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SKUP³: 6 and 24 Months Follow-up of Changes in Respiration and Sleepiness After Modified UPPP

Nanna Browaldh, MD, PhD ; Johan Bring; Danielle Friberg, MD, PhD

Objective: Our previous randomized controlled trial of patients with obstructive sleep apnea syndrome (OSAS) showed that modified uvulopalatopharyngoplasty (UPPP), including tonsillectomy, significantly improved nocturnal respiration, daytime sleepiness, and quality of life in the intervention group compared to controls who had delayed surgery after 6 months. This is the continuous report with the 6- and 24-month postoperative results.

Study Design: Single-center prospective cohort study.

Methods: Sixty-five patients with apnea-hypopnea index (AHI) ≥ 15 , body mass index (BMI) < 36 , Epworth Sleepiness Scale (ESS) ≥ 8 , and Friedman stage I or II underwent UPPP after failing nonsurgical treatment. The results from polysomnography and ESS at 6 and 24 months were compared to baseline.

Results: Eight percent and 20% dropped out from the 6- and 24-month follow-ups, respectively. The AHI value decreased significantly from mean (standard deviation) 52.9 (20.5) at baseline to 23.6 (20.2) after 6 months, and to 24.1 (20.9) after 24 months ($P < 0.001$). Patients with tonsil size 2, and 3 to 4, had significant reductions in the AHI after both follow-ups. The median ESS score decreased significantly from 13 (range 8–21) to 6.5 (1–18) after 6 months, and to 5 (2–17) after 24 months ($P < 0.001$). The BMI remained unchanged. There were significant modest correlations for the reductions in AHI and ESS after 24 months.

Conclusion: Modified UPPP was effective in improving nocturnal respiration and daytime sleepiness in OSAS patients at both 6- and 24-month follow-up. Patients with tonsil size 2, and 3 to 4, benefitted similarly from surgery with improved respiration.

Key Words: Obstructive sleep apnea syndrome, Epworth sleepiness scale, uvulopalatopharyngoplasty, daytime sleepiness.

Level of Evidence: 2b.

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INTRODUCTION

The prevalence of moderate to severe obstructive sleep apnea syndrome (OSAS) in adults has been estimated to be 49.7% in males and 23.4% in females.¹ OSAS is a general health problem that causes daytime sleepiness and impaired quality of life,² as well as increased morbidity and mortality.^{3–5} Patients with OSAS can be treated with nonsurgical alternatives, but up to 56% to 68% of patients do not accept or adhere to continuous positive airway pressure (CPAP) and/or mandibular retaining device (MRD) treatment after 4 to 5 years.^{6,7}

Uvulopalatopharyngoplasty (UPPP) was the predominant treatment for OSAS before CPAP was

generally available, but different surgical techniques and multilevel procedures have been used over the years, making it difficult to compare their effectiveness in treating OSAS. There has been a question about insufficient scientific evidence concerning the long-term efficacy of UPPP.

The main anatomical obstructive sites in OSAS are retropalatal, retroglossal, and hypopharyngeal—or a combination of multiple sites. Friedman et al. found in a nonrandomized study that their staging system based on palate position, tonsil size, and body mass index (BMI) predicted a positive treatment effect of UPPP.^{8,9} At the study start in 2007, the Friedman staging system was the predominant technique used for selection of OSAS patients for surgical treatment.

In our previous Sleep apnea Karolinska UPPP (SKUP³) randomized controlled trial (RCT), we used the Friedman staging system and found a highly significant and clinically relevant difference in respiratory disturbances, daytime sleepiness, and quality of life in favor of UPPP compared to controls (delayed surgery).^{2,10} Few studies have investigated the effect of UPPP from a long-term perspective. In the study by Janson et al.,¹¹ 48% of the 34 patients were responders to UPPP 4 to 8 years after treatment, and a low preoperative apnea hypopnea index (AHI) was a success factor. A 15-year follow-up of 50 OSAS patients after UPPP by our group

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Fig. 1. Flow of participants. Single center (June 2007–May 2011). Patients from the second center (n = 4) who deviated from the study protocol were excluded in the per protocol analysis but included in the intention-to-treat analyses. ESS = Epworth Sleepiness Scale; PSG = polysomnography; UPPP = uvulopalatopharyngoplasty. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

showed a stable and significant decrease in oxygen desaturation index (ODI), and 65% of the patients had a postoperative ODI < 20 and a 50% reduction.¹² The aim of the present study was to investigate the results from polysomnography after 6 and 24 months from all 65 operated patients in the SKUP³ cohort, to evaluate whether their results were stable, and to determine whether there were any success factors that could help to refine the assessment concerning to which OSAS patients we should offer UPPP surgery.

MATERIALS AND METHODS

This is the continuous report, with 6- and 24-month follow-up results in patients who were randomized to receive either modified UPPP within 1 month (intervention group, n = 32) or no treatment at all for 7 months (control group, n = 33). The patients in the control group received delayed surgery after 6 months. In the present study, we have analyzed the postoperative results for all 65 patients together 6 and 24 months after UPPP. The patients underwent several full-night in-lab polysomnography (PSG) procedures and filled out the Epworth Sleepiness Scale (ESS) questionnaires (Fig. 1).

The single-center prospective study has been presented in detail previously¹⁰ and briefly is described below.

Participants

All OSAS patients referred to the Oto-Rhino-Laryngology (ORL) Department at Karolinska University Hospital in Huddinge, Stockholm, Sweden, from June 2007 to May 2011 for UPPP were eligible candidates for the study. The inclusion criteria were: 1) males and females > 18 years of age; 2) AHI ≥ 15 events/hour of sleep (from PSG); 3) ESS score ≥ 8; 4) marked

daytime sleepiness three times a week or more; 5) BMI < 36 kg/m²; 6) Friedman stage I or II^{8,9}; and 7) having tried and failed or withholding of CPAP and MRD treatments, and no benefit from these treatments during the last 3 months. According to our clinical routines at study start, patients with Friedman stage I and BMI < 30 kg/m² were not required to have failed CPAP/MRD treatment before inclusion (three patients). Stratified randomization with four strata according to BMI < 30 or ≥ 30.0 and Friedman stage I or II was used.

The exclusion criteria were: 1) serious psychiatric, cardio-pulmonary, or neurological disease, or an American Society of Anesthesiologists (ASA) classification of > 3; 2) patients who declined surgery; 3) insufficient knowledge of Swedish; 4) night-shift workers; 5) patients who could pose a danger in traffic according to responses in our local questionnaire; 6) severe nasal congestion (could be included after corticoid nasal treatment); 7) previous tonsillectomy; 8) Friedman stage III; and 9) severe clinical worsening of OSAS during the study. For baseline characteristics, see Table I.

Intervention

Our method was a modification of the method described by Fujita,¹³ using the cold steel technique for tonsillectomy and minor resections of the soft palate and uvula, with sutures placed to lift up the anterior and posterior pillars.¹⁰ See Figure 2. There were 11 different surgeons, all ORL specialists, using the same technique in the study.

Outcomes

Outcomes were changes in respiratory parameters with polysomnography and subjective sleepiness with ESS questionnaire, 6 and 24 months after modified UPPP.

TABLE I.
Baseline Characteristics.

	Mean	SD	Median	Minimum	Maximum
Age (years)	42.3	11.5	41.4	20.4	64.3
Body mass index (kg/m ²)	28.0	3.1	28.2	21.1	33.8
Apnea-hypopnea index (events/hour sleep)	52.9	20.5	49.4	17.0	99.5
Oxygen desaturation index (events/hour sleep)	42.8	22.7	37.5	5.1	102.0
Nadir of oxygen saturation (%)	80.5	6.0	82.0	63.0	89.3
Epworth Sleepiness Scale	12.7	3.1	13.0	8	21

n = 65.

SD = standard deviation.

Polysomnography

Polysomnography was performed three and four times for the intervention and control groups, respectively: at baseline, pre-UPPP surgery (controls), 6 months after UPPP surgery, and 24 months after UPPP surgery. An in-lab, full-night PSG, using the Embla technology (Flaga Medical; Reykjavik, Iceland) was used, and the measurements were interpreted manually by a blinded single scorer. Sixteen channels were recorded: electroencephalography (sensors C3-A2, O1-A2, O2-A1, C4-A1), electrooculography (left and right), electromyogram chin and tibialis (left and right), oronasal thermistor and flowmetry, transcutaneous oxygen saturation, respiratory

movements (abdomen and thorax), snoring, ECG (electrocardiogram), pulse, and body position. Parameters were defined according to American Academy of Sleep Medicine (AASM) 2007,¹⁴ using criteria B for the hypopnea: at least a 50% flow reduction leading to either a 3% oxygen desaturation or arousal. There were two different certified scorers of the PSG recordings: one scored the baseline and 6-month values for the intervention and control groups; and the other scored the post-operative values for the controls at 6 months and for all at 24 months. Both scorers used the rules according to AASM 2007 criteria B for hypopnea¹⁴ and were blinded to the patients' score of previous recordings.

Fig. 2. Method of uvulopalatopharyngoplasty (1) Marked excision line laterally to the uvula. (2) Excision of the anterior tonsillar pillar 2 to 3 mm, and the mucosa between the pillars. (3) Tonsillectomy with cold steel (Henke). (4) Single sutures (the loop consists of needle and thread) lift up the posterior pillar, together with the palatopharyngeal muscle, to the anterior pillar, and also with suturing of the soft palatal mucosa. (5) Amputation of the uvula, leaving approximately 1 cm. 6. Final result.

TABLE II.
Results From Polysomnography and Epworth Sleepiness Questionnaire at Baseline, Preoperative (Controls), 6-Month, and 24-Month Follow-Ups.

	Baseline		Preoperative (controls)		Postoperative 6 Months		Postoperative 24 Months		Comparison Between Baseline and 6 Months <i>P</i>	Comparison Between Baseline and 24 Months <i>P</i>	Comparison Between 6 and 24 Months <i>P</i>
	n		n		n		n				
Apnea-hypopnea index (events/hour sleep)	65	52.9 (20.5)	33	46.8 (22.8)	60	23.6 (20.2)	52	24.1 (20.9)	< 0.001	< 0.001	0.810
Oxygen desaturation index (events/hour sleep)	65	42.8 (22.7)	33	35.6 (21.3)	60	16.0 (16.4)	51	18.0 (17.4)	< 0.001	< 0.001	0.178
Nadir of oxygen saturation (%)	65	80.5 (6.0)	33	82.1 (5.7)	60	85.3 (4.8)	51	84.0 (7.0)	< 0.001	< 0.001	0.307
Epworth Sleepiness Scale	65	13.0 (8–21)	33	12 (5–21)	60	6.5 (1–18)	50	5 (2–17)	< 0.001	< 0.001	0.358

The above data are the mean (standard deviation) for polysomnography data and median (minimum–maximum) for ESS. *P* values from the paired *t* test for AHI, ODI, and nadir of oxygen saturation and Wilcoxon signed-rank test for ESS for within-group comparisons.

Significant differences, *P* < 0.05, are shown in bold type.

AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; n = number of patients; ODI = oxygen desaturation index.

Epworth Sleepiness Scale

The ESS is a self-administered eight-item questionnaire pertaining to the tendency to fall asleep in different situations in daily life, and the result is presented in a scale of 0 to 24.¹⁵ The ESS questionnaire was administrated the morning after the PSG recording.

Statistical Analysis

The AHI data is presented as mean and standard deviation, and the ESS as median and range. Parametric statistical analyses were chosen for the analyses for AHI, oxygen desaturation index (ODI), and nadir oxygen saturation. Nonparametric statistical analyses were used for analyses of tonsil size, Friedman stage, and ESS: *P* values from the Wilcoxon signed-rank test for within-group comparisons, and Mann Whitney U for between-group comparisons. Correlation tests between changes in AHI and ESS after 6 and 24 months compared to baseline were performed with the Spearman correlation test. *P* < 0.05 was considered significant.

Success factors were tested for age, gender, BMI, AHI, tonsil size, Friedman stage, tongue position, percentage of sleep in supine position, and surgeon with regression analysis.

Sensitivity analyses were performed for all 71 included patients, as well as for the six excluded patients (Fig. 1). The missing variables were imputed to “no change from baseline” or “no change from follow-up.” In the six excluded patients with missing values at both baseline and follow-up, the median values for the subscale score for the group were used.

Due to the nature of the Wilcoxon signed-rank test, only patients with complete ESS data (baseline and follow-up) were included in the within-group comparisons for *P* values in Table II.

All statistical calculations were performed using Statistica 10.0, and the significance level was determined to be *P* < 0.05.

Ethics

The study was first rejected by the Swedish Regional Ethics Committee, 2007/449-31/3. After an appeal, it was approved by the Central Ethics Committee, Ö21-2007.

RESULTS

Altogether, there were 65 patients included in the study. Because there only were three patients with tonsil size 4, patients with tonsil size 3 and 4 were analyzed together.

Changes in Respiratory Parameters

Five out of 65 patients did not perform the PSG recording at the 6-month postoperative follow-up (8% dropouts). At the 24-month follow-up, there were 13 dropouts (20%).

The mean AHI value decreased significantly from 52.9 (20.5) at baseline to 23.6 (20.2) at the 6-month follow-up, a mean reduction of 55%; and to 24.1 (20.9) at the 24-month follow-up, a mean reduction of 54% (*P* < 0.001) (Fig. 3). The ODI and nadir values followed the same pattern as the AHI (Table II). The mean reduction of ODI was 63% at the 6-month follow-up, and 58% at the 24-month follow-up (Table II).

The success rate defined as an AHI reduction of > 50%, and a postoperative value of AHI < 20.0 was 15 of 24 (62.5%) at the 6-month follow-up, and 13 of 23 (56.5%) at the 24-month follow-up for Friedman stage I. For Friedman stage II, the corresponding values were 16 of 36 (44.4%) and 13 of 29 (44.8%). When comparing Friedman stages I and II, the AHI results at 6- and 24-month follow-up showed no statistically significant difference, *P* = 0.341 and *P* = 0.559, respectively. For Friedman stage I and II analyzed together, the success rate was 31 of 60 (52%) at the 6-month follow-up and 26 of 52 (50%) at the 24-month follow-up.

The AHI for the patients with tonsil size 1 was non-significantly decreased from mean 47.1 (SD 18.4) at baseline (n = 11) to 39.8 (26.1) at 6-month follow-up (n = 11), and to 27.8 (22.4) at the 24-month follow-up (n = 9), *P* = 0.213 and *P* = 0.086, respectively. For the patients with tonsil size 2 (n = 19), the AHI was

Fig. 3. Results from the AHI score with box plots (median, 25% and 75%), bars (10% and 90%), and outliers at baseline (all), at 6 months for controls, and for all operated on after 6 and 24 months.

AHI = apnea-hypopnea index; m = months; n = number of patients in each group; preop = preoperative; postop = postoperative.

significantly decreased from 51.5 (20.8) at baseline (n = 19) to 17.4 (14.0) at the 6-month follow-up (n = 19), and to 21.2 (18.5) at the 24-month follow-up (n = 15), $P < 0.001$ and $P = 0.002$, respectively. Patients with tonsil size 3 to 4 had a significant decrease in AHI from 55.6 (21.1) at baseline (n = 35) to 21.6 (18.5) at the 6-month follow-up (n = 30), and to 24.5 (22.0) at the 24-month follow-up (n = 28), $P < 0.001$ and $P < 0.001$, respectively (Fig. 4).

Changes in the Epworth Sleepiness Scale

There were five dropouts from the ESS questionnaire at the 6-month follow-up (8%). At the 24-month follow-up, there were 15 dropouts (23%).

The median ESS score had significantly decreased from 13 (range 8–21) to 6.5 (1–18) ($P < 0.001$), a mean reduction of 50% at the 6-month follow-up, and to 5 (2–17) at the 24-month follow-up, a mean reduction of 62% ($P < 0.001$). See Figure 5.

Success Factors

The test of success factors for percentage decrease in AHI from baseline after 6 months was only significant according to tonsil size. Compared to tonsil size 1, the AHI value for patients with tonsil size 2 decreased by 45% ($P < 0.001$). The corresponding value for patients with tonsil size 3 to 4 was a decrease of 43% ($P < 0.001$). The other factors (age, gender, BMI, AHI, Friedman stage, tongue position, percentage of sleep in supine position, and surgeon) did not show any significant difference according to percentage decrease in AHI. The BMI remained stable during the 24 months; the mean and standard deviation of the BMI at baseline was 28.0 (3.1.), after 6 months was 27.9 (3.3), and after 24 months

Fig. 4. Results from the AHI score with box plots (median, 25% and 75%), bars (10% and 90%), and outliers at baseline, after 6 and 24 months postoperatively for patients with tonsil size 1, 2 and 3 to 4.

AHI = apnea-hypopnea index; m = months; n = number of patients in each group.

was 28.0 (3.4). Also, the percentage of sleep in supine position remained stable, with the mean and standard deviation of 39.7 (24.9) at baseline, 43.0 (26.0) after 6 months, and 38.9 (24.9) after 24 months.

Correlation Analysis

There were no significant correlations in changes after 6 months between AHI, ODI, and nadir compared to ESS. However, there were significant correlations in changes after 24 months in AHI and ODI compared to

Fig. 5. Results from the ESS score with box plots (median, 25% and 75%), bars (10% and 90%), and outliers at baseline (all), at 6 months for controls, and for all operated on after 6 and 24 months.

ESS = Epworth Sleepiness Scale; n = number of patients in each group.

ESS, $r = 0.39$ and $r = 0.38$, $P = 0.005$ and $P = 0.007$, respectively.

Sensitivity Analysis

The sensitivity analysis for all 71 randomized patients did not change the results presented in Table II. Also, both parametric and nonparametric tests for all variables showed no difference in significance.

DISCUSSION

This SKUP³ follow-up study showed that both nocturnal respiration and excessive daytime sleepiness improved significantly 6 months after UPPP, and that the results were stable at the 24-month follow-up. Patients with tonsil size 2, and 3 to 4, had a similarly significant effect in terms of AHI value compared to patients with tonsil size 1. These patients also had a decrease after 24 months, but no conclusions can be drawn because they were few in number ($n = 9$).

The mean reduction of AHI was stable over time, 55% after 6 months and 54% after 24 months, which is higher than the mean AHI reduction of 33% in the meta-analysis of 15 UPPP studies from 2010.¹⁶ The corresponding values for ODI values in the present study were 63% and 58%, which are comparable with the results from a previous study of 158 patients from our group, with a mean reduction in ODI of 60% 1 year after UPPP,¹⁷ and of 52% at a 15-year follow-up of another cohort.¹² Thus, the results from three different patient cohorts undergoing UPPP at our department may be considered modest but consistent and long-lasting. This could be an effect of the surgical technique and selection criteria.

Regardless of Friedman stage I or II, the patients in the present study benefitted from the UPPP, but the AHI improvement only was slightly superior for Friedman stage I, with a 62% to 56% success rate compared to 44% for stage II. This is a lower difference between stages than in Friedman's original study from 2002 of 134 patients,⁸ which showed an 80% success rate in stage I and 38% in stage II. There are several explanations for this difference, one of which could be that the Friedman staging system is difficult to perform in clinical use and may differ between colleagues recruiting patients for this study. Other explanations are that there were only 65 patients in our study, and that the Friedman system does not evaluate other anatomical factors, for example, epiglottitis obstruction. It would be desirable to have a more refined system to select OSAS patients for UPPP. Drug-induced sleep endoscopy (DISE) could be used to evaluate the upper airway obstruction sites. DISE was used in the study by Raveslout et al.,¹⁸ who found that multilevel, complete, or tongue-base collapse all were associated with a higher AHI value before surgery. In the retrospective study by Koutsourelakis et al.,¹⁹ 49 OSA patients underwent DISE, upper airway surgery, and PSG. Their conclusion was that complete circumferential collapse at the velum or complete anterior-posterior collapses at the tongue base were the only independent predictors of upper airway surgery failure.

However, DISE is much more resource-demanding than the Friedman staging system.

UPPP includes tonsillectomy per definition, and it always is difficult to evaluate a two-stage treatment. Only about 6% of adult OSAS patients have large tonsils, according to the study by Dahlqvist et al.²⁰ Very few studies have evaluated tonsillectomy in adults. In the nonrandomized study by Holmlund et al.,²¹ 28 OSAS patients with tonsil size 3 to 4 were investigated with polygraphy before and 6 months after tonsillectomy. The preoperative AHI was lower than in our study because patients with mild OSAS were also included, and the mean AHI was reduced from 40 to 7. Their ESS was reduced from mean 11 to 6, which is very similar to our results. Also, the study by Verse et al. of nine adult OSAS patients with large tonsils who underwent tonsillectomy showed an 80% success rate of AHI reduction, using the same success criteria as in the present study.²²

However, in the 1-year follow-up from our group of 158 patients who had UPPP surgery by Lundkvist et al.,¹⁷ the success factor was young age and not tonsil size. This is in line with the results from the present study. These studies, together with the meta-analyses by Caples of UPP without tonsillectomy showing a mean AHI reduction of 32%,¹⁶ indicate that the lateralization of the tonsillar pillars and uplifting of the soft palate also improve nocturnal respiration. However, because our study population was small and the study was not designed to analyze success factors as primary outcome, the results have to be interpreted with precaution. More studies, including RCTs comparing tonsillectomy and UPPP, are needed to further clarify the question of which parts of the surgery are necessary in patients with different tonsil size, as well as longer follow-ups.

Although other studies have shown poor correlations between objective and subjective outcomes in OSAS patients after treatment,²³ in the present study there were modest but statistically significant correlations between improvements in respiration and sleepiness at the 24-month follow-up, as also was found after 6 months in the same cohort in our previous RCT.² However, no such correlation was found at the present 6-month follow-up in all operated patients, which could be explained by some outliers. Still, because the results were somewhat divergent, it cannot be excluded that the outcome from the questionnaires may not only be an effect of surgery but also a placebo effect.

Strengths and Weaknesses

The strengths of this study include the prospective design and the investigation of the OSAS patients with in-laboratory PSG. The dropout rate was rather low at both follow-ups, considering the large number of PSG procedures that the patients underwent. Furthermore, our main results were verified by sensitivity analyses. Additionally, both parametric and nonparametric tests for all variables showed no difference in significance.

A limitation of this study is that the PSG recordings were interpreted by two different scorers at baseline

and follow-ups. However, they used the same scoring rules and both were blinded to the patients' previous results. We also used very strict inclusion and exclusion criteria; only six women were included, which make the gender generalizability low. Further, our small study population was slightly younger and had a lower BMI than the general OSAS population. Another weakness is the absence of a control group at the follow-ups, but it would have been unethical to leave the patients untreated for a time longer than 6 months. Patients with residual OSAS after 24-month follow-up were referred to private sleep apnea clinics for discussion of complimentary treatments according to our clinical routines.

CONCLUSION

Modified UPPP was effective in improving nocturnal respiration and excessive daytime sleepiness. The results strengthen the body of evidence for modified UPPP that could be offered to selected OSAS patients. The results were stable at both the 6- and 24-month follow-ups. Patients with tonsil size 2, and 3 to 4, had a similarly significant effect in terms of respiration; however, larger studies are needed to confirm these results.

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