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SCIENTIFIC ARTICLE

Upper airway morphology in Down Syndrome patients under dexmedetomidine sedation

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Abstract
Background and objectives: Children with Down Syndrome are vulnerable to significant upper airway obstruction due to relative macroglossia and dynamic airway collapse. The objective of this study was to compare the upper airway dimensions of children with Down Syndrome and obstructive sleep apnea with normal airway under dexmedetomidine sedation.
Methods: IRB approval was obtained. In this retrospective study, clinically indicated dynamic sagittal midline magnetic resonance images of the upper airway were obtained under low (1 mcg/kg/h) and high (3 mcg/kg/h) dose dexmedetomidine. Airway anteroposterior diameters and sectional areas were measured as minimum and maximum dimensions by two independent observers at soft palate (nasopharyngeal airway) and at base of the tongue (retroglossal airway).
Results and conclusions: Minimum anteroposterior diameter and minimum sectional area at nasopharynx and retroglossal airway were significantly reduced in Down Syndrome compared to normal airway at both low and high dose dexmedetomidine. However, there were no significant differences between low and high dose dexmedetomidine in both Down Syndrome and normal airway. The mean apnea hypopnea index in Down Syndrome was 16 ± 11. Under dexmedetomidine sedation, children with Down Syndrome and obstructive sleep apnea when compared to normal airway children show significant reductions in airway dimensions most pronounced at the narrowest points in the nasopharyngeal and retroglossal airways.

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PALAVRAS-CHAVE
Vias aéreas;
Dexmedetomidina;
Imagem;
Síndrome de Down;
Apneia obstrutiva do sono;
Sedação

Morfologia das vias aéreas superiores em pacientes com síndrome de Down sob sedação com dexmedetomidina

Resumo
Justificativa e objetivos: As crianças com síndrome de Down (SD) são vulneráveis à obstrução significativa das vias aéreas superiores devido à macroglossia relativa e colapso dinâmico das vias aéreas. O objetivo deste estudo foi comparar as dimensões das vias aéreas superiores de crianças com SD e apnéia obstrutiva do sono (AOS) com vias aéreas normais (VAN) sob sedação com dexmedetomidina (DEX).
Métodos: Aprovação IRB foi obtida. Neste estudo retrospectivo, imagens clinicamente indicadas de ressonância magnética da dinâmica das vias aéreas superiores em plano sagital na linha média foram obtidas sob dose baixa (1 mcg/kg/h) e dose alta (3 mcg/kg/h) de DEX. Os diâmetros ânteroposteriores das vias aéreas e as áreas seccionais foram medidas como dimensões mínimas e máximas por dois observadores independentes, no palato mole (região nasofaríngea) e na base da língua (região retroglossal).
Resultados e conclusões: O diâmetro mínimo anteroposterior e a área seccional mínima das regiões nasofaríngea e retroglossal estavam significativamente reduzidos na SD em comparação com VAN, tanto com a dose baixa quanto com a dose alta de DEX. Contudo, não houve diferenças significativas entre as doses baixa e alta de DEX em SD e VAN. A média do índice de apneia e hipopneia na SD foi de 16 ± 11. Sob sedação com DEX, as crianças com SD e AOS quando comparadas com as crianças com VAN apresentaram reduções significativas nas dimensões das vias aéreas, mais pronunciadas nos pontos mais estreitos das regiões nasofaríngea e retroglossal.

Introduction

Down Syndrome (DS) or trisomy 21 is the most common genetic disorder in humans with an estimated birth rate of 6000 infants/year (1 in 691 live births) in the United States.[1] Obstructive sleep apnea (OSA) is common and noted in 79% of children with DS (95% confidence interval, 54–94%).[2] Risk factors for OSA in these children include midface hypoplasia, macroglossia, adenoid and tonsillar hypertrophy, laryngotracheal anomalies, obesity, and muscular hypotonia.[3] Even in the absence of OSA, children with DS have reduced airway size caused by soft tissue crowding within a smaller facial skeletal anatomy.[4]

Children with OSA, with or without DS, are sensitive to respiratory depression by opioids, sedatives, and hypnotics. They are especially vulnerable to the development of upper airway obstruction during sedation and anesthesia.[5] Dexmedetomidine (DEX) is an α-2 receptor agonist currently being used off-label for sedation in pediatric patients at many institutions. In contrast to other sedative agents, DEX has been shown to have sedative properties that parallel natural non-rapid eye movement sleep, without significant respiratory depression.[6,7] These advantages make DEX an attractive agent for sedating children with OSA.[8] We have previously used magnetic resonance imaging (MRI) to assess the effect of increasing doses of DEX on airway dimensions in children with normal upper airways (age range 3–10 years) and showed that increasing doses of DEX in these children is not associated with significant increase in the degree of airway obstruction.[9] We recently used a similar methodology to compare the dose–response effects of DEX and propofol on airway morphology in children with OSA (age range 1–16 years). We found that as the dosage increased, average airway dimensions were typically unchanged or slightly increased with DEX compared to unchanged or slightly decreased with propofol.[10]

Our aim in the present study was to test the hypothesis that DS children with OSA have significant upper airway collapsibility even at low doses of DEX compared to children with normal airway (NA). We therefore designed a retrospective cohort study comparing the upper airway morphologies of children aged 3–10 years with DS and OSA to those with NA under increasing doses of DEX sedation.

Materials and methods

After institutional review board approval, the data were obtained in children aged 3–10 years with DS and children with NA who underwent MRI airway analysis with DEX. Written informed consent had been obtained for sedation. The need for a separate informed consent for the retrospective review was waived by our IRB.

Down Syndrome (DS) group

The methodology used in children with DS is described in our previous study that examined the dose–response effects of DEX and propofol on airway morphology. This was done in 22 children and adolescents aged 3–16 years with a history of OSA scheduled for MRI sleep study.[10] Out of the 22 patients who completed the study, a subgroup of 7 patients, aged 3–10 years, had the diagnosis of DS. No premedication was given. Intravenous access was obtained in the

induction room with sevoflurane and/or nitrous oxide in oxygen. Atropine 10 mcg/kg IV was administered and sevoflurane and/or nitrous oxide were discontinued. DEX was started and MR imaging performed as described below.

Normal airway (NA) group

The methodology used for evaluation of children with normal airways was describe in a previously study.[9] In brief, children aged 3–10 years who presented for an elective MRI examination under sedation were included. Children with history of OSA or snoring, American Society of Anesthesiology classification >2, allergy to DEX, presence of airway or craniofacial abnormality, obesity, or severe developmental delay were excluded.

Dexmedetomidine protocol

Baseline airway images were obtained during the Low DEX infusion (1 mcg/kg/h). If the subject moved, a bolus of 0.5 mcg/kg over 10 min was given and the DEX infusion rate was increased to 1.5 mcg/kg/h. If the subject moved a second time, the research study was terminated and additional anesthesia was provided with propofol infusion. After the initial set of airway images were obtained, a bolus dose of DEX 2 mcg/kg was given over 10 min followed by an increase in the infusion rate to 3 mcg/kg/h (high dose DEX). University of Michigan Sedation Scale (UMSS) was used to assess sedation.[11] UMSS is a simple to use, validated tool to assess the depth of sedation in children.[11] Standard monitoring and spontaneous breathing with 2 L/min of oxygen via nasal cannula was used. Level of sedation was assessed after initial low dose of DEX before and after imaging. Sedation was not assessed during imaging as this may have necessitated changing the patient's head position and subsequently biasing airway measurement comparisons. Patients were transferred to the post anesthesia care unit following imaging and discharged home after meeting criteria.

MR imaging protocol

All patients underwent clinically indicated MRI under DEX sedation. Once adequate sedation was achieved, the cervical spine was maintained in a neutral position by placing the patient's head and neck in a vascular coil. No artificial airway (e.g., oral airway or nasal trumpet) or positioning aid (e.g., shoulder roll) was used during imaging. No attempt was made to open or close the mouth. Children with DS were transferred to the imager after the sevoflurane end-tidal concentration was reduced to <0.1%. MRI was performed on a 1.5 Tesla imager (GE Healthcare, Milwaukee, WI, USA) with an 8-channel receiver only neurovascular phased array coil (MEDRAD, Inc., Indianola, PA, USA). The primary images for analysis were rapidly acquired in a midline, sagittal plane using fast gradient echo imaging (1 image every 800 ms).[9] The scan parameters were: Repetition time/Echo time: 6.98/3.6, Field of view: 24 cm, slice thickness: 5 mm, matrix 256×128, number of excitations: 1, flip angle: 80°, receiver bandwidth 244.1 Hz/pixel, baseline resolution: 256, phase resolution: 128. By playing a cine loop of the images, a movie of airway motion was created (Figs. 1 and 2 with associated video). Upper airway images were obtained during low (1 mcg/kg/h) and high (3 mcg/kg/h) dose DEX sedation. The images were stored on the PACS (Picture Archiving and

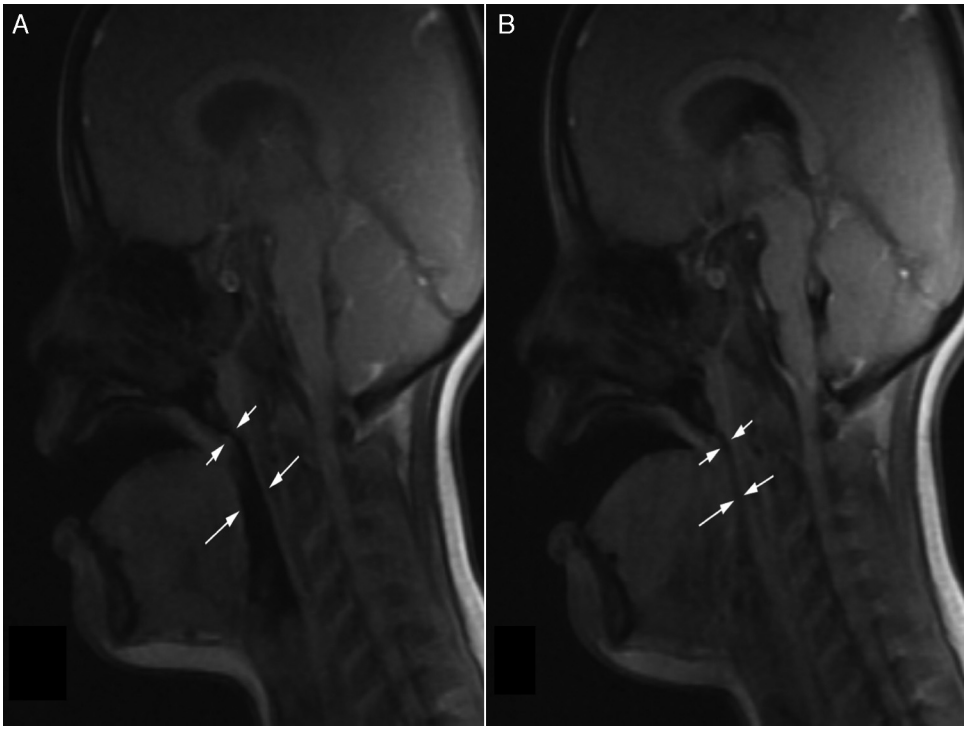

Figure 1 Still image (A) from a sagittal cine clip shows the nasopharynx airway (short arrows) and the retroglossal airway (long arrows) as open and the still image (B) shows the retroglossal airway as collapsed.

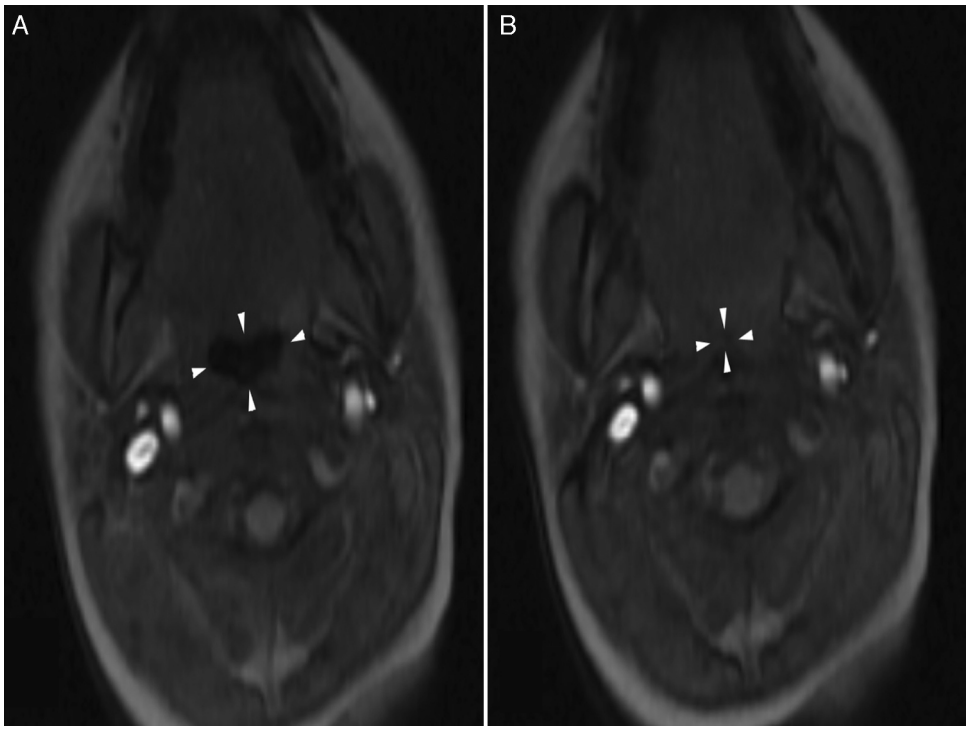

Figure 2 Still image (A) from the cine clip shows the retroglossal airway in cross-section while open (arrowheads) and the still image (B) shows the airway completely collapsed centrally compatible with hypopharyngeal collapse.

Communication System) and reviewed by two scorers who were blinded to the DEX doses.

The airway was measured at the level of the soft palate (nasopharyngeal airway) and the base of the tongue (retroglossal airway) (Figs. 1 and 2). The sectional area and anterior-posterior diameter were measured in the nasopharyngeal area (NPA) and the retroglossal area (RGA). The nasopharyngeal area (NPA) was defined anteriorly by a vertical line tangential to the posterior inferior nasal turbinate, posteriorly by the posterior wall of nasopharynx, superiorly by the superior wall of nasopharynx, and inferiorly by superior and posterior part of hard and soft palate. The retroglossal airway area (RGA) was defined anteriorly by the back of tongue, posteriorly by the posterior pharyngeal wall, superiorly by a horizontal line drawn at the inferior margin of the soft palate, and inferiorly by a horizontal line drawn at the base of the tongue. The sectional area and anteroposterior diameter were measured in the NPA and RGA on images of minimum and maximum expansion of the airway.

Power analysis

Analyses performed with R statistical software indicated that a sample size of 7 patients would have an 80% power to detect a 100 mm^2 difference in the mean sectional areas of NA and DS airways in children under low dose DEX.[12] A difference of 100 mm^2 was chosen because children with DS have baseline narrow airways and was based on a 95% confidence level in the mean differences.[13] Low dose DEX was chosen in order to determine the most conservative estimate of sample size necessary to adequately power the study. This was done under the assumption that high dose DEX would cause more significant airway narrowing than low dose DEX and, subsequently, the mean difference in airway measurements would be larger. A post hoc power analysis was performed to verify this assumption.

Statistical analysis

Statistical analysis was performed with R statistical software.[12] Normality of distribution of data was checked by Shapiro–Wilks test. Descriptive statistics are provided as mean and standard deviation or numbers as appropriate. Age, weight, and polysomnography derived variables between children with NA and children with DS were compared with Welch two-sample *t*-test. Gender was compared with the Fischer exact test. Hemodynamic data were compared with the unpaired *t*-test. The minimum and maximum anteroposterior diameter and sectional areas in the NPA and RGA were compared between children with DS and children with NA using the unpaired *t*-test. The difference between 'low dose DEX' and 'high dose DEX' between children with DS and children with NA was compared using the paired *t*-test. A *p*-value of <0.05 was considered statistically significant.

Results

We studied 7 children with DS and 23 children with NA. The age, weight, and polysomnography findings for the groups are presented in Table 1. The UMSS sedation scale showed that children with DS had significantly higher sedation scores during induction, but similar scores in the post anesthesia care unit (Table 1). Heart rate and blood pressure were statistically similar between both the groups (Table 2).

Table 1 Demographic and polysomnography findings.

	Down Syndrome ($n=7$)	Normal airway ($n=23$)	p
Age (years)	5 ± 1	6 ± 2	0.27
Weight (kg)	26 ± 11	22 ± 5	0.42
Male/females	4/3	12/11	1
Sedation score			
Induction	3 ± 1	2 ± 1	0.003
Post anesthesia care unit	3 ± 0	3 ± 0	0.36
Obstructive sleep apnea (n)	7	0	
Polysomnography findings			
Apnea hypopnea index (events/hour)	17 ± 11 (5.2–37.6)	–	
Minimal oxygen saturation (%)	81 ± 5 (72–85)	–	

All data in mean ± standard deviation or absolute numbers. Ranges are mentioned in parenthesis. –, not applicable.

Airway anteroposterior diameter and sectional area measurements are summarized in Table 3.

The following three dimensions were reduced significantly in children with DS as compared to NA at both low and high dose DEX: minimum RGA sectional area, minimum anteroposterior NPA diameter, and minimum anteroposterior RGA diameter. Sedation with DEX did not yield a statistically significant dose-dependent (low vs. high) difference in the airway measurements of children with DS and NA (Table 4).

Discussion

Our study showed that children with DS and OSA exhibited significant reductions in anatomical airway dimensions when compared to children with NA under DEX sedation. The safe sedation of children especially those with a history of OSA requires a clear understanding of the pharmacokinetic and pharmacodynamic effects of the sedative used as well as an appreciation of the effect of the chosen sedative on airway collapsibility. All practitioners providing sedation must have an in depth understanding of the interaction between depth of sedation and airway dynamics, remembering that depth of sedation is a continuum from minimal, moderate, and deep sedation to general anesthesia.

Table 2 Hemodynamic data.

	Baseline		p	First scan		p	High dose DEX		p
	Down Syndrome	Normal children		Down Syndrome	Normal children		Down Syndrome	Normal children	
HR (bpm)	101 ± 12	93 ± 14	0.15	97 ± 19	78 ± 15	0.03	84 ± 9	82 ± 19	0.88
SBP (mm Hg)	110 ± 10	107 ± 14	0.50	125 ± 14	111 ± 15	0.13	137 ± 14	112 ± 14	0.08
DBP (mm Hg)	64 ± 9	56 ± 19	0.16	69 ± 9	59 ± 12	0.15	84 ± 2	66 ± 12	<0.001

HR, heart rate; SBP, non-invasive systolic blood pressure; DBP, non-invasive diastolic blood pressure.

Table 3 Comparison of airway dimensions between children with Down Syndrome and children with normal airway under both low and high dose dexmedetomidine.

Dimensions	Low dose dexmedetomidine				High dose dexmedetomidine			
	Down	Normal	95% CI	p-Value	Down	Normal	95% CI	p-Value
Nasopharyngeal								
AP (mm)								
Minimum	1 ± 1	5 ± 2	2.6–4.9	<0.001	1 ± 1	5 ± 2	2.3–4.7	<0.001
Maximum	2 ± 1	5 ± 2	2.6–5.1	<0.001	2 ± 1	5 ± 2	2.0–4.7	<0.001
Sectional area (mm^2)								
Minimum	157 ± 41	265 ± 80	59.5–154.7	<0.001	171 ± 69	262 ± 75	7.2–175.0	0.04
Maximum	198 ± 28	279 ± 82	39.8–122.1	<0.001	199 ± 78	281 ± 71	−12.2 to 175.8	0.08
Retroglossal								
AP (mm)								
Minimum	2 ± 2	10 ± 4	5.7–9.9	<0.001	4 ± 3	9 ± 4	1.5–9.2	0.01
Maximum	7 ± 4	10 ± 4	−0.0 to 7.5	0.05	8 ± 4	10 ± 5	−2.2 to 6.7	0.27
Sectional area (mm^2)								
Minimum	108 ± 63	245 ± 79	74.3–199.7	<0.001	121 ± 48	247 ± 104	60.1–191.5	0.001
Maximum	227 ± 129	266 ± 89	−81.8 to 160.1	0.48	210 ± 78	268 ± 108	−37.8 to 153.9	0.2

AP, Antero-posterior; 95% CI, 95% confidence interval for the mean differences.

Table 4 Comparison of mean differences in airway dimensions between low and high dose dexmedetomidine in children with normal airway and children with Down Syndrome.

Dimensions	Down (low vs. high dose DEX)			Normal (low vs. high dose DEX)		
	Mean difference	95% CI	*p*-Value	Mean difference	95% CI	*p*-Value
Nasopharyngeal						
AP (mm)						
Minimum	−0.4	−2.0 to 1.3	0.56	0.1	−0.4 to 0.5	0.79
Maximum	−0.2	−1.9 to 1.5	0.76	0.3	−0.1 to 0.7	0.31
Sectional area (mm^2)						
Minimum	−1.5	−120.5 to 117.5	0.97	2.2	−8.7 to 13.2	0.67
Maximum	6.3	−114.9 to 127.6	0.89	−2.4	−13.7 to 8.9	0.67
Retroglossal						
AP (mm)						
Minimum	−1.5	−5.4 to 2.3	0.33	0.7	−0.0 to 1.5	0.06
Maximum	−2.0	−9.4 to 5.5	0.51	0.3	−0.5 to 1.2	0.41
Sectional area (mm^2)						
Minimum	3.1	−109.4 to 115.7	0.94	−1.9	−17.8 to 14.0	0.81
Maximum	4.9	−168.0 to 177.8	0.94	−1.9	−19.8 to 16.0	0.83

The mean differences in this table are obtained as a paired analysis from the dataset and do not represent simply the difference of two corresponding means from Table 3.

Sedating or anesthetizing a child known to have OSA is a challenge because anesthetic agents blunt arousal mechanisms, decrease respiratory drive, and reduce pharyngeal muscle tone. More than half of all children with DS have OSA, and these children are at higher risk of adverse airway events during procedural sedation. Our study examined the anatomical sagittal sectional areas and diameter at the critical part of the airway. We show that airway sectional areas and diameters were significantly reduced in children with DS compared to those children with NA at both low and high dose DEX. The changes in airway dimensions were not dose-dependent within the patient groups. The seeming independence of airway dimensions and DEX dose can be explained by the relationship between consciousness and upper airway collapsibility. Profound changes in upper airway muscle activity and collapsibility occur proximate to the loss of consciousness and relatively modest changes occur with increasing depth of anesthesia/sedation.[14]

Furthermore, we quantitate the effect of DEX sedation on airway morphology in children with DS. It is our hope that practitioners can utilize this information to better assess the depth of sedation of their DS patients and ultimately avoid the adverse effects of over sedation (e.g. hypoventilation, airway obstruction). As pediatric DS patients can rapidly obstruct their airways even at low doses of sedation, providers should also confirm that airway management instruments are readily available before sedating these children.

Patients with DS also have a higher chance of persistent OSA following tonsillectomy due to recurrent enlargement of lingual tonsils and adenoid tissue, reduced muscular tone, hypopharyngeal collapse, and glossoptosis.[15,16] MRI of the airway in adolescents for evaluation of OSA revealed that children with DS have disproportionately large tongues in comparison to the craniofacial parameters of age- and gender-matched controls.[3] The findings from the present study show that airway size was stable between the dosage levels of DEX studied. This suggests that the airway collapsibility is probably caused by reduced muscular tone and hypopharyngeal collapse, glossoptosis, midface hypoplasia, and relative macroglossia.[3,15,16] Pharyngeal collapse is more severe in children with DS compared to controls, independent of age, gender, and body mass index.[17] The augmented upper airway dilator activity present in the awake state is reduced at sleep onset, and is further attenuated during rapid eye movement sleep, contributing to pharyngeal collapse in children with OSA.[18,19] Additional contributors to airway obstruction during sedation with intravenous pentobarbital in children with moderate OSA include large soft palate, and, large adenoids and tonsils.[20]

The airway sectional area and anteroposterior diameter were measured as minimum and maximum, which represent dimensions during inhalation and exhalation respectively. This was done to interpret relative changes in the airway during the respiratory cycle. The peak image acquisition rate of 800 ms was performed and allowed for random sampling during the respiratory cycle. Segmentation of the airway size over the breathing cycle and the use of the peak size and minimal size obviated the need for synchronization to the respiratory cycle. The airway is largest during expiration and smallest during inspiration unless tongue/jaw thrusting is present and the airway is more dynamic in OSA.[21]

The baseline caliber of the airway is an important factor in the dynamics of the airway movement and is related to the flow structure interaction between the flowing air and the surrounding soft tissues.[22] Thus, the narrowest portions of the airway are most important in inducing airway collapse than the larger caliber segments of the airway. The change from maximum to minimum size during a respiration is physiological breathing-related and the greater degree in DS is linked to both the OSA and the smaller size. The end result is a significantly lower functional performance and

higher fatigability seen in inspiratory muscles in patients with OSA.[23]

There are a few limitations with our study. Although our sample size remains a limitation and may limit our statistical significance particularly with high dose DEX group nasopharyngeal area measurements (post hoc power 71%), our preliminary findings are relevant in defining and applying interventions to improve airway outcomes in children undergoing sedation outside the operating room. Second, all of the patients with DS in our study had moderate to severe OSA. The findings may be different in the minority of those patients with DS with no OSA. While it would be ideal to study DS patients with no OSA as a third group, the availability of an adequate number of DS patients having MRI of airway for non-OSA indications is a major limiting factor. Last, the mean sedation score in children with DS was significantly higher during induction as compared to children with NA and may have affected measurements during low dose DEX. Although UMSS captures changes in the depth of sedation, the inability of the scale to discriminate moderate and deep levels of sedation may limit its usefulness in such situations.[24]

Conclusions

In summary, children with DS with OSA exhibited significant reductions in anatomical airway dimensions when compared to children with NA under DEX sedation, supporting our hypothesis. The relative reduction in airway dimensions is equal at both low dose and high dose DEX, which suggests that the observed differences are unique to DS and not due to differences in sedation. These changes are most significant at the narrowest points in the nasopharyngeal and retroglossal airways.

Conflicts of interest

The authors declare no conflicts of interest.

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