Drug Induced Sleep Endoscopy-Directed Tongue Surgery to Treat Persistent Pediatric Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis

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Abstract

Objective: To systematically review the literature for articles evaluating outcomes of drug-induced sleep endoscopy (DISE) directed tongue surgery in children with prior adenotonsillectomy and persistent or recurrent obstructive sleep apnea (OSA), and to perform a meta-analysis on the polysomnographic (PSG) data. **Design**: Systematic review and metanalysis in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement guidelines. **Outcome Measures:** Primary, post-operative apnea-hypopnea index (AHI) and lowest oxygen saturation (LSAT); Secondary, surgical response rate. **Results:** Seven studies (283 patients) met criteria and reported PSG outcome data for the systematic review. The mean ± standard deviation surgical response rate was 70.0 ± 17.0% [95% CI 67.6, 71.6]. Six of the seven studies (270 patients) reported specific pre- and post-operative PSG data included in our meta-analysis. The pre- and post-operative AHI decreased from 9.5 ± 12.1 to 4.2 ± 6.9 events/hr ($p < 0.04$) with a mean difference (MD) of -5.13 [95% CI -7.13, -3.13], Z-score 5.02 ($P<0.00001$). LSAT improved from 87.8 ± 5.7 to 90.1 ± 5.1% ($p < 0.02$) with a MD of 2.71 [95% CI 1.53, 3.89], Z-score 4.51 ($P<0.0001$). **Conclusion:** Existing literature demonstrates DISE-directed tongue surgery in children with persistent OSA can reduce AHI by approximately 50%, improve LSAT by nearly 3%, and have an overall positive response to surgery rate of 70%. There is collective evidence that DISE-directed tongue surgery is effective, but there is heterogeneity in reported outcomes influenced by confounding factors. **Key Words:** Drug Induced Sleep Endoscopy; Pediatric Sleep Apnea; Tongue Surgery

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difference (MD) of -5.13 [95% CI -7.13, -3.13], Z-score 5.02 (P<0.00001). LSAT improved from 87.8 ± 5.7 to 90.1 ± 5.1% (p < 0.02) with a MD of 2.71 [95% CI 1.53, 3.89], Z-score 4.51 (P<0.0001).

Conclusion: Existing literature demonstrates DISE-directed tongue surgery in children with persistent OSA can reduce AHI by approximately 50%, improve LSAT by nearly 3%, and have an overall positive response to surgery rate of 70%. There is collective evidence that DISE-directed tongue surgery is effective, but there is heterogeneity in reported outcomes influenced by confounding factors.

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Key Points:

1. DISE-directed tongue surgery in children with prior adenotonsillectomy and persistent/recurrent OSA demonstrates a statistically significant reduction in post-operative AHI.
2. DISE-directed pediatric tongue surgery demonstrates a statistically significant increase in post-operative LSAT.
3. Patients who underwent DISE-directed tongue surgery demonstrated statistically significant surgical response.
4. There is a paucity of prospective data for DISE-direct tongue surgery.
5. There is a paucity of long-term PSG outcome data for DISE-directed tongue surgery.

Rationale

Pediatric obstructive sleep apnea (OSA) is a condition of upper airway resistance obstructing air flow and oxygen delivery into the lungs during sleep. It is characterized by prolonged partial or complete upper airway obstruction that disrupts normal ventilation during sleep and interferes with normal sleep patterns.[1] OSA impacts upwards of 1.2-5.7% of the pediatric population with higher prevalence among children with morbid obesity, Down syndrome, craniofacial abnormalities, cerebral palsy, and hypotonia.[2,3]

Adenotonsillectomy is the first-line recommendation by the American Academy of Otolaryngology for treatment of pediatric OSA.[4] Despite its success, the persistence of OSA remains an issue for about 25-40% patients following surgery for a multitude of reasons including obesity, medical comorbidities, and other sites of airway obstruction.[2,5,6] Drug Induced Sleep Endoscopy (DISE) has become an indispensable tool to provide anatomic targets for the surgical management of persistent OSA. In patients with persistent or recurrent OSA, DISE directed surgeries have demonstrated statistically significant improvement in both lowest saturation of oxygen (LSAT) and apnea-hypopnea index (AHI).[7] Indeed the 2023 Expert Consensus statement by Ishman et al. recommends DISE for recurrent or persistent pediatric OSA after adenotonsillectomy.[2]

Among the anatomic subsites evaluated with DISE, lingual tonsil hypertrophy/tongue base have consistently been one of the most frequent sites of obstruction making it a very common surgical target.[7] Given the increasing trend toward performing DISE and the expected concomitant rise is surgical management of the tongue, it is imperative that we better understand the effectiveness of this intervention.

Objective

The goal of this study is to determine the efficacy of DISE-directed tongue base surgery in pediatric patients with persistent obstructive sleep apnea despite adenotonsillectomy by performing a systematic review of the literature and metanalysis comparing pre- and post-operative AHI and LSAT based on PSG data.

Methods

Eligibility Criteria We reviewed articles regarding the treatment of recurrent or persistent OSA which we defined as residual disease after complete or partial tonsillectomy with or without adenoidectomy, as determined by overnight PSG. We also included surgically naïve pediatric patients with small Brodski 1+ tonsils on exam with PSG-confirmed OSA. We defined tongue surgery as surgery addressing the posterior or base of tongue, lingual tonsils, suprahyoid epiglottis, or hyoid bone or musculature. Studies including multi-level upper airway surgery involving the tongue were included.

Articles were included if they:

1) reported on pediatric patients under 18 years of age who underwent DISE for recurrent or persistent OSA confirmed on PSG;

2) contained pre- and post-operative PSG data regarding DISE-directed tongue surgery;

3) contained an abstract;

4) were published in English;

5) were not classified as review articles or consensus statements.

Information Sources

We searched the PubMed, EMBASE, Web of Science, and Google Scholar databases from 1 MAY 2024 – 20 JUNE 2024.

Search Strategy and Selection Process

The search strategy was created in conjunction with a medical librarian using Medical Subject Headings intended for PubMed, and then tailored for the other databases. To facilitate this study, Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards were followed in accordance with the PRISMA checklist.[8]

Search categories combined the following terms and their synonyms to filter for the initial article screening: "Pediatric," "DISE," "OSA," "Adenotonsillectomy," and "Tongue Surgery" (see Appendix 1). Two independent investigators (KS and GJ) reviewed all identified titles, abstracts, and full-text articles to determine if they met inclusion criteria (Figure 1). In the event of disagreement regarding study inclusion, reviewers discussed among one another to reach a consensus on inclusion or exclusion.

Data Items and Collection Process

Information obtained from each article pertaining to the primary outcomes of interest included authors, year of publication, number of study participants, mean age, BMI, pre- and post-op AHI and LSAT (Table 1). BMI was documented in terms of either kg/m^2, percentile, or Z-score across all studies; for consistency, we converted BMI units to either "normal," "overweight," or "obese." Normal BMI is defined as BMI < 85 percentile for age or a Z-score < 1, overweight is defined as BMI between 85 and 95 percentile for age or a Z-score between 1 and 2, and obese is defined as BMI > 95 percentile for age or a Z-score > 2.[9] For studies which included a variety of single or multi-level surgical sites (e.g., lingual tonsillectomy alone, or revision adenoidectomy plus turbinoplasty), only outcome measures that involved tongue surgery were extracted for review. These measures were primarily from PSG data including mean AHI change or LSAT change after surgery (primary outcome), and the percentage of subjects who were successfully treated by surgery (responders, secondary outcome). The definition of a responder in this study depends on preoperative AHI. If the preoperative AHI > 5 events/hr then response was defined as post-operative AHI < 5 and/or a 50% reduction in AHI. Patients with a preoperative AHI of < 5 were considered responders if postoperative AHI was <1 which is considered surgical cure. This definition was adapted from the definition used by He et al.[15]

Ethical Considerations

This study was exempt from evaluation by our institutional review board because it is a review of published studies.

Study Quality Assessment

The level of evidence for each study was determined in accordance with the guidelines outlined by the Center for Evidence-Based Medicine (http://www.cebm.net/index). Non-randomized article quality was assessed with The National Institute for Health and Clinical Excellence (NICE) criteria: [?] 2 metrics met ("Yes") was considered poor quality, 3 – 5 was fair quality, [?] 6 considered good quality.

Statistical Analysis

Statistical analysis was performed with Microsoft Excel (Microsoft 365 MSO, Version 2405 Build 16.0.17628.20006, 64-bit). If means and standard deviations were not reported in the study of interest, they were manually calculated from the data provided if possible. For combining data, means were weighted based on study population size and standard deviations were pooled based on unequal study population sizes, and a two-tailed paired t-test was performed with $P < 0.05$ as the cutoff for significance. Reported data was converted to common units of measurement if possible, however some data was incomplete and unable to be converted without additional information. Review Manager (Version: 8.0.0, REVMAN) was used for the metanalysis. A random effects model was used if heterogeneity existed. When pooling the data in the studies, the means, standard deviations, p-values, and 95% confidence intervals (CI) were calculated in either Microsoft Excel or REVMAN. Heterogeneity was assessed with the I^2 statistic (inconsistency levels: low = 25%, moderate = 50%, high = 75%) and the Cochran Q statistic, with significant heterogeneity considered when $P < 0.1$ was obtained. If heterogeneity existed, a sensitivity analysis was performed by removing each of the studies to identify the source(s). The null hypothesis for this study was that no difference exists between pre- and post- DISE-directed tongue surgery PSG outcomes for our study population.

Results

Search terms "Pediatric," "DISE," "OSA," "Tongue Surgery," and their synonyms individually yielded tens of thousands of articles. There was significant filtration when combined in PubMed: ultimately a total of 89 articles were screened for relevance, and 49 were excluded. After identification of 40 potentially relevant articles, they were downloaded and reviewed. Eight articles met initial inclusion and exclusion criteria, but one paper[18] was excluded due to duplicate patient data published by the same author (screening flowchart, Figure 1).

In total, seven articles were used in the systematic review (284 patients, age 9.5 +- 3.9

years, normal/overweight status) and six of the studies (271 patients, age 8.5 +- 3.8 years, majority normal weight status) were suitable for metanalysis.[10–16] See Table 1 and S1 for a summary of the studies. Individual patient data tended to be reported in studies with lower population sizes (Esteller et al, Kanotra et al, Maksimoski et al, Ulualp et al); means and standard deviations were included.[10,11,13,16] Demographic data was reported in most studies but not clearly linked to individual patient PSG outcomes. The majority of DISE-directed tongue surgery involved multi-level airway surgery (e.g. lingual tonsillectomy plus revision adenoidectomy).

He et al reported pre- and post- operative PSG data but did not specify which data corresponds to which type of surgery; however, the study did include responder and non-responder data directly linked to the type of surgery, so it was included in the systematic review but not primary outcome metanalysis.[15] Only three of the seven studies (185 patients, 65% of pooled study population) documented post-operative PSG timeline with an average of minimum 2.1 months post-op.[10,14,16]

Primary Outcomes

The pre- and post-operative AHI weighted mean +- pooled standard deviation (M +- SD; 270 patients) decreased from 9.5 +- 12.1 to 4.2 +- 6.9 events/hr ($p < 0.04$) (Table 1) with a mean difference (MD) of -5.13 [95% CI -7.13, -3.13], Z-score 5.02 ($P<0.00001$) (Figure 2). The I^2 statistic (54%) demonstrated moderate heterogeneity, and the Q statistic ($P = 0.05$) indicated heterogeneity of significance. Studies were individually excluded to identify the source(s) of heterogeneity: for AHI primary outcome, Ulualp et al was determined to be the main contributor of heterogeneity when sensitivity was investigated.[16] With this study removed, $I^2 = 7\%$ and $P = 0.37$. The mean difference of the remaining studies was -4.51 [95% CI -5.66, -3.35].

The pre- and post-operative LSAT M +- SD (263 patients) increased from 87.8 +- 5.7 to 90.1 +- 5.1% ($p < 0.02$) (Table 1) with a MD of 2.71 [95% CI 1.53, 3.89], Z score 4.51 ($P<0.0001$) (Figure 3). The I^2 statistic (44%) demonstrated moderate heterogeneity, and the Q statistic ($P = 0.13$) indicated no heterogeneity of

significance (Figure 3). Studies were individually excluded to identify the source(s). For LSAT, the primary contributor to heterogeneity found during sensitivity investigation was Kanotra et al. When this study was removed, $I^2 = 0\%$ and $P = 0.66$. The mean difference of the remaining studies was 2.21% [95% CI 1.29, 3.14].

Overall response to treatment

Response to treatment was evaluated as a secondary outcome. If the preoperative AHI > 5 events/hr then response was defined as post-operative AHI < 5 and/or a 50% reduction in AHI. Patients with a preoperative AHI of < 5 were considered responders if postoperative AHI was <1 which is considered surgical cure. All seven studies (283 patients) were included in this analysis with a M +- SD of 70.0 +/- 17.0% [95% CI 67.6, 71.6], and non-response rate of 30.0 +- 17.0% [95% CI 28.4, 32.4] (Table 2).

Individual Studies

While all studies selected for the systematic review and metanalysis offered informative pre- and post-operative PSG data, the goals and designs of the studies themselves were not ubiquitously tailored to demonstrating DISE-directed tongue surgery efficacy. Some data sets required careful extraction of relevant data for the purposes of this review and meta-analysis.

Esteller et al conducted a prospective cohort study with 20 pediatric patients comparing pre- and post-operative AHI and snoring intensity visual analog scale (VAS) data. Only 7 of the 20 patients had DISE-guided tongue surgery, all of which were multi-level (i.e. radiofrequency lingual tonsillectomy plus revision adenoidectomy, pharyngoplasty, and/or revision tonsillectomy). Determined by DISE, tongue base obstruction was present in 40% of the patients. AHI improved with tongue surgery, LSAT was not reported (Table 1). The study reported significant decrease in the VAS score for snoring after (1.55 +- 1.701) compared to before (6.75 +- 2.337) DISE-directed surgery ($p < 0.05$), with 80% of the patients' parents reporting VAS > 6 prior to surgery, but this data is confounded with upper airway surgery not involving the tongue.[10]

He et al's retrospective study also assessed a variety of multi-level airway surgeries for persistent/recurrent OSA; including lingual tonsillectomy, midline posterior glossectomy, or hyoid myotomy/suspension. Similar to Esteller et al, the article does not directly link PSG data to the specific type of surgery performed so it is unclear how tongue surgery independently affected AHI. However, the study described overall outcomes by surgery: the responder data showed four (57%) patients who underwent lingual tonsillectomy were responders, and three (43%) were non-responders, as previously defined. For partial midline glossectomy, there was one (25%) responder and three (75%) non-responders. Hyoid suspension/myotomy included one responder (50%) and one non-responder (50%).

Ulualp et al conducted a small retrospective series with ten patients who underwent combined tongue base reduction and lingual tonsillectomy, half of which were syndromic, and the majority were overweight or obese. There was overall statistically significant improvement in AHI post-operatively, but 60% of the patients had residual OSA, and there was no statistically significant improvement in LSAT. It is unsurprising there was residual OSA in most patients given the high proportion of overweight-obese patients, and it is well-understood in the literature that this is a risk factor for persistent OSA.[16]

Williamson et al evaluated post-operative PSG outcomes of 168 children. Of these patients, 101 underwent lingual tonsillectomy alone; 25, midline posterior glossectomy alone; and 42, both. Concurrent procedures included turbinate reduction, revision adenoidectomy, and/or supraglottoplasty. Their mean AHI improvement was 3.52 +- 8.39, 2.55 +- 5.59, and 3.70 +- 6.07 events/hr, respectively. Each surgical group experienced significant improvement in sleep apnea when pre- and postoperative AHI was compared ($P < 0.01$). Overall, 126 (75%) patients experienced surgical success.[14]

[List of Tables and Figures]

Table 1: Pre- and post-DISE directed pediatric tongue surgery polysomnography outcomes.

Table 2: Overall response to DISE-directed tongue surgery.

Table S1: General characteristics of included studies and quality assessment.

Figure 1: Study Selection Flow Chart.

Figure 2: Pre- and post- DISE-directed tongue surgery apnea-hypopnea index outcomes (forest plot).

Figure 3: Pre- and post- DISE-directed tongue surgery lowest oxygen saturation outcomes (forest plot).

Appendix 1: PubMed combined search terms.

Discussion

This systematic review and metanalysis of seven and six studies, respectively, has three main findings. First, DISE-directed tongue surgery in children with persistent OSA (or surgically naive with small tonsils) reduces AHI by approximately 50%. The pre- and post-tongue surgery AHI decreased from 9.5 +- 12.1 to 4.2 +- 6.9 events/hr ($p < 0.04$) (Table 1) with an MD of -5.13 [95% CI -7.13, -3.13], Z-score 5.02 (P<0.00001) (Figure 2). There was moderate heterogeneity for AHI data largely owing to the heterogeneity of the patient population studied in Ulualp et al. This retrospective study assessed ten children with a broad BMI range and variable syndromic status. They found PSG parameters improved in both syndromic and non-syndromic patients after lingual tonsillectomy and tongue base reduction, but the majority of overweight and obese children did not experience normalization of parameters.[16]Post-operative PSG timelines were not consistently reported, but the studies that did reported an overall average of 2.1 months after surgery, which may not be enough time to permit healing leading to possible under or over-estimation of OSA.[2]

Second, DISE-directed surgery improves lowest oxygen saturation (LSAT) by almost 3%. The pre- and post-operative LSAT increased from 87.8 +- 5.7 to 90.1 +- 5.1% ($p < 0.02$) (Table 1) with a MD of 2.71 [95% CI 1.53, 3.89], Z score 4.51 (P<0.0001) (Figure 3). Similar to AHI, post-op LSAT may have continued to change as well since post-op PSG was completed on average less than 3 months after surgery, and no conclusion can be made about objective long-term outcome. He et al and Esteller et al did not report LSAT data so the LSAT analysis was lower in power compared to AHI but still included 264 patients.[10,15] The LSAT data had moderate heterogeneity which appeared to stem from the small retrospective study published by Kanotra et al, but overall less heterogeneity compared to AHI and had a Cochrane Q statistic > 0.1, signifying heterogeneity may exist between studies rather than within each study. Kanotra et al evaluated five patients who underwent lingual tonsillectomy with epiglottopexy, and its primary objective was to assess swallowing outcomes. PSG data was available for four of the patients.[11]

Third, DISE-directed tongue surgery has an overall positive response rate. Nearly 70% of children either had an AHI reduction from moderate or severe to mild, reduced their AHI by 50%, or were completely cured of OSA. This collective evidence confirms the efficacy of the common clinical practice to use DISE to identify levels of obstruction and modify the surgical plan for children with persistent OSA, specifically for tongue surgery, which is an often-implicated site of obstruction especially in children with hypotonia or Down syndrome.

Methodological Quality of the Included Studies

Supplemental Table 1 depicts NICE Quality Assessment and general characteristics of the studies included in this review. The studies included in the review were six retrospective and one prospective study. Five retrospective and one prospective study had data usable for meta-analysis pertaining to pre- and post-operative AHI. Four retrospective studies had data usable for meta-analysis for pre- and post- operative LSAT. All studies ranked as fair quality besides Esteller et al,[10] which ranked as good quality. This is due to the study's prospective design with consecutive recruitment of participants.

Limitations

Several factors must be understood when interpreting the results of this study. While the largest study included 168 patients the majority had less than 15 subjects. Additionally, all but one of these studies were retrospective reviews. There was also heterogeneity among the studies with some measuring a more obese

and medically complex patients, multilevel airway surgery, and PSG results as secondary outcomes. This was accounted for in our statistical process described above. Within each study, demographic data and multi-level surgical targets were not always clearly linked to PSG data, presenting a source of confounding bias and potential selection bias. Finally, postoperative PSG data was collected on average 2.1 months postoperatively which may not be enough time to permit healing leading to possible under or over-estimation of OSA.[2]

Conclusion

The results of this study are in agreement with existing literature regarding DISE-directed surgery, and each individual study in this review carries the same theme of DISE-directed surgery being successful. We were able to suggest that DISE directed tongue surgery has a statistically significant improvement in PSG outcomes. While there is objective collective evidence that DISE-directed surgical decision making is effective, there is heterogeneity in reported outcomes and variety in patient demographics as well as confounding variables.

The existing literature demonstrates DISE-directed tongue surgery in children with persistent OSA can statistically improve AHI and LSAT levels. However, it does not necessarily cure OSA, as the average AHI level is 4.2 events/hr after DISE-directed surgical intervention. Overall, the existing pooled literature demonstrates DISE-directed tongue surgery can reduce AHI by approximately 50%, improve LSAT by nearly 3%, and have an overall positive response to surgery rate of 70%.

Conflict Of Interest

None to declare.

Data Availability

The data used for this study are available from the corresponding author upon request.

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