

Effect of Weight and Obstructive Sleep Apnea Severity on Sleep Surgery Outcomes in Children with Down Syndrome

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Abstract

Objectives: To assess the effect of weight status and obstructive sleep apnea (OSA) severity on polysomnographic (PSG) outcomes following sleep surgery inclusive of adenotonsillectomy (AT) in children with Trisomy 21.

Methods: A retrospective chart review was completed on thirty-six children ages 1-13 years with Trisomy 21 and OSA who underwent at a tertiary care academic hospital between 2005 to 2015 and had both preoperative and postoperative PSGs. Postoperative changes in apnea hypopnea index (AHI) and other PSG parameters, including percentage of various sleep stages, were compared between children who were normal weight, overweight and obese.

Results: The mean preoperative AHIs for normal weight, overweight and obese children were 15.6, 12.2 and 15.0, respectively while the mean postoperative AHIs were 10.6, 9.4 and 10.2, respectively. Improvement in AHI was significant only among children with severe OSA (AHI >10), but not among children with mild (AHI 1.5 to 5) or moderate OSA (AHI 5 to 10), both with and without controlling for weight status ($p=0.01$, $p=0.009$). There were no significant differences in postoperative PSG parameters comparing obese vs. non-obese and overweight vs. normal weight children.

Conclusion: Weight status does not appear to affect sleep surgery outcomes in children with Trisomy 21. This subset of children was found to have persistent OSA following sleep surgery regardless of weight. Other factors associated with Trisomy 21, such as macroglossia, glossoptosis and hypotonia, may play a greater role in the pathogenesis of OSA in this patient population. Only those children with severe OSA were found to have a significant improvement in AHI after sleep surgery, inclusive of AT.

Keywords: Down syndrome; Sleep surgery; Adenotonsillectomy; Obstructive sleep apnea

anomalies, retrognathia and neuromuscular disorders with associated hypotonia of upper airway musculature.

Introduction

The incidence of obstructive sleep apnea (OSA) in the general pediatric population is 1-4% [1,2]. OSA is characterized by recurrent episodes of prolonged partial or complete upper airway obstruction associated with arousals and/or oxyhemoglobin desaturations during sleep. Sequelae of untreated OSA include failure to thrive, endothelial dysfunction, systemic inflammation, systemic and pulmonary hypertension, cor pulmonale, developmental delay and hematologic changes including a significantly higher red cell distribution width, neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios [3]. In addition, untreated OSA has been associated with excessive daytime sleepiness, hyperactivity, cognitive dysfunction, and poor school performance. The most common source of airway obstruction among children with OSA is adeno-tonsillar hypertrophy. Other factors associated with upper airway obstruction include obesity, craniofacial

Trisomy 21 (Down's syndrome) is a genetic disorder caused by a trisomy of all, or part of, chromosome 21 and is observed in 1 in 650 to 1000 live births in the United States [4-6]. There is a high prevalence of OSA (30-70%) among children with Trisomy 21 [7-9]. Characteristics of children with Trisomy 21 that predispose to this high prevalence include hypotonia, macroglossia, midface hypoplasia, a narrowed pharyngeal inlet and increased incidence of upper respiratory tract anomalies, such as laryngomalacia [10-13].

During the past few decades, a significant increase in the prevalence of childhood obesity has been observed in the United States [14]. Obese children are at higher risk for persistent OSA following adenotonsillectomy (AT). Children with Trisomy 21 have a higher body mass index (BMI) in comparison to the general pediatric population, which may account, in part, for the higher prevalence of OSA in this population [15-17].

The initial step in treatment of OSA among children with or without Trisomy 21 is sleep surgery, inclusive of AT. The success rate of AT is higher among children who do not have co-morbidities and are of normal weight. There is a higher incidence of persistent OSA after AT among obese children and children with Trisomy 21 [18,19]. This study was designed to evaluate the relative efficacy of sleep surgery, inclusive of AT among children with Trisomy 21 and OSA as a function of their weight status and OSA severity. Specifically, changes in polysomnographic parameters including apnea hypopnea index (AHI), percentage of sleep stages and extent of oxygen desaturation were assessed.

Methods

Study design

The retrospective chart review was approved by the Institutional Review Board (IRB) at University of Michigan Health System (UMHS). The electronic medical record was reviewed for all children aged 1-13 years with Trisomy 21 and a diagnosis of OSA based on in-lab diagnostic PSG conducted between January 2005 and December 2015.

Only children who underwent AT at UMHS and had a postoperative in-lab PSG at the same institution were included in the study. Children who did not have both preoperative and postoperative PSGs were excluded.

Data recorded included patients' demographic information, BMI, as well as pre- and postoperative PSG measures. Data analyzed included changes in AHI and changes in sleep architecture including percent of N1, N2, N3 and REM sleep stages, arousal index, end tidal CO₂ (ETCO₂) or transcutaneous CO₂ (TCO₂) and the degree of oxygen desaturation. Changes in PSG parameters were compared between children of varying weight categories.

Weight status determinations (normal weight, overweight, and obese) were made using age and gender specific norms from the Centers for Disease Control and Prevention (CDC) growth charts.

BMI percentiles were used for children two years of age or older, while weight-for-length (WFL) percentiles were used for children under two years of age. According to the CDC's definitions, obesity was defined as BMI or WFL $\geq 95^{\text{th}}$ percentile, overweight as BMI or WFL $\geq 85^{\text{th}}$ percentile but $<95^{\text{th}}$ percentile, and normal weight as BMI or WFL $<85^{\text{th}}$ and $<85^{\text{th}}$ percentiles.

Polysomnography

All subjects underwent standard clinical overnight PSG using Profusion Sleep software (Compumedics, USA) and the electrodes were placed according to the 10-20 international system. This included six channel electroencephalogram (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1), left and right electro-oculograms, chin electromyogram, left and right leg electromyograms, electrocardiogram, thoracic and abdominal wall movement (piezoelectric strain gauges), oronasal airflow (thermocouple and nasal pressure), carbon dioxide (ETCO₂ or TCO₂) and pulse oximetry.

Sleep architecture and associated events were scored by standard techniques based on the American Academy of Sleep Medicine scoring manual (AASM) for pediatric patients [20].

Measurements included total sleep time (TST), percentage of sleep time in N1, N2, N3 and REM stage, arousal index, ETCO₂ or TCO₂, AHI, obstructive apnea index (OAI), central apnea index (CAI), and oxygen saturation nadir. Using both the previous and current AASM scoring guidelines, hypopneas were defined as events lasting ≥ 2 respiratory cycles with at least 50% decrease in oronasal flow with $\geq 3\%$ oxyhemoglobin desaturation or associated arousal, and events lasting ≥ 2 respiratory cycles with $\geq 30\%$ drop of peak signal excursions from the baseline and 4% oxygen desaturation or arousal, respectively. The criteria used for diagnosis of OSA was an OAI >1 event/hour or AHI >1.5 events/hour, further delineating the OSA severity as mild (AHI between 1.5-5 events/hour), moderate (AHI between 5-10 events/h, or severe (AHI >10 events/h). We defined a successful outcome of surgery as postoperative AHI <1.5 events/hour or OAI <1.0 events/h. Postoperative PSGs were obtained between 2 and 4 months following surgery.

Statistical analysis

Absolute change in sleep parameters was calculated by subtracting the preoperative value from the postoperative value.

Repeated measures ANOVA were used to test for changes in sleep parameters over time (preoperative vs. postoperative) and to examine whether weight status or severity of OSA moderated the impact of surgery.

To test for the potential moderation of surgery's impact by weight status, we tested an interaction term of weight status x time period (pre- or postoperative). To test for the potential moderation of surgery's impact by severity of OSA, we tested an interaction term of OSA severity x time period (pre- or postoperative).

When the interaction term was significant, we performed subgroup analysis to examine the effect of surgery within specific groups of interest.

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). A 2-tailed α level of ≤ 0.05 was considered statistically significant.

Results

Demographics

Thirty-six children, 14 boys and 22 girls with a mean age of 44.36 months (range 6-118 months), with Trisomy 21 and OSA who underwent sleep surgery, inclusive of AT and had both preoperative and postoperative PSGs were included in the study. The preoperative and postoperative mean BMI were not significantly different at 18.2 (range, 14.5-24.6) and 18.6 kg/m² (range 14.1-26.2), respectively.

Among the 36 children included in the study, 47% (n=17) were normal weight, 28% (n=17) were overweight and 25% (n=9) were obese. There were a higher proportion of children with severe OSA (53%) than moderate (22%) or mild OSA (25%). Of the 36 children who underwent AT, 11 had additional concurrent surgery at the discretion of the operative surgeon: Eight underwent uvulopalatopharyngoplasty (UPPP), one underwent UPPP with supraglottoplasty, one underwent lingual tonsillectomy and one underwent supraglottoplasty.

The median hospital length of stay was 1 day, although 1 subject had a prolonged hospitalization lasting 76 days due to aspiration pneumonia and resultant respiratory failure (Table 1).

Variables	n
Total	36
Males	14
Females	22
Normal weight	17
Overweight	10
Obese	9
Mild OSA	9
Moderate OSA	8
Severe OSA	19

Polysomnographic parameters

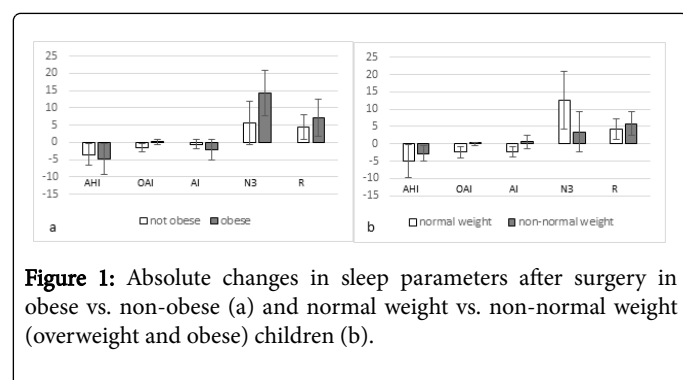
Mean preoperative and postoperative PSG parameters are shown in Table 2. There were high percentages of N3 sleep both pre- and postoperatively, at 40.0% and 47.8%, respectively, with an increase in percentage of N3 sleep following surgery. An increase in the percentage of REM sleep and a decrease in percentage of stage N1 and N2 sleep was also observed postoperatively, but was not found to be statistically significant. Comparisons were made between obese *vs.* non-obese (n=9 *vs.* 27) and normal weight *vs.* non-normal weight (overweight and obese) children (n=17 *vs.* 19). There were no significant differences in absolute change of sleep parameters (Figures 1a and 1b) or relative change of sleep parameters, including AHI, OAI, arousal index, percentage of N3 and percentage of REM, in both obese *vs.* non-obese and normal weight *vs.* non-normal weight groups.

Table 1: Patient demographics.

PSG Parameters	Pre-operative	Post-operative
TST, min	420.4	435.8
W, min	68.1	61.8
N1, %	5.2	3.5
N2, %	40	29
N3, %	40	47.8
REM, %	14.4	19.5
Arousal Index	13.1	13.2
OAI	1.8	0.7
AHI	13.8	10
CAI	1.3	1.2
Mean SpO ₂ (%)	96.2	95

TST: Total Sleep Time; W: Wake Stage; N1, N2, N3, Non-REM Sleep Stages 1, 2 And 3; REM: Rapid Eye Movement Sleep Stage; OAI: Obstructive Apnea Index; AHI: Apnea-Hypopnea Index; CAI: Central Apnea Index; SpO₂: Oxygen Saturation.

Table 2: Comparison of mean pre-operative and post-operative polysomnographic parameters.



Mean AHI and OAI values prior to and after surgery in both normal weight *vs.* non-normal weight (overweight and obese) and non-obese (normal and overweight) *vs.* obese are shown in Table 3. The mean pre- and postoperative AHI were 12.2 and 9.4, respectively, for non-normal weight (overweight and obese) children and 15.0 and 10.2 for obese children. There was no significant improvement in AHI and OAI following surgery among either non-normal weight or normal weight children ($p>0.05$) and there were no significant differences in the change in AHI and OAI in normal weight children compared to non-normal weight children ($p>0.05$). Similarly, AHI and OAI were not improved significantly after surgery in either obese or non-obese children ($p>0.05$) and there were no significant differences in the change of AHI and OAI following surgery when comparing obese to non-obese children ($p>0.05$).

	Normal Weight		Non-Normal Weight		p-value	Non-obese		Obese		p-value
	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-		
AHI (SD)	15.6 (14.2)	10.6 (11.6)	12.2 (10.1)	9.4 (9.0)	NS	13.4 (12.2)	9.9 (10.0)	15.0 (12.6)	10.2 (11.5)	NS
OAI (SD)	2.9 (6.8)	0.5 (0.9)	0.9 (1.1)	0.5 (0.9)	NS	2.0 (5.5)	0.5 (0.9)	1.2 (1.4)	1.3 (3.4)	NS

AHI: Apnea-Hypopnea Index; OAI: Obstructive Sleep Apnea; NS: Not Significant P>0.05.

Table 3: Comparison of mean pre-operative and post-operative AHI and OAI in normal weight vs. non-normal weight (overweight and obese) and obese vs. non-obese.

Comparisons between the preoperative and postoperative AHI and OAI respiratory parameters based on OSA severity both with and without controlling for weight status are shown in Table 4. When children are not categorized by OSA severity, there were no statistically significant changes in AHI and OAI following surgery with or without controlling for weight status. When the children were classified by OSA severity, there were no statistically significant changes in respiratory parameters among children with mild and moderate OSA

($p>0.05$). In children with severe OSA, the mean preoperative AHI was 21.6 while their mean postoperative AHI was 11.5. Children with severe OSA were found to have a significant improvement in AHI, both with and without controlling for overweight status ($p=0.01$ and $p=0.009$, respectively). There was also a significant difference between pre- and postoperative AHI comparing severe vs. mild/moderate OSA patients ($p=0.006$) indicating that the change in AHI following AT depended on the initial severity of OSA.

Preoperative (SD)		Postoperative (SD)	p-Value not controlling for weight	p-value, controlling overweight vs. normal weight
All severities				
AHI	13.8 (12.2)	10.0 (10.2)	0.15	0.15
OAI	1.8 (4.8)	0.7 (1.9)	0.20	0.2
Mild OSA				
AHI	3.3 (1.4)	8.8 (15.5)	0.33	0.32
OAI	0.2 (0.2)	0.5 (1.1)	0.43	0.42
Moderate OSA				
AHI	7.1 (1.0)	7.8 (4.9)	0.70	0.72
OAI	0.2 (0.3)	0.7 (1.2)	0.26	0.26
Severe OSA				
AHI	21.6 (12.1)	11.5 (9.0)	0.009	0.01
OAI	3.3 (6.3)	0.8 (2.4)	0.12	0.12
AHI: Apnea-Hypopnea Index; OAI: Obstructive Apnea Index.				

Table 4: Respiratory parameter changes based on severity of OSA and weight control.

Discussion

This is the first study to evaluate the effect of weight status on the efficacy of sleep surgery inclusive of AT for treatment of OSA in children with Trisomy 21. The first line treatment among healthy children with OSA is AT. However, a high proportion of obese children have residual OSA following AT [21,22]. Mitchell et al. demonstrated that obese children had higher AHI than normal weight children and that 76% of obese children had residual OSA after AT compared to only 28% of normal weight children [23]. Similarly, children with Trisomy 21 have a high likelihood of persistent OSA following AT. In 2007, Merrell et al. showed that only one third of children with Trisomy 21 had a normal postoperative AHI on PSG following AT.21

A recent systematic review of AT outcomes in children with Trisomy 21 confirmed that the majority of these patients do not have resolution of OSA (defined as $AHI<1$) after AT [22]. It may be expected then, that children with Trisomy 21 who are also obese would be even less likely to benefit from sleep surgery. However, the results of the current study did not support this premise as no significant difference in surgical outcomes were identified between obese vs. non-obese and normal vs. non-normal weight children with Trisomy 21.

In addition, no significant change in OSA severity was observed following sleep surgery, with or without controlling for weight status, in Trisomy 21 children with mild and moderate OSA. Only children with severe OSA demonstrated a statistically significant improvement

in AHI following sleep surgery. However, there was still significant residual disease, as measured by AHI, in this subset of patients.

Besides weight status, there are several other potential factors that may contribute to persistent OSA following sleep surgery for children with Trisomy 21 including the presence of upper airway abnormalities such as macroglossia, midface hypoplasia, increased upper airway fat distribution and hypotonia [10,12]. Donnelly et al. found that of Trisomy 21 patients with persistent OSA following AT 74% had macroglossia, 63% had glossoptosis and 30% had enlarged lingual tonsils [24]. Scott et al. proposed a mechanism to explain how pubertal changes modify determinants of OSA severity between childhood and adolescence, since BMI becomes a more important predictor of severe OSA in older children [25]. OSA severity in younger children has been linked to increased lymphoid hyperplasia, instead of parapharyngeal fat pad size. However, among children with Trisomy 21, studies have noted fatty infiltration in the muscular portion of the tongue on T1-weighted signal magnetic resonance imaging (MRI), as well as fat deposits in the lateral pharyngeal wall and uvula, similar to the fat distribution that increases the risk of OSA among adults [6,25,26]. These factors may also help explain the current study findings of no significant change in AHI and OAI following sleep surgery in both obese vs. non-obese and overweight vs. normal weight children.

Both the Muller's maneuver (MM) and drug induced sleep endoscopy (DISE) have been utilized to help identify potential site (s) of obstruction in patients diagnosed with OSA. This information is useful in determining which procedure (s) should be recommended for each individual patient. Although there is a reasonable concordance between the results of MM and DISE for the pattern of collapse at the velum (73-92%), there is a poor concordance between the results of the two examinations at the base of the tongue (24%) [27-38]. Therefore, DISE is a potentially invaluable tool for determining the need for additional surgery directed at the base of tongue in children with Trisomy 21 and OSA [27].

The current study demonstrates that sleep surgery inclusive of AT as primary treatment for children with Trisomy 21 and OSA is, at best, partially effective. Marcus et al. has suggested using CPAP as first line management among children with OSA and complex diagnoses [3]. However, achieving high levels of CPAP compliance among children, with or without developmental disabilities, can be challenging and may make this treatment option impractical for some. Prosser et al. recently found that lingual tonsillectomy significantly improved AHI and sleep outcomes in Trisomy 21 patients with persistent OSA after AT. Only one of the 36 children in the current study underwent concurrent lingual tonsillectomy [28].

When considering surgical treatment options including AT and additional procedures such as UPPP, lingual tonsillectomy, genioglossus muscle advancement, and supraglottoplasty, one must consider that these procedures may still not address the underlying hypotonia associated with Trisomy 21. Hypoglossal nerve stimulation therapy has recently been shown to have a significant impact on upper airway patency by increasing both the retropalatal and retrolingual air space [29-31]. At present, there is only one published report on the use of hypoglossal nerve stimulation therapy in an adolescent with Trisomy 21 and OSA who had significant improvement in AHI from 48.5 to 3.4 [32].

Previous studies have reported an increase in stage N3 sleep after AT in children with OSA and Trisomy 21 [33-36]. These findings are similar to the results of the current study. An increase in the

percentage of REM sleep and decrease in percentages of N1 and N2 sleep were also observed in the current study, although these changes were not found to be statistically significant.

There are several limitations to the current study. First, this was a retrospective study. The sample size is relatively small because only children who had both pre- and postoperative PSGs were included in the study, which risks inclusion bias. One possible explanation for the limited improvement in AHI found in our study is that only those with severe or clinically persistent disease underwent postoperative PSG, as patients' families may have forgone additional testing if symptomatic improvement was achieved. In addition, PSG data was collected over a 10-year period so two different PSG scoring methods were used in accordance with the American Academy of Sleep Medicine Scoring Guidelines. Finally, children included in this study were evaluated and treated by more than Otolaryngologist, who elected to perform AT with or without additional surgery based on their clinical impression regarding the likely additional site (s) of obstruction.

Conclusion

Weight status does not appear to affect sleep surgery outcomes in children with Trisomy 21. This subset of children was found to have persistent OSA following sleep surgery regardless of weight. Other factors associated with Trisomy 21, such as macroglossia, glossoptosis and hypotonia, may play a greater role in the pathogenesis of OSA in this patient population. Only those children with severe OSA were found to have a significant improvement in AHI after sleep surgery, inclusive of adenotonsillectomy [37,38].

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