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Cochrane Corner: Tonsillectomy or adenotonsillectomy versus non-surgical management for obstructive sleep-disordered breathing in children

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COCHRANE CORNER:

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Tonsillectomy or adenotonsillectomy versus non-surgical management for obstructive sleep-disordered breathing in children

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ABSTRACT

The “Cochrane Corner” is a section in the journal that highlights systematic reviews relevant to otolaryngology–head and neck surgery, with invited commentary to aid clinical decision making. This installment features a Cochrane Review on tonsillectomy for obstructive sleep-disordered breathing (oSDB) in children, which finds moderate quality evidence that surgery improves symptoms, behavior, and quality of life compared to non-surgical management. The results apply to non-syndromic children with SDB confirmed by polysomnography and must be balanced against a favorable natural history in many cases.

INTRODUCTION

Tonsillectomy is a common surgery in children, with more than 530,000 procedures annually in the United States.[1] Most surgery is performed for sleep disordered breathing (SDB), characterized by abnormalities of respiratory pattern or the adequacy of ventilation during sleep, which include snoring, mouth breathing, and pauses in breathing.[2] SDB encompasses a spectrum of obstructive disorders that increases in severity from primary snoring to obstructive sleep apnea (OSA). Although current practice guidelines offer recommendations on tonsillectomy for SDB and OSA,[1-2] they were published before a recent large randomized efficacy trial.[3] The Cochrane Review in this installment puts the findings of this trial, and other related studies, in context to help clinicians and patients make more informed surgical decisions.

Review abstract: Tonsillectomy or adenotonsillectomy versus non-surgical management for obstructive sleep-disordered breathing in children. Venekamp RP, Hearne BJ, Chandrasekharan D, Blackshaw H, Lim J, Schilder AGM.[4]

Disclaimer

This is an abstract of a Cochrane Review published in the Cochrane Database of Systematic Reviews 2015, Issue 10 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Library should be consulted for the most recent version of the review.

Background

Obstructive sleep-disordered breathing (oSDB) is a condition that encompasses breathing problems when asleep, due to an obstruction of the upper airways, ranging in severity from simple snoring to obstructive sleep apnea syndrome (OSAS). It affects both children and adults. In children, hypertrophy of the tonsils and adenoid tissue is thought to be the commonest cause of oSDB. As such, tonsillectomy—with or without adenoidectomy—is considered an appropriate first-line treatment for most cases of pediatric oSDB.

Objectives

To assess the benefits and harms of tonsillectomy with or without adenoidectomy compared with non-surgical management of children with oSDB.

Search methods

We searched the Cochrane Register of Studies Online, PubMed, EMBASE, CINAHL, Web of Science, Clinicaltrials.gov, ICTRP and additional sources for published and unpublished trials. The date of the search was 5 March 2015.

Selection criteria

Randomized controlled trials comparing the effectiveness and safety of (adeno)tonsillectomy with non-surgical management in children with oSDB aged 2 to 16 years.

Data collection and analysis

We used the standard methodological procedures expected by The Cochrane Collaboration.

Main results

Three trials (562 children) met our inclusion criteria. Two were at moderate to high risk of bias and one at low risk of bias. We did not pool the results because of substantial clinical heterogeneity. They evaluated three different groups of children: those diagnosed with mild to moderate OSAS by polysomnography (PSG) (453 children aged five to nine years; low risk of bias; CHAT trial), those with a clinical diagnosis of oSDB but with negative PSG recordings (29 children aged two to 14 years; moderate to high risk of bias; Goldstein) and children with Down syndrome or mucopolysaccharidosis (MPS) diagnosed with mild to moderate OSAS by PSG (80 children aged six to 12 years; moderate to high risk of bias; Sudarsan). Moreover, the trials included two different comparisons: adenotonsillectomy versus no surgery (CHAT trial and Goldstein) or versus continuous positive airway pressure (CPAP) (Sudarsan).

Disease-specific quality of life and/or symptom score (using a validated instrument): first primary outcome

In the largest trial with lowest risk of bias (CHAT trial), at seven months, mean scores for those instruments measuring disease-specific quality of life and/or symptoms were lower (that is, better quality of life or fewer symptoms) in children receiving adenotonsillectomy than in those managed by watchful waiting:

- OSA-18 questionnaire (scale 18 to 126): 31.8 versus 49.5 (mean difference (MD) -17.7, 95% confidence interval (CI) -21.2 to - 14.2);
- PSQ-SRBD questionnaire (scale 0 to 1): 0.2 versus 0.5 (MD -0.3, 95% CI -0.31 to -0.26);
- Modified Epworth Sleepiness Scale (scale 0 to 24): 5.1 versus 7.1 (MD -2.0, 95% CI -2.9 to -1.1).

No data on this primary outcome were reported in the Goldstein trial.

In the Sudarsan trial, the mean OSA-18 score at 12 months did not significantly differ between the adenotonsillectomy and CPAP groups. The mean modified Epworth Sleepiness Scale scores did not differ at six months, but were lower in the surgery group at 12 months: 5.5 versus 7.9 (MD -2.4, 95% CI -3.1 to -1.7).

Adverse events: second primary outcome

In the CHAT trial, 15 children experienced a serious adverse event: 6/194 (3%) in the adenotonsillectomy group and 9/203 (4%) in the control group (RD -1%, 95% CI -5% to 2%).

No major complications were reported in the Goldstein trial.

In the Sudarsan trial, 2/37 (5%) developed a secondary hemorrhage after adenotonsillectomy, while 1/36 (3%) developed a rash on the nasal dorsum secondary to the CPAP mask (RD -3%, 95% CI -6% to 12%).

Secondary outcomes

In the CHAT trial, at seven months, mean scores for generic caregiver-rated quality of life were higher in children receiving adenotonsillectomy than in those managed by watchful waiting. No data on this outcome were reported by Sudarsan and Goldstein.

In the CHAT trial, at seven months, more children in the surgery group had normalization of respiratory events during sleep as measured by PSG than those allocated to watchful waiting: 153/194 (79%) versus 93/203 (46%) (RD 33%, 95% CI 24% to 42%). In the Goldstein trial, at six months, PSG recordings were similar between groups and in the Sudarsan trial resolution of

OSAS (Apnea/ Hypopnea Index score below 1) did not significantly differ between the adenotonsillectomy and CPAP groups.

In the CHAT trial, at seven months, neurocognitive performance and attention and executive function had not improved with surgery: scores were similar in both groups. In the CHAT trial, at seven months, mean scores for caregiver-reported ratings of behavior were lower (that is, better behavior) in children receiving adenotonsillectomy than in those managed by watchful waiting, however, teacher reported ratings of behavior did not significantly differ.

No data on these outcomes were reported by Goldstein and Sudarsan.

Authors' conclusions

In otherwise healthy children, without a syndrome, of older age (five to nine years), and diagnosed with mild to moderate OSAS by PSG, there is moderate quality evidence that adenotonsillectomy provides benefit in terms of quality of life, symptoms and behavior as rated by caregivers and high quality evidence that this procedure is beneficial in terms of PSG parameters. At the same time, high quality evidence indicates no benefit in terms of objective measures of attention and neurocognitive performance compared with watchful waiting. Furthermore, PSG recordings of almost half of the children managed non-surgically had normalized by seven months, indicating that physicians and parents should carefully weigh the benefits and risks of adenotonsillectomy against watchful waiting in these children. This is a condition that may recover spontaneously over time.

For non-syndromic children classified as having oSDB on purely clinical grounds but with negative PSG recordings, the evidence on the effects of adenotonsillectomy is of very low quality and is inconclusive.

Low-quality evidence suggests that adenotonsillectomy and CPAP may be equally effective in children with Down syndrome or MPS diagnosed with mild to moderate OSAS by PSG.

We are unable to present data on the benefits of adenotonsillectomy in children with oSDB aged under five, despite this being a population in whom this procedure is often performed for this purpose.

COMMENTS ON THE COCHRANE REVIEW

Comments by Goldstein

While adenotonsillectomy is generally considered the first line treatment of pediatric oSDB, evidence for its success predominately consists of uncontrolled and non-randomized studies demonstrating subjective improvement and improvements in sleep study indices. Using Cochrane methodology, the literature was systematically reviewed for randomized controlled trials comparing the benefits and harms of adenotonsillectomy with medical treatment. There is a paucity of trials on this subject because of ethical concerns, so only three unrelated studies were identified. Due to the substantial heterogeneity between the studies, pooling of the results and meta-analysis could not be performed.

In the early OSAS literature, reports described children presenting with cardiorespiratory failure, cor pulmonale, failure to thrive, severe neurocognitive disturbances, coma and even death.[5] As adenotonsillar hypertrophy is the most common cause of pediatric OSAS and adenotonsillectomy has been considered first-line treatment, there has been a reluctance to conduct randomized trials. In the three identified studies, one excluded children with severe OSAS, one placed all children with positive PSG into an adenotonsillectomy group and excluded

them from randomization and one randomized children to either adenotonsillectomy or nasal CPAP with no option for watchful waiting.

The largest trial, the CHAT trial,[3] took place at six US clinical sites and required PSG for diagnosis of sleep apnea. This study, which included 453 generally healthy children aged five to nine years with mild to moderate obstructive sleep apnea randomized to adenotonsillectomy versus watchful waiting, had the lowest risk of bias and moderate to high quality evidence for the outcomes measured. At 7 month follow-up, the children randomized to the surgical arm had significant improvements in disease-specific quality-of-life, global quality-of-life, symptoms, parent-reported behavior and sleep study indices compared to the watchful waiting group. However, there was no significant difference in the study's primary outcome measure, a measure of attention and executive function, between groups. In addition, 46% of the watchful waiting group normalized their PSG indices as compared to 79% of the surgery group. Serious adverse events occurred in 3% of the adenotonsillectomy patients and 4% of the watchful waiting patients, mostly postoperative complications that occurred in both groups, including patients in the watchful waiting group that crossed over.

Despite its scientific rigor, the CHAT study had several shortcomings that include restricting the entry criteria to children aged five to nine year, excluding children with severely positive sleep study indices, and limiting the outcome assessment to short-follow-up. The study may not apply to clinical practice because PSG is not routinely performed in children with signs and symptoms of SDB due to its high cost and limited availability.

The primary aim of the second study[6] was not to determine the efficacy of adenotonsillectomy as a treatment of pediatric oSDB, but to evaluate the utility of clinical assessment in diagnosing upper airway obstruction. This study was conducted from 1999 to

2001 at one US site. At the time, studies were emerging documenting the inaccuracy of clinical assessment in predicting a positive PSG, PSG was even less available than it is currently and the definition of what constituted a positive PSG was in evolution, The goal of the study was to document improvement in the signs and symptoms of oSDB after adenotonsillectomy even if the pre-operative PSG was negative, thus validating clinical assessment in determining the need for adenostonsillectomy.

Fifty-nine otherwise healthy children (mean [SD] age of 6.3 [3.0] years) with a clinical diagnosis of oSDB were evaluated by a standardized assessment consisting of history, physical examination, voice recording, tape recording of breathing during sleep, lateral neck radiograph and echocardiogram and assigned a clinical assessment score. A minimum clinical assessment score (40) was required for entry. PSG was then performed. Children with positive PSG (AHI $\geq$ 5 or at least 10% of the night was spent with oxygen saturation < 90%) underwent adenotonsillectomy while children with negative PSG were randomized to adenotonsillectomy versus no surgery (watchful waiting). The identical assessment, including PSG, was performed 6 to 8 months later by investigators blinded to treatment group.

In the randomized subjects, children who underwent adenotonsillectomy had a significant improvement in the median clinical assessment score as compared to the nonsurgery subjects. 82% of the adenotonsillectomy children were asymptomatic as compared to 22% of the nonsurgery children. A major weakness of this study was that at the time of the study, the clinical assessment score was not a validated measure. Formal validation of the history and physical examination items was subsequently performed by the first author and led to the development of the Clinical Assessment Score -15 (CAS-15).[7]

The Cochrane review presents the sleep study results that, not surprisingly, do not differ between groups at follow-up as they were normal at baseline, and presents adverse events that were not reported in either group. The review does not present the clinical scores as this was not an a priori outcome measure determined by the Cochrane reviewers. At the time of design of the Goldstein study, disease-specific quality of life measures for pediatric oSDB were not available as the OSA-18 was first described in 1999, the Obstructive Sleep Disorders-6 in 2000 and the Tonsil and Adenoid Health Status Instrument (TAHSI) in 2001. The study is considered of low quality as the sample size was small (29 randomized patients), there was a high rate of attrition (follow-up was only available for 11 surgery patients and nine control patients), there was a high risk of bias and there were concerns that treatment received by the control group was not representative of current practice. The concerns regarding treatment received by the control group seem odd as watchful waiting implies no active treatment, and watchful waiting was also the strategy used for the control group in the CHAT trial.

The third included trial[8] compared 80 children with Down syndrome or mucopolysaccharidoses with mild to moderate obstructive sleep apnea as determined by PSG who were randomized to adenotonsillectomy or treatment with continuous positive airway pressure. Normalization of sleep study indices was similar in both groups as was improvement in the OSA-18 and Epworth Sleepiness Scale scores. The evidence was judged to be low quality due to uncertainties regarding the method of randomization and allocation concealment and unblinded outcome assessments, but the results suggested that the treatments were equally effective.

The disparate nature of the included studies highlights the lack of evidence supporting adenotonsillectomy for treatment of pediatric oSDB. School-aged children with positive PSG

benefit from surgery, but there is a natural resolution rate of close to 50% in unoperated children. Although generally safe, risks of surgery must be considered when recommending adenotonsillectomy to affected children. Unanswered questions include treatment of younger children, which comprise the largest group of children with oSDB, and the role of medical therapies such as topical nasal steroids and leukotriene modifiers. As PSG is not routine in many practices, the role of clinical assessment in determining treatment decisions is of yet unknown.

Comments by Burton

Why are there so few randomized trials evaluating the treatment of children with SDB? Is it—as Dr Goldstein suggests—due to ethical concerns? If so, what are those concerns?

We know that there are many areas of uncertainty in the field of oSDB. These relate to both diagnosis and treatment. What is the "best" way of diagnosing oSDB, and in particular its most severe form—obstructive sleep apnea syndrome (OSAS)? But also, to be pragmatic, what is the easiest and most practical way to make that diagnosis? Once a child has been placed in the appropriate diagnostic category, how are they best managed? Do they need any active treatment at all, or will "watchful-waiting" or "active monitoring" suffice? For some if not for all; and for how long? In those who need active treatment, what intervention is best and what outcomes are being sought? What concerns parents the most and what specific aspects of the child's life and health are we trying to make better? With so much uncertainty, and clear equipoise about the effects of surgery compared with active monitoring (certainly in some children with some expressions of oSDB) can it be ethical not to conduct appropriately rigorous controlled evaluations of the management options?

The authors of the Cochrane review[4] conclude that in "otherwise healthy children, without a syndrome, of older age (5-9 years),…diagnosed with mild to moderate OSAS by PSG"

adeno-tonsillectomy provides benefit in terms of quality of life, symptoms and behavior as rated by caregivers (the CHAT trial[3]). Goldstein interprets the results of the trial as showing "significant improvements" from surgery. Are they saying the same thing? The results are indeed statistically significant. The questions must be this: how clinically significant are differences between surgery and watchful waiting of 17.7 points on a 108-point disease-specific quality of life scale, or 5.9 points on a 100-point generic quality of life scale, or 5.1 points on a 24 point "sleepiness" scale?

In considering the results of a systematic review, it is important to remember that the reviewers make choices about the participants, interventions, comparators and the primary and secondary outcomes before they start to look for studies to include in the review, and they set these out in a published protocol. The panel of peer referees for protocols of Cochrane ENT reviews always includes a lay person/consumer. This process is designed to ensure that the most relevant and important outcomes are considered first and reviewers are encouraged to have no more than three primary outcomes of which one should be the most significant adverse effect(s) of treatment.

Reviewers may seek to answer questions about a particular type of participant and their choice may be to focus very narrowly (looking for studies carried out in particular types of children, of a certain age, with a diagnosis made using very specific criteria and methods) or more broadly. If the review is framed too narrowly, there may be no relevant studies to find, and even if there are, the generalizability and applicability of the results of those studies may be restricted. Cast the net too widely, and a set of studies may be identified that is so disparate that they cannot be combined in a meta-analysis and each study must simply be reported separately. Whatever the reviewers decide in their protocol, when they go to the literature to look for studies

to include, they can of course only find those studies that have actually been done, and the types of participants in those studies may—as in this case—be very specific.

Goldstein provides a commentary on the study on which she herself was the first author (Goldstein, 2004) and in my view goes beyond considering its place in the Cochrane review that is the subject of this Corner. She points out that the *primary* purpose of the study was not to determine the efficacy of adeno-tonsillectomy as a treatment of oSDB. Nonetheless, *some* information on efficacy was available and the conclusion drawn by the authors of the Cochrane review was that "the evidence on the effects of adeno-tonsillectomy is of very low quality and is inconclusive."

This conclusion has arisen for two reasons. Firstly, because the Goldstein study did not evaluate the main primary outcomes chosen by the reviewers (the study used as its primary outcome a "change in clinical assessment score") no data were available to be included in the primary outcomes section of the systematic review, other than information on "adverse events". Secondly, the GRADE approach was used to rate the overall quality of evidence for each outcome, as is usual in current Cochrane reviews. The GRADE rating of "very low quality evidence" implies that the authors' confidence in the effect estimate is very uncertain. It is helpful to know that the control group in Goldstein's study was managed by watchful waiting; the publication reporting the trial simply refers to "no surgery" without further explanation.

When I was a resident tonsillectomy was frequently performed for recurrent throat infections and—occasionally—for "sleep apnea." Now infection is much less often an indication for surgery and data suggest that it is more usually undertaken for oSDB. But there is still—and always will be—morbidity associated with adeno-tonsillectomy and it is critical to determine

which children will really benefit significantly from surgery, and to understand by how much those benefits outweigh the risks.

Comments by Rosenfeld

This Cochrane Corner offers insight into how different individuals can reach different conclusions from the same trial set, by juxtaposing comments from Cochrane reviewers (Venekamp and colleagues),[4] an author of one of the included trials (Goldstein),[6] and a senior Cochrane editor (Burton). As an additional commentator, I will close by offering some observations on two study outcomes: quality of life and normalization of PSG recordings.

Dr. Burton rightly questions the clinical relevance of an 18 point change on a 108-point disease-specific quality of life scale. For the OSA-18 survey, however, the relevance has been well documented by comparing caregiver-reported change with change scores after intervention.[9] Change scores of 10, 15, 21, and 23 points correlated with clinical changes of none, small, moderate, and large, respectively. Therefore, the 4.5 point change score in the CHAT trial watchful waiting group equates to no change in quality of life but the 21.4 change score in the surgical group equates to a moderate clinical change. The difference between groups of 17.7 points would be a small to moderate change.

When analyzing results of a randomized trial I have always enjoyed scrutinizing the control group outcomes, which can be more interesting and important than the treatment group. In the CHAT trial, for example, 46% of children in the *watchful waiting* group normalized their PSG findings at 7 months compared with 79% in the adenotonsillectomy group.[3] The "efficacy" of watchful waiting was higher for non-obese children and those with an apnea-hypopnea index (AHI) less than the median of 4.7, with normalization rates of 54% and 65%, respectively.[3] This

favorable natural history suggests a healthy role for watchful waiting in children similar to those enrolled in the CHAT study, especially if non-obese and with mild OSA (AHI < 5.0). Similarly, surgery is not a cure-all for OSA, since 1 in 5 children had persistent abnormalities on PSG.

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