Effects and Side-Effects of Surgery for Snoring and Obstructive Sleep Apnea – A Systematic Review

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Study Objectives: Many patients undergo surgery for snoring and sleep apnea, although the efficacy and safety of such procedures have not been clearly established. Our aim was systematically to review studies of the efficacy and adverse effects of surgery for snoring and obstructive sleep apnea.

Design: Systematic review.

Measurements: PubMed and Cochrane databases were searched in September 2007. Randomized controlled trials of surgery vs. sham surgery or conservative treatment in adults, with daytime sleepiness, quality of life, apnea-hypopnea index, and snoring as outcomes were included. Observational studies were also reviewed to assess adverse effects. Evidence of effect required at least two studies of medium and high quality reporting the same result.

Results: Four studies of benefits and 45 studies of adverse effects were included. There was no significant effect on daytime sleepiness and quality of life after laser-assisted uvulopalatoplasty and radiofrequency ablation. The apnea-hypopnea index and snoring was reduced in one trial after laser-assisted uvulopalatoplasty but not in another trial. Subjective snoring was reduced in one trial after radiofrequency ablation. No trial investigating the effect of any other surgical modality met the inclusion criteria. Persistent side-effects occurred after uvulopalatopharyngoplasty and uvulopalatoplasty in about half the patients and difficulty in swallowing, globus sensation and voice changes were especially common.

Conclusions: Only a small number of randomized controlled trials with a limited number of patients assessing some surgical modalities for snoring or sleep apnea are available. These studies do not provide any evidence of effect from laser-assisted uvulopalatoplasty or radiofrequency ablation on daytime sleepiness, apnea reduction, quality of life or snoring. We call for research of randomized, controlled trials of surgery other than uvulopalatopharyngoplasty and uvulopalatoplasty, as they are related to a high risk of long-term side-effects, especially difficulty swallowing.

Keywords: Sleep apnea syndromes, snoring, surgery, adverse effects, meta-analysis

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SNORING IS A SIGN OF INCREASED UPPER AIRWAY RESISTANCE, AND OBSTRUCTIVE SLEEP APNEA IS CHARACTERIZED BY RECURRENT EPISODES OF UPPER airway obstruction during sleep. Excessive daytime sleepiness is common among heavy snorers and among patients with obstructive sleep apnea syndrome.[1-3] A number of recent prospective studies report than patients with obstructive sleep apnea run an increased risk of stroke and early death.[4-8]

Surgical treatment for snoring and obstructive sleep apnea aims to increase the upper airway cross-sectional area, remove obstructive tissues, such as enlarged tonsils, or bypass the upper airway. Uvulopalatopharyngoplasty became popular shortly after its introduction in 1981.[9] The uvula, the distal part of the soft palate and the tonsils are removed, with the aim of enlarging the oropharyngeal airspace and thereby reducing sleep apneas, snoring, and daytime sleepiness. Laser-assisted uvulopalatoplasty and temperature-controlled radiofrequency tissue ablation were subsequently introduced, and these surgical modalities could be performed under local anesthesia. Other surgical modalities include tracheostomy, inferior sagittal mandibular osteotomy and genioglossus advancement with hyoid myotomy and suspension, laser midline glossectomy and lingual plasty, maxillo-mandibular osteotomy and advancement, expansion sphincter pharyngoplasty, palatal implants, nasal surgery, epiglottoplasty for selected cases of laryngomalacia, and so on. The efficacy of surgical modalities has, however, been questioned in systematic reports, and laser-assisted uvulopalatopharyngoplasty is not recommended for the treatment of sleep disordered breathing.[10-14] There is a lack of systematic reviews of adverse effects, as many subjects still undergo surgery because of snoring and sleep apnea.

The present aim was systematically to review studies of the efficacy and adverse effects of surgery for snoring and obstructive sleep apnea in adults.

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METHODS

Search Strategy

PubMed and the Cochrane Controlled Trials Register were searched on 1 September 2007; ("Sleep apnea syndromes"

[Mesh] OR "Snoring" [Mesh]) AND ("Surgery" [Mesh] OR "Surgery" [Subheading] or Radiofrequency) Limits: English, Randomized Controlled Trial, Meta-Analysis.

PubMed was searched on 1 September 2007 for side-effects; sleep apnea syndromes/surgery [Mesh] OR snoring/surgery [Mesh] AND (adverse effects [Mesh Subheading] OR complications [Mesh subheading] OR complication [Text Word] OR complications [Text Word]) NOT (comment [Publication Type] OR editorial [Publication Type] OR news [Publication Type]) Limits: English.

Reference lists of all the identified articles were searched for additional studies.

Inclusion Criteria for the Selection of Articles and Study end Points

Two reviewers independently screened abstracts according to inclusion criteria. For all possibly relevant articles, full reports were requested. Randomized, controlled studies of medium and high quality comparing surgery for snoring or obstructive sleep apnea with sham operations or conservative treatment were included. The primary outcomes were daytime sleepiness measured using the Epworth Sleepiness Scale, Multiple sleep latency test or Maintenance of wakefulness test and Quality of life. Secondary outcomes were the apnea-hypopnea index and severity of snoring.

The review of adverse effects included randomized, controlled studies and observational studies of medium and high quality reporting complications and side-effects of surgery other than post-operative pain. All studies reporting life-threatening side effects and deaths in relation to surgery were included.

Quality Assessment and Evidence Grading

A modified JADAD ranking scale from 0-5 was used to assess the quality of randomized, controlled trials.[13,15] We used questions on single blinding instead of double blinding, with the following questions: Was the trial described as randomized? Was the allocation concealed? Were patients blinded to treatment alternative? Were investigators blinded to treatment alternative? Was there a description of withdrawals? A score of 0-2 was rated as poor quality, 3 as medium quality, and 4-5 as high quality.

The following scores were used for observational studies reporting side-effects. High quality required a prospective study; before and after data for adverse effects; defined groups of patients and a detailed description of methods and adverse effects; loss to follow-up of less than 30%. Medium quality required a prospective design or consecutive patients; a summary description of patients and methods; a detailed description of adverse effects; loss to follow-up of less than 30%.

Strong evidence required at least two studies of high quality reporting the same result. Moderate evidence required at least one study of high quality and two of medium quality, while limited evidence required at least two studies of medium quality.

Data Abstraction

The data were independently abstracted by two reviewers and the authors were contacted in the event of questions. The number of participants, baseline characteristics, type of surgery, time of follow-up, design, benefits and adverse effects were extracted.

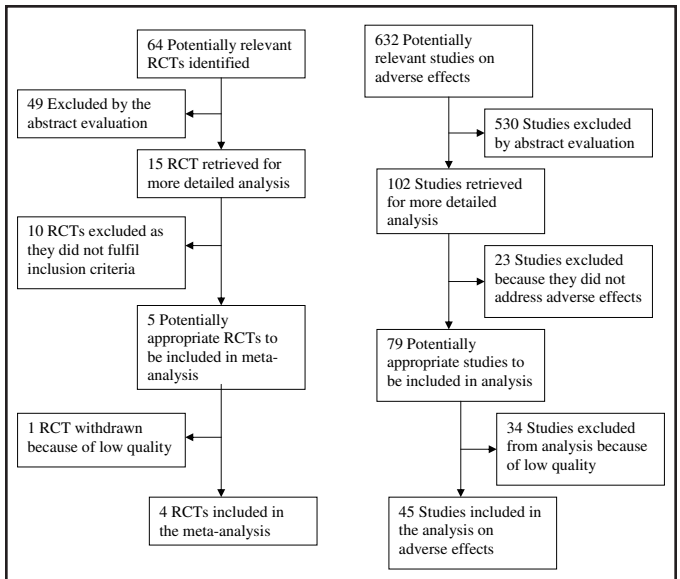

Figure 1—Flowchart of the process of study selection.

Statistical Analysis

Means and 95% confidence interval (CI) for change in active treated patients compared with control patients was calculated from mean of change (after - before) and standard deviation of change (SD). Differences of mean change between active treatment and control treatment were presented with 95% confidence interval (95% CI). A significant effect was regarded when 0 was not included in the confidence interval. For meta-analysis, we used Cochrane Review Manager software (version 5.0; Cochrane Library Software, Oxford, England). Means and SD for change in outcome was entered in the analysis. The weighted mean difference was used for comparisons of change in difference between active treatment and control. A P-value of < 0.05 was considered significant. Weighted means for adverse effects were calculated as $= \Sigma\, n_i/n * p_i$. Where n_i = number of treated patients, n = sum of all treated patients and p_i = proportion of patients with an adverse effect.

RESULTS

Efficacy

There were 64 hits in the search, and 15 potentially relevant articles were read. Five randomized controlled trials comparing surgery with sham surgery or conservative treatment were identified (Figure 1). One trial comparing uvulopalatopharyngoplasty and conservative treatment was excluded from further analysis due to low quality and a modified JADAD score of 2.[16] Four parallel, randomized, controlled trials of high quality met the inclusion criteria, 2 studies investigated the effect of laser-assisted uvulopalatoplasty and 2 the effect of radiofrequency ablation (Table 1).[17-20]

A summary of the effects on outcome for the difference in change is presented in Table 2. These studies show no sig-

Table 1—Description of Included Studies of Medium and High Quality

Source	Location	Study design	Sample size*	Operation	Outcomes	Quality
Ferguson et al., 2003[17]	Canada	RCT, parallel	46 (45)	LAUP	ESS, AHI, SAQLI, Snoring, Side-effects	High
Woodson et al., 2003[18]	USA	RCT, parallel	60 (52)	TCRAFTA	ESS, AHI, SF36, FOSQ, Side-effects	High
Larossa et al., 2004[19]	Spain	RCT, parallel	28 (25)	LAUP	ESS, AHI, SF36, Snoring, Complications	High
Stuck et al., 2005[20]	Germany	RCT, parallel	26 (23)	TCRAFTA	ESS, Snoring, Side-effects	High
Studies of adverse effects						
Esclamado et al., 1989[23]	USA	Consecutive patients	132	UPPP	Perioperative complications	Medium
Harmon et al., 1989[24]	USA	Consecutive patients	132	UPPP	Peri- and postoperative complications	Medium
Walker et al., 1996[25]	USA	Consecutive patients	275	LAUP	Postoperative complications	Medium
Riley et al., 1997[26]	USA	Prospective	182 (182)	Different operations	Postoperative complications	Medium
Mickelson et al., 1998[27]	USA	Consecutive patients	347	UPPP	Postoperative complications	Medium
Terris et al., 1998[28]	USA	Consecutive patients	109 (109)	UPPP	Peri- and postoperative complications	Medium
Hultcrantz et al., 1999[29]	Sweden	Consecutive patients	55	UPP	Long-term side-effects	Medium
Levring-Jäghagen et al., 1999[30]	Sweden	Consecutive patients	76 (68)	UPP	Persistent dysphagia	Medium
Powell et al., 1999[31]	USA	Prospective	20 (18)	TCRAFTA tongue	Postoperative complications, swallowing function	Medium
Remacle et al., 1999[32]	Belgium	Prospective	89	LAUP UPPP	Complications	Medium
Boudewyns et al., 2000[33]	Belgium	Prospective	103 (44)	TCRAFTA soft palate	Postoperative complications	Medium
Coleman et al., 2000[34]	USA	Prospective	12	TCRAFTA soft palate	Postoperative complications	Medium
Grontved et al., 2000[35]	Denmark	Consecutive patients	69	UPPP	Complications	Medium
Hagert et al., 2000[36]	Sweden	Consecutive patients	457 (415)	UPPP LAUP	Long-term side-effects	Medium
Hukins et al., 2000[37]	Australia	Prospective	20	TCRAFTA soft palate	Postoperative complications	Medium
Li et al., 2000[38]	USA	Prospective	22	TCRAFTA soft palate	Long term side-effects	Medium
Osman et al., 2000[39]	UK	Prospective	47 (47)	UPPP LAUP	Postoperative complications	Medium
Bäck et al.. 2001[40]	Finland	Prospective	21 (16)	TCRAFTA soft palate	Postoperative complications	Medium

(continued on following page)

Table 1—Description of Included Studies of Medium and High Quality (continued from previous page)

Source	Location	Study design	Sample size*	Operation	Outcomes	Quality
Brown et al., 2001[41]	Canada	Prospective	12	TCRAFTA soft palate	Postoperative complications	Medium
Pazos et al., 2001[42]	USA	Consecutive patients	30 (30)	TCRAFTA soft palate, tongue	Postoperative complications	Medium
Sher et al., 2001[43]	USA	Prospective	112 (105)	TCRAFTA soft palate	Postoperative complications	Medium
Terris et al., 2001[45]	USA	Prospective	23	TCRAFTA soft palate	Postoperative complications	Medium
Woodson et al., 2001[46]	USA	Prospective	73 (69)	TCRAFTA tongue	Postoperative complications	Medium
Haraldsson et al., 2002[47]	Sweden	Prospective	16	TCRAFTA soft palate	Speech evaluation	Medium
Lysdahl et al., 2002[48]	Sweden	Consecutive patients	150 (121)	UPPP LAUP	Long-term side-effects	Medium
Stuck et al., 2002[44]	Germany	Prospective	20 (18)	TCRAFTA soft palate, tongue	Postoperative complications	Medium
Berger et al., 2003[49]	Israel	Prospective	49	UPPP LAUP	Early and long-term side-effects	Medium
Rombaux et al., 2003[50]	Belgium	Prospective	49	UPPP LAUP TCRAFTA soft palate	Postoperative complications	Medium
Said et al., 2003[51]	USA	Consecutive patients	50 (39)	TCRAFTA soft palate	Postoperative complications	Medium
Jäghagen et al., 2004[22]	Sweden	Prospective	46 (42)	UPPP UPP	Swallowing function	High
Kezirian et al., 2004[21]	USA	Prospective	3130	UPPP	Postoperative serious side-effects	High
Kim et al., 2005[52]	South Korea	Consecutive patients	90	UPPP	Postoperative complications	Medium
Li et al.,[54]	China	Consecutive patients	108	UPPP	Taste disturbances	Medium
Pavelec et al., 2006[53]	Czech Republic	Prospective	63	LAUP	Postoperative complications	Medium

Abbreviations: RCT, randomized, controlled trial; ESS, Epworth sleepiness scale; SF36 Short Form 36; AHI, Apnea-hypopnea index; FOSQ, functional outcome of sleep questionnaire; SAQLI, Calgary Sleep Apnea Quality of Life Index; LAUP, laser-assisted uvulopalatoplasty; UPP, uvulopalatopharyngoplasty; UPPP, uvulopalatopharyngoplasty; TCRAFTA, temperature-controlled radiofrequency tissue ablation. *Numbers in parentheses denote the number of patients analyzed after withdrawals.

nificant effect on daytime sleepiness measured with the Epworth sleepiness scale after laser-assisted uvulopalatoplasty and temperature-controlled, radiofrequency tissue ablation (Figure 2). The apnea-hypopnea index and snoring was reduced in one trial after laser-assisted uvulopalatoplasty[17] but not in another trial.[19] Subjective snoring was reduced, but not the apnea-hypopnea index in one trial after radiofrequency ablation.[18] There was no effect on quality of life in any trial. No trial investigating the effect of any other surgical modality met the inclusion criteria.

Laser-Assisted Uvulopalatoplasty

Ferguson et al. randomized 46 snoring patients with an apnea-hypopnea index of between 10 and 27 to laser-assisted uvulopalatoplasty or no treatment and followed them for 7 months.[17] There was no significant between-group difference in the Epworth Sleepiness Scale or the Calgary Sleep Apnea Quality of Life Index. The mean apnea-hypopnea index was reduced from 19 to 15 in the actively treated patients and increased from 16 to 23 in non-treated patients, P = 0.04 for the between-group difference in change. Snoring intensity estimated by a bedroom

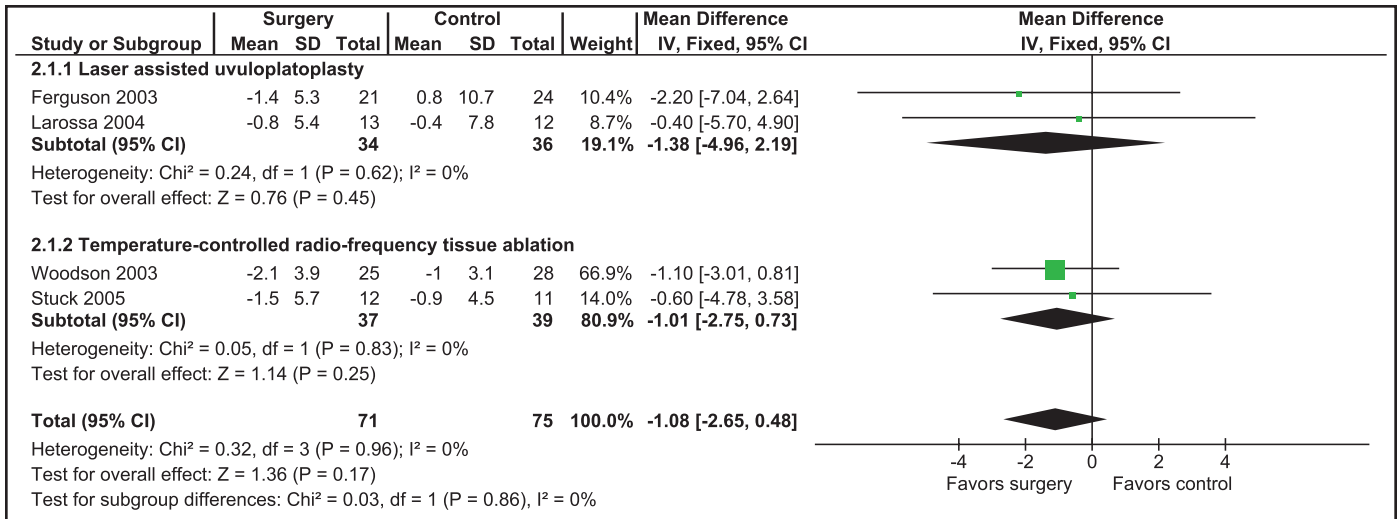

Figure 2—Effect of surgery on daytime sleepiness using the Epworth sleepiness scale.

Table 2—Effects of Surgery Compared to Placebo or No Treatment

	LAUP Ferguson et al., 2003[17]	LAUP Larossa et al., 2004[19]	TCRAFTA Woodson et al., 2003[18]	TCRAFTA Stuck et al., 2005[20]
ESS	-2.2 (-15, 9.3)	-0.4 (-13, 12)	-1.2 (-3.1, 0.8)	-0.6 (-1.2, 2.3)
FOSQ			-0.9 (-0.1, 1.9)	
SAQLI	0.2 (-0.6, 1.0)			
SF-36 Physical		1.4 (-38, 41)	-1.0 (-5.1, 3.1)	
SF-36 Mental		-2 (-49, 45)	2.5 (-1.4, 6.4)	
AHI	-10.5, P = 0.04	7 (-76, 90)	-2.7 (-9.9, 4.5)	
Snoring intensity	-4.0 (-5.5, -2.5)*	-1.1 (-12, 10)		
Snoring frequency	-3.6 (-1.3, -5.9)*	-106 (-8753, 8541)		
Snoring subjective		-0.5 (-3.8, 2.8)		-2.5 (-4.6, -0.4)*

*Significant as 0 was not included in the confidence interval.
Abbreviations: LAUP, laser-assisted uvulopalatoplasty; TCRAFTA, temperature-controlled radiofrequency tissue ablation; ESS, Epworth sleepiness scale; NS, No significant change. SF36 Short Form 36; FOSQ, functional outcome of sleep questionnaire; SAQLI, Calgary Sleep Apnea Quality of Life Index; AHI, Apnea-hypopnea index

partner on a VAS scale from 0-10 was reduced by surgery from a mean of 9.2 to 4.8 and by no treatment from 8.9 to 8.5, P < 0.0001 for the between-group difference in change. Snoring frequency was reduced from a mean of 9.4 to 5.5 in surgically treated patients and from 8.8 to 8.5 in non-treated patients, P < 0.005.

Larossa et al. randomized 28 snoring patients with an apnea-hypopnea index < 30 to laser-assisted uvulopalatoplasty or sham surgery and followed them for 3 months.[19] They found no significant difference in change in any of the outcomes, i.e. the Epworth Sleepiness Scale, Short-Form 36 Physical component summary, Short-Form 36 Mental component summary, Subjective snoring intensity, Snoring index or Decibels of snoring (Table 2).

Temperature-Controlled Radiofrequency Tissue Ablation

Woodson et al. performed the largest study and randomized 60 patients with daytime sleepiness, an apnea-hypopnea index of 5 to 40 and a body-mass index < 35 kg/m^2 to radiofrequency ablation or sham surgery.[18] They report that radiofrequency ablation, compared with sham surgery, improved Functional Outcomes of Sleep Questionnaire with a mean of 0.9 (95% CI -0.1, 1.9) P = 0.04 and reduced the apnea index with a mean of –4.8 (–9.3, 0.4) P = 0.02. These P-values were, however, significant only in one sided *t*-test but not in 2-sided nonparametric test, and 0 was included in confidence interval (Table 2). They found no significant difference in change for the Epworth Sleepiness Scale, Short-Form 36 Physical component summary, Short-Form 36 Mental component summary or the apnea-hypopnea index.

Stuck et al. randomized 26 non-sleepy snorers with an apnea-hypopnea index < 15, a body-mass index < 35 kg/m^2 and a mean Epworth sleepiness scale of 8.2 (1.4) to temperature-controlled radiofrequency ablation or sham surgery.[20] There was no between-group difference in change in the Epworth Sleepiness Scale. The authors report that snoring estimated by a bedroom partner on a VAS scale from 0-10 was reduced by surgery compared with sham surgery from a mean of 8.1 to 5.2 and by sham surgery from 8.4 to 8.0, P = 0.045 for the difference in change.

Table 3—Deaths in the Peri- and Postoperative Period

Author	Operation	Death case numbers	Source population numbers	Reasons for death	Quality
Esclamado 1989[23] USA	UPPP	1	135	Intubation problems	Medium
Harmon 1989[24] USA	UPPP	2	132	Bleeding (n = 1) Pulmonary embolism (n = 1)	Medium
Fairbanks 1990[57] USA	UPPP	16		Bleeding (n = 1) Loss of airway (n = 12) Unknown (n = 3)	Low
Carenfelt 1993[58]	UPPP	3	9000	Cardiac arrest (n = 2)	Low
Sweden	LAUP	1	2900	Bleeding (n = 1) Infection (n = 1)	
Haavisto 1994[60] Finland	UPPP	1	101	Breathing difficulties and asystole (n = 1)	Low
Lee 1997[62] UK	UPPP or LAUP	6		Respiratory arrest (n = 1) Cardiac arrest (n = 1) Unknown (n = 4)	Low
Kezirian 2004[21] USA	UPPP	7	3130	Unknown (n = 4) Respiratory problems (n = 2) Cardiac arrest (n = 1)	High

Abbreviations: UPPP, uvulopalatopharyngoplasty; LAUP, laser-assisted uvulopalatoplasty.

Adverse Effects

There were 632 hits in the search and 102 potentially relevant articles were read. Seventy-nine trials met the inclusion criteria. Five of the included studies were of high quality,[17,18,20-22] and 33 were of medium quality (Table 1).[19,23-54]. Forty-one studies were of low quality and they were excluded from further analysis, except for 7 studies reporting life-threatening side-effects and deaths[55-95] (Figure 1).

Uvulopalatopharyngoplasty

Uvulopalatopharyngoplasty was followed by severe complications in the peri- and post-operative period, including death, bleedings and respiratory compromise, in 0% to 16% of patients, with higher frequencies in studies published during the 1980s and lower complication frequencies in studies in recent years.[21,23,24,26-28,39,50,52,58,60,77,94]

A total of 30 cases of death were reported from six studies published between 1989 and 2004 (Table 3). One high-quality study comprising 3,130 operations reported peri- and post-operative death in 0.2% (95% CI 0.1 to 0.4) and serious complications other than death in 1.5% (95% CI 1.1 to1.9).[21] Respiratory compromise, bleedings, intubation difficulties, infections, and cardiac arrest were the main causes of death. Persistent side-effects occurred in a mean (range) of 58% (42%–62%) (limited evidence; Table 4).[35,36] Difficulty swallowing, including nasal regurgitation, occurred in 31% (13% to 36%) of operated patients (moderate evidence), voice changes in 13% (7% to 14%) (limited evidence), and taste disturbances in 5% (1% to 7%) (limited evidence).[22,35,36,48,54] Other reported side-effects were globus sensation, smell disturbances, and single cases of velopharyngeal insufficiency.[36,55]

Uvulopalatoplasty

Uvulopalatoplasty performed with a scalpel or laser was followed by peri- and post-operative complications in up to 5%, including post-operative bleedings and infections, with one report of death from septicemia (Tables 3).[17,19,25,39,50,58] Persistent side-effects were reported in a mean (range) of 59% (48% to 62%) (limited evidence; Table 5).[29,36,49] Difficulty swallowing including nasal regurgitation was reported in 27% (19% to 31%) (strong evidence) and globus sensation in 27% (16% to 36%) (limited evidence).[17,22,29,30,32,36,48,53] Other reported side-effects included voice changes, smell disturbances, taste disturbances, and single cases of velopharyngeal stenosis.[36,49]

Temperature-Controlled Radiofrequency Tissue Ablation

There were no reported changes in speech or swallowing one to two months after surgery.[18,20,38,47] Side-effects of temperature-controlled, radiofrequency tissue ablation of the soft palate included hemorrhage, infections and velopharyngeal fistula in single cases.[33,50] Radiofrequency ablation of the base of the tongue was followed by severe infections or tongue abscesses in 0% to 8% of patients (moderate evidence).[18,31,42,44,46] Single cases of mouth floor edema, severe tongue swelling, and a case of pseudo-aneurysm of the lingual artery and heavy bleeding 14 days after surgery have also been reported.[42,44,46,92]

Other Surgical Modalities

No studies of any other surgical modality meeting the inclusion criteria for adverse effects were found.

Table 4—Side-Effects After Uvulopalatopharyngoplasty

	Author	Frequency	Weighted mean	Evidence grade
Persistent side-effects	Hagert 2000[36]	62%	58%	Limited
	Grontved 2000[35]	42%		
Difficulty swallowing	Hagert 2000[36]	35%	31%	Moderate
	Grontved 2000[35]	13%		
	Lysdahl 2002[48]	36%		
	Jäghagen 2004[22]	29%		
Voice changes	Hagert 2000[36]	14%	13%	Limited
	Grontved 2000[35]	7%		
Taste disturbances	Hagert 2000[36]	7%	5%	Limited
	Li 2006[54]	1%		

Table 5—Side-Effects After Uvulopalatoplasty

	Author	Frequency	Weighted mean	Evidence grade
Persistent side-effects	Hultcranz 1999[29]	56%	59%	Limited
	Hagert 2000[36]	62%		
	Berger 2003[49]	48%		
Difficulty swallowing	Levring-Jäghagen 1999[30]	20%	27%	Strong
	Hultcranz 1999[29]	19%		
	Hagert 2000[36]	31%		
	Lysdahl 2002[48]	27%		
	Ferguson 2003[17]	19%		
	Jäghagen 2004[22]	29%		
Globus sensation in throat	Hultcranz 1999[29]	19%	27%	Limited
	Hagert 2000[36]	36%		
	Pavelec 2006[53]	16%		

DISCUSSION

Randomized, controlled trials do not support any benefit from surgery in the form of laser-assisted uvulopalatoplasty and temperature-controlled radiofrequency tissue ablation when it comes to daytime sleepiness or quality of life. Studies do not provide any evidence of effect on apnea-hypopnea index or snoring as there is a need of at least two trials reporting effect for evidence grading. One study reported a reduction in the apnea-hypopnea index and snoring after laser-assisted uvulopalatoplasty, while no such effects were found in another trial. A single study reported a reduction in snoring after radiofrequency tissue ablation. No evidence of effect was established for any other surgical modality, as no randomized, controlled trial meeting the inclusion criteria was found for any other surgical modality. Persistent side-effects were reported in a majority of the patients undergoing uvulopalatopharyngoplasty and uvulopalatoplasty, especially in the form of difficulty swallowing, globus sensation in the throat, and voice changes.

Only four controlled trials randomizing a total of 141 patients to either laser-assisted uvulopalatopharyngoplasty and sham/no treatment, or temperature-controlled radiofrequency tissue ablation and sham surgery met the present inclusion criteria. From this small sample of trials, it is not possible to exclude any effect of surgery. However, the many reports of swallowing difficulties after uvulopalatopharyngoplasty and uvulopalatoplasty suggest that other surgical modalities than these two should be further tested. Tonsillectomy is one suggested modality as large tonsils are associated with sleep apnea.[96] One disadvantage of surgery, especially more invasive surgery, is the problem of performing placebo or sham surgery in the control group. Instead of placebo, we suggest that control patients should be randomized to delayed surgery. In subsequent systematic reviews we suggest that other quality criteria than pure JADAD should be used in quality assessments. We used a modified JADAD focusing on the quality of single blinding instead of double blinding. If patients and surgeons cannot be blinded, one can always try to blind the assessors.

To date, the best study of peri- and post-operative mortality was published by Kezirian et al. in 2004. They reported a mortality of 0.2% among all Veterans Affairs inpatient uvulopalatopharyngoplasty surgery from 1991 to 2001 and serious peri- and post-operative complications in 1.5% of patients.[21] However, without evidence of effects of the surgical procedures, it is difficult to accept mortality related to surgery. Two cohort studies followed long-term mortality after uvulopalatopharyngoplasty and they report low mortality in the long term for these patients compared with untreated patients and patients on CPAP.[97,98] These studies were, however, not randomized controlled trials, and surgically treated patients were younger and had less comorbidity than those treated with CPAP.

This systematic review included only randomized, controlled trials of medium and high quality regarding the efficacy of surgery. The lack of evidence of benefits of surgery is in agreement with a Cochrane review[11] and recent reviews by Elshaug et al.[12,14] Only a few randomized controlled trials were, however, available, even though surgery for obstructive sleep apnea was introduced more than 25 years ago. To evaluate adverse effects, we included observational studies of medium and high qual-

ity in accordance with the GRADE working group.[99] When attempting to estimate the risk of side-effects, sources other than randomized trials have to be searched, since randomized controlled trials are seldom designed to evaluate the risk of side-effects. Observational studies may provide better evidence of rare adverse effects and well-designed case series in particular may provide high-quality evidence of the complication rates for surgery.[99] These are the main reasons why different inclusion criteria were used for studies of efficacy and studies of side-effects. With the present design, it was found that the evidence of harm was greater than the evidence of benefits in relation to surgery on the soft palate involving the removal of the uvula, i.e., uvulopalatopharyngoplasty and uvulopalatoplasty.

In conclusion, only a small number of randomized controlled trials with a limited number of patients assessing some surgical modalities for snoring or sleep apnea are available. These studies do not provide any evidence of effect from laser-assisted uvulopalatoplasty or radiofrequency ablation on daytime sleepiness, apnea reduction, quality of life or snoring. We call for research of randomized controlled trials of surgery other than uvulopalatopharyngoplasty and uvulopalatoplasty, as they are related to a high risk of long-term side-effects, especially difficulty swallowing.

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DISCLOSURE STATEMENT

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REFERENCES

1. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667-89.
2. Whitney CW, Enright PL, Newman AB, Bonekat W, Foley D, Quan SF. Correlates of daytime sleepiness in 4578 elderly persons: the Cardiovascular Health Study. Sleep 1998;21:27-36.
3. Zielinski J, Zgierska A, Polakowska M, et al. Snoring and excessive daytime somnolence among Polish middle-aged adults. Eur Respir J 1999;14:946-50.
4. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005;353:2034-41.
5. Sahlin C, Sandberg O, Gustafson Y, et al. Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up. Arch Intern Med 2008;168:297-301.
6. Valham F, Mooe T, Rabben T, Stenlund H, Wiklund U, Franklin KA. Increased risk of stroke in patients with coronary artery disease and sleep apnea: a 10-year follow-up. Circulation 2008;118:955-60.
7. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008;31:1071-8.
8. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. Sleep 2008;31:1079-85.
9. Fujita S, Conway W, Zorick F, Roth T. Surgical correction of anatomic azbnormalities in obstructive sleep apnea syndrome: uvulopalatopharyngoplasty. Otolaryngol Head Neck Surg 1981;89:923-34.
10. Littner M, Kushida CA, Hartse K, et al. Practice parameters for the use of laser-assisted uvulopalatoplasty: an update for 2000. Sleep 2001;24:603-19.
11. Sundaram S, Bridgman SA, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea. Cochrane Database Syst Rev. 2005:CD001004.
12. Elshaug AG, Moss JR, Southcott AM, Hiller JE. Redefining success in airway surgery for obstructive sleep apnea: a meta analysis and synthesis of the evidence. Sleep 2007;30:461-7.
13. SBU. Obstructive sleep apnoea syndrome. Report of a joint Nordic project. Stockholm: Statens beredning för medicinsk utvärdering (SBU) 2007.
14. Elshaug AG, Moss JR, Hiller JE, Maddern GJ. Upper airway surgery should not be first line treatment for obstructive sleep apnoea in adults. BMJ 2008;336:44-5.
15. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled clinical trials 1996;17:1-12.
16. Lojander J, Maasilta P, Partinen M, Brander PE, Salmi T, Lehtonen H. Nasal-CPAP, surgery, and conservative management for treatment of obstructive sleep apnea syndrome. A randomized study. Chest 1996;110:114-9.
17. Ferguson KA, Heighway K, Ruby RR. A randomized trial of laser-assisted uvulopalatoplasty in the treatment of mild obstructive sleep apnea. Am J Respir Crit Care Med 2003;167:15-9.
18. Woodson BT, Steward DL, Weaver EM, Javaheri S. A randomized trial of temperature-controlled radiofrequency, continuous positive airway pressure, and placebo for obstructive sleep apnea syndrome. Otolaryngol Head Neck Surg 2003;128:848-61.
19. Larrosa F, Hernandez L, Morello A, Ballester E, Quinto L, Montserrat JM. Laser-assisted uvulopalatoplasty for snoring: does it meet the expectations? Eur Respir J 2004;24:66-70.
20. Stuck BA, Sauter A, Hormann K, Verse T, Maurer JT. Radiofrequency surgery of the soft palate in the treatment of snoring. A placebo-controlled trial. Sleep 2005;28:847-50.
21. Kezirian EJ, Weaver EM, Yueh B, et al. Incidence of serious complications after uvulopalatopharyngoplasty. Laryngoscope. 2004;114:450-3.
22. Jaghagen EL, Berggren D, Dahlqvist A, Isberg A. Prediction and risk of dysphagia after uvulopalatopharyngoplasty and uvulopalatoplasty. Acta Otolaryngol. 2004;124:1197-203.
23. Esclamado RM, Glenn MG, McCulloch TM, Cummings CW. Perioperative complications and risk factors in the surgical treatment of obstructive sleep apnea syndrome. Laryngoscope. 1989;99:1125-9.
24. Harmon JD, Morgan W, Chaudhary B. Sleep apnea: morbidity and mortality of surgical treatment. South Med J. 1989;82:161-4.
25. Walker RP, Gopalsami C. Laser-assisted uvulopalatoplasty: postoperative complications. Laryngoscope. 1996;106:834-8.
26. Riley RW, Powell NB, Guilleminault C, Pelayo R, Troell RJ, Li KK. Obstructive sleep apnea surgery: risk management and complications. Otolaryngol Head Neck Surg 1997;117:648-52.
27. Mickelson SA, Hakim I. Is postoperative intensive care monitoring necessary after uvulopalatopharyngoplasty? Otolaryngol Head Neck Surg. 1998;119:352-6.
28. Terris DJ, Fincher EF, Hanasono MM, Fee WE, Jr., Adachi K. Conservation of resources: indications for intensive care monitor-

ing after upper airway surgery on patients with obstructive sleep apnea. Laryngoscope. 1998;108:784-8.
29. Hultcrantz E, Johansson K, Bengtson H. The effect of uvulopalatopharyngoplasty without tonsillectomy using local anaesthesia: a prospective long-term follow-up. J Laryngol Otol 1999;113:542-7.
30. Levring-Jäghagen E, Nilsson ME, Isberg A. Persisting dysphagia after uvulopalatoplasty performed with steel scalpel. Laryngoscope 1999;109:86-90.
31. Powell NB, Riley RW, Guilleminault C. Radiofrequency tongue base reduction in sleep-disordered breathing: A pilot study. Otolaryngol Head Neck Surg 1999;120:656-64.
32. Remacle M, Betsch C, Lawson G, Jamart J, Eloy P. A new technique for laser-assisted uvulopalatoplasty: decision-tree analysis and results. Laryngoscope 1999;109:763-8.
33. Boudewyns A, Van De Heyning P. Temperature-controlled radiofrequency tissue volume reduction of the soft palate (somnoplasty) in the treatment of habitual snoring: results of a European multicenter trial. Acta Otolaryngol 2000;120:981-5.
34. Coleman SC, Smith TL. Midline radiofrequency tissue reduction of the palate for bothersome snoring and sleep-disordered breathing: A clinical trial. Otolaryngol Head Neck Surg 2000;122:387-94.
35. Grøntved AM, Karup P. Complaints and satisfaction after uvulopalatopharyngoplasty. Acta Oto-laryngologica 2000;543:190-2.
36. Hagert B, Wikblad K, Odkvist L, Wahren LK. Side effects after surgical treatment of snoring. ORL J Otorhinolaryngol Relat Spec 2000;62:76-80.
37. Hukins CA, Mitchell IC, Hillman DR. Radiofrequency tissue volume reduction of the soft palate in simple snoring. Arch Otolaryngol Head Neck Surg 2000;126:602-6.
38. Li KK, Powell NB, Riley RW, Troell RJ, Guilleminault C. Radiofrequency volumetric reduction of the palate: An extended follow-up study. Otolaryngol Head Neck Surg 2000;122:410-4.
39. Osman EZ, Osborne JE, Hill PD, Lee BW, Hammad Z. Uvulopalatopharyngoplasty versus laser assisted uvulopalatoplasty for the treatment of snoring: an objective randomised clinical trial. Clin Otolaryngol Allied Sci 2000;25:305-10.
40. Back L, Palomaki M, Piilonen A, Ylikoski J. Sleep-disordered breathing: radiofrequency thermal ablation is a promising new treatment possibility. Laryngoscope 2001;111:464-71.
41. Brown DJ, Kerr P, Kryger M. Radiofrequency tissue reduction of the palate in patients with moderate sleep-disordered breathing. J Otolaryngol 2001;30:193-8.
42. Pazos G, Mair EA. Complications of radiofrequency ablation in the treatment of sleep-disordered breathing. Otolaryngol Head Neck Surg 2001;125:462-6; discussion 6-7.
43. Sher AE, Flexon PB, Hillman D, et al. Temperature-controlled radiofrequency tissue volume reduction in the human soft palate. Otolaryngol Head Neck Surg 2001;125:312-8.
44. Stuck BA, Maurer JT, Verse T, Hormann K. Tongue base reduction with temperature-controlled radiofrequency volumetric tissue reduction for treatment of obstructive sleep apnea syndrome. Acta Otolaryngol 2002;122:531-6.
45. Terris DJ, Chen V. Occult mucosal injuries with radiofrequency ablation of the palate. Otolaryngol Head Neck Surg 2001;125:468-72.
46. Woodson BT, Nelson L, Mickelson S, Huntley T, Sher A. A multiinstitutional study of radiofrequency volumetric tissue reduction for OSAS. Otolaryngol Head Neck Surg 2001;125:303-11.
47. Haraldsson PO, Karling J, Lysdahl M, Svanborg E. Voice quality after radiofrequency volumetric tissue reduction of the soft palate in habitual snorers. Laryngoscope 2002;112:1260-3.
48. Lysdahl M, Haraldsson PO. Uvulopalatopharyngoplasty versus laser uvulopalatoplasty: prospective long-term follow-up of self-reported symptoms. Acta Otolaryngol 2002;122:752-7.
49. Berger G, Stein G, Ophir D, Finkelstein Y. Is there a better way to do laser-assisted uvulopalatoplasty? Arch Otolaryngol Head Neck Surg 2003;129:447-53.
50. Rombaux P, Hamoir M, Bertrand B, Aubert G, Liistro G, Rodenstein D. Postoperative pain and side effects after uvulopalatopharyngoplasty, laser-assisted uvulopalatoplasty, and radiofrequency tissue volume reduction in primary snoring. Laryngoscope 2003;113:2169-73.
51. Said B, Strome M. Long-term results of radiofrequency volumetric tissue reduction of the palate for snoring. Ann Otol Rhinol Laryngol 2003;112:276-9.
52. Kim JA, Lee JJ, Jung HH. Predictive factors of immediate postoperative complications after uvulopalatopharyngoplasty. Laryngoscope 2005;115:1837-40.
53. Pavelec V, Polenik P. Use of Er,Cr:YSGG versus standard lasers in laser assisted uvulopalatoplasty for treatment of snoring. Laryngoscope 2006;116:1512-6.
54. Li HY, Lee LA, Wang PC, et al. Taste disturbance after uvulopalatopharyngoplasty for obstructive sleep apnea. Otolaryngol Head Neck Surg 2006;134:985-90.
55. Katsantonis GP, Friedman WH, Krebs FJ 3rd, Walsh JK. Nasopharyngeal complications following uvulopalatopharyngoplasty. Laryngoscope 1987;97:309-14.
56. Croft CB, Golding-Wood DG. Uses and complications of uvulopalatopharyngoplasty. The J Laryngol Otol 1990;104:871-5.
57. Fairbanks DN. Uvulopalatopharyngoplasty complications and avoidance strategies. Otolaryngol Head Neck Surg 1990;102:239-45.
58. Carenfelt C, Haraldsson PO. Frequency of complications after uvulopalatopharyngoplasty. Lancet 1993;341:437.
59. Stepnick DW. Management of total nasopharyngeal stenosis following UPPP. Ear Nose Throat J 1993;72:86-90.
60. Haavisto L, Suonpaa J. Complications of uvulopalatopharyngoplasty. Clin Otolaryngol Allied Sci 1994;19:243-7.
61. Jackson IT, Kenedy D. Surgical management of velopharyngeal insufficiency following uvulopalatopharyngoplasty: report of three cases. Plast Reconstr Surg 1997;99:1151-3.
62. Lee WC, Skinner DW, Prichard AJ. Complications of palatoplasty for snoring or sleep apnoea. J Laryngol Otol 1997;111:1151-4.
63. Coleman JA, Jr. Laser-assisted uvulopalatoplasty: long-term results with a treatment for snoring. Ear Nose Throat J 1998;77:22-4, 6-9, 32-4.
64. Isberg A, Levring-Jäghagen E, Dahlström M, Dahlqvist Å. Persistent dysphagia after laser uvulopalatoplasty: a videoradiographic study of pharyngeal function. Acta Otolaryngol 1998;118:870-4.
65. O'Reilly BF, Simpson DC. A comparison of conservative, radical and laser palatal surgery for snoring. J R Coll Surg Edinb 1998;43:194-5.
66. Pinczower EF. Globus sensation after laser-assisted uvulopalatoplasty. Am J Otolaryngol 1998;19:107-8.
67. Powell NB, Riley RW, Troell RJ, Li K, Blumen MB, Guilleminault C. Radiofrequency volumetric tissue reduction of the palate in subjects with sleep-disordered breathing. Chest 1998;113:1163-74.
68. Tytherleigh MG, Thomas MA, Connolly AA, Bridger MW. Patients' and partners' perceptions of uvulopalatopharyngoplasty for snoring. J Otolaryngol 1999;28:73-5.
69. Tegelberg Å, Wilhelmsson B, Walker-Engström ML, et al. Effects and adverse events of a dental appliance for treatment of obstructive sleep apnoea. Swed Dent J 1999;23:117-26.
70. Andsberg U, Jessen M. Eight years of follow-up--uvulopalatopharyngoplasty combined with midline glossectomy as a treatment for obstructive sleep apnoea syndrome. Acta Oto-laryngologica 2000;543:175-8.

71. Emery BE, Flexon PB. Radiofrequency volumetric tissue reduction of the soft palate: a new treatment for snoring. Laryngoscope 2000;110:1092-8.
72. Ferguson M, Smith TL, Zanation AM, Yarbrough WG. Radiofrequency tissue volume reduction: multilesion vs single-lesion treatments for snoring. Arch Otolaryngol Head Neck Surg 2001;127:1113-8.
73. Blumen MB, Dahan S, Fleury B, Hausser-Hauw C, Chabolle F. Radiofrequency ablation for the treatment of mild to moderate obstructive sleep apnea. Laryngoscope 2002;112:2086-92.
74. Finkelstein Y, Stein G, Ophir D, Berger R, Berger G. Laser-assisted uvulopalatoplasty for the management of obstructive sleep apnea: myths and facts. Arch Otolaryngol Head Neck Surg 2002;128:429-34.
75. Walker-Engstrom ML, Tegelberg A, Wilhelmsson B, Ringqvist I. 4-year follow-up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea: a randomized study. Chest 2002;121:739-46.
76. Fischer Y, Khan M, Mann WJ. Multilevel temperature-controlled radiofrequency therapy of soft palate, base of tongue, and tonsils in adults with obstructive sleep apnea. Laryngoscope 2003;113:1786-91.
77. Gessler EM, Bondy PC. Respiratory complications following tonsillectomy/UPPP: is step-down monitoring necessary? Ear Nose Throat J 2003;82:628-32.
78. Isono S, Shimada A, Tanaka A, Ishikawa T, Nishino T, Konno A. Effects of uvulopalatopharyngoplasty on collapsibility of the retropalatal airway in patients with obstructive sleep apnea. Laryngoscope 2003;113:362-7.
79. Li HY, Li KK, Chen NH, Wang PC. Modified uvulopalatopharyngoplasty: The extended uvulopalatal flap. Am J Otolaryngol 2003;24:311-6.
80. Riley RW, Powell NB, Li KK, Weaver EM, Guilleminault C. An adjunctive method of radiofrequency volumetric tissue reduction of the tongue for OSAS. Otolaryngol Head Neck Surg 2003;129:37-42.
81. Stuck BA, Starzak K, Verse T, Hormann K, Maurer JT. Complications of temperature-controlled radiofrequency volumetric tissue reduction for sleep-disordered breathing. Acta Otolaryngol 2003;123:532-5.
82. Tatla T, Sandhu G, Croft CB, Kotecha B. Celon radiofrequency thermo-ablative palatoplasty for snoring - a pilot study. J Laryngol Otol 2003;117:801-6.
83. Kamel UF. Hypogeusia as a complication of uvulopalatopharyngoplasty and use of taste strips as a practical tool for quantifying hypogeusia. Acta Otolaryngol 2004;124:1235-6.
84. Kania RE, Schmitt E, Petelle B, Meyer B. Radiofrequency soft palate procedure in snoring: influence of energy delivered. Otolaryngol Head Neck Surg 2004;130:67-72.
85. Kieff DA, Busaba NY. Same-day discharge for selected patients undergoing combined nasal and palatal surgery for obstructive sleep apnea. Ann Otol Rhinol Laryngol 2004;113:128-31.
86. Madani M. Complications of laser-assisted uvulopalatopharyngoplasty (LA-UPPP) and radiofrequency treatments of snoring and chronic nasal congestion: a 10-year review of 5,600 patients. J Oral Maxillofac Surg 2004;62:1351-62.
87. Uppal S, Nadig S, Jones C, Nicolaides AR, Coatesworth AP. A prospective single-blind randomized-controlled trial comparing two surgical techniques for the treatment of snoring: laser palatoplasty versus uvulectomy with punctate palatal diathermy. Clin Otolaryngol Allied Sci 2004;29:254-63.
88. Jones LM, Guillory VL, Mair EA. Total nasopharyngeal stenosis: treatment with laser excision, nasopharyngeal obturators, and topical mitomycin-c. Otolaryngol Head Neck Surg 2005;133:795-8.
89. Kezirian EJ, Powell NB, Riley RW, Hester JE. Incidence of complications in radiofrequency treatment of the upper airway. Laryngoscope 2005;115:1298-304.
90. Spiegel JH, Raval TH. Overnight hospital stay is not always necessary after uvulopalatopharyngoplasty. Laryngoscope 2005;115:167-71.
91. Hathaway B, Johnson JT. Safety of uvulopalatopharyngoplasty as outpatient surgery. Otolaryngol Head Neck Surg 2006;134:542-4.
92. Herzog M, Schmidt A, Metz T, et al. Pseudoaneurysm of the lingual artery after temperature-controlled radiofrequency tongue base reduction: a severe complication. Laryngoscope 2006;116:665-7.
93. Iyngkaran T, Kanagalingam J, Rajeswaran R, Georgalas C, Kotecha B. Long-term outcomes of laser-assisted uvulopalatoplasty in 168 patients with snoring. J Laryngol Otol 2006;120:932-8.
94. Pang KP. Identifying patients who need close monitoring during and after upper airway surgery for obstructive sleep apnoea. J Laryngol Otol 2006;120:655-60.
95. Roosli C, Schneider S, Hausler R. Long-term results and complications following uvulopalatopharyngoplasty in 116 consecutive patients. Eur Arch Otorhinolaryngol 2006;263:754-8.
96. Dahlqvist J, Dahlqvist A, Marklund M, Berggren D, Stenlund H, Franklin KA. Physical findings in the upper airways related to obstructive sleep apnea in men and women. Acta Otolaryngol 2007;127:623-30.
97. Marti S, Sampol G, Munoz X, et al. Mortality in severe sleep apnoea/hypopnoea syndrome patients: impact of treatment. Eur Respir J 2002;20:1511-8.
98. Weaver EM, Maynard C, Yueh B. Survival of veterans with sleep apnea: continuous positive airway pressure versus surgery. Otolaryngol Head Neck Surg 2004;130:659-65.
99. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ Clinical research ed 2004;328:1490.