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Drug-Induced Sleep Endoscopy Compared to Systematic Adenotonsillectomy in the Management of Obstructive Sleep Apnea in Children: A Systematic Review and Meta-Analysis Protocol.

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Date of the study

We are planning to start the study in October 2018.

Abstract

Introduction: Obstructive sleep apnea affects up to 6% of children worldwide. Although current guidelines recommend systematic tonsillectomy and adenoidectomy, many children do not benefit from these interventions. Drug-Induced Sleep Endoscopy (DISE) allows the dynamic evaluation of patients' airway in order to identify the specific anatomic sites of obstruction. This intervention can potentially guide subsequent invasive procedures in order to optimize outcomes and minimize the number of children exposed to unnecessary operations.

Methods and analysis: We will identify randomized controlled trials and controlled observational studies comparing DISE-directed interventions and systematic tonsillectomy and adenoidectomy in pediatric population. We will search MEDLINE, EMBASE, CINAHL, CENTRAL as well as clinical trial registries and conference proceedings. Screening, data extraction and risk of bias assessments will be performed in duplicate by independent reviewers. We will use the GRADE approach to assess the overall quality of evidence and present our results.

Ethics and dissemination: Ethics approval is not required for this systematic review of published data. This review will be presented according to PRISMA guidelines. We will present our findings at otorhinolaryngology conferences and publish a report in a peer-reviewed journal.

Registration number (PROSPERO): CRD42018085370.

Strengths and limitations of this study:

- This is the first review to compare DISE-guided interventions to standard adenotonsillectomy in the treatment of pediatric obstructive sleep apnea.
- This review is prospectively registered, includes detailed search strategy and explicit, prespecified inclusion and exclusion criteria.
- We will provide transparent and clear reporting of our findings using the GRADE approach.

INTRODUCTION

Obstructive sleep apnea (OSA) affects 1 to 6 % of school-aged children [1, 2]. Left untreated, this condition is associated with neurocognitive and behavioral disorders, cardiovascular consequences, failure to thrive and poor quality of life [2-6].

Nocturnal laboratory polysomnography (PSG) is the diagnostic gold standard for obstructive sleep apnea in children with either an obstructive apnea index (OAI) > 1/h or an obstructive apnea and hypopnea index (AHI) of > 1.5/h [2, 7-9]. Tonsillectomy and adenoidectomy (T&A) is recommended by the American Academy of Pediatrics as the first-line therapy for children diagnosed with obstructive sleep apnea and adenotonsillar hypertrophy [2]. However, published data on obstructive sleep apnea improvement following adenotonsillectomy remain inconclusive, with a variable success rate between 12 and 83% [10, 11]. Other potential treatment approaches include medications (e.g. nasal corticosteroids, leukotriene antagonists), life style interventions for obese patients, CPAP, hypoglossal nerve stimulation, myofunctional therapy, supraglottoplasty, lingual tonsillectomy, nasal surgery, maxillofacial surgery and orthodontic treatment [2, 12, 13]. Accordingly, tests predicting the response to adenotonsillectomy may help distinguish patients who will benefit from those in whom adenotonsillectomy is more likely to be inefficient and potentially harmful.

Drug-Induced Sleep Endoscopy (DISE) consists in the direct examination of the upper airway using flexible endoscopy under deep sedation in order to identify specific anatomic sites of obstruction. Drugs that induce a hemodynamically stable near-normal sleep are administered, and sleep and snoring must be maintained by ensuring anesthetics are within appropriate concentration ranges. DISE can be used as a first-line diagnostic tool to select the best candidates for surgery and reduce the rate of unsuccessful invasive interventions. DISE can also be of benefit to children who fail to improve following adenotonsillectomy [12].

OBJECTIVES

Our primary objective is to evaluate whether children with obstructive sleep apnea in whom the first-line therapy is guided by DISE have a higher cure rate (normal polysomnography) than children with obstructive sleep apnea who undergo adenotonsillectomy without pre-operative DISE. Our secondary objective is to determine if children diagnosed with obstructive sleep apnea who are selected for surgery after DISE have a higher cure rate (normal polysomnography) than children with obstructive sleep apnea who undergo adenotonsillectomy without pre-operative DISE.

METHODS AND ANALYSIS

Protocol and registration

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement guided the design of this protocol [14] (CRD42018085370).

Eligibility criteria

Participants

Our population is limited to surgically naïve children (≥ 1 and < 18 years of age) with confirmed obstructive or mixed sleep apnea, defined by an obstructive apnea index (OAI) > 1/h or an obstructive apnea and hypopnea index (oAHI) >1.5/h ascertained by PSG. We will exclude studies whose population includes infants with < 1 year of age, congenital craniofacial malformations, neurologic or muscular disease impacting respiratory function (e.g. cerebral palsy, muscular dystrophy) and patients with previous airway surgery unless these patients account for less than 10% of the total sample size or there is data available for the subgroup of patients without these characteristics. Patients with laryngomalacia with no exclusion criteria are included in the study. We will exclude animal studies.

Interventions

The intervention of interest is DISE performed before a first-line surgical therapy for obstructive sleep apnea is attempted.

Outcome measures

The primary outcome will be the normalization of either the obstructive apnea index (OAI ≤ 1/h) or apnea hypopnea index (≤ 1.5/h). We will stratify secondary outcomes according to GRADE recommendations as “critical”, “important but not critical” or “low importance”. Those outcomes of interest will be the proportion of patients undergoing a tonsillectomy, postoperative bleeding, perioperative bleeding, postoperative pain, velopharyngeal insufficiency, dehydration requiring intra-venous fluid therapy, number of interventions under general anesthesia, length of hospital stay, overall cost, quality of life, neurobehavioral development, neurocognitive development, growth, days missed at school/kindergarten during postoperative period, infections requiring antibiotic therapy and other minor surgical complications (e.g. dental damage, mouth/lips burn). These outcomes will be rated for importance in consultation with otorhinolaryngologists, pediatricians, community members, and parents of children with obstructive sleep apnea.

Type of studies

We will include randomized controlled trials and observational studies that allow comparisons between DISE-guided interventions and adenotonsillectomy for all patients (cohort or case-control). Case series and case reports will be excluded. We will impose no restriction based on language or publication status.

Search strategy

We will perform a search in MEDLINE, MEDLINE In-Process, CINAHL, EMBASE, PUBMED and The Cochrane Library (CENTRAL database). An example of this search strategy is included (Appendix A). Other sources that will be searched are ClinicalTrials.gov, reference lists of included studies, and conference proceedings from the following major scientific meetings since 1988: American Academy of Otolaryngology-Head and Neck Surgery, International Congress on Pediatric Pulmonology, American Thoracic Society, American Pediatric Societies Meeting and European Respiratory Society Meeting.

Study records

Two reviewers will independently screen titles and abstracts in duplicate using the Rayyan electronic platform (Qatari Computing Research Institute): https://rayyan.qcri.org/.

We will proceed to full-text review unless both reviewers agree to exclude a report. Disagreements will be resolved by consensus or third-reviewer adjudication.

Data collection

Both reviewers will use pre-tested data collection forms to collect data independently and in duplicate. Data of interest include study design, population baseline characteristics, intervention characteristics, clinical outcomes and variables necessary for risk of bias assessment. Disagreements will be resolved by consensus or third-reviewer adjudication.

Risk of bias assessment

We will use a modified version of the Cochrane Collaboration's tool to assess the risk of bias in randomized controlled trials [15]. This tool evaluates reports for randomization, allocation concealment, blinding, loss to follow-up, selective outcome reporting, as well as other risks of bias.

We will use the grading tool developed by the "Clinical Advances through Research and Information Technology" (CLARITY) group to evaluate the risk of bias in observational studies (McMaster University, https://distillercer.com/resources/). These tools evaluate reports for experimental and control group selection, assessment of prognostic factors, exposure and outcomes, statistical methods, follow-up, co-intervention similarity between groups, as well as other risks of bias.

If any domain presents a potential source of bias, then the report will be graded as high risk of bias. We will evaluate the overall quality of data across studies for each outcome using GRADE methodology [16].

Summarizing data and treatment effect

We will include comparably homogeneous studies in a random-effects meta-analysis, using the inverse-variance method to assign study weights [17]. We will use the Review Manager software made available by the Cochrane Collaboration (Review Manager 5.3).

Dichotomous variables will be calculated using individual study odds ratios and presented as risk ratios with 95% confidence intervals. Outcomes reported on different scales, such as quality of life, will be presented as number needed to treat according to the previously published recommendations of *Thorlund et al.* [18]. Continuous outcomes will be presented as mean differences with associated 95% confidence intervals. These recommendations encourage the use of two or more complimentary methods to present such results, in order to facilitate their interpretation. We will analyze and present randomized trials and observational studies separately.

If we identify no studies homogeneous enough to be included in a meta-analysis, we will provide a qualitative summary of our findings and justify our rationale.

Investigations of heterogeneity

We will evaluate study heterogeneity qualitatively by assessing whether or not study populations, interventions and settings are comparable across studies. The following characteristics will be considered: baseline apnea hypopnea index, Brodsky score, body mass index (BMI), age, sex and ethnicity. These categories will constitute the basis for subgroup analyses.

We will evaluate heterogeneity quantitatively using a chi-squared test for homogeneity as well as Higgins and Thomson's I^2 statistic. Regardless the degree of heterogeneity identified, we will perform the following limited subgroup analyses:

(1) Baseline obstructive sleep apnea severity: mild (1.5 < apnea hypopnea index < 5 OR 1 ≤ obstructive apnea index < 2), moderate (5 ≤ apnea hypopnea index or obstructive apnea index < 10) and severe (apnea hypopnea index or obstructive apnea index ≥ 10/h), hypothesizing that more severe obstructive sleep apnea will be more likely to benefit from DISE-directed therapy;

(2) Patients Brodsky score from 0 to 4, hypothesizing that patients with a lower Brodsky score will be more likely to benefit from DISE-directed interventions;

(3) Obese (≥ 95th percentile for body mass index) vs non-obese patients, hypothesizing that obese patients will be less likely to benefit from DISE-directed interventions;

(4) Age (1 to 8 years-old or > 8 years-old), hypothesizing that older patients will be more likely to benefit from DISE-directed interventions [19];

(5) Sex, hypothesizing that male patients will be more likely to benefit from DISE-directed interventions;

(6) Ethnicity (white, black or other), hypothesizing that African American patients will be more likely to benefit from DISE-directed interventions.

We will evaluate the credibility of subgroup effects according to the following: if the subgroup characteristic is present at baseline, whether the comparison is within or between studies, whether the result is statistically significant, whether the result is found consistently across studies and outcomes, and whether or not there exists other evidence to support the result [20]. We will require five or more studies for comparisons between different studies, with each group represented by two or more studies. If the comparison is between subgroups within the same studies, we will require only two studies to perform the analysis.

Sensitivity analyses

We will conduct a sensitivity analysis excluding studies published as abstracts as well as another excluding studies with "unclear" or "high risk of bias".

Assessment of reporting bias

If we identify ten or more eligible studies in a meta-analysis, we will present a funnel plot and either the Egger's test (continuous outcomes) or the Arcsine test (dichotomous outcomes) to assess the risk of publication bias.

Interpretation of results

The Grading of Recommendations, Assessment, Development and Evaluation framework will be used to report the overall quality of evidence and our confidence in estimates of effect. This framework considers the overall risk of bias, imprecision, inconsistency across studies, indirectness and the likelihood of publication bias. We will classify the quality of evidence as being "very low", "low", "moderate", or "high".

We will present our results in a Summary of Findings table to represent individual outcomes across studies as well as the quality of evidence for each outcome.

Protocol amendments

Any amendments to this protocol will be reported with the justification and date of modification.

Patients and public involvement

Our research question was guided by the lack of consensus on the management of pediatric obstructive sleep apnea. We aim to provide guidance on the most effective treatment that minimizes adverse effects and risks to patients. Patients were not directly

involved in the study design, but a few parents and members of the public will be involved in the classification of secondary outcomes.

Ethics and dissemination

No confidential data will be used, therefore approval by an ethic committee will not be necessary. This systematic review will provide an accurate portrait of the impact of DISE-directed management compared to systematic adenotonsillectomy in the management of pediatric obstructive sleep apnea. We will publish our results in a peer-reviewed journal.

The review will be reported according to PRISMA guidelines [14].

DISCUSSION

Obstructive sleep apnea is a common condition that, left untreated, can have profound consequences on future development. The routine adoption of adenotonsillectomy as a first-line treatment aims to mitigate this impact. However, disparities in cure rates between different reports suggest that this approach is not optimal for all subgroups of patients. DISE is a promising intervention that may both help select surgical candidates and avoid unnecessary surgeries in children least likely to benefit from adenotonsillectomy.

If we identify high quality evidence suggesting that preoperative DISE is beneficial, this conclusion will have important implications for practice. In contrast, if we find that the existing evidence is insufficient to provide definitive inferences regarding the effect of DISE before adenotonsillectomy, this review will expose a knowledge gap and provide a strong rationale for further prospective research.

Contributors

ASP, MG, FL, MCB, JPP and MH conceived the research question. MH and FL conceptualized methodological analyses. ASP and MH wrote the draft protocol. All authors reviewed and approved the protocol. ASP and MH will review articles. All authors will contribute to the writing of the publication.

Acknowledgements

The search strategy was developed in collaboration with Rachel Couban (McMaster University medical librarian).

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Competing interests

None.

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Appendix A – Sample search strategy (MEDLINE)

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
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1 sleep apnea syndromes/ or exp sleep apnea, obstructive/ (29977)
2 (obstruct* adj2 hypopn?ea*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (438)
3 apn?e*-hypopn*.mp. (8934)
4 (nocturnal adj2 hypoxemia).mp. (411)
5 apn?eic.mp. (3195)
6 (upper airway adj3 (resistan* or obstruct*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5042)
7 (sleep* adj3 (apne* or apnoe* or hypopn* or obstruct* or disorder* or disturb*)).mp. (75865)
8 (osa or osas or osahs).tw. (15457)
9 ((apn?e* or hypopn?ea) adj1 index).mp. (7834)
10 (airway adj1 (resistan* or obstruct* or collapsib*)).mp. (42933)
11 or/1-10 (118935)
12 *ENDOSCOPY/ (26578)
13 DISE.mp. (224)
14 ((sleep or sedation) and (endoscop* or nas?endoscop*)).mp. (4384)
15 or/12-14 (30540)
16 11 and 15 (1237)
17 Pediatrics/ or adolescent/ or child/ or child, preschool/ or exp infant/ (3295505)
18 (child* or children or pediat* or paediat* or infan* or youth* or toddler* or adolesc* or teen* or boy or boys or boyfriend or boyhood or girl* or preschool* or pre-school* or minors or minors* or kid or kids or schoolchild* or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3818207)
19 school child*.ti,ab. (21272)
20 (Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1425311)
21 or/17-20 (4018110)
22 11 and 15 and 21 (398)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A		
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	X		
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		
Sponsor	5b	Provide name for the review funder and/or sponsor	X		
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X		
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for	X		

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		eligibility for the review			
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X		
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		

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Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Anaesthesia, Paediatrics, Respiratory medicine
Keywords:	Paediatric otolaryngology < PAEDIATRIC SURGERY, SLEEP MEDICINE, Anaesthesia in otolaryngology < ANAESTHETICS, Paediatric anaesthesia < ANAESTHETICS, Paediatric otolaryngology < OTOLARYNGOLOGY

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Date of the study

Study start date is October 2018.

Abstract

Introduction: Obstructive sleep apnea affects up to 6% of children worldwide. Although current guidelines recommend systematic tonsillectomy and adenoidectomy, many children do not benefit from these interventions. Drug-Induced Sleep Endoscopy (DISE) allows the dynamic evaluation of patients' airway to identify the specific anatomic sites of obstruction. This intervention can potentially guide subsequent invasive procedures to optimize outcomes and minimize the number of children exposed to unnecessary operations.

Methods and analysis: We will identify randomized controlled trials and controlled observational studies comparing DISE-directed interventions and systematic tonsillectomy and adenoidectomy in pediatric population. We will search MEDLINE, EMBASE, CINAHL, CENTRAL as well as clinical trial registries and conference proceedings (initial electronic search date 2018-10-09). Screening, data extraction and risk of bias assessments will be performed in duplicate by independent reviewers. We will use the GRADE approach to assess the overall quality of evidence and present our results.

Ethics and dissemination: Ethics approval is not required for this systematic review of published data. This review will be presented according to PRISMA guidelines. We will present our findings at otorhinolaryngology conferences and publish a report in a peer-reviewed journal.

Registration number (PROSPERO): CRD42018085370.

Strengths and limitations of this study:

- This review is prospectively registered, includes detailed search strategy and explicit, prespecified inclusion and exclusion criteria.
- We will provide transparent and clear reporting of our findings using the GRADE approach.
- This systematic review will offer a rigorous, comprehensive assessment of the literature pertaining to the use of Drug-Induced Sleep Endoscopy for a common pediatric condition.
- One of our main outcome measures, the apnea hypopnea index, is an imperfect metric which does not consider variables such as cardiovascular complications and daytime functioning, but it is nonetheless rigorously standardized and commonly used.
- The number and methodological quality of available studies will likely limit our conclusions.

INTRODUCTION

Obstructive sleep apnea (OSA) affects 1 to 6 % of school-aged children [1, 2]. Left untreated, this condition is associated with neurocognitive and behavioral disorders, cardiovascular consequences, failure to thrive and poor quality of life [2-6].

Nocturnal laboratory polysomnography (PSG) is the diagnostic gold standard for obstructive sleep apnea in children with either an obstructive apnea index (OAI) > 1/h or an obstructive apnea and hypopnea index (AHI) of > 1.5/h [2, 7-9]. The AHI an imperfect metric, as it does not consider relevant variables such as cardiovascular complications or daytime functioning. It is nonetheless the outcome most likely to be consistently reported, given the standardization of scoring rules by the American Academy of Sleep Medicine [10]. Tonsillectomy and adenoidectomy (T&A) is recommended by the American Academy of Pediatrics as the first-line therapy for children diagnosed with obstructive sleep apnea and adenotonsillar hypertrophy [2]. However, published data on obstructive sleep apnea improvement following adenotonsillectomy remain inconclusive, with a variable success rate between 12% and 83% [11, 12]. Other potential treatment approaches include medications (e.g. nasal corticosteroids, leukotriene antagonists), lifestyle interventions for obese patients, CPAP, hypoglossal nerve stimulation, myofunctional therapy, supraglottoplasty, lingual tonsillectomy, nasal surgery, maxillofacial surgery and orthodontic treatment [2, 13, 14]. Accordingly, tests predicting the response to adenotonsillectomy may help distinguish patients who will benefit from those in whom adenotonsillectomy is more likely to be inefficient and potentially harmful.

Drug-Induced Sleep Endoscopy (DISE) consists in the direct examination of the upper airway using flexible endoscopy under deep sedation to identify specific anatomic sites of obstruction. Drugs that induce a hemodynamically stable near-normal sleep are administered, and sleep and snoring must be maintained by ensuring anesthetics are within appropriate concentration ranges. DISE can be used as a first-line diagnostic tool to select the best candidates for surgery and reduce the rate of unsuccessful invasive interventions. DISE can also be of benefit to children who fail to improve following adenotonsillectomy [13].

It is conceivable that DISE may improve rates of OSA cure, if the ensuing surgical intervention is better tailored to a patient's specific anatomic abnormality. Alternatively, it is possible that DISE will only avoid unnecessary adenotonsillectomy in patients who would not have benefited from a surgical intervention either way. In this latter scenario, we would expect similar rates of OSA improvement and decreased surgical morbidity in patients undergoing DISE.

OBJECTIVES

Our primary objective is to determine whether children with OSA should undergo DISE followed by targeted therapy, or routine adenotonsillectomy without additional preoperative workup. The latter case reflects the current standard of care. Our primary research question is therefore as follows: In children with OSA, does DISE-guided management (surgical and/or non-surgical) lead to improved cure rates (normal polysomnography), compared to first-line adenotonsillectomy without additional preoperative workup?

Our secondary objective is to determine, within the more limited subgroup of patients that ultimately undergo a surgical procedure, whether those selected with preoperative DISE have improved outcomes. Our secondary research question is therefore as follows: In children with OSA, do surgical interventions guided by pre-operative DISE lead to improved cure rates (normal polysomnography), compared to first-line adenotonsillectomy without further preoperative workup?

METHODS AND ANALYSIS

Protocol and registration

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement guided the design of this protocol (Appendix B) [15]. PROSPERO registration number: CRD42018085370.

Eligibility criteria

Participants

Our population is limited to surgically naïve children (≥ 1 and < 18 years of age) with confirmed obstructive or mixed sleep apnea, defined by an obstructive apnea index (OAI) > 1/h or an obstructive apnea and hypopnea index (oAHI) >1.5/h ascertained by PSG. We will exclude studies whose populations include congenital craniofacial malformations, neurologic or muscular disease impacting respiratory function (e.g. cerebral palsy, muscular dystrophy) and patients with previous airway surgery unless these patients account for less than 10% of the total sample size or there is data available for the subgroup of patients without these characteristics. We will not exclude patients with laryngomalacia.

Intervention/Comparator

The intervention of interest is DISE performed before a first-line surgical therapy for OSA is attempted. The comparator is adenotonsillectomy for all patients presenting with OSA without preoperative DISE. This procedure removes tissue in the nasopharynx and oropharynx, thereby potentially relieving OSA when these are the sites of obstruction [16]. Multiple techniques (e.g. cold steel, monopolar or bipolar diathermy, coblation) are reported in the literature [17-20]. Complications of adenotonsillectomy include post-

operative bleeding, pain, dehydration, post-obstructive pulmonary edema, velopharyngeal insufficiency and death.

Outcome measures

The primary outcome will be the normalization of either the obstructive apnea index (OAI ≤ 1/h) or apnea hypopnea index (AHI≤ 1.5/h). Given that we anticipate that there will be few comparative studies addressing our specific research question, we will not exclude studies based on outcomes assessed. However, we will prespecify which secondary outcomes to include in our formal analysis and GRADE summary tables. Outcomes were selected and prioritized following a consultation with otorhinolaryngologists and patient advocates. We followed GRADE recommendations and favored patient-important outcomes and those that are not surrogate outcomes [21]. Outcomes of "low importance" will not be included in our analysis. Outcomes graded as "critical" were death and acute postoperative respiratory failure. Outcomes deemed to be "important but not critical" included the proportion of patients cured of OSA, the proportion of patients undergoing an adenotonsillectomy, post-operative bleeding, the number of interventions requiring general anesthesia, overall cost and quality of life.

Type of studies

We will include randomized controlled trials and observational studies that allow comparisons between DISE-guided interventions and adenotonsillectomy for all patients (cohort or case-control). Case series and case reports will be excluded. We will impose no restriction based on language or publication status.

Search strategy

We will perform a search in MEDLINE, MEDLINE In-Process, CINAHL, EMBASE and The Cochrane Library (CENTRAL database). The initial electronic search was performed on October 9th 2018 and will be updated as we near the publication of our review. An example of this search strategy is included (Appendix A). Other sources that will be searched are ClinicalTrials.gov, reference lists of included studies, and conference proceedings from the following major scientific meetings since 1988: American Academy of Otolaryngology-Head and Neck Surgery, International Congress on Pediatric Pulmonology, American Thoracic Society, American Pediatric Societies Meeting and European Respiratory Society Meeting.

Study records

Two reviewers will independently screen titles and abstracts in duplicate using the Rayyan electronic platform (Qatari Computing Research Institute): https://rayyan.qcri.org/.

We will proceed to full-text review unless both reviewers agree to exclude a report. Both reviewers will assess full-text reports independently and in duplicate using the same electronic platform. Disagreements will be resolved by consensus or third-reviewer adjudication.

Data collection

Both reviewers will use pre-tested data collection forms to collect data independently and in duplicate. Data of interest include study design, population baseline characteristics, intervention characteristics, clinical outcomes and variables necessary for risk of bias assessment. Disagreements will be resolved by consensus or third-reviewer adjudication.

Risk of bias assessment

We will use a modified version of the Cochrane Collaboration's tool to assess the risk of bias in randomized controlled trials [22]. This tool evaluates reports for randomization, allocation concealment, blinding, loss to follow-up, selective outcome reporting, as well as other risks of bias.

For non-randomized trials, we will use the Cochrane Collaboration's ROBINS-I tool [23, 24]. This tool is based on the principle that each non-randomized study seeks to reproduce the results of an "ideal" randomized controlled trial. Sources of bias are defined as the differences between the two studies that significantly alter the results of the non-randomized study. ROBINS-I addresses the following domains as potential sources of bias: confounding, selection bias, intervention classification, deviation from anticipated interventions, missing outcome data, method of measuring outcomes, and selective outcome reporting.

For both randomized and non-randomized studies, if any domain presents a potential source of bias (unclear or high risk of bias), then the report will be graded as high risk of bias. [25].

Summarizing data and treatment effect

We will include comparably homogeneous studies in a random-effects meta-analysis, using the inverse-variance method to assign study weights [26]. We will use the Review Manager software made available by the Cochrane Collaboration (Review Manager 5.3).

Dichotomous variables will be calculated using individual study odds ratios and presented as risk ratios with 95% confidence intervals. Continuous outcomes will be presented as mean differences with associated 95% confidence intervals. Outcomes reported on different scales, such as quality of life, will be presented according to the previously published recommendations of *Thorlund et al.* [27]. These recommendations include the use of two or more complimentary methods to present results in units that are easily interpreted by clinicians, for example as natural units of a familiar instrument or as a Number Needed to Treat. We will also present these data as standardized mean differences, as a sensitivity analysis. We will analyze and present randomized trials and observational studies separately. There are no conditions under which we will pool results from randomized and non-randomized studies.

If we identify no studies homogeneous enough to be included in a meta-analysis, we will provide a qualitative summary of our findings and justify our rationale.

Prespecified subgroup analyses

We will evaluate study heterogeneity qualitatively by assessing whether study populations, interventions and settings are comparable across studies. The following characteristics will be considered: baseline apnea hypopnea index, Brodsky score, body mass index (BMI), age, sex, ethnicity and socioeconomic status. These categories will constitute the basis for subgroup analyses.

We will evaluate heterogeneity quantitatively using a chi-squared test for homogeneity as well as Higgins and Thomson's I^2 statistic. Regardless the degree of heterogeneity identified, we will perform the following limited subgroup analyses:

(1) Baseline obstructive sleep apnea severity: mild (1.5 < apnea hypopnea index < 5 OR 1 ≤ obstructive apnea index ≤5), moderate (5 ≤ apnea hypopnea index or obstructive apnea index < 10) and severe (apnea hypopnea index or obstructive apnea index ≥ 10/h), hypothesizing that more severe obstructive sleep apnea will be more likely to benefit from DISE-directed therapy.

If the number of eligible studies is sufficient, we will also explore heterogeneity using quantile regression to analyze apnea severity as a continuous variable. We will require at least ten studies in the meta-analysis in order to perform a quantile regression, as recommended by Cochrane guidelines [22]. Moreover, studies included in this analysis will need to report the estimated treatment effect, associated variance, and covariate values [28]. In order to account for the residual heterogeneity between studies, we will perform a random-effects meta-regression.

(2) Patients Brodsky score from 0 to 4, hypothesizing that patients with a lower Brodsky score will be more likely to benefit from DISE-directed interventions

(3) Obese ($\geq 95^{th}$ percentile for body mass index) vs non-obese patients, hypothesizing that obese patients will be less likely to benefit from DISE-directed interventions

(4) Age (1 to 8 years-old or > 8 years-old), hypothesizing that older patients will be more likely to benefit from DISE-directed interventions [29]

(5) Sex, hypothesizing that male patients will be more likely to benefit from DISE-directed interventions

(6) Ethnicity (white, black or other), hypothesizing that African American patients will be more likely to benefit from DISE-directed interventions

(7) Socioeconomic status (higher vs. lower, as defined by individual study authors), hypothesizing that patients of lower socioeconomic status will be more likely to benefit from DISE-directed interventions

We will evaluate the credibility of subgroup effects according to the following: if the subgroup characteristic is present at baseline, whether the comparison is within or between studies, whether the result is statistically significant, whether the result is found consistently across studies and outcomes, and whether or not there exists other evidence to support the result [30]. We will require five or more studies for comparisons between different studies, with each group represented by two or more studies. If the comparison is between subgroups within the same studies, we will require only two studies to perform the analysis.

Sensitivity analyses

We will conduct a sensitivity analysis excluding studies published as abstracts as well as another excluding studies with "unclear" or "high risk of bias".

Assessment of reporting bias

If we identify ten or more eligible studies in a meta-analysis, we will present a funnel plot and either the Egger's test (continuous outcomes) or the Arcsine test (dichotomous outcomes) to assess the risk of publication bias, with statistical significance set at $p<0.05$ for both tests.

Interpretation of results

The Grading of Recommendations, Assessment, Development and Evaluation framework will be used to report the overall quality of evidence and our confidence in estimates of effect. This framework considers the overall risk of bias, imprecision, inconsistency across studies, indirectness and the likelihood of publication bias [31]. We will classify the quality of evidence for each outcome across studies as being "very low", "low", "moderate", or "high".

Confidence in effect estimates will be rated down for overall risk of bias if any study included in the analysis is graded as "high risk of bias" [32] .

Imprecision refers to the width of the 95% confidence interval surrounding the overall estimate of effect for an outcome. If clinical decision-making would differ based on whether the upper or lower bound of the confidence interval represented the truth, then the outcome will be rated down for imprecision [33].

Inconsistency refers to the variation in results across different studies. We will explore inconsistency by assessing the similarity of estimates, overlap of 95% CIs, as well as the Chi-squared test (with significance established at $p<0.05$) and I2 statistic (with "substantial heterogeneity" defined as an I2 greater than 50%) [34, 35]. We will present

a transparent rationale justifying the decision to rate down for inconsistency based on these factors and on whether it is explained by our *a priori* subgroup effects.

Indirectness refers to the degree to which clinical outcomes are surrogate rather than patient-important outcomes [36]. We will rate down for indirectness if studies fail to address patient-important outcomes directly.

Publication bias refers to the bias that is introduced to a body of evidence if positive studies are more likely to have been published than negative studies. We will rate down for publication bias if the arcsine test, Egger's test or a visual funnel plot are suggestive of significant publication bias [37].

We will present our results in a Summary of Findings table to represent individual outcomes across studies as well as the quality of evidence for each outcome [38]. Results from observational studies and randomized trials will be presented separately as different rows within the same table. Our final interpretation of results will rely on the estimate of effect providing the highest degree of certainty (e.g., data from high-quality clinical trials if available).

Protocol amendments

Any amendments to this protocol will be reported with the justification and date of modification.

Patients and public involvement

Our research question was guided by the lack of consensus on the management of pediatric obstructive sleep apnea. We aim to provide guidance on the most effective treatment that minimizes adverse effects and risks to patients. Patients were not directly involved in the study design, but a few parents and members of the public were involved in the classification of secondary outcomes.

Ethics and dissemination

No confidential data will be used, therefore approval by an ethic committee will not be necessary. This systematic review will provide an accurate portrait of the impact of DISE-directed management compared to systematic adenotonsillectomy in the management of pediatric obstructive sleep apnea. We will publish our results in a peer-reviewed journal.

The review will be reported according to PRISMA guidelines [15].

DISCUSSION

Obstructive sleep apnea is a common condition that, left untreated, can have profound consequences on future development. The routine adoption of adenotonsillectomy as a first-line treatment aims to mitigate this impact. However, disparities in cure rates between different reports suggest that this approach is not optimal for all subgroups of

patients. DISE is a promising intervention that may both help select surgical candidates and avoid unnecessary surgeries in children least likely to benefit from adenotonsillectomy.

If we identify high quality evidence suggesting that preoperative DISE is beneficial, this conclusion will have important implications for practice. In contrast, if we find that the existing evidence is insufficient to provide definitive inferences regarding the effect of DISE before adenotonsillectomy, this review will expose a knowledge gap and provide a strong rationale for further prospective research.

Contributors

ASP, MG, FL, MCB, JPP and MH conceived the research question. MH and FL conceptualized methodological analyses. ASP and MH wrote the draft protocol and will review articles. All authors (ASP, MH, MG, FL, MCB, SDM and ML) reviewed and approved the protocol and will contribute to the writing of the publication.

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Competing interests

None.

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Appendix A - PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A		
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	X		
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		
Sponsor	5b	Provide name for the review funder and/or sponsor	X		
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X		
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X		
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		

Appendix B – Sample search strategy (MEDLINE)

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
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1 sleep apnea syndromes/ or exp sleep apnea, obstructive/ (29977)
2 (obstruct* adj2 hypopn?ea*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (438)
3 apn?e*-hypopn*.mp. (8934)
4 (nocturnal adj2 hypoxemia).mp. (411)
5 apn?eic.mp. (3195)
6 (upper airway adj3 (resistan* or obstruct*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5042)
7 (sleep* adj3 (apne* or apnoe* or hypopn* or obstruct* or disorder* or disturb*)).mp. (75865)
8 (osa or osas or osahs).tw. (15457)
9 ((apn?e* or hypopn?ea) adj1 index).mp. (7834)
10 (airway adj1 (resistan* or obstruct* or collapsib*)).mp. (42933)
11 or/1-10 (118935)
12 *ENDOSCOPY/ (26578)
13 DISE.mp. (224)
14 ((sleep or sedation) and (endoscop* or nas?endoscop*)).mp. (4384)
15 or/12-14 (30540)
16 11 and 15 (1237)
17 Pediatrics/ or adolescent/ or child/ or child, preschool/ or exp infant/ (3295505)
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20 (Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1425311)
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Drug-Induced Sleep Endoscopy Compared to Systematic Adenotonsillectomy in the Management of Obstructive Sleep Apnea in Children: A Systematic Review and Meta-Analysis Protocol.

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Abstract

Introduction: Obstructive sleep apnea affects up to 6% of children worldwide. Although current guidelines recommend systematic tonsillectomy and adenoidectomy, many children do not benefit from these interventions. Drug-Induced Sleep Endoscopy (DISE) allows the dynamic evaluation of patients' airway to identify the specific anatomic sites of obstruction. This intervention can potentially guide subsequent invasive procedures to optimize outcomes and minimize the number of children exposed to unnecessary operations.

Methods and analysis: We will identify randomized controlled trials and controlled observational studies comparing DISE-directed interventions and systematic tonsillectomy and adenoidectomy in pediatric population. We will search MEDLINE, EMBASE, CINAHL, CENTRAL as well as clinical trial registries and conference proceedings (initial electronic search date 2018-10-09). Screening, data extraction and risk of bias assessments will be performed in duplicate by independent reviewers. We will use the GRADE approach to assess the overall quality of evidence and present our results.

Ethics and dissemination: Ethics approval is not required for this systematic review of published data. This review will be presented according to PRISMA guidelines. We will present our findings at otorhinolaryngology conferences and publish a report in a peer-reviewed journal.

Registration number (PROSPERO): CRD42018085370.

Strengths and limitations of this study:

- This review is prospectively registered, includes detailed search strategy and explicit, prespecified inclusion and exclusion criteria.
- We will provide transparent and clear reporting of our findings using the GRADE approach.
- This systematic review will offer a rigorous, comprehensive assessment of the literature pertaining to the use of Drug-Induced Sleep Endoscopy for a common pediatric condition.
- One of our main outcome measures, the apnea hypopnea index, is an imperfect metric which does not consider variables such as cardiovascular complications and daytime functioning, but it is nonetheless rigorously standardized and commonly used.
- The number and methodological quality of available studies will likely limit our conclusions.

INTRODUCTION

Obstructive sleep apnea (OSA) affects 1 to 6 % of school-aged children [1, 2]. Left untreated, this condition is associated with neurocognitive and behavioral disorders, cardiovascular consequences, failure to thrive and poor quality of life [2-6].

Nocturnal laboratory polysomnography (PSG) is the diagnostic gold standard for obstructive sleep apnea in children with either an obstructive apnea index (OAI) > 1/h or an obstructive apnea and hypopnea index (AHI) of > 1.5/h [2, 7-9]. The AHI an imperfect metric, as it does not consider relevant variables such as cardiovascular complications or daytime functioning. It is nonetheless the outcome most likely to be consistently reported, given the standardization of scoring rules by the American Academy of Sleep Medicine [10]. Tonsillectomy and adenoidectomy (T&A) is recommended by the American Academy of Pediatrics as the first-line therapy for children diagnosed with obstructive sleep apnea and adenotonsillar hypertrophy [2]. However, published data on obstructive sleep apnea improvement following adenotonsillectomy remain inconclusive, with a variable success rate between 12% and 83% [11, 12]. Other potential treatment approaches include medications (e.g. nasal corticosteroids, leukotriene antagonists), lifestyle interventions for obese patients, CPAP, hypoglossal nerve stimulation, myofunctional therapy, supraglottoplasty, lingual tonsillectomy, nasal surgery, maxillofacial surgery and orthodontic treatment [2, 13, 14]. Accordingly, tests predicting the response to adenotonsillectomy may help distinguish patients who will benefit from those in whom adenotonsillectomy is more likely to be inefficient and potentially harmful.

Drug-Induced Sleep Endoscopy (DISE) consists in the direct examination of the upper airway using flexible endoscopy under deep sedation to identify specific anatomic sites of obstruction. Drugs that induce a hemodynamically stable near-normal sleep are administered, and sleep and snoring must be maintained by ensuring anesthetics are within appropriate concentration ranges. DISE can be used as a first-line diagnostic tool to select the best candidates for surgery and reduce the rate of unsuccessful invasive interventions. DISE can also be of benefit to children who fail to improve following adenotonsillectomy [13].

It is conceivable that DISE may improve rates of OSA cure, if the ensuing surgical intervention is better tailored to a patient's specific anatomic abnormality. Alternatively, it is possible that DISE will only avoid unnecessary adenotonsillectomy in patients who would not have benefited from a surgical intervention either way. In this latter scenario, we would expect similar rates of OSA improvement and decreased surgical morbidity in patients undergoing DISE.

OBJECTIVES

Our primary objective is to determine whether children with OSA should undergo DISE followed by targeted therapy, or routine adenotonsillectomy without additional preoperative workup. The latter case reflects the current standard of care. Our primary research question is therefore as follows: In children with OSA, does DISE-guided management (surgical and/or non-surgical) lead to improved cure rates (normal polysomnography), compared to first-line adenotonsillectomy without additional preoperative workup?

Our secondary objective is to determine, within the more limited subgroup of patients that ultimately undergo a surgical procedure, whether those selected with preoperative DISE have improved outcomes. Our secondary research question is therefore as follows: In children with OSA, do surgical interventions guided by pre-operative DISE lead to improved cure rates (normal polysomnography), compared to first-line adenotonsillectomy without further preoperative workup?

METHODS AND ANALYSIS

Protocol and registration

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement guided the design of this protocol (Appendix A) [15]. PROSPERO registration number: CRD42018085370.

Eligibility criteria

Participants

Our population is limited to surgically naïve children (≥ 1 and < 18 years of age) with confirmed obstructive or mixed sleep apnea, defined by an obstructive apnea index (OAI) > 1/h or an obstructive apnea and hypopnea index (oAHI) >1.5/h ascertained by PSG. We will exclude studies whose populations include congenital craniofacial malformations, neurologic or muscular disease impacting respiratory function (e.g. cerebral palsy, muscular dystrophy) and patients with previous airway surgery unless these patients account for less than 10% of the total sample size or there is data available for the subgroup of patients without these characteristics. We will not exclude patients with laryngomalacia.

Intervention/Comparator

The intervention of interest is DISE performed before a first-line surgical therapy for OSA is attempted. The comparator is adenotonsillectomy for all patients presenting with OSA without preoperative DISE. This procedure removes tissue in the nasopharynx and oropharynx, thereby potentially relieving OSA when these are the sites of obstruction [16]. Multiple techniques (e.g. cold steel, monopolar or bipolar diathermy, coblation) are reported in the literature [17-20]. Complications of adenotonsillectomy include post-

operative bleeding, pain, dehydration, post-obstructive pulmonary edema, velopharyngeal insufficiency and death.

Outcome measures

The primary outcome will be the normalization of either the obstructive apnea index (OAI ≤ 1/h) or apnea hypopnea index (AHI≤ 1.5/h). Given that we anticipate that there will be few comparative studies addressing our specific research question, we will not exclude studies based on outcomes assessed. However, we will prespecify which secondary outcomes to include in our formal analysis and GRADE summary tables. Outcomes were selected and prioritized following a consultation with otorhinolaryngologists and patient advocates. We followed GRADE recommendations and favored patient-important outcomes and those that are not surrogate outcomes [21]. Outcomes of "low importance" will not be included in our analysis. Outcomes graded as "critical" were death and acute postoperative respiratory failure. Outcomes deemed to be "important but not critical" included the proportion of patients cured of OSA, the proportion of patients undergoing an adenotonsillectomy, post-operative bleeding, the number of interventions requiring general anesthesia, overall cost and quality of life.

Type of studies

We will include randomized controlled trials and observational studies that allow comparisons between DISE-guided interventions and adenotonsillectomy for all patients (cohort or case-control). Case series and case reports will be excluded. We will impose no restriction based on language or publication status.

Search strategy

We will perform a search in MEDLINE, MEDLINE In-Process, CINAHL, EMBASE and The Cochrane Library (CENTRAL database). The initial electronic search was performed on October 9th 2018 and will be updated as we near the publication of our review. An example of this search strategy is included (Appendix B). Other sources that will be searched are ClinicalTrials.gov, reference lists of included studies, and conference proceedings from the following major scientific meetings since 1988: American Academy of Otolaryngology-Head and Neck Surgery, International Congress on Pediatric Pulmonology, American Thoracic Society, American Pediatric Societies Meeting and European Respiratory Society Meeting.

Study records

Two reviewers will independently screen titles and abstracts in duplicate using the Rayyan electronic platform (Qatari Computing Research Institute): https://rayyan.qcri.org/.

We will proceed to full-text review unless both reviewers agree to exclude a report. Both reviewers will assess full-text reports independently and in duplicate using the same electronic platform. Disagreements will be resolved by consensus or third-reviewer adjudication.

Data collection

Both reviewers will use pre-tested data collection forms to collect data independently and in duplicate. Data of interest include study design, population baseline characteristics, intervention characteristics, clinical outcomes and variables necessary for risk of bias assessment. Disagreements will be resolved by consensus or third-reviewer adjudication.

Risk of bias assessment

We will use a modified version of the Cochrane Collaboration's tool to assess the risk of bias in randomized controlled trials [22]. This tool evaluates reports for randomization, allocation concealment, blinding, loss to follow-up, selective outcome reporting, as well as other risks of bias.

For non-randomized trials, we will use the Cochrane Collaboration's ROBINS-I tool [23, 24]. This tool is based on the principle that each non-randomized study seeks to reproduce the results of an "ideal" randomized controlled trial. Sources of bias are defined as the differences between the two studies that significantly alter the results of the non-randomized study. ROBINS-I addresses the following domains as potential sources of bias: confounding, selection bias, intervention classification, deviation from anticipated interventions, missing outcome data, method of measuring outcomes, and selective outcome reporting.

For both randomized and non-randomized studies, if any domain presents a potential source of bias (unclear or high risk of bias), then the report will be graded as high risk of bias. [25].

Summarizing data and treatment effect

We will include comparably homogeneous studies in a random-effects meta-analysis, using the inverse-variance method to assign study weights [26]. We will use the Review Manager software made available by the Cochrane Collaboration (Review Manager 5.3).

Dichotomous variables will be calculated using individual study odds ratios and presented as risk ratios with 95% confidence intervals. Continuous outcomes will be presented as mean differences with associated 95% confidence intervals. Outcomes reported on different scales, such as quality of life, will be presented according to the previously published recommendations of *Thorlund et al.* [27]. These recommendations include the use of two or more complimentary methods to present results in units that are easily interpreted by clinicians, for example as natural units of a familiar instrument or as a Number Needed to Treat. We will also present these data as standardized mean differences, as a sensitivity analysis. We will analyze and present randomized trials and observational studies separately. There are no conditions under which we will pool results from randomized and non-randomized studies.

If we identify no studies homogeneous enough to be included in a meta-analysis, we will provide a qualitative summary of our findings and justify our rationale.

Prespecified subgroup analyses

We will evaluate study heterogeneity qualitatively by assessing whether study populations, interventions and settings are comparable across studies. The following characteristics will be considered: baseline apnea hypopnea index, Brodsky score, body mass index (BMI), age, sex, ethnicity and socioeconomic status. These categories will constitute the basis for subgroup analyses.

We will evaluate heterogeneity quantitatively using a chi-squared test for homogeneity as well as Higgins and Thomson's I^2 statistic. Regardless the degree of heterogeneity identified, we will perform the following limited subgroup analyses:

(1) Baseline obstructive sleep apnea severity: mild (1.5 < apnea hypopnea index < 5 OR 1 ≤ obstructive apnea index ≤5), moderate (5 ≤ apnea hypopnea index or obstructive apnea index < 10) and severe (apnea hypopnea index or obstructive apnea index ≥ 10/h), hypothesizing that more severe obstructive sleep apnea will be more likely to benefit from DISE-directed therapy.

If the number of eligible studies is sufficient, we will also explore heterogeneity using quantile regression to analyze apnea severity as a continuous variable. We will require at least ten studies in the meta-analysis in order to perform a quantile regression, as recommended by Cochrane guidelines [22]. Moreover, studies included in this analysis will need to report the estimated treatment effect, associated variance, and covariate values [28]. In order to account for the residual heterogeneity between studies, we will perform a random-effects meta-regression.

(2) Patients Brodsky score from 0 to 4, hypothesizing that patients with a lower Brodsky score will be more likely to benefit from DISE-directed interventions

(3) Obese ($\geq 95^{th}$ percentile for body mass index) vs non-obese patients, hypothesizing that obese patients will be less likely to benefit from DISE-directed interventions

(4) Age (1 to 8 years-old or > 8 years-old), hypothesizing that older patients will be more likely to benefit from DISE-directed interventions [29]

(5) Ethnicity (white, black or other), hypothesizing that African American patients will be more likely to benefit from DISE-directed interventions

(6) Socioeconomic status (higher vs. lower, as defined by individual study authors), hypothesizing that patients of lower socioeconomic status will be more likely to benefit from DISE-directed interventions

We will evaluate the credibility of subgroup effects according to the following: if the subgroup characteristic is present at baseline, whether the comparison is within or between studies, whether the result is statistically significant, whether the result is found consistently across studies and outcomes, and whether or not there exists other evidence to support the result [30]. We will require five or more studies for comparisons between different studies, with each group represented by two or more studies. If the comparison is between subgroups within the same studies, we will require only two studies to perform the analysis.

Sensitivity analyses

We will conduct a sensitivity analysis excluding studies published as abstracts as well as another excluding studies with "unclear" or "high risk of bias".

Assessment of reporting bias

If we identify ten or more eligible studies in a meta-analysis, we will present a funnel plot and either the Egger's test (continuous outcomes) or the Arcsine test (dichotomous outcomes) to assess the risk of publication bias, with statistical significance set at $p<0.05$ for both tests.

Interpretation of results

The Grading of Recommendations, Assessment, Development and Evaluation framework will be used to report the overall quality of evidence and our confidence in estimates of effect. This framework considers the overall risk of bias, imprecision, inconsistency across studies, indirectness and the likelihood of publication bias [31]. We will classify the quality of evidence for each outcome across studies as being "very low", "low", "moderate", or "high".

Confidence in effect estimates will be rated down for overall risk of bias if any study included in the analysis is graded as "high risk of bias" [32] .

Imprecision refers to the width of the 95% confidence interval surrounding the overall estimate of effect for an outcome. If clinical decision-making would differ based on whether the upper or lower bound of the confidence interval represented the truth, then the outcome will be rated down for imprecision [33].

Inconsistency refers to the variation in results across different studies. We will explore inconsistency by assessing the similarity of estimates, overlap of 95% CIs, as well as the Chi-squared test (with significance established at $p<0.05$) and I2 statistic (with "substantial heterogeneity" defined as an I2 greater than 50%) [34, 35]. We will present a transparent rationale justifying the decision to rate down for inconsistency based on these factors and on whether it is explained by our *a priori* subgroup effects.

Indirectness refers to the degree to which clinical outcomes are surrogate rather than patient-important outcomes [36]. We will rate down for indirectness if studies fail to address patient-important outcomes directly.

Publication bias refers to the bias that is introduced to a body of evidence if positive studies are more likely to have been published than negative studies. We will rate down for publication bias if the arcsine test, Egger's test or a visual funnel plot are suggestive of significant publication bias [37].

We will present our results in a Summary of Findings table to represent individual outcomes across studies as well as the quality of evidence for each outcome [38]. Results from observational studies and randomized trials will be presented separately as different rows within the same table. Our final interpretation of results will rely on the estimate of effect providing the highest degree of certainty (e.g., data from high-quality clinical trials if available).

Protocol amendments

Any amendments to this protocol will be reported with the justification and date of modification.

Patients and public involvement

Our research question was guided by the lack of consensus on the management of pediatric obstructive sleep apnea. We aim to provide guidance on the most effective treatment that minimizes adverse effects and risks to patients. Patients were not directly involved in the study design, but a few parents and members of the public were involved in the classification of secondary outcomes.

Ethics and dissemination

No confidential data will be used, therefore approval by an ethic committee will not be necessary. This systematic review will provide an accurate portrait of the impact of DISE-directed management compared to systematic adenotonsillectomy in the management of pediatric obstructive sleep apnea. We will publish our results in a peer-reviewed journal.

The review will be reported according to PRISMA guidelines [15].

DISCUSSION

Obstructive sleep apnea is a common condition that, left untreated, can have profound consequences on future development. The routine adoption of adenotonsillectomy as a first-line treatment aims to mitigate this impact. However, disparities in cure rates between different reports suggest that this approach is not optimal for all subgroups of patients. DISE is a promising intervention that may both help select surgical candidates and avoid unnecessary surgeries in children least likely to benefit from adenotonsillectomy.

If we identify high quality evidence suggesting that preoperative DISE is beneficial, this conclusion will have important implications for practice. In contrast, if we find that the existing evidence is insufficient to provide definitive inferences regarding the effect of DISE before adenotonsillectomy, this review will expose a knowledge gap and provide a strong rationale for further prospective research.

Contributors

ASP, MG, FL, MCB, JPP and MH conceived the research question. MH and FL conceptualized methodological analyses. ASP and MH wrote the draft protocol and will review articles. All authors (ASP, MH, MG, FL, MCB, SDM and ML) reviewed and approved the protocol and will contribute to the writing of the publication.

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The search strategy was developed in collaboration with Rachel Couban (McMaster University medical librarian).

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Competing interests

None.

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Appendix A - PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A		
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		2
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		1 & 10
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A		N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		10
Sponsor	5b	Provide name for the review funder and/or sponsor	X		10
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X		10
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		3

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		4
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		4-5
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		5-6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		5
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		5
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		5
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		6
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		6

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		6-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X		6-8
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		6-8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		6-8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		5

Appendix B – Sample search strategy (MEDLINE)

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
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1 sleep apnea syndromes/ or exp sleep apnea, obstructive/ (29977)
2 (obstruct* adj2 hypopn?ea*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (438)
3 apn?e*-hypopn*.mp. (8934)
4 (nocturnal adj2 hypoxemia).mp. (411)
5 apn?eic.mp. (3195)
6 (upper airway adj3 (resistan* or obstruct*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5042)
7 (sleep* adj3 (apne* or apnoe* or hypopn* or obstruct* or disorder* or disturb*)).mp. (75865)
8 (osa or osas or osahs).tw. (15457)
9 ((apn?e* or hypopn?ea) adj1 index).mp. (7834)
10 (airway adj1 (resistan* or obstruct* or collapsib*)).mp. (42933)
11 or/1-10 (118935)
12 *ENDOSCOPY/ (26578)
13 DISE.mp. (224)
14 ((sleep or sedation) and (endoscop* or nas?endoscop*)).mp. (4384)
15 or/12-14 (30540)
16 11 and 15 (1237)
17 Pediatrics/ or adolescent/ or child/ or child, preschool/ or exp infant/ (3295505)
18 (child* or children or pediat* or paediat* or infan* or youth* or toddler* or adolesc* or teen* or boy or boys or boyfriend or boyhood or girl* or preschool* or pre-school* or minors or minors* or kid or kids or schoolchild* or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3818207)
19 school child*.ti,ab. (21272)
20 (Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1425311)
21 or/17-20 (4018110)
22 11 and 15 and 21 (398)