Improving sleep in severe CRSwNP: an RCT on the effect of mepolizumab and FESS on OSA, sleep disturbances and quality of life

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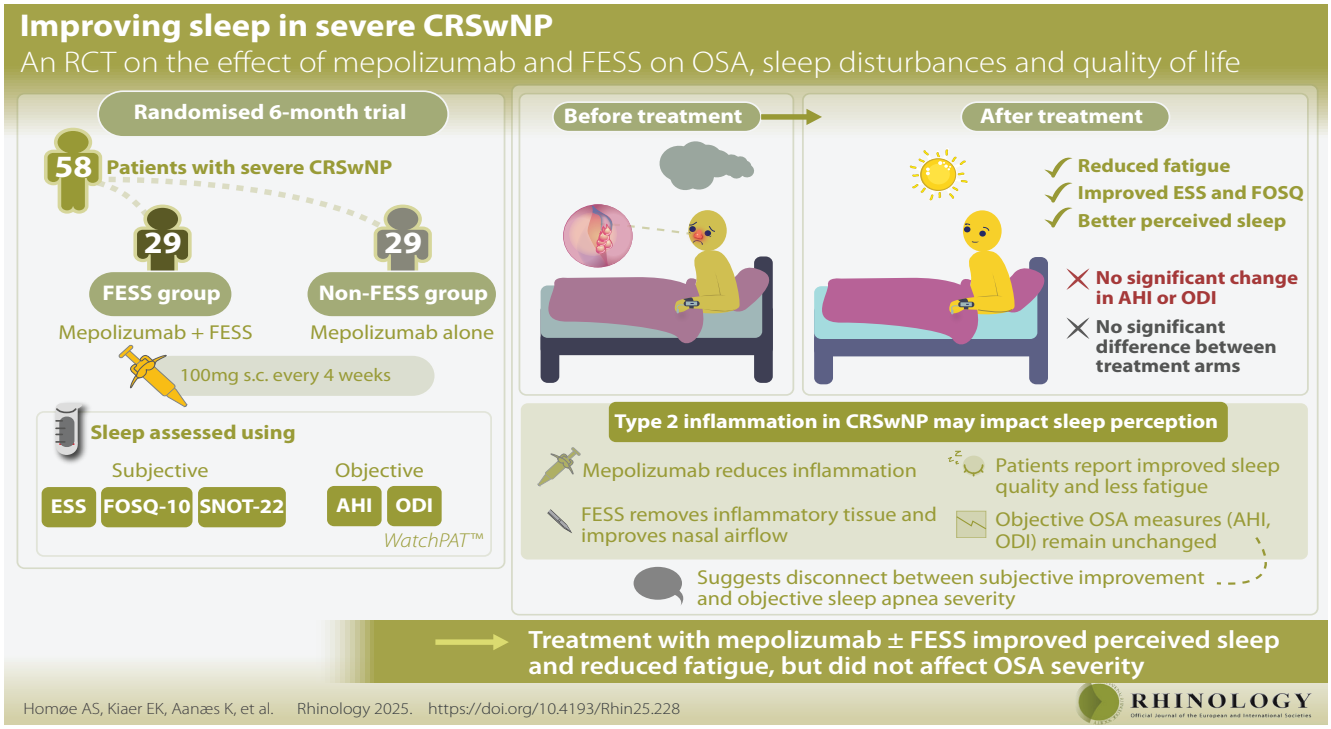

Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) often leads to poor sleep quality and fatigue. Many patients with CRSwNP are also at risk for obstructive sleep apnea (OSA). This study examined how mepolizumab and/or endoscopic sinus surgery (FESS) affect sleep quality and OSA in patients with severe uncontrolled CRSwNP.

Methods: In a randomised trial with 58 patients, participants received mepolizumab alone or combined with FESS. Sleep quality was measured using FOSQ-10 and ESS, and OSA severity via AHI from home sleep apnea tests.

Results: At baseline, 70% of participants had OSA (AHI ≥ 5), with 34.6% having moderate-to-severe OSA. After six months, there were significant improvements in sleep quality (SNOT-22, FOSQ-10, ESS) in both groups but no significant change in objective OSA measures (AHI, ODI). Patients with OSA showed a reduction in severity, however non-significant. There were no severe adverse events (SAE) during the follow-up.

Conclusions: Mepolizumab, with or without FESS, improved subjective sleep quality and reduced fatigue but did not significantly affect OSA severity. This suggests that while treatment eases sleep-related symptoms, it may not resolve underlying OSA, particularly in more severe cases.

Key words: biologics, CRSwNP, OSA sinus surgery, sleep

Introduction

Chronic rhinosinusitis with nasal polyposis and type-2 inflammation (CRSwNP) affects 2 – 4 % of the European population [1]. It is characterized by nasal obstruction, facial pain/pressure, postnasal drip, and loss of smell, and poses a heavy disease burden on many patients and thus a poor quality of life (QoL) [1]. Many of these patients also suffer from poor sleep quality, fatigue, depression, reduced concentration, impaired memory, and productivity, which often is attributed their sinonasal symptoms even though it is known, that people with CRSwNP are more susceptible to suffer from sleep dysfunction such as obstructive sleep apnea (OSA) [2–5]. Previous studies have not been able to show an association between poor sleep quality and nasal polyp score (NPS), whereas a high CRS-specific burden of disease scored by the sino-nasal outcome test (SNOT-22-score) has been shown to be associated with sleepiness [6]. Former studies have shown that reduction of the nasal resistance improves subjective symptoms of fatigue, but reduction of the nasal resistance in patients with OSA with sleepiness does not significantly improve objective measures [7]. The degree of OSA should be documented using objective measures, as subjective reports show poor correlation. Additionally, subjective sleepiness symptoms require objective nighttime measurements, given the low association between feeling tired and the degree of OSA [4,8]. Generally, sleep complaints and fatigue are often reported by patients suffering from chronic diseases and sleep disturbances are associated with a poor QoL [9]. Patients with CRSwNP suffer from Type-2 inflammation with a high number of eosinophilic cells in the nasal polyps (NP) and blood. The mechanisms underlying the sleep disturbances in CRSwNP are considered multifactorial with an increasing understanding that both local and systemic inflammation may have a greater impact on sleep physiology [9,10]. Previous findings have shown an improvement in sleep-related symptoms following functional endoscopic sinus surgery (FESS), though it has been argued this is not solely due to an improvement of nasal passage but potentially due to the removal of extensive inflammatory tissue and a general improvement of CRS symptoms [5,7,11]. Recent studies have investigated the impact of biologic treatments on sleep quality, revealing significant improvements as measured by patient reported outcomes (PROMs) [3,4]. Still, there is a lack of knowledge about the impact on objective measures for identification of OSA. In this study we performed home sleep apnea tests (HSAT) on all patients. We wanted to examine the prevalence of OSA among patients from the FESSnonFESS study [12] and aimed to investigate the impact of a) mepolizumab and b) mepolizumab combined with FESS, on patients with severe CRSwNP regarding their sleep related symptoms including apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) based on questionnaires and HSAT.

Materials and methods

Eligibility criteria

Patients ≥ 18 years with severe uncontrolled CRSwNP , NPS ≥ 2+2 (using the Meltzer NPS scoring system), a SNOT-22-score ≥ 35, type 2 inflammation (blood or polyp tissue eosinophilia) and previously ≥ one FESS in general anesthesia were considered eligible to participate. Patients were excluded if they had previously been treated with biologics for CRS or asthma, had received prednisone (> 10 mg per day) three months prior to inclusion, had a history of malignant lung disease or cardiac disease of clinical importance, had allergic or significant reactions to mepolizumab or were pregnant or planning a pregnancy during the study period. Asthma diagnosis was based on respiratory symptoms and a positive bronchial provocation test (metacholine and/or mannitol) [13,14].

Randomisation

The study encompassed 58 patients in total [12]. Patients were assigned to one of two blocks: NPS 4-5 (small) or NPS 6-8 (large). Patients were randomly assigned to either a) mepolizumab only (n=29), or b) mepolizumab and FESS (n=29), in addition to ongoing standard care. Both groups received 100 mg of mepolizumab subcutaneously on the same day of the randomisation, and continued treatment every four weeks for six months regardless of randomisation. The group randomised to FESS had the procedure performed 14 days after randomisation and the first injection to avoid redundancy due to potential early NPS improvement [15–17]. The randomisation was generated automatically by using a randomisation tool in REDCap. One patient dropped out immediately after randomisation, wishing to participate in a different study.

Sleep monitoring

Patient reported sleepiness was measured by using validated questionnaires (Functional Outcomes of Sleep Questionnaire (FOSQ-10), Epworth Sleepiness Scale (ESS) and SNOT-22 including the sleep domains (Difficulty falling asleep, Waking up at night, Lack of a good night's sleep, Fatigue) [18–20]. A change of 1.8–2.2 points on the FOSQ-10 and ≥2 points on the ESS is considered clinically relevant, though not formally validated [21,22]. Overnight sleep monitoring to detect possible OSA was made by using the clinically validated WatchPAT 300 technology. The advantage of this technology is that the sleep period is considered when measuring potential respiratory abnormality. Data collected for this study were AHI (apnea-hypopnea index), level of snoring and oxygen desaturation index (ODI). The examination was conducted for one night after inclusion and repeated after six months with a minimum of 4 hours of sleep to establish a reliable AHI.

Table 1. The demographics of both groups.

	FESS	non-FESS	p
n	29	28	
Age yrs (mean (SD))	51.1 (13.8)	53.0 (14.3)	0.619
Sex (%)			
Female	7 (24.1)	7 (25)	1.000
Male	22 (75.9)	21 (75)	
BMI (mean (SD))	26.7 (5.2)	25.9 (3.1)	0.474
Asthma (%)	24 (83%)	20 (71%)	0.308

Data and statistical analysis

All data were handled in a RedCap database. The study was approved by the Danish Research Ethics Committee no 2212460, Eudract no 2022-002923-37, Pactius Jn P-2022-773, Clinicaltrial.gov no NCT05598814 and the GCP Unit Capital region: Initiation 23.02.2023.

Based on the predefined power calculation in the study protocol, the target sample size was 50 patients (25 per treatment arm), assuming an alpha level of 0.05 and a statistical power of 80% [NCT05598814]. To make the study less vulnerable to drop-outs, we included four more patients in each treatment arm.

The WatchPat™ analysis were made by the same consultant at the department of clinical neuro-physiology, Rigshospitalet, University Hospital Copenhagen. Data analysis was performed using R-studio with default settings. If data were normally distributed, a student's t-test was used. Most data were not normally distributed. Wilcoxon signed rank test was used for paired T-testing. Mann Whitney-U was used for independent samples. Categorical variables were compared using Fisher's exact test, Chi-squared test or McNemars test, as appropriate. The significance level was set at 0.05. For correlation testing, Fishers Z-test was used. Logistic regression was used to assess possible associations between clinical variables and AHI and ODI. The few missing values (7%) in AHI, ODI and snoring were excluded from the analyses. This ensured calculations were based only on complete data, maintaining result integrity without imputation.

Results

There were no demographic differences between the groups (FESS and nonFESS). Mean age was 51 and 53 years, respectively (Table 1). At baseline, the frequency of OSA (AHI≥ 5) was 70% in total, with 71% and 68% in the two groups, respectively (p=1). Of those with OSA 34.6% had Moderate-Severe (AHI≥15) at baseline. The median NPS score was 6.0 in both groups. There was no difference in mean BMI between the treatment modalities (26.7 and 25.9, respectively). In our cohort, there was a statistically significant correlation between higher BMI and higher NPS ($p<0.05$) at baseline, and between higher BMI and higher AHI and ODI ($p<0.001$). Whereas we found no statistical correlations between AHI or ODI and age, blood eosinophilia and FeNO. Also, no correlation between AHI or ODI and: ESS nor FOSQ was found.

Sleep quality

The total SNOT-22-score improved significantly in both treatment modalities (Table 2, MCID ≥ 8.9 points) as did the FOSQ-10-score and ESS score (Table 2) after six months of treatment. Overall, patients in both groups reported sleep disturbing symptoms (from SNOT-22: difficulty falling asleep, lack of good sleep, awakening during the night, waking up tired, fatigue, reduced productivity, and concentration) as a moderate problem at baseline (Table 2). For both treatment modalities there was a significant improvement in all sleep symptoms (SNOT-22, ESS and FOSQ) after six months of treatment without any differences between the two groups (Table 2). Patients also significantly improved their NCS in both groups.

Objective parameters

There was a statistically significant correlation between NPS and AHI in the FESS group at baseline ($p<0.001$). This was not found in the nonFESS group. At six months follow-up there was no correlation between NPS and AHI in either of the groups.

We observed no significant change in AHI nor ODI among any of the groups during the six months follow-up (Table 3). Snoring did not change significantly either. FeNO and blood eosinophilia improved significantly in both groups after six months of treat-ment (Table 2). There were no differences between the groups. No significant correlation was found between blood eosinophilia and ESS or FOSQ scores at baseline. At six months the FOSQ score correlated to a higher level of blood eosinophilia in the FESS group ($p<0.001$), though not in the nonFESS group ($p=0.746$). There was a statistically significant difference between the treatment modalities at six months (<0.05).

OSA

Overall, 39 patients (70%) had an AHI ≥ 5 at baseline, and Figure 1 shows the distribution of OSA severity. Of those with OSA (AHI ≥ 5), 82% were male (OR 3.12, 95% CI [0.74, 13.54], $p = 0.094$). Figure 2 illustrates individual transitions in OSA severity from baseline to six months in the FESS and nonFESS groups, respectively. In both groups, some patients improved, while others remained stable or worsened slightly. The changes in severity were non-significant in both treatment modalities. There was no statistically significant difference in the distribution of OSA severity between the treatment modalities at baseline ($p = 0.440$, Fisher's exact test) or at six months ($p = 0.950$, Fisher's exact test). Moreover, there were no associations between changes in AHI and NPS or NCS.

Table 2. Changes from baseline to 6 months in SNOT-22, selected sleep-related items, nasal congestion score (NCS), nasal polyp score (NPS), ESS, FOSQ-10, blood eosinophil count, and FeNO.

Outcome	Group	Baseline	6 months	Δ (Change)	p (within)	p (between)
SNOT-22 Total	FESS	57.0 [48.0–70.0]	16.0 [9.0–25.0]	42.0 [32.0–51.0]	<0.001	0.055
	non-FESS	60.0 [51.8–70.8]	24.0 [18.5–43.3]	27.5 [21.3–43.5]	<0.001	
Difficulty falling asleep	FESS	2.0 [1.0–4.0]	0.0 [0.0–1.0]	2.0 [1.0–3.0]	<0.001	0.279
	non-FESS	2.5 [1.0–4.0]	1.0 [0.0–1.0]	1.0 [0.0–2.3]	<0.001	
Awakening	FESS	3.0 [1.0–4.0]	1.0 [0.0–2.0]	2.0 [1.0–2.0]	<0.001	0.851
	non-FESS	3.0 [2.0–4.0]	1.0 [0.0–1.3]	2.0 [1.0–3.0]	<0.001	
Lack of good sleep	FESS	4.0 [2.0–5.0]	1.0 [0.0–2.0]	3.0 [1.0–3.0]	<0.001	0.861
	non-FESS	3.0 [2.0–4.3]	1.0 [0.0–3.0]	1.0 [0.8–2.3]	<0.001	
Wake up tired	FESS	4.0 [2.0–4.0]	1.0 [0.0–1.0]	3.0 [1.0–4.0]	<0.001	0.311
	non-FESS	4.0 [3.0–4.0]	1.0 [0.0–2.3]	2.0 [0.0–3.0]	<0.001	
Fatigue	FESS	3.0 [1.0–4.0]	1.0 [0.0–1.0]	2.0 [1.0–3.0]	<0.001	0.763
	non-FESS	3.5 [3.0–4.3]	2.0 [1.0–3.0]	1.0 [0.0–2.0]	<0.001	
Reduced productivity	FESS	2.0 [2.0–4.0]	1.0 [0.0–1.0]	1.0 [1.0–2.0]	<0.001	0.883
	non-FESS	3.0 [2.0–3.3]	1.0 [0.8–2.0]	2.0 [0.0–2.3]	0.001	
Reduced concentration	FESS	2.0 [1.0–4.0]	1.0 [0.0–1.0]	1.0 [1.0–2.0]	<0.001	0.694
	non-FESS	2.0 [2.0–4.0]	1.0 [1.0–2.0]	1.0 [0.0–2.0]	<0.001	
ESS	FESS	7.0 [5.0–10.0]	5.0 [2.0–6.0]	3.0 [1.0–5.0]	<0.001	0.436
	non-FESS	7.0 [4.0–12.0]	5.5 [3.0–8.0]	2.0 [0.0–5.0]	0.011	
FOSQ-10	FESS	16.0 [14.0–18.5]	18.5 [16.5–19.5]	2.0 [0.5–4.0]	0.002	0.128
	non-FESS	14.8 [12.3–17.8]	17.0 [14.8–19.0]	1.5 [0.5–3.3]	0.002	
NPS	FESS	6.0 [4.5–6.0]	1.5 [1.0–3.5]	4.0 [2.0–5.0]	<0.001	<0.001
	non-FESS	6.0 [5.0–6.0]	5.0 [3.8–6.0]	0.5 [0.0–1.0]	0.003	
NCS	FESS	3.0 [2.0–3.0]	0.0 [0.0–1.0]	2.0 [1.0–3.0]	<0.001	<0.001
	non-FESS	3.0 [2.0–3.0]	1.0 [1.0–2.0]	1.0 [1.0–1.3]	<0.001	
Blood eosinophils (10^9/L)	FESS	0.4 [0.3–0.6]	0.0 [0.0–0.1]	0.3 [0.2–0.6]	<0.001	0.225
	non-FESS	0.5 [0.4–0.7]	0.1 [0.0–0.1]	0.4 [0.3–0.6]	<0.001	
FeNO (ppb)	FESS	32.0 [18.0–57.0]	25.0 [15.0–34.0]	8.0 [−2.0–18.0]	0.003	0.861
	non-FESS	40.5 [29.5–60.5]	30.0 [22.5–43.5]	9.5 [−2.0–19.5]	0.017	

Values are presented as median [IQR]. Within-group changes were analysed using the Wilcoxon signed-rank test; between-group comparisons were assessed using the Mann–Whitney U test.

Table 3. Objective sleep parameters from home sleep monitoring at baseline and 6-month follow-up.

Outcome	Group	Baseline	6 months	Δ (Change)	p (within)	p (between)
AHI	FESS	11.0 [3.6–24.4]	7.9 [3.5–17.8]	−0.4 [−2.5–2.9]	1.000	0.848
	non-FESS	7.6 [4.6–14.6]	6.5 [3.4–17.0]	−0.8 [−4.1–5.0]	0.990	
ODI	FESS	11.1 [3.9–23.7]	7.5 [3.6–18.0]	−0.7 [−1.8–3.2]	0.939	0.763
	non-FESS	8.1 [4.9–14.2]	6.5 [4.4–16.8]	−0.5 [−4.0–4.7]	1.000	
Snoring (%)	FESS	6.0 [5.0–13.0]	10.0 [3.5–15.5]	1.0 [−2.0–4.0]	0.375	0.563
	non-FESS	5.5 [3.8–20.3]	7.0 [4.3–13.8]	0.0 [−3.0–3.0]	0.972	

Values are presented as median [IQR]. Within-group changes were analysed using the Wilcoxon signed-rank test; between-group comparisons were assessed using the Mann–Whitney U test.

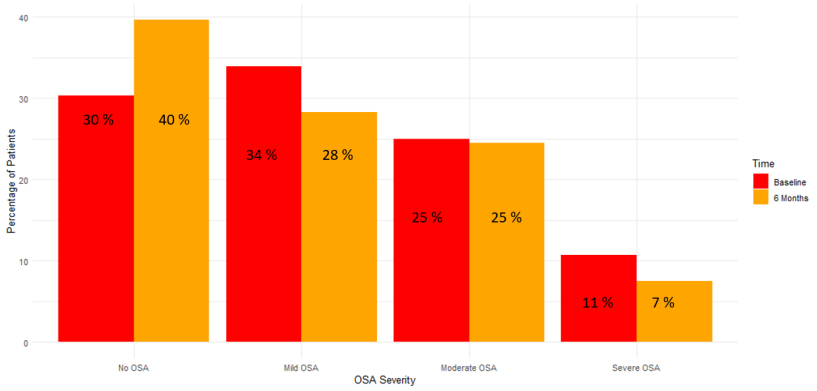

Figure 1. Change of total OSA severity from baseline to 6 months. There were no differences in OSA severity between the FESS group and nonFESS group at baseline nor 6 months. The group of no OSA significantly increased after 6 months ($p<0.05$).

Discussion

Based on our current knowledge, this is the first study to investigate the effects of mepolizumab, both as a standalone treatment and in combination with FESS, on objective sleep parameters. Patients with CRSwNP are known to have a poor quality of life, poor sleep quality, and daytime fatigue [2–5,23]. We found that a significant proportion of CRSwNP suffered from sleep disturbances and OSA at baseline. Patients with CRSwNP not only suffer from nasal congestion and other CRS symptoms, but often also from type-2 inflammation, which is also associated with sleep disturbances [9]. Six months of treatment with mepolizumab reduced daytime fatigue, improved sleep quality and reduced OSA severity independent of combination with FESS.

Initially, both groups had elevated levels of AHI and ODI (Table 3) [24]. There was no significant nor clinical important change in AHI after six months of treatment no matter the treatment modality. This suggests, that neither FESS nor biologic treatment have an impact on AHI and ODI, which is in alignment with previous studies examining the effect of FESS on sleep [5]. There was a reduction in NPS in both groups and patients also reported a clinically and statistically significant improvement in NCS (Table 2). It has previously been shown that a reduction in nasal resistance does improve daytime fatigue, but has no effect on AHI, which is consistent with our findings [6,9]. This indicate that despite experiencing a significantly better nasal airflow, this does not affect objective sleep parameters based on our findings.

At baseline, patients in both groups reported poor sleep quality, daytime fatigue, and experience of sleep disturbances (Table 2). At six months follow-up both groups had improved significantly in both SNOT-22-score (overall and sleep domain), ESS and FOSQ-10 (Table 2). The improvement of the SNOT-22 sleep domain is in alignment with other studies [3,4,23]. For all three parameters, the FESS group improved the most, but without significant differences between the treatment modalities (Table 2). Thus, despite not improving objective nighttime measurements, patients still report less daytime fatigue and overall, a feeling of improved sleep. This confirms previous demonstrations of low association between feeling tired, QoL, and objective findings [8,9].

Although many patients (and their partners) reported reduced snoring, this was not reflected in the overall objective scores from baseline to six months (Table 3). However, in patients with a large polyp burden (NPS 6-8), greater reductions in nasal polyp score were significantly associated with improved snoring ($\beta = 2.77$, $p = 0.003$), adjusted for BMI.

This association was only seen in the FESS group ($\beta = 3.76$, $p = 0.001$), suggesting that surgery may be key to improving snoring in CRSwNP.

Based on the initial nighttime monitoring, 70% of the patients were suffering from some level of OSA (at least AHI≥5) and this was more frequent among men than women (77% of the males (n=33) vs 50% of the females (n=7). Though, without a significant difference as the study has a higher proportion of male participation (75% males vs 25% females, Table 1). Of the males with OSA, 55% (n=18) had Moderate-Severe disease while among the females with OSA, this was 47% (n=3). Of those with OSA, 46% had a BMI>27. No change in BMI was found after six months of treatment, which could explain why they did not decrease more in AHI. After six months of treatment, only 60% had an AHI≥5 ($p<0.05$). There was no difference between the treatment modalities. A trend towards improvement in OSA severity was observed in both groups (Figure 2). This may support the hypothesis that reducing upper airway inflammation with biologic treatment—alone or combined with surgery—can improve sleep-related breathing. However, the results must be interpreted cautiously due to the small sample size and absence of statistically significant between-group differences.

It is well known that chronic inflammatory disease is associated with daytime fatigue and poor QoL [3–5,9,23]. However, we did not find any correlation between increased inflammatory parameters (FeNO, blood eosinophilia) and increased AHI at baseline. Both blood eosinophilia and FeNO significantly reduced in both groups after six months with no differences between the

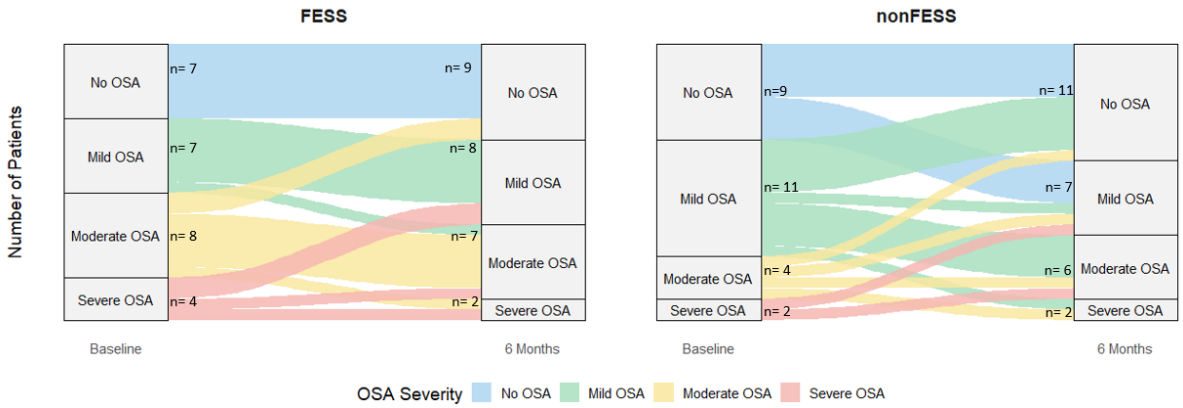

Figure 2. Individual change (n values shown) in OSA severity after six months of treatment divided by treatment group. There are no significant changes within the groups nor between FESS and nonFESS after six months of treatment (p=0.776).

groups.

It is interesting to note the improvement in patients' experience of sleep quality and QoL, meanwhile there is no improvement in overall AHI. Alt et al. argued in a review from 2013 that we should distinguish more between "fatigue" and "sleepiness" (sleep dysfunction) [9]. Patients with CRSwNP generally have a low QoL which results in lack of energy physically and mentally, which cannot solely be attributed to poor sleep.

It is also worth shedding light on NPS and the association with AHI which has been widely discussed in previous studies [9]. Initially, it seemed there was a correlation between NPS and AHI, where a higher NPS correlated with higher AHI, though this was only the case in the FESS group. At six months follow-up, we did not find any significant correlation between higher NPS and higher AHI in any of the groups. Thus, the finding at baseline likely indicates a random finding rather than a meaningful correlation. This is consistent with previous findings: that NPS does not correlate with higher AHI (OSA) [9].

Strengths and limitations

This study's main strength is its randomised controlled design, providing a robust comparison between treatment modalities. It is the first RCT to evaluate both subjective and objective sleep outcomes in patients with severe CRSwNP treated with mepolizumab with or without FESS. The use of validated questionnaires (FOSQ-10, ESS) alongside home sleep monitoring (WatchPAT™) offers a comprehensive view of treatment effects. Sleep data were analysed by a blinded neurophysiologist, reducing interpretation bias. The inclusion of real-world patients and inflammatory biomarkers (FeNO, eosinophils) enhances generalisability.

However, the relatively small sample size may limit the ability to detect group differences, particularly in objective measures. Sleep monitoring was limited to one night, potentially underestimating night-to-night variability. The study lacked a FESS only group. The cohort was male-dominated, which may limit generalisability, and follow-up was limited to six months. Full polysomnography was not used, which may have missed subtle sleep disturbances.

Conclusion

In this study, we found that patients with severe uncontrolled CRSwNP suffer from poor sleep quality and increased sleep disturbances. The patients in this study significantly improved their experience of sleep quality as well as QOL after six months of treatment with mepolizumab – regardless of sinus surgery. However, this improvement could not be significantly objectified by AHI or ODI. Treatment with combined therapy (FESS and mepolizumab) did not further improve sleep quality compared to treatment with mepolizumab alone. The etiology of the sleep dysfunction amongst patients with CRSwNP remains multifactorial, though it seems inflammatory control reduces fatigue and improves sleep quality despite not influencing objective sleep parameters. It is important to acknowledge that patients with severe CRSwNP, despite reporting improved sleep and QoL, remain at high risk for sleep disturbances such as OSA with the health-related risks it entails. Therefore, relevant treatment of underlying OSA is important.

Authorship contribution

AH: study design, collection of data, analysis of results, drafting manuscript. EK: study design, revision of manuscript, critical review of all contents. JT: collection of data, revision of manuscript. KA: revision of manuscript, critical review of all contents. PJ: study design, analysis of data, revision of manuscript, critical review of all contents. VB: study design, revision of manuscript, critical review of all contents.

Conflict of interest

The study was funded by GlaxoSmithKline.

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