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Judging Sleep Apnea Surgery

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It is a fact that surgery usually does not cure obstructive sleep apnea. That is where the consensus ends and controversy abounds.

The lack of consistent cure has led some to conclude recently that surgery should not be considered in the treatment of obstructive sleep apnea (1-4). This conclusion warrants scrutiny, as highlighted by two articles in this issue of Sleep Medicine Reviews (5, 6). These two articles reviewed two surgical therapies, one established therapy (maxillomandibular advancement) and one investigational therapy (hypoglossal nerve stimulation). Neither therapy cures sleep apnea consistently, but each potentially improves sleep apnea significantly (5, 6).

This conflict raises questions about how one should judge surgical success. Three of the questions about judging surgical success include: 1) Conceptually what defines success? 2) How should we measure success? 3) How should we judge the surgical outcomes studies?

What Is Success?

To some, cure defines success and lack of cure defines failure.(2, 3, 7) In the world of sleep apnea surgery, in fact in the world of sleep medicine or even of most medical or surgical therapies for any chronic condition, cure alone often is not the appropriate criterion to judge success or failure. For the sleep apnea patient with severe disease and in whom the main therapy offers no benefit (e.g., when the patient is unable to use continuous positive airway pressure [CPAP] therapy), the significant physiological and moreover clinical improvement offered by surgical therapy make it compelling to at least consider, even in the absence of cure. To deny this therapy because it does not fully eliminate sleep apnea is counter-productive as it would leave patients untreated when they could have achieved important health benefits. While obvious, it is sometimes ignored that CPAP also does not cure sleep apnea, but rather it manages the disorder (when used). Anti-hypertensive medications do not cure hypertension. Anti-inflammatory medications do not cure arthritis.

For the sake of argument, let’s consider the logical conclusion of requiring cure by sleep apnea therapy for it to be deemed appropriate for clinical use. The logical conclusion is nihilistic. Since none of the main sleep apnea therapies offers consistent cure, the

requirement for cure would logically lead to the conclusion that one should not treat sleep apnea patients. CPAP therapy can manage severe sleep apnea well, but it offers no cure. Of course, any time the patient does not wear CPAP its effectiveness deteriorates. Even when worn, CPAP often does not completely eliminate sleep apnea,(8) which can vary by sleep position, sleep stage, sleep hygiene, nasal congestion, other factors, and combinations of factors not always captured during CPAP titration. Nor does oral appliance therapy always cure sleep apnea, even in ideal candidates. While weight loss improves sleep apnea, it rarely eliminates the disorder. Radical airway reconstructive surgery such as maxillomandibular advancement does not always cure (<50%) (5). Following the logic as proposed, tracheotomy might be the only appropriate treatment for sleep apnea if cure were required. Unfortunately, tracheotomy is not acceptable to most sleep apnea patients.

As an alternative to cure alone defining success, improvement without cure may also define a successful outcome in many cases. Maxillomandibular advancement is an established therapy, and the meta-analysis by Holty et al. confirms that while maxillomandibular advancement often does not cure sleep apnea, it usually has a major positive impact on the disorder (5). Hypoglossal nerve stimulation is an emerging therapy under development, and the review by Kezirian et al. suggests that it too may have an important physiological impact on sleep apnea while not curing the disorder (6). Other forms of sleep apnea surgery have been shown to produce important physiological improvements (7, 9) and, more importantly, clinical improvements in sleep apnea (10-16), even without necessarily curing sleep apnea.

Thus, both logically and practically, true cure is not viable as a sole criterion to judge the success of any sleep apnea therapy, including surgical therapy. In fact, any single, arbitrary success criterion based on a surrogate measure poses important difficulty in judging the appropriateness for a therapy, especially when the surrogate and clinical outcomes are discordant. The use of arbitrary cut-offs of surrogate outcomes has presented a major hurdle to understanding the truly important role of surgical therapy in the treatment of sleep apnea.

Thus, success includes *improvement*, even in the absence of cure.

How Should We Measure Success?

Part of the confusion of how to judge success has been complicated by the method of measuring sleep apnea severity. Polysomnography provides numerous physiological measures of sleep apnea, but unfortunately no single parameter represents a comprehensive measure of sleep apnea disease burden or treatment outcome (17). Sleep apnea is unusual in that the whole complicated disorder often gets summarized by a single number, the apnea-hypoponea index (AHI). AHI alone is used to define success or cure (7, 18), but it appears not to capture the full burden of the disorder nor to reflect clinical outcomes of therapy in sleep apnea patients (17). It turns out that it is possible for a therapy to have an important clinical benefit while measurable sleep apnea persists. The physiological measurements are important surrogate measures of sleep apnea burden, especially for future cardiovascular risk (19). Unfortunately, these measures as currently formulated do not reflect other clinical burdens of sleep apnea, such as symptoms, performance, and quality of life.(17)

A rhetorical question might best illustrate the relative importance of clinical versus surrogate outcome measures: Would a patient rather have improved clinical outcomes (e.g., improved survival, reduced cardiovascular risk, reduced car accident risk, improved performance, reduced symptoms, and improved quality of life) *or* a normal AHI? The patient can choose one or the other, but not both. Of course, most would choose the clinical improvement over the AHI (surrogate) improvement. Polysomnography parameters as outcome measures are important surrogates of some clinical outcomes, such as cardiovascular risk, but they should not be mistaken for clinical outcomes themselves. This is true of all surrogate outcome measures.

When possible, it is always preferred to measure the clinical outcomes directly rather than relying solely on surrogate measures. The maxillomandibular advancement data have focused on its physiological success (albeit not necessarily cure), but Holty's review also revealed the important clinical improvement in subjective sleepiness (5). As highlighted by Holty et al., clinical outcomes should be the focus of future clinical studies of maxillomandibular advancement, as they should be for other sleep apnea therapies.

Thus, measures of *clinical improvement*, by a variety of methods, provide important measures of success.

How Should We Judge the Surgical Outcomes Studies?

One of the barriers to accepting surgery as a viable treatment option has been the relative paucity of the most rigorous study designs in testing surgical therapies. In the parlance of evidence-based medicine, study designs are assigned evidence levels: level 1 = good randomized controlled clinical trial (ideally double-blinded and placebo-controlled), level 2 = good cohort study, level 3 = good case-control study, level 4 = case series or poor quality cohort study, and level 5 = opinion or animal/laboratory research (20). Level 1 studies are considered the gold standard. Because of the paucity of level 1 evidence comparing invasive surgical therapy to placebo or to other therapies, some have drawn the conclusion that there are no data to support a role for surgery (21), or worse, there is evidence of no effect of surgery (4). Both of these conclusions are fallacies.

To depend solely on level 1 evidence and deny all other evidence risks missing completely what a therapy might offer. In fact, level 1 evidence in isolation often suffers an important bias (external validity, or generalizability), so is best complemented by controlled observational studies (e.g., level 2 evidence) (22). The benefit of randomization in a trial is to balance known and unknown confounding variables, but there are other forms of bias, such as placebo effect, investigator bias, ascertainment bias, external validity, and others that are not necessarily controlled in a randomized trial.

The maxillomandibular advancement article illustrates the importance of considering all of the evidence. If one were to rely only on randomized, double-blinded, placebo-controlled trials to judge the value of this therapy, then there would be no data to support maxillomandibular advancement. And there probably never will be. It does not appear feasible to double-blind maxillomandibular advancement, because patients can see the

treatment effect on the anatomy and feel the acute effects of surgery. Finding a viable placebo may be impossible. And the nature of the subset of patients willing to let the decision to proceed with maxillomandibular advancement be left to random assignment is likely to be very different from the usual patient considering surgical care. The alternative of randomizing to invasive therapy now versus later limits outcomes to short-term only and does nothing to control for the placebo-effect, investigator bias, and other biases when unblinded. The practical limitation of identifying enough patients willing to let the treatment choice, or timing of treatment, be determined at random may be prohibitive.

The maxillomandibular advancement review relies heavily on case series data (level 4 evidence). However, there are features that argue for the validity of its measured effectiveness. The results are consistent across multiple studies and a large pool of patients. The effect sizes are huge (>2.0 for AHI, and >1.0 for apnea index, oxyhemoglobin nadir, and daytime sleepiness). The results appear generalizable across centers, surgeons, and patient populations. There is a dose-response effect, where greater advancement is associated with greater effect. The favorable outcomes are seen on objective measures, which are less prone to the placebo effect. It can be argued that even the level 4 evidence makes a strong case for the treatment effect in light of all those favorable findings. Nevertheless, higher level, controlled, observational studies such as good cohort studies or non-randomized trials with appropriate adjustment for confounding variables will strengthen the evidence for maxillomandibular advancement (or any surgical therapy) as the authors suggest.

It turns out that some of the maxillomandibular advancement studies are controlled studies (non-randomized trials or cohort studies) where maxillomandibular advancement is compared to CPAP therapy. The patients served as their own controls in a non-randomized cross-over study design. Surgery cannot be washed out, so always comes second in these trials. In examples of these comparisons, polysomnography outcomes after maxillomandibular advancement were comparable to outcomes while using CPAP therapy in the laboratory (23).

While the hypoglossal nerve stimulation therapy is also supported by case series (and animal research), the authors appropriately do not make the claim that it should be considered as an established treatment. The distinction from maxillomandibular advancement is that the studies are small and few, the effect sizes are smaller, and the experience with the therapy is limited. Its effect on clinical outcomes, its generalizability, and its long-term effect are not clear. Yet, the early data are compelling and warrant further study.

Thus, the worthwhile evaluation of a therapy is not limited exclusively to randomized trials. Holty et al. and Kezirian et al. each provides a thorough review of a surgical therapy where no randomized trial (let alone placebo-controlled and double-blinded) exists, yet where the physiological and lower level clinical studies are compelling in informing us of the importance or potential importance of each therapy. Ideally, a combination of high level studies, including randomized trials when feasible and complemented by observational studies, will ultimately provide the most robust assessment of clinical treatment effects.

Conclusion

Maxillomandibular advancement should be available to patients. Hypoglossal nerve stimulation should be developed. Various other surgical therapies should also be considered, in indicated cases, because they can provide important clinical benefits. As with CPAP, oral appliance, and weight loss therapies, surgical therapy has shown an important role in the treatment of the complicated disorder of sleep apnea while usually not curing sleep apnea.

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