Temporomandibular Disorder (TMD) Pain in Response to Jaw Advancement in People with TMD and Obstructive Sleep Apnea

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SPECIFIC AIMS

Two chronic health conditions are treated with oral appliances during sleep. One condition is temporomandibular disorder (TMD); a musculoskeletal disorder characterized by pain in the masseter muscle and temporomandibular joint. TMD pain is treated with a stabilization splint which operates by limiting abnormal muscle activity. The other condition is obstructive sleep apnea (OSA). Mild to moderate OSA is treated with a mandibular advancement splint (MAS) which holds the mandible in a protruded position to increase the pharyngeal airway space and reduce upper airway collapsibility.

The comorbidity of the two conditions is high. Approximately one in four patients with clinically diagnosed TMD has polysomnographic-diagnosed OSA.[1] This comorbidity poses a problem for management because neither appliance is considered effective in treating both conditions. In fact, mandible advancement is assumed to worsen TMD pain.[2] However this assumption is not well supported by scientific evidence, with some studies finding that mandibular advancement actually *reduces* TMD pain,[3,4,5], albeit after a transient increase in TMD pain in some patients. Furthermore, anecdotal evidence suggests that mandibular advancement reduces TMD pain because it first alleviates OSA severity, implying a causal relationship.

The overall objective of this study is to characterize the temporal nature of TMD pain in adults with comorbid TMD/OSA treated with MAS therapy. It is the first study to monitor adherence to MAS therapy objectively in this study population, using a microsensor embedded in the MAS.

Aim 1: To describe the frequency, duration, and severity of TMD pain symptoms during MAS therapy in people with comorbid TMD and OSA. *Hypothesis 1: TMD pain symptoms increase at MAS treatment onset, then resolve quickly with continued therapy, to decline below baseline levels.*

Aim 2: To examine temporal aspects of the therapeutic response. *Hypothesis 2: A reduction in OSA severity—determined by a reduction in the apnea hypopnea index (AHI)—precedes a reduction in TMD pain.*

Aim 3: To explore the relationship between TMD pain intensity and adherence to MAS therapy. *Hypothesis 3: Greater pain intensity at enrollment is associated with worse adherence. Hypothesis 4: Change in pain over time is correlated with change in adherence.*

Our collaboration has expertise in dental sleep medicine, epidemiology and biostatistics. The short-term goal is to collect preliminary evidence in support of a NIH Planning Grant (R34) proposal. The long-term goal is to translate research findings into clinical practice guidelines to address an unmet need in chronic TMD/OSA pain management.

SIGNIFICANCE

The study is significant because findings will provide the first detailed information of the course of pain and sleep-disordered breathing in people with comorbid TMD/OSA. People rate the severity of TMD pain as 4.3, on average, on a 0–10 numeric rating scale; similar to ratings for chest pain and back pain.[6] Prevalence of TMD is 12% [7] and the disorder accounts for 17.8 million lost work days per year for every 100 million U.S. working adults.[8] As many as 1 in 4 people with TMD have comorbid OSA.[1] In the U.S. adult population, prevalence of OSA is 26%,[9] and OSA has public health significance as a risk factor for hypertension,[10] stroke,[11] cardiovascular disease[12] depression[13] and all-cause mortality.[11,12] Clinical trials comparing mandibular advancement to CPAP, conclude that the two therapies have equivalent effectiveness to prevent airway obstructions[14,15,16,17,18,19, 20] because the better adherence to mandibular advancement therapy offsets its lesser efficacy.

The study is significant for its potential to translate research findings into clinical practice guidelines. There is clinical equipoise in the research questions since mandibular advancement is typically contraindicated with TMD, yet the degree of jaw movement in mandibular advancement is insufficient to exacerbate TMD pain,[3] and any initial increase in pain is transient, [4] and that mandibular advancement decreases TMD pain over time.[5]

INNOVATION

Fig 1. An example of a micro-recorder, aka "compliance chip", sealed into the upper right side of a MAS. Image copied from Vanderveken et al., 2013). [21]

It is innovative to investigate treatment of comorbid TMD/OSA with mandibular advancement. These conditions are rarely studied together, despite their frequent coexistence and shared risk factors[22]. It is innovative to begin to explore the basis for a possible causal relationship between sleep-disordered breathing and TMD pain. Thirdly, it is innovative to objectively assess adherence to MAS therapy using a micro-recorder (Figure 1). To our knowledge adherence has not previously evaluated objectively in TMD patients being treated with a MAS.

APPROACH

Design: This is an interventional study of 12 patients receiving non-standard of care therapy for comorbid TMD/OSA. There is no comparison group.

Setting: Recruitment and MAS therapy will be conducted at *Lane and Associates Family Dentistry;* a group of 27 dental practices located throughout the Triangle and Triad region of North Carolina. Advantages of using *Lane & Associates* are: large influx of new dental patients every month, fast recruitment, well-established protocols for screening for TMD and OSA and for referral of patients to sleep physicians for evaluation and PSG, standardized protocols for oral appliance therapy, and a Dental Sleep Medicine director (Dr. Spencer) who is highly experienced also in the management of TMD. The study coordinator, Ms. Kristin Dillow, is a dental hygienist in the UNC School of Dentistry Dental Sleep Clinic who works with Dr. Essick in delivering oral appliance therapy. She will travel to the Lane & Associates offices to assist in clinical and administrative activities and will manage all data collection for the 12 subjects. The Dental Sleep Clinic at the UNC School of Dentistry is not considered adequate to serve as the study site because it currently operates only one day a week and accepts referrals for only patients without TMD pain.

Inclusion criteria are men or women aged 30–64 years of any race or ethnicity who meet research diagnostic criteria for TMD,[23] who rate their TMD pain severity as ≥4 on a 0–10 numeric rating scale and have no history of treatment for OSA. If taking a prescription medication (with the exception of prescription formulations of NSAIDs, acetaminophen, and aspirin) episodically for the management of pain, the subject must agree to discontinue its use prior to or at the baseline visit. If taking a prescription medication daily for the management of pain, must agree to continue the daily use of the medication throughout the 16-week observation period. If taking an over-the-counter pain medication daily, the subject must agree to continue the daily use throughout the study. Exclusion criteria are <8 retained teeth per arch; tooth mobility; unmanaged periodontal disease; skeletal Class III occlusion; central sleep apnea; hypoventilation syndromes; congestive heart failure; and chronic obstructive pulmonary disease.

Pre-enrollment activities: Patients at *Lane and Associates Family Dentistry* complete a standard TMD screening questionnaire. Those screening positive will be clinically examined against Research Diagnostic Criteria for TMD to confirm Group II: Masticatory Muscle Disorders, 1A: Myalgia.[24] They will also be screened for OSA using the validated STOP-BANG questionnaire.[25] Those at high risk will be referred for evaluation by a sleep physician and a diagnostic PSG, as is the standard of care at *Lane and Associates*. If the PSG reveals mild to moderate OSA (apnea-hypopnea index (AHI) ≥5 and <30), the patient is a candidate for oral appliance therapy, pending confirmation of the sleep physician, and thus eligible to enroll in the study.

Enrollment: Subjects will be consented and assessed for demographics, medical history, and medication use. Impressions of the upper and lower dental arches will be recorded, poured in dental stone and sent to the lab. A George Gauge will record a protrusive bite registration with the jaw advanced 60% from the most retruded position. The custom-made MAS will be fitted with a micro-recorder (Braebon DentiTrac Monitor) to assess adherence. We define adherence as use of the splint 4 hours/night for ≥70% of nights as is standard practice for CPAP therapy. Home sleep test (HST): Subjects will complete a series (from 2 to 5) two-night HSTs using the portable AccuSom device by NovaSom, which collects sleep parameters of AHI, minimum oxygen saturation, and snoring indices (Figure 2). Novosom arranges shipment of the device and offers 24-hour technical support during the sleep test. Sleep data are uploaded wirelessly from the recorder to an online portal for statistical analysis. Drs. Essick and Sanders have experience using this device in dental sleep medicine research.

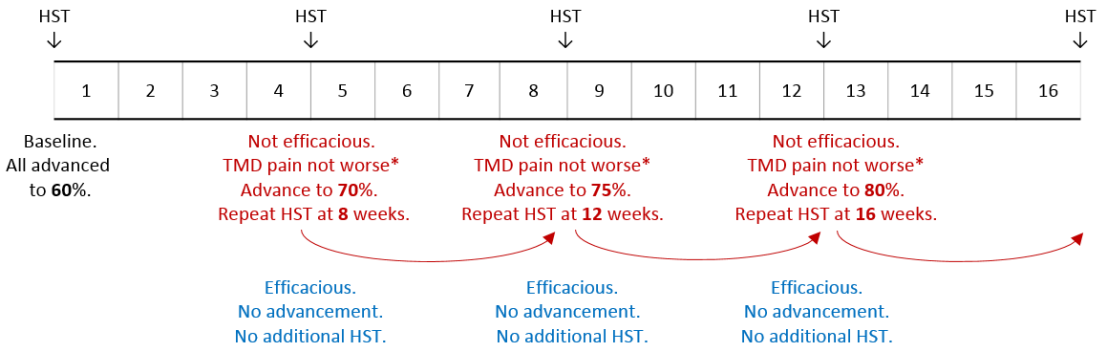

Figure 2. Following a baseline home sleep test (HST), 12 participants will enter the study wearing a MAS during sleep that protrudes the mandible to 60% of its maximal advancement. This approximates the minimum amount of jaw advancement that is expected to be efficacious. A HST will be repeated at the end of Week #4. If that HST shows that the MAS is not efficacious (i.e. has not reduced baseline AHI by ≥50% or the AHI is ≥10**), and if TMD pain is not worse, the mandible will be advanced to 70% and the participant will repeat the HST at the end of Week #8. Once efficacy is achieved, there is no need for further HSTs. If efficacy is not achieved at the end of Week #8 and if TMD pain is not worse, the mandible will be advanced to 75% and the participant will repeat the HST at the end of Week #12. If efficacy is not yet achieved and if TMD pain is not worse, the mandibular will be further advanced to 80% and the participant will undergo a final HST at the end of Week #16. Once a HST indicates that the MAS is efficacious in reducing the AHI, the participant will maintain that level of advancement. The minimum number of HSTs for any one participant is 2 (baseline and 4-week follow-up) and the maximum number is 5.

* If TMD pain symptoms have worsened the study dentist will determine whether jaw advancement should be decreased, maintained or increased. Subjects who cannot tolerate the minimum 60% jaw advancement after 8 weeks of treatment will return to their sleep physician for alternate therapies for OSA.

TMD symptoms are recorded daily by the subject and monitored weekly by the study coordinator.

**Criteria established by the American Board of Dental Sleep Medicine for a successful responder to oral appliance therapy include both a reduction in the AHI of ≥>50% from baseline and AHI<10.

The primary outcome is the course of TMD pain over 16 weeks, computed from the weekly mean pain index, and representing the arithmetic mean of daily pain index values in the preceding 7-day period. The pain index is the product of the pain intensity score multiplied by the pain duration score, each as reported in the Daily Symptom Diary kept by the subject. A second measure of pain, also recorded daily, is the Graded Chronic Pain Scale. This comprises 7 items and assesses 2 dimensions of pain: pain intensity and pain-related disability.

Fig 3. The AccuSom home sleep test provided by NovaSom.

Secondary outcomes are sleep breathing parameters evaluated by HSTs (Figure 3). Since MAS is a well-established therapy for OSA these outcomes are confirmatory only. We will also assess subjective sleepiness with the Epworth Sleepiness Scale.

Adverse effects: The most likely adverse effect is short-term increase in TMD pain in the first two weeks. Subjects will record TMD pain intensity on a 0-10 numeric rating scale in a daily log. Every week the study coordinator will contact each subject by phone to monitor the course of TMD pain symptoms. Subjects with increased TMD pain will be clinically assessed by the study dentist and, if indicated, the jaw will be returned to a neutral position until TMD pain symptoms resolve.

Data analysis: The overall analytic approach will emphasize to Aim 1 is to produce basic descriptive statistics and graphic plots to explore within-subject temporal changes in TMD pain over 16 weeks. For Aim 1, the time course of the primary outcome of TMD pain will be fitted with a linear mixed model applied to the sixteen repeated measures on the twelve subjects using a Kenward-Roger degrees of freedom correction for the small number of patients. Observed and model-predicted TMD pain estimates will be plotted for each patient over time. The approach for Aim 2 is to use time-lagged correlation analysis by adding to the model of Aim 1 a time-varying indicator variable for whether AHI has been reduced > 50% from baseline and that AHI < 10; for missing HST's by design (Figure 3), last observation carried forward will be used to impute this variable so that for the sixteen time points AHI reduction will be characterized by a sequence of zeros, and then, when and if AHI is reduced, by a sequence of ones of the two time series (i.e. OSA severity, pain trajectory,) to test hypothesis 2 that a reduction in mean AHI precedes a reduction in mean TMD pain. Finally, for Aim 3, pain intensity at enrollment and change in pain over time will be compared between patients who satisfy the definition for adherence versus those who do not.

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