

# Surgical Treatment of Obstructive Sleep Apnea

## Upper Airway and Maxillomandibular Surgery

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Upper airway surgery is an important treatment option for patients with obstructive sleep apnea (OSA), particularly for those who have failed or cannot tolerate positive airway pressure therapy. Surgery aims to reduce anatomical upper airway obstruction in the nose, oropharynx, and hypopharynx. Procedures addressing nasal obstruction include septoplasty, turbinectomy, and radiofrequency ablation (RF) of the turbinates. Surgical procedures to reduce soft palate redundancy include uvulopalatopharyngoplasty, uvulopalatal flap, laser-assisted uvulopalatoplasty, and RF of the soft palate with adenotonsillectomy. More significant, however, particularly in cases of severe OSA, is hypopharyngeal or retrolingual obstruction related to an enlarged tongue, or more commonly due to maxillo-mandibular deficiency. Surgeries in these cases are aimed at reducing the bulk of the tongue base or providing more space for the tongue in the oropharynx so as to limit posterior collapse during sleep. These procedures include genioglossal advancement, hyoid suspension, distraction osteogenesis, tongue RF, lingualplasty, and maxillo-mandibular advancement. Successful surgery depends on proper patient selection, proper procedure selection, and experience of the surgeon. Most surgeries are done in combination and in a multistep manner, with maxillo-mandibular advancement typically being reserved for refractory or severe OSA, or for those with obvious and significant maxillo-mandibular deficiency. Although not without risks and not as predictable as positive airway pressure therapy, surgery remains an important therapeutic consideration in all patients with OSA. Current research aims to optimize the success of these procedures by identifying proper candidates for surgery, as well as to develop new invasive procedures for OSA treatment.

**Keywords:** uvulopalatopharyngoplasty; radiofrequency; adenotonsillectomy; maxillary expansion

Obstructive sleep apnea (OSA), defined as an apnea-hypopnea index (AHI) of at least five events per hour, is a major public health problem in the United States that affects 24% of adult males and 9% of adult females (1). The gold standard treatment for adults is positive airway pressure (PAP). Although extremely effective, tolerance and compliance remain considerable hurdles. Certain interventions may promote compliance to PAP, such as correction of nasal obstruction, attention to mask-fit, desensitization for claustrophobia, heated humidification, patient education, regular follow-ups, compliance software, and support groups (2). Despite these measures, PAP therapy remains a considerable challenge for many individuals, and surgical intervention is often an effective therapeutic alternative (3).

Surgery aims to alleviate anatomic sites of obstruction in the naso-, oro-, and hypopharynx. In adults, surgical options include phase I surgeries (nasal, palate reduction, and tongue advancement or reduction surgeries), and phase II surgery (maxillo-mandibular advancement [MMA]). Other surgical therapies for OSA

include distraction osteogenesis of the maxilla and mandible, and finally, tracheotomy. Phase I and II surgeries are generally performed sequentially, although some surgeons will perform phase II surgery initially or, less commonly, combine phase I and II surgeries. In children, tonsillectomy and adenoidectomy (TNA) represent the major surgical intervention and, if needed, radiofrequency treatment of the nasal turbinates combined with aggressive treatment of allergies. Adjunctive treatment in children includes maxillary and mandibular distraction via orthodontics.

Surgical success for OSA is often unpredictable and less effective than PAP (with the exception of tracheotomy). Surgical success depends on appropriate patient selection, the type of procedure performed, and the experience of the surgeon. In general, phase I surgeries have a reported success rate of 50–60% in significantly improving OSA by greater than 50% in select patients, whereas phase II surgeries have a success rate of greater than 90% (4, 5).

Surgery is considered appropriate on a case-by-case basis in patients with usually moderate to severe OSA with associated symptoms of excessive daytime sleepiness or with significant medical morbidities.

### DEFINING SURGICAL SUCCESS

It should be emphasized that no currently available treatment modality completely eliminates OSA. PAP is considered the gold standard therapy for OSA, yet even PAP users achieve only approximately 50% of ideal use (6). Therefore, today's definition of surgical success is achieving a greater than 50% reduction of the AHI and/or an AHI of less than 20 events per hour. The surgical success rate defined in this review will follow the above definition.

### SPECIFIC SURGICAL PROCEDURES

#### Nasal Reconstruction

The goal of nasal reconstructive surgery is to improve nasal airway blockage caused by bony, cartilaginous, or hypertrophied tissues to restore normal breathing as well as to optimize nasal CPAP use. A patent nasal airway is important for minimizing mouth breathing, because mouth breathing worsens upper airway obstruction by forcing the lower jaw to rotate downward and backward and pushing the tongue into the posterior pharyngeal space. Nasal reconstructive surgeries include septal and/or bony intranasal reconstruction, alar valve or alar rim reconstruction, and turbinectomy. Radiofrequency treatments for turbinate hypertrophy may also be done in the outpatient office setting. These procedures are generally low in risk and successful at achieving nasal patency. However, by themselves, they are not likely to make a significant impact on moderate or severe sleep disordered breathing. Nonetheless, it remains an essential part of treating OSA, and more importantly, a means of improving nasal PAP tolerance and compliance.

#### Uvulopalatopharyngoplasty

The palatal and lateral pharyngeal tissues are highly compliant and collapsible during sleep in certain patients. Uvulopalatophar-

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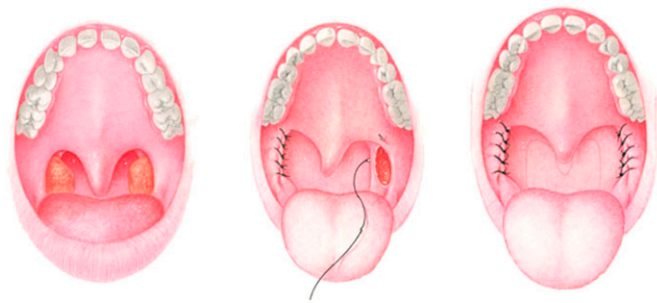
Uvulopalatopharyngoplasty (UPPP) aims to enlarge the retropalatal airway by trimming and reorienting the posterior and anterior lateral pharyngeal pillars, and by excising the uvula and posterior portion of the palate (Figure 1). This surgery is often performed in conjunction with adenotonsillectomy, or combined with limited resection, advancement, or RF of the tongue base to achieve maximal enlargement of the retropalatal and retrolingual airway (7–9). UPPP has a reported success rate of approximately 40–50% for improving mild to moderate OSA, although surgical efficacy appears to decrease over time (10). It is recommended that the procedure be performed by experienced surgeons, as it may be associated with significant complications, including velopharyngeal insufficiency, dysphagia, persistent dryness, and nasopharyngeal stenosis (11–13).

### Uvulopalatal Flap

Uvulopalatal flap (UPF), a modification of the UPPP, involves retraction of the uvula superiorly toward the hard–soft palate junction after a limited removal of the uvula, lateral pharyngeal wall, and mucosa, thereby widening the oropharyngeal airway (14) (Figure 2). Indications for this procedure are similar to UPPP, except that it is contraindicated in the case of an excessively long or bulky palate or uvula in which such a flap could create an abnormal thickness to the palate and diminish or reverse any favorable outcomes (15, 16). UPF is preferred over UPPP in most cases because it reduces the risk of nasopharyngeal incompetence by using a potentially reversible flap that could be taken down in the early postoperative period. Additionally, because there are no sutures along the free edge of the palate, there is reportedly less postoperative pain compared with traditional UPPP or laser therapy. Complications are similar to those of UPPP (14).

### Laser-Assisted Uvulopalatoplasty

Laser-assisted uvulopalatoplasty (LAUP) is an office-based surgical procedure that was introduced in 1990 as a new approach for the treatment of snoring. This technique progressively shortens and tightens the uvula and palate through a series of carbon dioxide laser incisions and vaporizations. Most of the uvula is amputated, and the soft palate is incised by vertical trenches up to the muscular sling 1–2 cm lateral to the uvula. Surrounding mucosal or tonsillar pillar tissue may also be vaporized. Studies evaluating the efficacy of LAUP for OSA suggest a near 50% success rate in reducing respiratory disturbance index (RDI) to less than 10 events per hour (17, 18). There are some concerns, however, regarding the safety of performing this surgery on an ambulatory basis, because of possible early postoperative edema of the upper airway (19–21). As a result of these



**Figure 1.** Uvulopalatopharyngoplasty reduces upper airway obstruction by shortening the uvula, trimming the soft palate, and suturing back the anterior and posterior pharyngeal pillars. Tonsillectomy is performed at the same time if tonsils are found to be enlarged.



**Figure 2.** Uvulopalatal flap is a modification of uvulopalatopharyngoplasty. Instead of removing the uvula and soft palate, the uvula is retracted and tugged superiorly under the soft palate. The pharyngeal pillars are sutured back and tonsils are removed in this procedure as well.

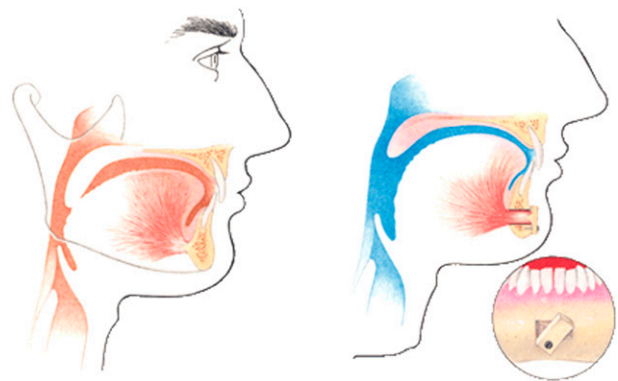
concerns, as well as significant postoperative pain, LAUP has become less popular for the treatment of OSA.

### Mandibular Osteotomy with Genioglossus Advancement

Mandibular osteotomy with genioglossus advancement (GA) addresses upper airway obstruction at the base of the tongue. The genioglossus muscle is attached to the lingual surface of the mandible at the geniotubercle and also to the hyoid complex just above the larynx. Movement forward of either or both of these anatomic structures will stabilize the tongue base along with the associated pharyngeal dilators. GA enlarges the retrolingual airway specifically by advancing forward the geniotubercle of the mandible through a limited parasagittal mandibular osteotomy, thereby forcing an anterior advancement of the tongue base (22) (Figure 3). The procedure achieves a greater hypopharyngeal space, much as in the typical “jaw thrust” used in cardiopulmonary resuscitation. The responder or cure rate ranges from 35–60% depending on the severity of the disorder (23, 24). The most serious complication of this procedure is mandibular fracture, which occurs when the osteotomy violates the inferior border of the mandible or induces lesions at the roots of the teeth. Other complications include infection, permanent anesthesia, and seroma (24).

### Hyoid Myotomy Suspension

The hyoid complex helps to maintain the upper airway space, and forward movement of the complex improves the airway space behind the tongue (25, 26). Hyoid myotomy suspension (HMS) is part of phase I treatment, but is not always included at



**Figure 3.** Genioglossus advancement enlarges the hypopharyngeal space by pulling forward the tongue base at the geniotubercle through a mandibular osteotomy.

the same time as GA (27). In patients with severe OSA (RDI > 40 or SaO<sub>2</sub> nadir < 80–85%), a multilevel approach is taken and GA is usually combined with UPPP to address both palatal and retrolingual levels of obstruction. The addition of HMS has been found to be very difficult to tolerate by many of these patients, and often GA with UPPP has been found to sufficiently improve the upper airway space and obviate the need for a hyoid procedure. In cases where HMS is performed, the procedure may be combined instead with radiofrequency to the ventral surface and base of tongue. Currently, however, HMS is not considered primary therapy, and is performed instead as adjunctive surgical therapy for tongue base obstruction (28).

### Laser Midline Glossectomy and Lingualplasty

The removal of the center part of the tongue base using a laser evaporation technique or lingualplasty was described by Fujita and Woodson (29). They reported a 77% success rate in their series (30). However, protective tracheotomy and an extended hospital stay were occasionally required due to postoperative edema as well as excessive bleeding. Tongue reduction surgery is currently seldom undertaken due to these significant morbidities, and is recommended in a select group of patients in whom other phase I surgeries are not options or are failures.

### MMA Osteotomy

Patients usually undergo phase II surgical management only after they have undergone phase I surgery and are found to be incompletely treated due to continued base-of-tongue obstruction. However, some surgeons advocate MMA osteotomy as the initial intervention, especially for those with severe OSA or significant maxillomandibular deficiency.

The first reports of mandibular skeletal surgery for OSA were done by Kuo and colleagues (31) in 1979 and Bear (32) in 1980. This surgery specifically addresses hypopharyngeal or base-of-tongue obstruction. The maxilla and mandible are advanced simultaneously by means of LeFort I maxillary and sagittal-split mandibular osteotomies to enlarge the retrolingual and retro-palatal airway (Figure 4). Achieving such clearance, especially for long-term improvement, usually necessitates an advancement of 10 to 15 mm of the maxilla and mandible. MMA is perhaps the most effective surgery for improving OSA when performed on appropriately selected patients. Studies report reduction in post-operative RDI by at least 50%, with an average improvement of greater than 85%, in approximately 90% of patients (33–38).

In 80% of patients, temporary numbness of the cheek and chin area can occur, and usually resolves within 6 to 12 months after surgery. Skeletal relapse resulting in malocclusion can also occur in up to 15% of patients, and therefore, coordinated treatment with an orthodontist may be necessary when indicated (33).

### Radiofrequency Ablation

The advantages of radiofrequency ablation (RF) over electrocautery and laser energy surgery reside in its precision and safety. With RF, the targeted tissue temperatures stay within 60 to 90°C, thus limiting heat dissipation and damage to adjacent tissue. Electrocautery and laser temperatures are significantly greater (750–900°C) and in excess of the desired therapeutic need. This difference allows for a more accurate, minimally invasive, and less morbid procedure without compromising treatment efficacy. One disadvantage of this procedure, however, is that it requires multiple treatments over several weeks.

RF can be performed on the nasal turbinates, tongue base, and palate. RF of hypertrophied turbinates for patients with nasal obstruction is highly successful, minimally invasive, and with very few risks (39). RF of the tongue base is useful for

treating snoring and OSA in select patients (40, 41). Factors that influence its success include age, health, weight, tongue size, the presence of other areas of obstruction, and severity of OSA. At present, RF of the tongue base is considered adjunctive and not necessarily a primary procedure. RF of the soft palate has similarly been used to treat OSA with limited success, but again is considered adjunctive rather than primary therapy. Neither speech nor swallowing is affected by any of these ablations.

### TNA

Childhood OSA is typically recognized at age 2–8 years when the tonsils and adenoids are the largest in relation to the underlying airway size (42). Adenotonsillar hypertrophy in the presence of a narrow airway, and/or decreased oropharyngeal muscle tone, is considered the most common cause of OSA in children, and, therefore, TNA is considered first-line therapy for OSA in children. The goal is to maximize the size of the upper airway by removing tonsillar and adenoid tissue, as well as to prevent collapse of the soft palate and lateral pharyngeal walls. Suturing the tonsillar wound to reduce collapsibility of the pharynx and to prevent scarring and narrowing of the posterior pharynx are performed by some surgeons in an attempt to maximize success (Figure 5).

A controversial issue is how early to perform this surgery. Most agree that TNA can be performed successfully and without complications after 24 months of age. However, OSA can occur as early as 3 weeks of age, and TNA has been performed successfully as early as 6 months of age (43).

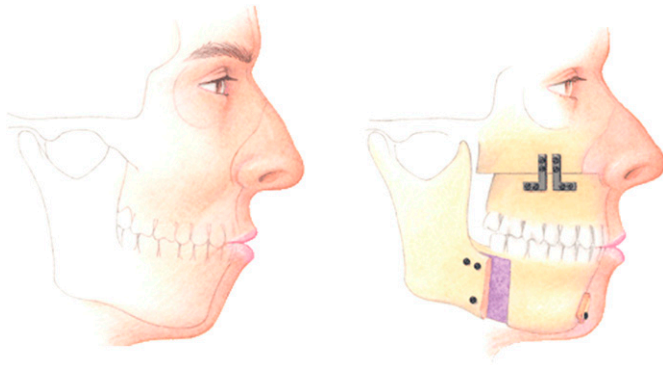
TNA is considered highly effective for treating OSA. Polysomnographic parameters improve after TNA in approximately 75–100% of children, and OSA is reportedly cured in 60–80% of cases, although the definition of cure varies somewhat between studies (44–46). Behavioral and health consequences of OSA also improve starting as early as 1 month postoperatively. The majority of children experience improvement in growth (47), quality of life (45), behavior (48), right ventricular function (49), neurocognitive function (50), and school grades (51). Children experiencing other sleep-related disturbances, such as night terrors, sleepwalking, or nocturnal enuresis, also improve after TNA (52, 53).

It is important to mention, however, that a multidisciplinary approach involving a sleep specialist, otolaryngologist, maxillofacial surgeon, and orthodontist should be used when evaluating a child suspected of having sleep-disordered breathing. Because children with OSA often have enlarged tonsillar and adenoid tissue in the setting of a narrowed or floppy airway, even though TNA has a high initial success rate for improving OSA and associated symptoms of OSA, if not curative, the procedure may do little to affect craniofacial development in the long-term, and the child remains at risk for worsening OSA in adulthood. The multidisciplinary approach assures a comprehensive plan to address all aspects of the child's orofacial anatomy, and to positively affect craniofacial and upper airway development in a child at risk for OSA in adolescence or adulthood.

The most common perioperative complication of TNA is bleeding (54). Morbidly obese children undergoing TNA may be considered at a higher risk of postoperative respiratory compromise, requiring interventions in the form of supplemental oxygen, aggressive suctioning, and nasal PAP (55).

### Tracheotomy

Tracheotomy, because it bypasses the entire upper airway, is considered curative for OSA (56). However, despite being the



**Figure 4.** Maxillomandibular advancement osteotomy, or phase II surgery, advances the maxilla and mandible to enlarge the retrolingual and retropalatal spaces.

most effective treatment for OSA, patient acceptance is low due to the associated morbidity and social implications. The current use of tracheostomy primarily serves as a temporary measure for airway protection in patients with severe sleep apnea with either morbid obesity or significant craniofacial anomalies that pose a high risk for airway compromise in the perioperative period. Permanent tracheostomy as a long-term treatment of OSA remains an option in morbidly obese patients with obesity hypoventilation syndrome, or in patients with significant craniofacial anomaly for whom all other forms of nonsurgical and surgical treatments have failed.

#### Distraction Osteogenesis

Rapid maxillary distraction in conjunction with TNA has shown to be successful in treating children with OSA and maxillary contraction (high-arched palate and unilateral or bilateral cross-bite) (57). Rapid maxillary distraction requires an orthodontic device anchored to two upper molars on each side of the jaw, which applies daily pressure causing each half of the maxilla to grow apart. Bone grows into the spaces bordering the midline cartilage (Figure 6). This technique aims to expand the hard palate laterally, raise the soft palate, and widen the nasal passage. This provides more space for the tongue and prevents it from falling posterior and occluding the oropharynx during sleep. Rapid maxillary distraction needs to occur before the cartilage becomes bone, and is therefore most often performed between the ages of 5 and 16 years. Rapid maxillary distraction may result in a limited widening of the mandibular arch due to dental compensation. For mandibular manipulation, mandibular repositioning splints and other dental appliances may also be used as a noninvasive form of therapy.

Orthognathic surgery, or mandibular distraction osteogenesis, may be required if noninvasive orthodontic procedures is not able to achieve sufficient mandibular widening. The procedure is performed by a surgeon with close communication with the



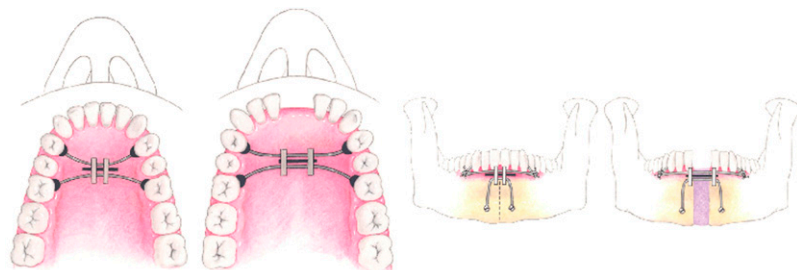
**Figure 5.** Adenotonsillectomy is first-line therapy for obstructive sleep apnea in children. Both adenoid and tonsillar tissue are removed, and the lateral pharyngeal walls are sutured to prevent collapse.

orthodontist. The concept of mandibular distraction osteogenesis is very similar to that of rapid maxillary distraction, except that the surgeon uses a saw to create osteotomies in the mandible where either an internal (intraoral) device or an external device is used to expand the bones. Patients accept internal devices better than external ones, but the former are difficult to use in patients with small bones. External devices offer flexibility and vector selection, but often cause scarring of the skin. Widening of 12 to 14 mm can be obtained easily in 3 weeks (58). This approach is normally postponed until 10 to 13 years of age, and by 12 to 13 years of age both rapid maxillary distraction and mandibular distraction osteogenesis can be performed simultaneously.

#### MEDICAL EVALUATION FOR SURGERY

A complete medical and sleep history and physical exam, including vital signs, neck circumference, body habitus, and skeletal facial pattern, are required in the surgical evaluation. This information should attest to OSA and not another sleep disorder as the cause of the patient's symptoms. The history and physical exam should also assess for any comorbid conditions, such as significant cardiac, pulmonary, or psychiatric disease, that support or preclude the patient from having a successful surgical outcome. The exam focuses on the three major anatomic regions of potential upper airway obstruction: nose, palate (oropharynx), and base of tongue (hypopharynx). The nasal examination should be done during quiet breathing and during deep inspiration to assess alar support and nasal valve function. Mallampati score is noted because it has been shown to correlate with the severity of OSA, and indicates palatal redundancy and oropharyngeal crowding. A high-arched hard palate signals maxillomandibular deficiency and potentially chronic oral breathing due to nasal obstruction. A tongue too large for its space, as evidenced by teeth marks on the sides of the tongue, indicates macroglossia or mandibular deficiency.

A radiographic cephalometric analysis, along with fiberoptic nasopharyngoscopy, improves the ability to evaluate soft tissue and skeletal anatomy as part of the preoperative assessment. Lateral cephalometric radiographs are the simplest and most



**Figure 6.** Rapid maxillary distraction can be achieved by orthodontics in young children with midline cartilaginous tissue. Distraction creates more space for the tongue so as to prevent its collapse posteriorly during supine sleep.

**TABLE 1. OBSTRUCTIVE SLEEP APNEA SURGICAL COMPLICATIONS**

Procedure	Complications
Nasal surgeries (turbinectomy, septoplasty, alar reconstruction) UPPP, UPF, LAUP	Bleeding and infection (uncommon) Velopharyngeal insufficiency (2%), postoperative bleeding (1%), nasopharyngeal stenosis (0.8%), voice change (0.6%), foreign body sensation (0.1%), death (0.2%) (4, 11, 19, 23)
GA	Pathologic mandibular fracture, infection (<1%), permanent anesthesia (<6%), seroma (<2%) (63)
HMS	Airway edema, dysphagia, superior laryngeal nerve injury (uncommon) (28)
Glossectomy	Bleeding, odynophagia, change in taste (30)
MMA	Temporary numbness of cheek and chin (80%), malocclusion (4%), bleeding, edema with airway compromise
RF	Ulcer and infection (uncommon) (39)
TNA	Pain and bleeding (1%), subcutaneous emphysema, pneumomediastinum, taste disturbance due to glossopharyngeal nerve injury (rare)
Tracheotomy	Stoma infection (36%), hemorrhage (5%), tracheal stenosis (2%), psychosocial difficulties
Distraction osteogenesis	None reported

*Definition of abbreviations:* GA = genioglossus advancement; HMS = hyoid myotomy suspension; LAUP = laser-assisted uvulopalatoplasty; MMA = maxillomandibular advancement; RF = radiofrequency ablation; TNA = tonsillectomy and adenoidectomy; UPF = uvulopalatal flap; UPPP = uvulopalatopharyngoplasty.

practical upper airway imaging tool. Patients with OSA tend to demonstrate a long uvula and soft palate, less than 10-mm posterior airway space, and a low-lying hyoid bone. Fiberoptic nasopharyngolaryngoscopy during Mueller’s maneuver can be used to evaluate the dynamic properties of the upper airway to better identify sites of obstruction and to more accurately predict success of selected surgical procedures. Laryngoscopy also allows the anatomy of the epiglottis to be observed. An Ω-shaped (folded) epiglottis indicates “floppy” redundant supraglottic mucosa and tissue. Finally, a laryngoscopic exam is important to rule out other causes of upper airway obstruction, such as webs, cysts, tumors, or vocal cord paralysis.

As standard practice, the presurgical evaluation should include a nocturnal polysomnography to determine the severity of OSA, as the correlation between OSA severity and findings on physical exam are imperfect. A preoperative polysomnography is also important to compare and determine the success of the surgical procedure. The number of apneas or hypopneas, and degree of nocturnal desaturation on polysomnography, in conjunction with the patient’s complaints and anatomy will influence the types of procedures performed by the surgeon. Surgeons may opt to be more conservative and follow a stepwise protocol in cases of mild or moderate OSA, performing first nasal and/or phase I surgeries (pharyngoplasty, GA, HMS, glossectomy), followed by phase II surgery (MMA) only if necessary. In cases of severe OSA or severe craniofacial deformity, surgeons may proceed directly to phase II surgery or tracheotomy. However, it is recommended and cautioned that no one test or procedure should be relied upon to make a definitive surgical treatment plan. Physical exam, patient complaints, comorbidities, imaging tests, and disease severity are all taken into account when devising the surgical plan.

**RISK MANAGEMENT IN SURGERY FOR OSA**

The most important consideration in sleep apnea surgery is avoidance of complications. It is important that sleep specialists are familiar with the type and incidence of complications (Table 1).

Although fortunately rare, life-threatening complications have been associated with sleep apnea surgery (59, 60). Fatalities in the early postoperative period have been related to upper airway collapse or obstruction secondary to pharmacological sedation and surgical edema (61). Nasal PAP use during the perioperative period has shown to protect patients from airway obstruction and hypoxemia, and is highly encouraged, especially in cases of severe OSA (62, 63).

A postoperative polysomnogram is encouraged in all children for a period of 6 weeks to 3 months after TNA, particularly where there is a high likelihood of residual OSA, such as in cases of a narrow mandible or maxilla, obesity, neuromuscular disorder, trisomy 21, or craniofacial abnormalities (64). In adults, a postoperative polysomnogram is recommended after 4–6 months when healing, weight stabilization, and neurologic equilibration have most likely been achieved (65). The decision for further surgery is based on these results. In a small percentage of patients, phase I and II surgeries will fail and nasal PAP is required. However, although not always curative, sleep apnea surgeries will often achieve enough treatment effect to require significantly less therapeutic PAP, making tolerance and compliance more favorable (66, 67).

**CONCLUSIONS**

Innovative procedures are constantly being explored for OSA therapy. Electrical stimulation of the tongue muscles and palatal stiffening with pillar implants show promising preliminary results, although further research is necessary (68, 69). Other new surgical techniques have not been attempted within the last 5 years. Instead, development in this area appears to concentrate on combining previously known methods (so-called multilevel surgery) and on optimizing methods of patient selection. Combined surgical procedures can achieve success rates of about 70 to 99%. Even taking all these developments into account, however, nasal PAP continues to be the gold standard treatment for OSA (25, 36). Nevertheless, the disappointing long-term compliance rates of 40 to 60% among PAP users have to be regarded as a major challenge warranting more aggressive exploration of both surgical and nonsurgical alternatives for OSA therapy.

*Conflict of Interest Statement:* None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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