figure 4: Forest plot of Effect of myofunctional therapy on nadir oxygen saturations in children

Figure 5: Forest plot of Effect of myofunctional therapy on mouth breathing in children

Figure 6: Forest plot of Effect of passive myofunctional therapy on AHI in children

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Heterogeneity: \( \tau^2 = 0.62; \) \( \chi^2 = 28.84, \text{df} = 8 (P = 0.0003); I^2 = 72\%
Test for overall effect: \( Z = 4.36 (P < 0.0001) \)
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<tr>
<td>Huang 2019a</td>
<td>2.85</td>
<td>2.45</td>
<td>50</td>
<td>5.56</td>
<td>6.65</td>
<td>50</td>
<td>11.0%</td>
<td>-2.71</td>
<td>-4.67, -0.75</td>
</tr>
<tr>
<td>Lee 2015</td>
<td>1.2</td>
<td>0.34</td>
<td>9</td>
<td>2.7</td>
<td>0.36</td>
<td>9</td>
<td>0.0%</td>
<td>-4.08</td>
<td>-5.85, -2.31</td>
</tr>
<tr>
<td>Levrini 2018</td>
<td>0.7</td>
<td>0.69</td>
<td>9</td>
<td>3.2</td>
<td>2.2</td>
<td>9</td>
<td>18.7%</td>
<td>-2.50</td>
<td>-4.01, -0.99</td>
</tr>
<tr>
<td>Villa 2015</td>
<td>1.84</td>
<td>1.56</td>
<td>14</td>
<td>4.87</td>
<td>2.89</td>
<td>14</td>
<td>14.3%</td>
<td>-3.03</td>
<td>-4.75, -1.31</td>
</tr>
<tr>
<td>von Lukowicz 2019</td>
<td>6.4</td>
<td>10.8</td>
<td>18</td>
<td>6.4</td>
<td>8.6</td>
<td>18</td>
<td>1.0%</td>
<td>0.00</td>
<td>-6.38, 6.38</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>160</td>
<td></td>
<td>160</td>
<td>100.0%</td>
<td></td>
<td>-2.22</td>
<td>-2.87, -1.57</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 4.54, df = 5 (P = 0.48); I² = 0%

Test for overall effect: Z = 6.69 (P < 0.000001)
The table and graph provide a summary of the study results and their statistical significance. The table shows the mean differences in various studies, along with the mean, standard deviation, and total number of participants. The graph illustrates the mean differences with a forest plot, indicating the direction of the effect and the confidence intervals. The total mean difference, along with its 95% confidence interval, is also presented. The heterogeneity test indicates a low level of heterogeneity among the studies, with a tau squared of 0.00, chi-square of 5.14, df of 6 (P = 0.53), and I^2 of 0%. The test for the overall effect shows a Z value of 1.99 (P = 0.05), indicating a statistically significant difference favoring the post MT condition.
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>post MT Events</th>
<th>Total</th>
<th>pre MT Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee 2015</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>29.3%</td>
<td>0.00 [0.00, 0.15]</td>
</tr>
<tr>
<td>Villa 2015</td>
<td>4</td>
<td>14</td>
<td>3</td>
<td>14</td>
<td>30.1%</td>
<td>0.03 [0.00, 0.32]</td>
</tr>
<tr>
<td>Villa 2017</td>
<td>3</td>
<td>18</td>
<td>2</td>
<td>18</td>
<td>40.6%</td>
<td>0.04 [0.01, 0.23]</td>
</tr>
</tbody>
</table>

Total (95% CI)     | 41            | 41    | 100.0%       |       |        | 0.03 [0.01, 0.10]           |

Total events       | 7             | 37    |              |       |        |                             |

Heterogeneity: Chi² = 1.44, df = 2 (P = 0.49); |² = 0%
Test for overall effect: Z = 5.55 (P < 0.00001)
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chuang 2017</td>
<td>1.9</td>
<td>2.5</td>
<td>29</td>
<td>5.4</td>
<td>5.9</td>
<td>29</td>
<td>9.2%</td>
<td>-3.50 [-5.83, -1.17]</td>
<td></td>
</tr>
<tr>
<td>Chuang LC 2019</td>
<td>2.16</td>
<td>1.8</td>
<td>40</td>
<td>3.75</td>
<td>2.48</td>
<td>40</td>
<td>55.6%</td>
<td>-1.59 [-2.54, -0.64]</td>
<td></td>
</tr>
<tr>
<td>Huang 2019a</td>
<td>2.85</td>
<td>2.45</td>
<td>50</td>
<td>5.56</td>
<td>6.65</td>
<td>50</td>
<td>13.0%</td>
<td>-2.71 [-4.67, -0.75]</td>
<td></td>
</tr>
<tr>
<td>Levrini 2018</td>
<td>0.7</td>
<td>0.69</td>
<td>9</td>
<td>3.2</td>
<td>2.2</td>
<td>9</td>
<td>22.1%</td>
<td>-2.50 [-4.01, -0.99]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

| 128 | 128 | 100.0% | -2.11 [-2.82, -1.40] |

Heterogeneity: $\chi^2 = 3.13$, df = 3 ($P = 0.37$); $I^2 = 4\%$
Test for overall effect: $Z = 5.85$ ($P < 0.000001$)