Proceedings of the 2020 Design of Medical Devices Conference
DMD2020
April 6, 7-9, 2020, Minneapolis, MN, USA

DMD2020-9026

ADHERENCE OF UPPER AIRWAY STIMULATION IN US AND GERMAN MEDICAL CENTERS: A MULTICENTER META-ANALYSIS ON ADHERE REGISTRY

Jingxin Lei[1]
University of Minnesota, Twin Cities,
Minneapolis, MN, US

Kent Lee
Inspire Medical Systems, Inc.
Golden Valley, MN, US

ABSTRACT

Upper airway stimulation (UAS) is shown to be effective with high adherence for patients with moderate to severe obstructive sleep apnea. However, the consistency of adherence among medical sites remains to be verified. This study examines the adherence to UAS among medical sites in an international multicenter registry. A statistically significant adherence decrease between 6-month and 12-month visit was found in the study cohort as well as in most sites. No significant heterogeneity was found among sites with either all patients or only patients who had adherence at both visits recorded. In addition, there is no enough evidence that region and experience of sites influences the adherence. This study indicates that UAS therapy adherence is consistent among sites, regardless of region and experience of sites.

Keywords: UAS, sleep apnea, therapy adherence, meta-analysis

INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent sleep disorder diagnosed as the frequent partial or complete collapse of the upper airway during sleep[1]. Nasal continuous positive airway pressure (CPAP) is a conventional and effective therapy for OSA[2]. However, CPAP is not accepted by many patients due to patient dissatisfaction or poor adherence[3]. Upper airway stimulation (UAS; Inspire Medical systems, Golden Valley, MN, USA) is an alternative surgical option for moderate-to-severe OSA patients with CPAP intolerance. Consisting "an implantable pulse generator, stimulation lead placed on the hypoglossal nerve and respiratory sensing electrode"[4], the effectiveness of UAS has been verified by previous studies[5–7].

Studies have shown that UAS has a higher adherence than CPAP[4], however, the consistency of adherence among different medical sites has shown differing results. Previous research showed that the therapy usage was reported as 6.93 and 6.66 h per night at 6-months visit at two USA centers, but the adherence at the 12-months was 6.25 and 6.85 h per night respectively[8]. For these two sites, the time trend of adherence even had different directions. This can be a signal that the adherence change is inconsistent. In addition, the patient population, medical staff, patient training, and implantation technique might be different among sites. However, no comprehensive analysis of this heterogeneity was conducted to date. Therefore, this paper aims to compare the adherence change at multiple medical centers, as well as understand the reason behind this phenomenon. This study also examines the potential regional effect on the therapy adherence change, namely the difference between the United States and Germany, since different population and healthcare systems may have an impact on the therapy adherence.

1. Methods

1.1 Participants

The ADHERE registry is an international observational registry designed for monitoring the status of patients who have an implanted Inspire UAS device[4]. Patients received the Inspire II (Model 3024) or Inspire IV (Model 3028) Upper Airway Stimulation system. This registry has 32 medical centers in both the US and Europe, which can serve as a perfect platform for multicenter analysis. Patients were followed up to one year after the implantation. Enrolled patients are adults, with a moderate to severe degree of OSA (AHI 15-65 events·h^{-1}), a body mass index (BMI) < 35 kg·m^{-2} and intolerance to CPAP[7], which is defined as an inability or unwillingness to use CPAP[4].

1.2 Site Selection

As of September 2019, the ADHERE registry has 32 medical centers with surgical outcomes available. We selected 11 sites with more than 10 patients with therapy usage at both the 6-month and 12-month visits to reduce the variation of the analysis.

1.3 Adherence Measurements

Therapy usage was objectively measured by downloading the usage data calculated by the implantable pulse generator (IPG) with a programmer at both the 6-month and 12-month visits.

1.4 Statistical Analysis

Both unpaired t-test and paired t-test were conducted between therapy adherence measured at 6-month and 12-month visit. We matched the adherence at 6-month and 12-month visits

[1] Contact author: lei00011@umn.edu

for each patient to construct the paired data. Meta-analysis is designed for comparing and summarizing results of case-control studies from multiple resources[9], which performs well with more than 10 resources. Therefore, in this paper, a meta-analysis of therapy adherence was conducted with all available data as well as patient with data from both 6-month and 12-month visits. Most of the time, the meta-analysis compares the treatment effects in different publications. In this study, the therapy adherence at the 12-month visit was treated as the experimental group while the adherence at the 6-month visit at each site serves as its control, which can represent the effect of time after titration. Both fixed effect model and random effect model are used and compared, since the fixed effect model is more powerful if the assumption that all the observations came from the same population is met, and the random effect model is more realistic. The adherence changes are measured by the differences between average adherences at 6-month visit and 12-month visit. The tests of heterogeneity were conducted among all sites as well as between two regional subgroups. The null hypothesis for the test of heterogeneity is that the average adherence difference at all sites are the same.

In addition to the standard meta-analysis model, we also considered adding correlation terms as well as pairwise t-tests. These correlation terms represent the correlation between the 6-month observations and 12-month observations within each site. Paired data works better to control the confounders introduced by individual characteristics as well as eliminate patients who have not had their final visits. On the other hand, the completed registry has a larger sample size since both the 6-month and 12-month visit can be missing. Therefore, we take both models into consideration. We also built a meta-analysis model with site-specific correlation terms between 6-month and 12-month adherence as a validation. The addition of site-specific correlation terms can reduce potential bias due to the population heterogeneity among sites but may increase the variance. Pairwise tests like pairwise t-test with correction are also reasonable choices for multiple comparisons, so pairwise t-tests with Hochberg's, Hommel's and Holm's correction were also conducted.

R is used for all statistical analyses (https://www.r-project.org/).

2. Results

Between October 2016 to September 2019, 1018 patients from 32 sites had follow-up data in the study. For this analysis, only 700 patients from the 11 sites were included, because they had at least 10 patients with adherence data at both visits. This cohort population can be described as middle-aged, primarily male (78%) and White (97%), and overweight. The average severity of sleep apnea is "severe" measured by AHI or "mild excessive daytime sleepiness" measured by ESS. (Table 1)

The average therapy usages at both visits were considered adequate (≥ 4 h per night) at all sites regardless of whether the records are paired or not (Table 2 and Table 3). The overall average adherence decreased from 6.37 ± 2.03 hours/night to 5.52 ± 2.17 hours per night, this value was statistically significant (p-value < 0.001). Adherence in each site also decreased, and statistically significant usage decreases were found in 5 of 11 sites with all records (Table 2) and 7 of 11 sites with only paired therapy adherence records (Table 3). This finding is consistent with previous studies. However, previous studies failed to investigate site performance in terms of therapy adherence. Consequently, the focus of this paper is to summarize and compare the adherence among sites via multicenter meta-analysis.

TABLE 1: BASELINE CHARACTERISTICS OF SELECTED REGISTRY PATIENTS

Characteristics	
Subject (N)	700
Age at Consent year (Mean ± SD)	60.3 ± 11.0
Sex (N (%))	
Male	548 (78.3%)
Female	151 (21.6%)
Unknown	1 (0.1%)
Race (N (%))	
White	681 (97.3%)
Other	12 (1.7%)
Unknown	7 (1.0%)
BMI kg·m^{-2} (Mean ± SD)	29.4 ± 4.0
AHI events·h^{-1} (Mean ± SD)	36.5 ± 15.8
ESS (Mean ± SD)	11.7 ± 5.5

TABLE 2: THERAPY ADHERENCE AT 6-MONTH AND 12-MONTH VISIT WITH ALL RECORDS

Sites	6-Month Visit		12-Month Visit		P-values*
	N	Mean ± SD	N	Mean ± SD	
A	18	6.02 ± 2.69	26	6.19 ± 2.04	0.821
B	57	6.43 ± 1.62	42	5.33 ± 2.16	0.007
C	43	6.17 ± 2.09	28	5.52 ± 2.55	0.263
D	114	6.50 ± 1.92	103	5.68 ± 1.83	0.001
E	16	6.12 ± 1.76	15	4.55 ± 2.52	0.056
F	117	6.44 ± 1.91	107	5.50 ± 2.19	<0.001
G	52	6.32 ± 2.47	13	4.91 ± 1.96	0.039
H	61	5.85 ± 2.07	46	4.89 ± 1.97	0.017
I	34	6.73 ± 2.16	21	5.53 ± 2.53	0.080
J	36	6.38 ± 2.05	17	5.32 ± 2.60	0.151
K	61	6.61 ± 2.12	60	6.03 ± 2.31	0.150
Total	609	6.37 ± 2.03	478	5.52 ± 2.17	<0.001

*: P-values were from unpaired t-test

TABLE 3: THERAPY ADHERENCE AT 6-MONTH AND 12-MONTH VISIT WITH PAIRED RECORDS

Sites	N	6-Month Visit	12-Month Visit	P-values**
		Mean ± SD	Mean ± SD	
A	7	5.86 ± 2.70	5.55 ± 2.36	0.731
B	41	6.43 ± 1.54	5.27 ± 2.15	<0.001
C	21	6.22 ± 1.87	5.45 ± 2.70	0.186
D	101	6.43 ± 1.90	5.74 ± 1.80	<0.001
E	9	5.86 ± 1.93	5.14 ± 2.76	0.147
F	106	6.53 ± 1.83	5.51 ± 2.20	<0.001
G	13	5.74 ± 1.88	4.91 ± 1.96	0.027
H	45	6.03 ± 1.88	4.87 ± 1.99	<0.001
I	17	6.89 ± 1.76	5.86 ± 2.36	0.021
J	17	6.42± 1.54	5.32 ± 2.60	0.136
K	48	6.63 ± 1.95	6.02 ± 2.30	0.007
Total	425	6.40 ± 1.85	5.51 ± 2.16	<0.001

**: P-values were from paired t-test

Figure 1 shows the results of meta-analysis with (a) completed data, (b) paired data, and (c) paired data with correlation terms. The mean difference (MD) is the difference of therapy adherence (12-month visit – 6-month visit). The values of estimated average decrease of therapy adherence are significant and similar for the three models (0.90 per night for both model (a) and (b), and 0.85 per night for model (c), p-values < 0.001). The fixed effect models and random effect models give the same estimates because the No significant difference was found among these sites. The p-values of overall heterogeneity tests in all three models were 0.90, 0.99, and 0.99 respectively (based on heterogeneity statistic Q). Other model validations were done via pairwise t-tests with Hochberg's, Hommel's and Holm's correction (adjusted p-values for all pairs of sites are 0.98 or 0.99).

The heterogeneity between Europe and USA subgroups of sites was also checked for model (a) and (b). No significant differences were found between the Europe and USA subgroups as well as within each subgroup (p-values: between subgroups: 0.98, 0.96; within Europe subgroup: 0.94, 0.54; within USA subgroup: 0.69, 0.99).

3. Discussion

This study showed UAS adherence change was consistent among 11 sites and was not affected by region (US or EU) since no significant difference in UAS adherence among sites was found. This finding supports that the standard training programs for implementing UAS in both countries works well, despite of different healthcare systems in the US and Germany.

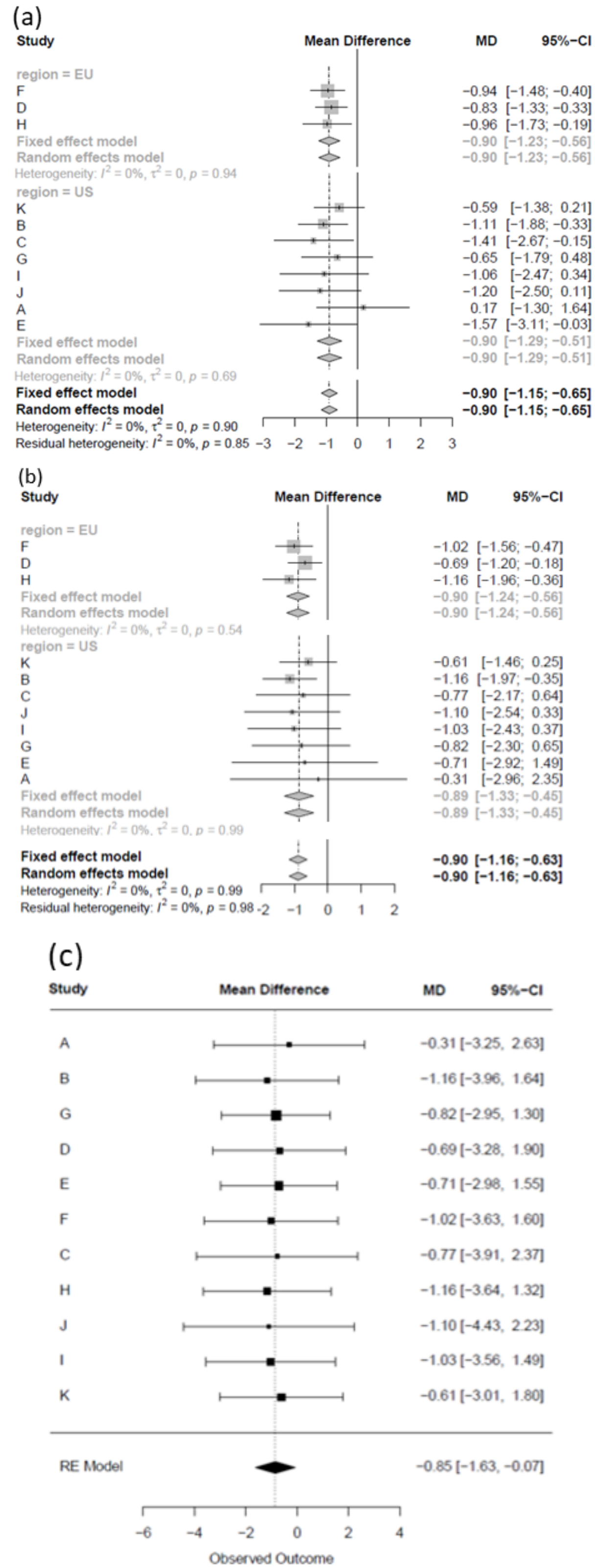

FIGURE 1: META-ANALYSIS FOR ADHERENCE WITH (a) COMPLETED DATA, (b) PAIRED DATA, AND (c) PAIRED DATA WITH CORRELATION TERMS

The average therapy adherence was found significantly decreased from 6.37 to 5.52 hours per night from 6-month to 12-month. The therapy is effective at opening the airway if the patient is using the therapy during sleep. For instance, if a patient sleeps for 7 hours, and his/her adherence decreases from 6.37 to 5.52, it means the device is not active for 0.8 hours/night, and the stimulator is not active in those hours, potentially means the sleep apnea is not treated for these times. Nevertheless, the average UAS usage was adequate (≥ 4 h per night) in all these sites.

Another potential factor that may influence adherence is the experience of the site. We further divided the sites into two subgroups equally based on whether the number of patients received in each site was larger than 40 at both visits (See Figure2. Expert: B, D, F, H, K vs Novice: C, E, G, J, I). The results from model (a) showed that the expert sites had 0.25 h per night less adherence decrease than novice sites, but the difference is not significant (p-value = 0.58). The adherence of expert and novice sites have no difference when we use only paired data. Since both models indicate no significant heterogeneity between experienced and inexperienced sites, we conclude that therapy adherence is consistent with respect to experience based on current data and analyses.

It is interesting that some cites showed no significant change of the therapy adherence. The reasons behind this phenomenon remain unclear and need further investigation. It is worth noted that the adherence decreases of patients in site A were smaller than other sites. A possible explanation is that the patients in site A are all veterans, who may be older, keep a regular sleep habit and have greater adherence to therapy instructions.

Previous studies of therapy adherence examined the cohort of specific medical sites but did not look at regional or site-based differences. This paper studies adherence by site and region to understand whether different implanting sites would have a difference in outcomes. Identifying differences in regions may help find sites who have above average outcomes and identifying reasons for their outperformance. These findings could be then taught to the other lower performing sites.

It should be noted that this analysis only includes patients who consent for the ADHERE study. Patients who do not consent may be also non-adherent with the therapy. In addition, the population of UAS patients is CPAP intolerant population, which may be pre-disposed to decreased adherence over time.

In conclusion, the UAS adherence remains adequate in the 12-month follow-up, even with nearly 1 hour per night decrease. No significant heterogeneity of adherence change was found among sites, and there is not enough evidence to claim that experience can influence the average adherence of sites. This suggests the adherence between sites is consistent and generalizable. This finding has an impact on therapy adoption that outcomes between different sites, whether new or very experienced, can be expected to be consistent. Future work can be done to find other explanations of the decrease of adherence, which makes it possible to achieve a more stable long-term adherence. Furthermore, it would be interesting to investigate the similarity and difference between model (a) and (b), and the reasoning behind it.

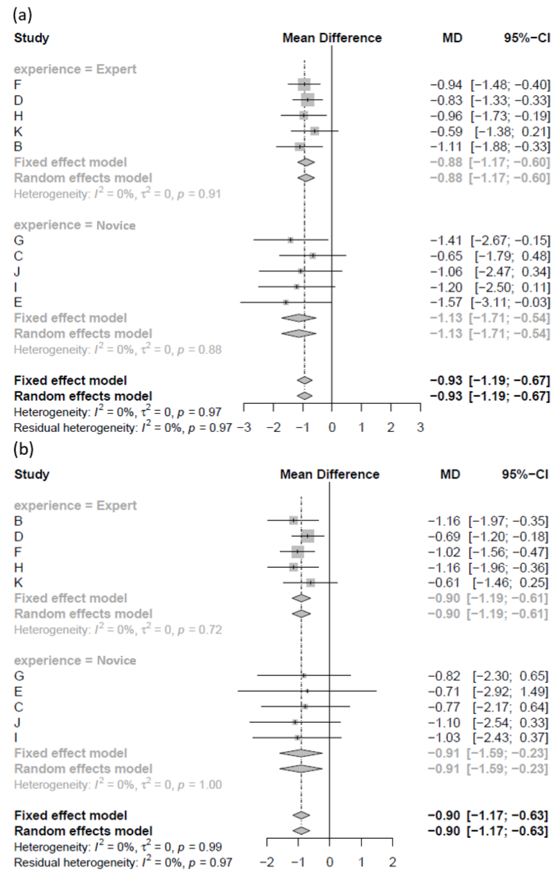

FIGURE 2: META-ANALYSIS FOR ADHERENCE FOR TESTING THE EFFECT OF EXPERIENCE WITH (a) COMPLETED DATA AND (b) PAIRED DATA

REFERENCES

[1] Punjabi, N. M., 2008, "The Epidemiology of Adult Obstructive Sleep Apnea," Proc. Am. Thorac. Soc., **5**(2), pp. 136–143.

[2] McARDLE, N., DEVEREUX, G., HEIDARNEJAD, H., ENGLEMAN, H. M., MACKAY, T. W., and DOUGLAS, N. J., 1999, "Long-Term Use of CPAP Therapy for Sleep Apnea/Hypopnea Syndrome," Am. J. Respir. Crit. Care Med., **159**(4), pp. 1108–1114.

[3] Verse, T., Dreher, A., Heiser, C., Herzog, M., Maurer, J. T., Pirsig, W., Rohde, K., Rothmeier, N., Sauter, A., Steffen, A., Wenzel, S., and Stuck, B. A., 2016, "Leitlinie: „HNO-Spezifische Therapie Der Obstruktiven Schlafapnoe Bei Erwachsenen`` Kurzfassung," HNO, **64**(5), pp. 310–319.

[4] Heiser, C., Steffen, A., Boon, M., Hofauer, B., Doghramji, K., Maurer, J. T., Ulrich Sommer, J., Soose, R., Strollo, P. J., Schwab, R., Thaler, E., Withrow, K., Kominsky, A., Larsen, C., Kezirian, E. J., Hsia, J., Chia, S., Harwick, J., Strohl, K., and Mehra, R., 2019, "Post-Approval Upper Airway Stimulation Predictors of Treatment Effectiveness in the ADHERE

Registry," Eur. Respir. J., **53**(1).
[5] Strollo, P. J. J., Soose, R. J., Maurer, J. T., de Vries, N., Cornelius, J., Froymovich, O., Hanson, R. D., Padhya, T. A., Steward, D. L., Gillespie, M. B., Woodson, B. T., Van de Heyning, P. H., Goetting, M. G., Vanderveken, O. M. O. M., Feldman, N., Knaack, L., Strohl, K. P., Malhotra, A., Soose, R. J., Maurer, J. T., de Vries, N., Cornelius, J., Hanson, R. D., Padhya, T. A., Steward, D. L., Woodson, B. T., Verbraecken, J., Vanderveken, O. M. O. M., Goetting, M. G., Feldman, N., Chabolle, F., Badr, M. S., Randerath, W., and Strohl, K. P., 2014, "Upper Airway Stimulation for Obstructive Sleep Apnea: Durability of the Treatment Effect at 18 Months.," Sleep, **370**(2), pp. 139–49.
[6] Woodson, B. T., Gillespie, M. B., Soose, R. J., Maurer, J. T., De Vries, N., Steward, D. L., Baskin, J. Z., Padhya, T. A., Lin, H.-S., Mickelson, S., Badr, S. M., Strohl, K. P., and Strollo, P. J., 2014, "Randomized Controlled Withdrawal Study of Upper Airway Stimulation on OSA: Short-and Long-Term Effect," Otolaryngol. Neck Surg., **151**(5), pp. 880–887.
[7] Heiser, C., and Hofauer, B., 2017, "Predictive Success Factors in Selective Upper Airway Stimulation," ORL, **79**(1–2), pp. 121–128.
[8] Huntley, C., Kaffenberger, T., Doghramji, K., Soose, R., and Boon, M., 2017, "Upper Airway Stimulation for Treatment of Obstructive Sleep Apnea: An Evaluation and Comparison of Outcomes at Two Academic Centers," J. Clin. Sleep Med., **13**(9), pp. 1075–1079.
[9]DerSimonian, R., and Laird, N., 1986, "Meta-Analysis in Clinical Trials," Control. Clin. Trials, **7**(3), pp. 177–188.

