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Adenotonsillectomy or Watchful Waiting in the Management of Childhood Obstructive Sleep Apnea

Commentary on Marcus CL, Moore RH, Rosen CL, Giordani B, et al. for the Childhood Adenotonsillectomy Trial (CHAT). A randomized trial of adenotonsillectomy for childhood sleep apnea. N Engl J Med 2013;368:2366-76.

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ARTICLE SUMMARY

Question: Compared with watchful waiting, does the treatment of childhood obstructive sleep apnea (OSA) with adenotonsillectomy improve cognitive outcomes, symptoms, behavior, quality of life, and polysomnography findings?

Design: Multicenter, single-blind, randomized, controlled trial conducted at seven academic sleep centers; ClinicalTrials.gov number, NCT00560859.

Allocation: Children were randomly assigned to early adenotonsillectomy (EAT-surgery within 4 weeks after randomization) or a strategy of watchful waiting with supportive care (WWSC). Randomization was performed centrally using a web-based system that required confirmation of eligibility criteria prior to providing the treatment assignment.

Blinding: Single-blind; personnel involved in conducting psychometric evaluations and measuring other study outcomes, as well as study investigators (other than the surgeons), were blinded to randomization assignments, study participants and families were not blinded.

Follow-Up Period: 7 months.

Setting: The study recruited children with symptoms of obstructive sleep apnea syndrome (OSAS) from primary care, otolaryngology, and sleep clinics at 7 academic centers in the United States.

Subjects: 453 children, mean age 6.5 ± 1.4 years, 49% male, were randomized.

Inclusion Criteria: Age between 5 to 9 years, polysomnographic diagnosis of OSAS without prolonged oxyhemoglobin desaturation, and considered to be suitable candidates for adenotonsillectomy. OSAS was defined as an apnea–hypopnea index (AHI) score of 2 or more events per hour or an obstructive apnea index (OAI) score of 1 or more events per hour.

Exclusion Criteria: Children with an AHI score of more than 30 events per hour, an OAI score of more than 20 events per hour, or arterial oxyhemoglobin saturation of less than 90% for ≥ 2% of total sleep time, recurrent tonsillitis, a BMI z score of ≥ 3, and use of medication for attention deficit–hyperactivity disorder (ADHD).

Intervention: Participants meeting eligibility criteria were randomized to early adenotonsillectomy or a strategy of watchful waiting with supportive care (WWSC). Children completed in lab polysomnography at baseline and 7 month follow-up. At both time points, caregivers were asked to complete survey instruments evaluating behavior, intellectual functioning, quality of life, symptoms of sleepiness and sleep apnea; teachers were mailed behavioral assessments. Neuropsychological testing was performed during a morning visit, on a separate day from the polysomnogram, to avoid the influence of atypical sleep related to overnight monitoring. Tests were administered by psychometrists, blinded to the polysomnographic results.

Outcomes: The primary outcome was the change in the attention (A) and executive-function (E) score on the Developmental Neuropsychological Assessment (NEPSY).

Secondary outcome measures were: 1) caregiver and teacher ratings of behavior measured by Conners' Rating Scale Revised: Long Version Global Index, comprising Restless–Impulsive and Emotional Lability factor sets and the Behavior Rating Inventory of Executive Function (BRIEF), comprising summary measures of behavioral regulation and metacognition; 2) symptoms of obstructive sleep apnea syndrome, as assessed by the Pediatric Sleep Questionnaire sleep-related breathing disorder scale (PSQ-SRBD); 3) sleepiness, assessed using the Epworth Sleepiness Scale modified for children; 4) global quality of life, evaluated by caregiver-rated total score from the Pediatric Quality of Life Inventory (PedsQL); 5) disease-specific quality of life measure based on the 18-item Obstructive Sleep Apnea assessment tool; 6) generalized intellectual functioning evaluated by the General Conceptual Ability score from the Differential Ability Scales-II (DAS); and 7) polysomnographic indexes.

A study sample size of 400 children, randomized 1:1 between the 2 study arms allowed for detection of an effect size, for the primary endpoint of the NEPSY A/E domain score, of ≥ 0.32 (an effect size estimated from one prior study) with 90% power.

Patient Follow-Up: 464 children were randomized between January 2008 and September 2011, 11 excluded due to lack of follow-up data, 35 were lost to follow-up, and 18 withdrew from the study. Follow-up visits were conducted for 400 children (86%), with 397 children having measurements of attention and executive function on the NEPSY (primary outcome) that could be evaluated. An intention to treat analysis was performed.

Main Results: The baseline attention and executive function score on the NEPSY (primary outcome) was close to the population mean of 100 in both groups. Average scores increased in both groups at 7 month follow-up, but there was no statistically significant difference between the groups in the primary outcome (7.1 ± 13.9 in the early-adenotonsillectomy group and 5.1 ± 13.4 in the watchful-waiting group, $p = 0.16$). The AHI score improved in both groups, but significantly more so in the early-adenotonsillectomy group (Effect size 0.57, $p < 0.001$). There were statistically significant improvements in behavioral, quality of life measures, and greater reduction in symptoms in the early adenotonsillectomy group than in the watchful-waiting group.

Neither obesity nor age significantly modified treatment responses for any of the outcomes reported. The relative improvements associated with

early-adenotonsillectomy were significantly lower for African American children compared to children of other ethnic/racial backgrounds for the caregiver completed behavioral questionnaires.

There were 15 post-randomization serious adverse events, six of which occurred in children randomized to early adenotonsillectomy and nine in the control group. Eight of the events were associated with peri-operative complications (bleeding, dehydration, and pain). Nine treatment failures were also considered adverse events, occurring in the watchful waiting group; treatment failures were attributed to: increased problems with sleep quality or sleepiness, school behavioral problems, morning headaches, asthma exacerbation, hypertension, and bacterial infections.

Conclusion: Among school age children with obstructive sleep apnea syndrome without prolonged oxygen desaturation, early adenotonsillectomy, as compared with a strategy of watchful waiting with supportive care, did not result in significantly greater improvement in scores on a formal test of attention and executive function after a period of 7 months. However, early adenotonsillectomy was associated with statistically significant improvements in polysomnographic findings, caregiver and teacher reported measures of behavior, quality of life, and sleep apnea symptoms.

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COMMENTARY

This elegant study raises several questions for the treating clinician, including:

1. Which children would benefit from watchful waiting, since there was no significant difference in the primary outcome (attention and executive function) between early adenotonsillectomy and watchful waiting with supportive care after 7 months of treatment?
2. Are the improved secondary outcomes sufficient to warrant adenotonsillectomy in children who have OSAS?
3. What are the implications of favoring surgery versus watchful waiting in children who have OSA?

This was a well-designed and rigorously conducted study evaluating multiple outcomes in a large group of otherwise healthy children aged 5-9 years across several academic centers across the United States. Efforts were made to include children from primary care clinics. The methodological rigor involved was impressively executed, with great efforts made towards appropriate screening, standardized testing and measurement, use of quality control measures, and ensuring surgery was also carried out in a standardized fashion among different centers. Factors that could exacerbate OSAS, including allergies and poorly controlled asthma, were assessed as part of the protocol, but did not affect randomization. The children were not tested formally for asthma and allergies, such that some children with either condition could have been randomized to the study, which could affect the severity of OSAS over time. Both groups were provided opportunity to improve sleep quality via good sleep structure and hygiene. However, medication was not included as an intervention or within the run-in period to determine how many children would benefit from medication alone.

Despite the rigorous methodology, there are several factors that must be considered for interpretation of these results. The children studied were those that were able to perform neurocognitive testing; however, OSAS in children starts at a much younger age and whether the timing of the surgery for younger children would result in different outcomes remains to be seen. In addition, for ethical reasons, the study group had very minimal intermittent hypoxemia (oxygen hemoglobin saturation less than 90% for $\geq$ 2% of the total sleep time). It is possible that the outcomes in children, who have more severe hypoxemia or more recurring desaturations, could have more noticeable changes in executive function to a certain extent; while those with very severe recurrent desaturations may not have any improvement, depending on the duration and severity of the disease. Furthermore, the primary outcome may be impacted by various factors including sleep deprivation, sleep apnea, sleep fragmentation, and genetic endowment to name a few, such that the lack of difference may be mitigated by other non-measurable factors. It is hoped that with randomization these non-measurable factors will also be equally distributed between the two groups. Nevertheless, this study did show significantly greater improvements in behavior, quality of life, and polysomnographic findings, as well as a reduction in symptoms in the children who underwent early adenotonsillectomy versus watchful waiting. A parent and the treating clinician may consider the secondary outcomes worthy enough to consider surgery, at least in some children. What is striking is that 46% of the children in the watchful waiting group did normalize their polysomnographic parameters, despite ongoing behavioral and quality of life impairment, which raises the question – which treatment outcomes should be considered of primary importance? Polysomnographic parameters may be evaluated within the context of clinical picture. In addition, it could be possible that the time at follow-up was too short to show differences in executive function and attention in those children that had watchful waiting versus surgery or that the subtle differences in function are not apparent in the neuropsychological testing. Finally, we eagerly await the data on physiological parameters that were measured within this study to determine if there are other criteria that would help decision making towards surgery versus watchful waiting.

Overall, not many children were treated medically prior to randomization and perhaps a period with medical treatment may also have been a viable option as some children with allergic rhinitis or poorly controlled asthma respond to treatment and the snoring may dissipate. This study suggests that children with OSAS warrant comprehensive evaluation to determine whether surgery is needed; ideally, after a trial of medical management. Additional large studies are needed to evaluate the role of medical management and surgery. If watchful waiting is chosen, the necessity for treatment should be considered after evaluation of neurocognitive and physical effects and potential impact to the child's functioning and quality of life with follow-up. Future studies should also consider economic analyses of either management option. In summary, this study highlights that OSAS is a disease that results in end-organ dysfunction across various domains, such as physical and neurocognitive func-

tion. The optimal timing and choice of intervention for children across the developmental trajectory is yet to be determined.

CITATION

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.