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Update on Hypoglossal Nerve Stimulation in Children With Down Syndrome and Obstructive Sleep Apnea

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Objectives/Hypothesis: Hypoglossal nerve (HGN) stimulation is a novel therapy for obstructive sleep apnea (OSA) in adults. Its efficacy and safety in children with Down syndrome (DS) was previously reported in a preliminary case series of six adolescents.

Study Design: Case series.

Methods: Twenty nonobese children and adolescents (aged 10–21 years) with DS and severe OSA (apnea-hypopnea index [AHI] >10 and <50 events/hr) despite prior adenotonsillectomy were enrolled. Participants had failed a trial of continuous positive airway pressure therapy and underwent sleep endoscopy confirming surgical candidacy. The primary outcome was to assess safety and monitor for adverse events. Secondary outcomes included efficacy in reducing AHI (% reduction in AHI), adherence to therapy, and change in a validated quality-of-life instrument, the OSA-18 survey.

Results: All 20 children (median age = 16.0 years [interquartile range = 13–17 years], 13 male) were implanted with no long-term complications. We report two interval adverse events, both of which were corrected with revision surgery. Twenty participants completed the 2-month polysomnogram, with median percent reduction in titration AHI of 85% (interquartile range = 75%–92%). The median nightly usage for these children was 9.21 hours/night. There was a median change in the OSA-18 score of 1.15, indicating a moderate, yet significant, clinical change.

Conclusions: HGN stimulation was safe and effective in the study population. Two minor surgical complications were corrected surgically. Overall, these data suggest that pediatric HGN stimulation appears to be a safe and effective therapy for children with DS and refractory severe OSA.

Key Words: Obstructive sleep apnea, hypoglossal nerve stimulator, Down syndrome, upper airway stimulation, Inspire.

Level of Evidence: 4

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INTRODUCTION

Down syndrome (DS) is one of the most common genetic disorders in the United States, with a prevalence estimated at 8.27 people with DS per 10,000 population in 2008.[1] This disorder is characterized by a decline of learning capacity during infancy and early childhood, speech and language delay, and impairments in cognitive flexibility and memory.[2] The prevalence of obstructive sleep apnea (OSA) is about 55% to 80%[3,4] in pediatric participants with DS compared to 1% to 5% in the general pediatric population.[5] This increased prevalence is thought to relate to anatomical factors seen in children with DS, including generalized hypotonia, macroglossia, midface hypoplasia, small tracheal caliber, and lingual tonsil hypertrophy.

Sequelae of OSA in all children include cardiopulmonary complications, adverse behavior, and reduced quality

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C.L.C. was involved in execution of the study, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the final manuscript as submitted. G.R.D., D.K., S.R.S., S.L.I., N.R., and C.J.H. were involved in the planning and execution of the study, as well as critical review and revision of the manuscript and approval of the final manuscript as submitted. D.K., R.S., and S.L.I. interpreted study-related polysomnograms. V.D. assisted in execution of the study and correspondence with regulatory oversight organizations. C.L.C. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This study is registered with ClinicalTrials.gov (NCT2344108) under the title "A Pilot Study to Evaluate the Safety and Efficacy of the Hypoglossal Nerve Stimulator in Adolescents With Down Syndrome and Obstructive Sleep Apnea." This study was approved under investigational device exemption G140209.

Inspire Medical Systems provided technical support and provided the nerve stimulators used in this study free of charge (if third-party payers did not). S.L.I. consulted with Genus LifeSciences in 2018. R.S. is a former STAR Trial Investigator for Inspire Medical Systems and participates in consulting for Inspire Medical Systems, Galvani Bioelectronics, Invicta Medical, Cryosa, Inc., and Enhale Medical.

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of life (QOL).[5,6] Additional adverse sequelae may be present in children with DS. OSA in children with DS has been shown to be associated with lower mean verbal IQ score and lower cognitive flexibility than in children with DS who do not have OSA.[7] These findings have highlighted the importance of adequate sleep quality in this population.

Adenotonsillectomy is the first-line treatment for children with OSA and has been shown to provide therapeutic benefit to children with DS and OSA who have tonsillar hypertrophy.[3] However, it is estimated that only 16% to 33% of children with DS have resolution of their OSA (defined as an apnea-hypopnea index [AHI] <1 event/hr) following adenotonsillectomy.[8] In the case of OSA refractory to adenotonsillectomy, sites of residual obstruction include base of tongue obstruction, pharyngeal collapse, and crowding associated with obesity and lingual tonsil hypertrophy. Approximately 63% of patients with DS who have persistent OSA following adenotonsillectomy have glossoptosis.[9] To overcome these additional levels of obstruction, continuous positive airway pressure (CPAP) may be trialed; however, it is sometimes not tolerated.

Further surgical options currently include tongue base surgery, oromaxillary surgery, and tracheostomy in severe cases. These options do impose varying degrees of risk.[10] For example, although midline posterior glossectomy with or without lingual tonsillectomy has been suggested to significantly reduce AHI in children with DS who have persistent OSA following adenotonsillectomy, these procedures can lead to postoperative bleeding as well as increased postoperative hospital stay due to poor oral intake.[11] In the case of tracheostomy, significant caregiver burden and reduced mental health are also encountered.[12]

Hypoglossal nerve stimulation has emerged as a novel therapy for OSA in adults. It has been proven safe and effective for upper airway stimulation for the treatment of moderate-to-severe OSA in select adults.[13] Prospective studies demonstrate that therapy remains well tolerated and effective up to 5 years after implantation.[14] In children, short-term results of an early efficacy and safety trial were favorable, demonstrating improvements in AHI and OSA-18 QOL survey scores as well as good tolerance of therapy.[10]

The current study reports the 2-month safety, including adverse events, following implantation of the Inspire (Inspire Medical Systems, Inc., Golden Valley, MN) implantable hypoglossal nerve stimulator in children with DS. Polysomnogram (PSG) titration outcomes, adherence to therapy, and OSA-related QOL data were also collected as secondary outcomes. Here we present data of the first 20 pediatric participants to undergo hypoglossal nerve stimulator implantation.

MATERIALS AND METHODS

The institutional review boards at the three enrolling sites approved this study. This study was also approved by the Food and Drug Administration (FDA), which issued an investigational device exemption. The trial is also registered with ClinicalTrials.gov (NCT2344108). Written consent was obtained from study participants or their legal guardians prior to study participation and nerve stimulator implantation.

Participants aged 10 to 21 years old with DS and OSA refractory to adenotonsillectomy who were unable to tolerate CPAP or were dependent on a tracheostomy at night were enrolled in a prospective manner. Participants were identified as candidates for implantation at each institution and underwent initial evaluation by the local surgical team. Participants with any medical conditions requiring future need for magnetic resonance imaging (MRI) were initially excluded before the current generation of MRI-conditional devices was made available. (Children still can not get an MRI of their chest and neck after implantation but can be safely imaged elsewhere.) Parents also had to attest to their child's ability to cooperate with exams and communicate discomfort. To participate, subjects had to be medically stable with a body mass index (BMI) <95% when adjusted for age and gender calculated using the normal values specified by the Centers for Disease Control and Prevention.[15] Participants without a PSG within 6 months of enrollment underwent polysomnography to identify baseline characteristics and verify inclusion criteria, including AHI between 10 and 50 events per hour and a central apnea contribution of <25%. Participants also underwent drug-induced sleep endoscopy (DISE) if this had not been performed within 6 months of enrollment. DISE was used to evaluate upper airway anatomy at the level of the velopharynx, oropharynx, tongue base, and hypopharynx. Exam findings were evaluated using the VOTE (velum, oropharyngeal lateral walls [including the tonsils], tongue, and epiglottis) classification scheme, which has been described previously.[16] Circumferential collapse at the level of the velopharynx resulted in exclusion from the study. Objective inclusion criteria, including BMI, PSG findings, and anatomic findings were based upon the inclusion criteria used in prior studies of the hypoglossal nerve stimulator in adult participants.[13]

Study participants meeting inclusion criteria then underwent hypoglossal nerve stimulator implantation using standard techniques, which have been described previously.[10] All participants underwent postoperative posterior–anterior and lateral chest radiography to rule out pneumothorax and to document device position. All participants received perioperative antibiotics and were hospitalized overnight for monitoring.

One month after implantation, participants underwent temporary activation of their stimulators in the clinic, and testing included recording the functional threshold as well as monitoring the respiratory sensor. Of note, this methodology differs from the protocol used in adults due to uncertainty of our ability to identify stimulation thresholds as well as the risk of postobstructive hypoventilation syndrome in this population. Therefore, all activations were performed while the patients were asleep and in a monitored setting. The evening of the clinic appointment, participants underwent titration of their devices during an overnight PSG. The patient with a tracheostomy was capped during the PSG. They were discharged with instructions to use therapy nightly to become acclimated to the device. A follow-up PSG with further device titrations was then performed at 2 months after implantation to allow additional device optimization. Throughout the study period, participants were monitored for any adverse events. Average use per week calculations were automatically registered by the device itself and recorded at the time of PSG. Average nightly use was calculated by dividing the average use per week by seven.

All PSGs were scored using American Academy of Sleep Medicine (AASM) pediatric standards.[17] The severity of OSA was defined by the AHI. Mild OSA was defined as 1 to ≤5 events per hour, moderate as 5 to <10, and severe as >10. Success was defined as a child who achieved a postoperative AHI of ≤5 events per hour at an optimal voltage. Hypopneas were scored using a 30% reduction in flow associated with either a 3% oxygen desaturation or an arousal. Preoperative AHI was reported as the AHI on the PSG performed prior to implantation, and the postoperative titration AHI was reported as the estimated AHI present at the optimal voltage on the 2-month postoperative PSG. The voltage at which the most optimal AHI was achieved and sustained was chosen as the

treatment voltage. All sleep studies and device titrations performed after implantation were conducted at one of the three participating institutions and interpreted using the AASM criteria by a board-certified sleep medicine specialist.

In addition to safety and efficacy data, OSA-related QOL data were obtained as a secondary outcome measure. The OSA-18 survey, a previously validated QOL instrument in children with sleep-disordered breathing,[18] was used to assess QOL at baseline and at 2 months after implantation. This is an 18-item survey graded 1 to 7, with 7 being the most severe impact on QOL. We calculated the survey score as the mean of the 18-item scores. A change score of <0.5 represents a trivial change, 0.5 to 0.9 indicates a small change, 1.0 to 1.4 demonstrate a moderate change, and ≥1.5 indicates a large change.[19] Continuous variables are reported using median and interquartile range (IQR). Categorical data are presented as percentages.

RESULTS

Two-month results of the first 20 participants to receive hypoglossal nerve stimulator implantation at three tertiary-care centers are presented here. Six- and 12-month follow-up results of the first six implant recipients at a single institution have been reported previously.[10]

Twenty participants, 13 male and seven female, with a median (IQR) age of 16.0 years (13.75–17.25 years) were enrolled in the study (Table I). The median (IQR) baseline AHI was 24.15 events per hour (19.88–35.10 events/hr) and the median (IQR) preoperative OSA-18 was 3.56 (2.61–4.40). All participants underwent hypoglossal nerve stimulator implantation without intraoperative complications. All participants received 24 hours of perioperative antibiotics. All participants were hospitalized overnight for observation, and pain was well controlled using acetaminophen and ibuprofen; use of narcotics after initial recovery in the post-anesthesia care unit was minimized.

Since our report of the first six patients, two participants experienced interval adverse events that required revision surgery. Neither patient experienced long-term deleterious effects. The first patient experienced extrusion of the stimulation lead through the submental incision almost 3 months following implantation. This required wound exploration with reimplantation of the lead and was not associated with a wound infection. The second patient experienced poor connectivity at the time of activation, which upon investigation was due to incomplete sensor lead insertion into the device. Wound exploration was needed to make adjustments to the device.

TABLE I.
Patient Demographics.

Patient Information	Total, n = 20
Sex, no. (%)	
Male	13 (65%)
Female	7 (35%)
Age, yr	
Median	16
IQR	13.75–17.25
Preoperative BMI	
Median	24.10
IQR	20.30–25.70

BMI = body mass index; IQR = interquartile range.

TABLE II.
Polysomnogram Results After Implantation.

	Preoperative AHI	Postoperative Titration AHI	% Reduction in AHI
Median	24.15	3.00	85.0%
IQR	19.88–35.10	2.42–7.74	75%–92%

AHI = apnea-hypopnea index; IQR = interquartile range.

All participants underwent activation 1 month after implantation. They all tolerated stimulation and initial titration without discomfort and were discharged to use the device nightly and become acclimated to stimulation. Further titration of therapy was carried out at a 2-month PSG. The median (IQR) length of follow-up for all participants was 68 days (61–70 days). All participants were able to tolerate titration to a lower AHI on their 2-month PSGs. At 2 months, the median (IQR) titration AHI dropped by 85% (75%–92%%), from 24.15 to 3.0 (Table II). It is important to note we interpreted our results for all of our participants strictly using pediatric criteria. Using the criteria for pediatric interpretation of AHI for all participants, 14 participants were titrated to an AHI equivalent of mild OSA (AHI ≤5 events/hr), two participants were titrated to an AHI equivalent of moderate OSA (AHI >5 and <10 events/hr), and four participants were at best titrated to an AHI equivalent of severe OSA. When these results are interpreted with success defined as titration to a mild OSA equivalent, our success rate with hypoglossal nerve stimulation implantation was then 70% (14 out of 20 participants) at 2 months.

Across all 20 participants, for the 1 month monitored between initial titration PSG and 2-month titration PSG, the median (IQR) nightly usage for the hypoglossal nerve stimulator was 9.21 hours/night (8.29–9.50 hr/night) (Table III). Caregivers completed OSA-18 questionnaires at available time points. The results indicate that all participants demonstrated significant improvement in their OSA-related QOL. There was a median (IQR) change in OSA-18 score of 1.15 (0.02–1.97), with >1.0 indicating a moderate change.

Two patients experienced high functional thresholds at the 2-month PSG, in that an acceptable, therapeutic AHI was not achieved within the range of stimulation patients could tolerate while asleep. They were offered the option of device interrogation to optimize tongue protrusion during DISE, which they and their families opted to pursue. Through titration of electrode configurations, both of these patients experienced significant clinical improvements using these techniques.

DISCUSSION

Here we present the results of the first 20 adolescents with DS to undergo hypoglossal nerve stimulation for refractory OSA. Overall, our results support the use of this therapy and reveal it to be safe and effective in acutely

TABLE III.
Nightly Usage of the Hypoglossal Nerve Stimulator.

Subject	Preimplantation AHI (Events/Hour)	2-Month Titration AHI (Events/Hour)	Average Device Use (Hours/Night)	Preoperative OSA-18	2-Month OSA-18
1	48.5	3.71	8.3	4.28	1.11
2	17.1	2.79	10.0	1.94	1.27
3	30.7	2.48	10.0	1.22	2.50
4	22.7	1.10	3.6	3.00	2.83
5	13.9	9.52	9.3	3.06	1.83
6	25.6	4.03	9.3	2.79	1.66
7	41.7	26.09	8.7	3.11	4.11
8	18	2.64	8.4	1.59	2.26
9	20.5	2.25	8.3	2.07	1.78
10	21.2	0.75	8.0	4.00	2.83
11	37	7.14	9.3	5.11	2.00
12	10.9	1.71	10.0	3.94	4.38
13	15.9	2.55	9.1	1.94	1.22
14	26.2	3.00	9.4	4.44	2.39
15	37	3.00	8.9	5.33	1.39
16	22	16.17	9.4	4.77	2.72
17	33	21.18	9.7	4.38	3.16
18	34.8	5.00	7.4	5.17	5.72
19	21.6	1.10	3.9	3.17	1.61
20	36	15.40	10.0	4.11	2.17

AHI = apnea-hypopnea index; OSA-18 = Obstructive Sleep Apnea-18 quality-of-life survey.

reducing AHI. Taken together, the median hours of use of 9.21 hours/night and the improvement in OSA-18 scores reflect good patient tolerance of and caregiver satisfaction with therapy, respectively. The median percent reduction in AHI (comparing preoperative to titration AHI) was 85%, and 70% of participants were corrected to mild OSA using these same comparisons. Lessons learned from our preliminary study include prevention and treatment of postoperative complications as well as reconfiguration of electrodes in the setting of suboptimal results to maximize therapeutic benefit. Future directions include interpretation of these results as well as investigation of potential speech and cognition benefits of therapy given overwhelming reports from caregivers of improvement in these categories.

We learned valuable lessons from the two adverse events requiring revision surgery. In the first case, extrusion of the stimulating lead wires connecting the device to the nerve cuff extruded through the submental incision. This occurred approximately 3 months postoperatively, and the family did note the patient had made a habit of picking at his incision site. At the time of implantation, the wound was closed in a multilayered fashion with absorbable sutures and dressed with steristrips, a nonadherent dressing, and an adhesive bandage. The family was instructed to remove this after 1 day. Since this event, participants have been instructed to keep their dressings on for 1 week following surgery, with the addition of fluff gauze taped over the wound overnight. In children prone to wound picking (and in the absence of infection), we have found temporarily covering the wound with a nonadherent dressing and adhesive bandage to be adequate to break the disruptive habit of picking.

The second adverse event was experienced following institution of a new, MRI-conditional version of the Inspire device. The sensor lead was not fully inserted into the implantable pulse generator (IPG) processor at the time of surgery according to the new technique required, and surgical re-exploration was required to fully insert the respiratory sensor lead into the device; activation was successful thereafter. Despite apparent full insertion at the time of the placement and good signal on interrogation of the device, it is hypothesized that a small air bubble at the insertion site prevented full insertion. Since that time, we hold pressure on the electrode to prevent any slippage while we screw it in place.

Our 2-month benchmark allowed us to intervene on two patients whose electrode placement required revised configurations to optimize therapy. Higher voltages during their 2-month PSG titration were not achieving optimal results, and therefore it was recommended we pursue exploration of patient comfort settings. Based on anecdotal experience from adult subjects, it is thought that hypoglossal nerve stimulation can be optimized not only by increasing the voltage of the stimulation, but also by adjusting a series of other parameters including electrode configuration, pulse width, and rates of pulsation. We reconfigured the devices for those subjects who were unable to be optimally titrated, delivering a lower voltage to achieve better tongue protrusion. Devices are initially configured in a +/–/+ configuration confining capture within the volume enveloped by the cuff; however, five permutations are available to achieve optimal stimulation of targeted muscles. By targeting a broader set of tongue protrusion muscles, we felt better

protrusion was achieved on DISE at a lower voltage. Of note, although the hypoglossal nerve stimulator solely targets motor neurons, muscle stimulation itself can cause soreness, and it is therefore very important to optimize patient comfort during device titration, taking care to avoid overtitration, especially during the acclimation to therapy phase.

Although several participants were either older than 18 years or turned 18 years old during their participation in the study, we chose to use pediatric criteria to score the severity of OSA in our study given that our population is likely more at risk to the effect of sleep disturbance than other adults. Adult scoring presumes that adults can tolerate more sleep disruption, apneas, hypopneas, and oxygen desaturations than pediatric patients (given ongoing growth and development in children). However, it is reasonable to consider pediatric criteria for all of our patients given the unique need of our study population for a novel treatment for their OSA given their propensity of failure with other interventions. Furthermore, pediatric criteria demand more strict interpretation of AHI and therefore allow us to interpret our data in a more conservative manner.

Although the traditional measurement of success in treating OSA in children is the rate of cure (AHI <1) and the lack of need for any adjunct treatment, our population is unique in that they have all failed CPAP due to poor compliance, are nonobese, and had DISE showing base of tongue collapse and subsequently underwent lingual tonsillectomy when indicated. Furthermore, studies focused on success of various surgical interventions for refractory OSA have often adopted AHI <5 as the threshold where no further surgical intervention would be necessary.[9,20] Thus, although some remain with clinically significant OSA and would typically be counseled to undergo further treatment, these alternative therapies were either not tolerated (i.e., CPAP) or carry significantly more morbidity (i.e., tracheostomy, tongue base reduction surgery, oromaxillary surgery). In this setting, it is important to note the percent reduction in AHI (median = 85.0%) and realize that improved AHI, even if not under the traditional benchmark, may be considered by families to hold less risk than the alternatives currently offered to this population. Given anecdotal reports from families of improvement in functioning capacity and behavior among recipients (even those whose AHI remained >5), we would consider future study into the neurocognitive benefits of AHI reduction with hypoglossal nerve stimulation, even when a complete cure of OSA is not achieved.

Limitations of this study include a mixed age group with an imperfect metric for success in correction of OSA. Given the short length of follow-up, our OSA-18 data did not capture QOL following the second titration sleep study. Furthermore, as our population was quite unique, the applicability of hypoglossal nerve stimulation to the general pediatric population or even those with DS who do not meet our criteria remains unknown. Finally, our AHI reporting in this interim analysis is based on sleep studies involving titration of treatment voltages rather than the gold standard of a full-night efficacy study. Full-night efficacy studies are performed at the 12-month PSG in our formal study.

CONCLUSION

We demonstrated that hypoglossal nerve stimulation is safe given the present but tolerable adverse events in children with DS and OSA refractory to conventional therapy. Our study further demonstrated the effectiveness of therapy in this population, given a significant average reduction of the AHI and improvement in OSA-related QOL. Continuing investigation is underway to collect further data on efficacy and outcomes with the goal of FDA approval of this device.

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