

Effect of comorbid migraine on propranolol efficacy for painful TMD in a randomized controlled trial

Cephalalgia

2021, Vol. 41(7) 839–850

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DOI: 10.1177/0333102421989268

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Abstract

Introduction: The migraine-preventive drug propranolol is efficacious in reducing pain from temporomandibular disorder, suggesting potential modifying or mediating effects of comorbid migraine.

Methods: In this randomized controlled trial, myofascial temporomandibular disorder patients were treated with propranolol or placebo for 9 weeks. The primary endpoint was change in a facial pain index derived from daily symptom diaries. Linear and logistic regression models tested for a migraine × treatment-group interaction in reducing facial pain index. Counterfactual models explored changes in headache impact and heart rate as mediators of propranolol's efficacy.

Results: Propranolol's efficacy in reducing facial pain index was greater among the 104 migraineurs than the 95 non-migraineurs: For example, for the binary $\geq 30\%$ reduction in facial pain index, odds ratios were 3.3 (95% confidence limits: 1.4, 8.1) versus 1.3 (0.5, 3.2), respectively, although the interaction was statistically non-significant ($p = 0.139$). Cumulative response curves confirmed greater efficacy for migraineurs than non-migraineurs (differences in area under the curve 26% and 6%, respectively; $p = 0.081$). While 9% of the treatment effect was mediated by reduced headache impact, 46% was mediated by reduced heart rate.

Conclusions: Propranolol was more efficacious in reducing temporomandibular disorder pain among migraineurs than non-migraineurs, with more of the effect mediated by reduced heart rate than by reduced headache impact.

Study identification and registration: SOPPRANO; NCT02437383; <https://clinicaltrials.gov/ct2/show/NCT02437383>

Keywords

Adrenergic beta-antagonists, chronic pain, facial pain, headache, sympathetic nervous system, autonomic nervous system

Date received: 24 June 2020; revised: 13 August 2020; 20 November 2020; accepted: 8 December 2020

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Introduction

Since Costen described “a syndrome dependent upon disturbed function of the temporomandibular joint” in 1934, painful temporomandibular disorder (TMD) has been separated from headache and treated primarily by dentists (1,2). However, TMD often co-occurs with primary headaches. In the US population, prevalence of TMD symptoms is elevated five-fold in the presence of severe headache or migraine (15.6% vs 2.6% in people without severe headache or migraine) (3). Presence of TMD was also associated with greater frequency of migraine attacks in the Finland Health 2000 Survey (4). Other studies showed greater headache comorbidity among TMD patients compared with dental patients, namely 74.0% versus 31.9% in a US study (5) and 85.5% versus 45.6% in a Brazilian study (6).

Myofascial TMD, the most frequent diagnosis in people with painful TMD, is often accompanied by migraine (4,6,7). In our prospective cohort study of TMD-free individuals, migraine, but not tension-type headache, was a major risk factor for the first onset of TMD (8). Both TMD pain and migraine pain are subserved by the trigeminal nerve, and pain referral between the divisions of this nerve is explained by the neuroanatomical connectivity as well as central sensitization (9). Both conditions are also associated with autonomic dysfunction, as evidenced by reduced heart rate variability (HRV) found in patients with migraine or TMD (10,11).

Clinical trials can provide further insight into the relationship between migraine and TMD (12). One interesting and important question is whether a proven therapy for one condition is beneficial for the other condition when both conditions are highly comorbid. This is especially so when the therapy in question affects the pathophysiological mechanisms akin to both conditions. It is, therefore, informative to learn whether the therapeutic efficacy differs in the presence of both conditions compared to the presence of only one condition. To answer this question, we conducted a randomized controlled trial (RCT) evaluating efficacy of propranolol in participants with painful TMD, half of whom had comorbid migraine.

Propranolol is a non-selective β -adrenergic receptor antagonist indicated for migraine prevention. Its analgesic effect has been attributed to inhibition of central pain processing in the trigeminal pathway (13,14) and blockade of peripheral nociception (15–17). In addition, propranolol reduces nociception through interaction with the cardiovascular system via reduction in heart rate and blood pressure (18), and through indirect parasympathomimetic effect via increase in HRV (19). The noradrenergic pathways are significant in both cardiovascular regulation and pain transmission

and serve as the basis for the extensive interaction between these two systems. These interactions can be modulated by changes in baroreflex sensitivity, impairment in descending noradrenergic pain inhibitory pathways, and/or activation of pain facilitatory pathways (18).

In our recent RCT entitled “Study of Orofacial Pain and Propranolol” (SOPPRANO), we demonstrated the efficacy of propranolol in achieving $\geq 30\%$ and $\geq 50\%$ reduction in TMD pain (20). However, potential variation in drug efficacy between migraineurs and non-migraineurs was not assessed, and the mechanisms that may mediate the effect of propranolol on TMD pain were not evaluated.

The current study evaluates two exploratory aims of the SOPPRANO trial: i) whether the efficacy of propranolol for TMD pain is greater in participants with comorbid migraine compared with those without migraine; ii) whether the efficacy of propranolol for TMD pain was mediated by the reduction in headache impact or the change in heart rate secondary to propranolol use.

Methods

The study’s methods have been described in detail (20) and are summarized below.

Study design

SOPPRANO was a multi-site, double-blind, placebo-controlled, parallel-group, phase 2b trial that investigated analgesic efficacy of propranolol in patients with painful TMD. The study was approved by the Institutional Review Boards at three sites: The University of North Carolina at Chapel Hill, the University of Florida, and the University at Buffalo. All participants provided informed consent at enrollment. The recruitment continued from August 2015 to January 2018 and the follow-up of the last participant was finished in April 2018. The study included a baseline period which ranged from 1–3 weeks, a 10-week treatment period following randomization, and a 1-week follow-up period.

Participants

The trial enrolled 200 participants aged 18–65 years with chronic myogenous TMD (with or without arthralgia) classified according to the Diagnostic Criteria for TMD (DC/TMD) (21). The intention-to-treat sample included 199 participants who provided at least one follow-up assessment of the primary outcome. Inclusion criteria aimed to identify persons with frequent and moderate-to-severe TMD pain, while exclusion criteria were based on contraindications to

propranolol therapy and health conditions that may bias pain rating. A complete list of inclusion and exclusion criteria is provided in Supplemental Materials.

Randomization and blinding

Staff at the data coordinating center administered the site-stratified blocked randomization scheme with fixed permuted blocks of four, allocating subjects in a 1:1 ratio to propranolol or placebo. Other study staff and participants were masked to the allocation. The active drug and matching placebo were dispensed by site pharmacies.

Interventions

Extended-release propranolol 60 mg or placebo were administered during the treatment period once daily for 1 week, followed by twice daily for 8 weeks, and then tapered to once daily for 1 week.

Outcomes

The primary outcome designed to assess TMD pain was a mean weekly facial pain index (FPI) computed as a 7-day average of the product of two ratings: Average facial pain intensity during the day (reported on a 0–100 numeric rating scale) multiplied by pain duration (reported as the percentage of waking day with pain), divided by 100. Both facial pain intensity and duration were recorded in the daily symptom diary. The FPI was computed for each of the 7-day periods preceding study visits at 1, 5, and 9 weeks after randomization.

Secondary outcomes included: Migraine and tension-type headache assessed at baseline using a structured headache interview (8) based on the International Classification of Headache Disorders, 3rd edition (beta version) (22); the Headache Impact Test-6 (HIT-6), which evaluated headache-related disability (23); the Graded Chronic Pain Scale (GCPS), which evaluated TMD pain-related disability (24); the Hospital Anxiety and Depression Scale (HADS) (25), and vital signs. The structured headache interview recorded details of up to three different types of headache in separate sections. Each section asked about location, intensity, characteristics, duration, frequency, and aggravating factors associated with each type of headache. The final question asked about an average number of days per month with headache of any type during the past 3 months.

At each visit, participants reported their use of all medications, including the study drug. Concomitant medications were coded using the World Health Organization Drug Dictionary (WHODrug) version 2015.01. Inclusion/exclusion criteria related to

concomitant medications are presented in Supplemental Materials.

Sample size

Calculations made during study planning indicated that the target sample size of 200 subjects would provide 90% statistical power for the primary aim, which investigated the overall analgesic efficacy of propranolol. Statistical power was not calculated for the current hypotheses of effect modification or mediation. This was an exploratory analysis, proposed *a priori* in the statistical analysis plan on the grounds that comorbid migraine is scientifically and clinically relevant in treatment of painful TMD with propranolol.

Statistical methods

To evaluate the pre-specified hypothesis that migraine status at baseline is associated with variation in efficacy of propranolol for painful TMD, regression models tested for an interaction of migraine and allocated treatment group in predicting study endpoints. The regression models used generalized estimating equations (GEE) to account for repeated visits by participants. Consistent with the modified intention-to-treat principle, the models used data from all available follow-up visits. For the primary endpoint of FPI, efficacy was quantified as change in FPI, computed by subtracting the baseline value from the value at each follow-up visit (i.e. weeks 1, 5 and 9). For this exploratory objective investigating efficacy stratified according to migraine, the Statistical Analysis Plan specified three forms of the primary endpoint: The continuous variable and dichotomized indicators of $\geq 30\%$ and $\geq 50\%$ thresholds of treatment response. We therefore used linear GEE models to analyze mean change in FPI, and binomial logistic GEE models to analyze the two dichotomized thresholds of response, both of which are clinically meaningful thresholds of improvement in pain (26). Predictor variables were a binary indicator for the presence or absence of migraine at baseline, treatment group (two groups), study visit (three post-baseline categories), and all 2-way and 3-way interactions of migraine, treatment group, and visit. Other covariates were baseline FPI (modeled as a continuous variable), study site (three categories), sex (two categories) and race/ethnicity (two categories: non-Hispanic white or Other). GEE models were likewise used to evaluate a binary indicator signifying a post-baseline reduction of ≥ 6 points in the HIT-6 scale, which is considered a clinically important change (27).

To evaluate effect modification, an “estimate” statement (28) tested for a two-way interaction of the

treatment group with migraine at week 9. When evaluating effect modification, the threshold for statistical significance was $p < 0.05$ for the two-tailed test of the null hypothesis of no interaction at week 9. Other estimate statements calculated treatment-group differences in the odds of response along with 95% confidence limits (95% CL), from which number needed to treat (NNT) was calculated.

To determine efficacy across the full range of clinically-meaningful thresholds of 20–70% FPI reduction, binary logistic regression GEE models for each threshold were used to construct cumulative response curves (29). The percentage of the area under the curve (%AUC) was calculated for both the propranolol and placebo groups, with the %AUC difference between treatment groups representing the efficacy estimate. AUC values were calculated using the trapezoid rule, and bootstrap estimates of the standard error were obtained from 1000 replicated samples generated by random sampling, with replacement, of the observed data. Wald's test evaluated pairwise treatment-group differences in AUC for migraineurs and non-migraineurs.

For the second aim, causal mediation within the counterfactual framework (30) was used to explore changes in headache impact and changes in heart rate as potential mediators of the analgesic effect of propranolol on TMD pain. The allocated treatment group was the treatment variable and binary response of $\geq 50\%$ reduction in FPI at week 9 was the outcome variable. The mediator variable was either the change in the HIT-6 score from baseline to week 5 or the change in heart rate from baseline to week 5. For descriptive purposes, we calculated Kendall's tau as a measure of correlation between the dichotomized mediator and the binary outcome. While the RCT design means that other baseline variables are not associated with treatment allocation, there is potential for baseline variables to confound the treatment-mediator and the mediator-outcome relationship. A regression approach (30) was therefore used to control for potential confounding due to study site, sex and race. The regression models estimated odds ratios of the natural direct effect of propranolol on FPI reduction and the natural indirect effect (e.g. the portion of propranolol's effect on FPI reduction that was mediated by change in headache impact); those effects were also expressed as a percentage of the total effect of propranolol on pain index reduction. The causal mediation analysis was implemented with the "causalmed" procedure in SAS v9.4 using data for all randomized subjects. Based on the findings from aim 1, the analysis was repeated for migraineurs only.

Results

Participants

Of the 199 randomized participants who provided follow-up data, 174 (87%) completed follow-up through week 9, with equal percentages of completers in each treatment group (see Tchivileva et al. 2020 (20) for the flowchart and analyses of efficacy and safety). Most of the participants were young, white females. While 52% of participants met criteria for definite or probable migraine, 29% and 30% of identified migraineurs met criteria for chronic migraine or migraine with aura, respectively (Table 1). The demographic and baseline TMD-related characteristics were similar among participants with and without migraine except for the time since TMD onset (12 years vs. 9 years, respectively) and the GCPS measures that indicated significantly higher TMD pain-related disability and pain intensity in the migraineurs. Migraineurs reported greater headache frequency than non-migraineurs (17 vs. 12 headache days per month), higher mean HIT-6 score (59 vs. 50), and greater anxiety and depression.

Concomitant medication for TMD pain was used by approximately 20% of participants independently of their migraine status. However, headache medication was used by a significantly higher percentage of migraineurs than non-migraineurs (66% vs. 41%, $p < 0.001$). Among migraineurs, 34% reported taking headache medication for treatment of migraine: Almost all of them used acute migraine medication and only 4% reported preventive migraine medication (Table 1).

Effect modification of the primary endpoint and HIT-6 secondary endpoint by migraine

When efficacy was analyzed as the difference between treatment groups in the mean change in FPI at week 9, there was a small difference for migraineurs (adjusted mean = -3.6 , 95% CL = -9.7 , 2.4) but effectively no difference for non-migraineurs, and the migraine by treatment group interaction was not statistically significant ($p = 0.381$, Table 2). In the analysis of $\geq 30\%$ reduction in FPI at week 9, the efficacy of propranolol was greater among migraineurs (adjusted odds ratio [AOR] = 3.3 ; 95% CL = 1.4 , 8.1 ; $p = 0.009$; NNT = 3.7) than non-migraineurs (AOR = 1.3 ; 95% CL = 0.5 , 3.2 ; $p = 0.631$; NNT = 18.7) although the test for migraine by treatment group interaction did not reach statistical significance ($p = 0.139$) (Table 2). A similar tendency was observed for $\geq 50\%$ reduction in FPI: NNT = 3.9 for migraineurs versus 12.5 for non-migraineurs ($p = 0.260$ for interaction). The odds of ≥ 6 -point reduction in the HIT-6 score at week 9 were greater in migraineurs (AOR = 2.8 ; 95%

Table 1. Baseline demographic and clinical characteristics of participants and use of concomitant medications (ITT population)*.

Characteristic	No migraine			Migraine			p-value
	Placebo (n = 46)	Propranolol (n = 49)	Total (n = 95)	Placebo (n = 53)	Propranolol (n = 51)	Total (n = 104)	
Age, years	35.2 (15.1)	33.7 (12.4)	34.4 (13.7)	33.5 (11.6)	34.2 (12.1)	33.8 (11.8)	0.754
Sex							
Female, n (%)	35 (76.1)	36 (73.5)	71 (74.7)	43 (81.1)	41 (80.4)	84 (80.8)	0.306
Male, n (%)	11 (23.9)	13 (26.5)	24 (25.3)	10 (18.9)	10 (19.6)	20 (19.2)	
Race							
White, n (%)	31 (67.4)	38 (77.6)	69 (72.6)	40 (75.5)	41 (80.4)	81 (77.9)	0.571
Black, n (%)	8 (17.4)	8 (16.3)	16 (16.8)	10 (18.9)	4 (7.8)	14 (13.5)	
Asian, n (%)	5 (10.9)	2 (4.1)	7 (7.4)	1 (1.9)	3 (5.9)	4 (3.8)	
Other, n (%)	2 (4.3)	1 (2.0)	3 (3.2)	2 (3.8)	3 (5.9)	5 (4.8)	
TMD							
Time since onset, years	9.6 (10.1)	8.3 (8.3)	8.9 (9.2)	10.2 (8.8)	13.2 (10.7)	11.7 (9.8)	0.054
TMD myalgia and arthralgia, n (%)	43 (93.5)	44 (89.8)	87 (91.6)	49 (92.5)	49 (96.1)	98 (94.2)	0.465
Weekly pain index, 0–100 scale	29.7 (19.4)	27.8 (19.2)	28.7(19.2)	32.5 (18.6)	32.0 (20.7)	32.3 (19.5)	0.195
Weekly pain intensity, 0–100 scale	44.4 (16.1)	47.0 (14.5)	45.7 (15.3)	49.9 (14.8)	48.8 (16.0)	49.4 (15.3)	0.094
Weekly pain duration, 0–100 scale	60.6 (23.8)	53.2 (26.1)	56.8 (25.2)	59.6 (25.5)	59.9 (26.9)	59.8 (26.0)	0.410
Painful days in the last 30 days, n	25.4 (6.0)	23.9 (7.4)	24.6 (6.8)	22.7 (6.9)	23.4 (7.1)	23.1 (7.0)	0.109
Pain-free jaw opening, mm	28.4 (11.1)	32.1 (9.8)	30.3 (10.6)	30.7 (11.9)	27.8 (11.4)	29.3 (11.7)	0.530
TMD Graded Chronic Pain Scale							
Grades I-IIa, n (%)	35 (76.1)	34 (69.4)	69 (72.6)	23 (43.4)	24 (47.1)	47 (45.2)	< 0.001
Grades IIb-IV, n (%)	11 (23.9)	15 (30.6)	26 (27.4)	30 (56.6)	27 (52.9)	57 (54.8)	
Characteristic pain intensity, 0–100 scale	58.0 (13.9)	56.1 (13.5)	57.0 (13.6)	61.0 (14.8)	63.3 (16.2)	62.1 (15.5)	0.014
Disability score, 0–100 scale	17.8 (16.9)	20.9 (21.8)	19.4 (19.5)	34.8 (24.9)	33.8 (26.0)	34.3 (25.3)	< 0.001
Headache							
Time since migraine onset (years)	NA	NA	NA	15.4 (10.6)	14.8 (11.2)	15.1 (10.9)	NA
Time since TTH onset (years)	14.2 (10.7)	14.3 (11.2)	14.2 (10.9)	13.5 (7.8)	14.4 (9.4)	13.9 (8.5)	0.836
Chronic migraine prevalence, n (%)	NA	NA	NA	12 (22.6)	18 (35.3)	30 (28.8)	NA
Migraine with aura prevalence, n (%)	NA	NA	NA	18 (34.0)	13 (25.5)	31 (29.8)	NA
TTH prevalence, n (%)	40 (87.0)	41 (83.7)	81 (85.3)	31 (58.5)	25 (49.0)	56 (53.8)	< 0.001
Headache frequency, days per month	12.6 (9.6)	11.3 (9.5)	12.0 (9.5)	17.9 (9.7)	16.2 (9.2)	17.1 (9.5)	< 0.001
Migraine frequency, days per month	NA	NA	NA	10.7 (9.7)	10.4 (9.5)	10.5 (9.6)	NA
TTH frequency, days per month	9.9 (10.2)	8.9 (9.5)	9.4 (9.8)	8.1 (10.3)	6.0 (8.6)	7.1 (9.5)	0.097
HIT-6, 36–78 scale	50.8 (8.7)	49.1 (8.0)	49.9 (8.4)	59.1 (6.6)	59.4 (7.0)	59.3 (6.8)	< 0.001
Emotional functioning							
HADS anxiety, 0–21 scale	5.9 (3.6)	6.2 (4.0)	6.0 (3.8)	8.9 (4.9)	7.6 (4.3)	8.3 (4.6)	< 0.001
HADS depression 0–21 scale	2.4 (2.6)	3.2 (3.2)	2.8 (2.9)	4.1 (3.4)	4.2 (3.8)	4.1 (3.6)	0.005
Vital signs							
Heart rate, beats per minute	72.7 (10.6)	71.5 (11.3)	72.1 (10.9)	73.8 (12.6)	76.4 (11.7)	75.1 (12.2)	0.070
Systolic blood pressure, mmHg	119.6 (10.7)	121.8 (10.0)	120.7 (10.4)	124.2 (18.0)	121.8 (14.8)	123.0 (16.5)	0.242
Diastolic blood pressure, mmHg	70.5 (10.0)	72.3 (7.8)	71.4 (8.9)	73.9 (11.4)	72.9 (11.4)	73.4 (11.3)	0.166
Medication use post randomization							
TMD-specific medication, n (%)	10 (21.7)	9 (18.4)	19 (20.0)	9 (17.0)	13 (25.5)	22 (21.1)	0.841
Any headache medication, n (%)	18 (39.1)	21 (42.9)	39 (41.1)	32 (60.4)	37 (72.5)	69 (66.3)	< 0.001
Migraine medication, n (%)	NA	NA	NA	19 (35.8)	16 (31.4)	35 (33.7)	NA
Acute migraine medication, n (%)	NA	NA	NA	19 (35.8)	15 (29.4)	34 (32.7)	NA
Preventive migraine medication, n (%)	NA	NA	NA	2 (3.8)	2 (3.9)	4 (3.8)	NA

*Data are means (SD) or numbers (%).

p-values are from chi-square and t-test analyses, comparing values between the no-migraine and migraine groups.

HADS: Hospital Anxiety and Depression Scale; HIT-6: Headache Impact Test-6; ITT: intention to treat; SD: standard deviation; TMD: temporomandibular disorder; TTH: tension-type headache.

Table 2. Efficacy estimates and tests for a migraine by treatment group interaction at 9 weeks of treatment*.

Continuous endpoint	Placebo, mean (95% CL)	Propranolol, mean (95% CL)	AEE, mean (95% CL)	AEE difference: Migraine vs. no-migraine, mean (95% CL)	Interaction p-value	
Change from baseline to week 9 in mean weekly pain index						
No migraine	-14.3 (-19.1, -9.6)	-14.0 (-18.6, -9.5)	0.3 (-6.1, 6.7)	-3.9 (-12.8, 4.9)	0.381	
Migraine	-10.4 (-14.7, -6.1)	-14.0 (-18.6, -9.5)	-3.6 (-9.7, 2.4)			
Binary endpoint	Placebo responders, % (95% CL)	Propranolol responders, % (95% CL)	AOR 95% CL	p-value	NNT	Interaction p-value
30% responders in mean weekly pain index						
No migraine	59 (42, 74)	64 (47, 78)	1.3 (0.5, 3.2)	0.631	18.7	0.139
Migraine	48 (33, 63)	75 (59, 87)	3.3 (1.4, 8.1)	0.009	3.7	
50% responders in mean weekly pain index						
No migraine	40 (25, 58)	48 (32, 65)	1.4 (0.6, 3.5)	0.483	12.5	0.260
Migraine	36 (23, 52)	62 (44, 77)	2.8 (1.2, 6.8)	0.019	3.9	
HIT-6 responders						
No migraine	36 (20, 56)	40 (24, 58)	1.2 (0.5, 3.2)	0.705	22.7	0.221
Migraine	20 (10, 35)	41 (25, 60)	2.8 (1.1, 7.5)	0.035	4.7	

*Estimates from generalized estimating equations for linear and logistic models with predictor variables of migraine status, treatment, visit, all two-way and three-way interactions; study site, sex, and race as fixed effects; and a baseline value of the endpoint as a covariate.

95% CL: 95% confidence limits; AEE: adjusted efficacy estimate (propranolol minus placebo) for continuous endpoint; AOR: adjusted odds ratio (propranolol relative to placebo) for binary endpoint; HIT-6: Headache Impact Test-6; NNT: number needed to treat.

CL = 1.1, 7.5; $p = 0.035$; NNT = 4.7) than non-migraineurs (AOR = 1.2; 95% CL = 0.5, 3.2; $p = 0.705$; NNT = 22.7) with the statistically non-significant interaction ($p = 0.221$). Responder percentages for the FPI and HIT-6 across all study visits are presented in Figure 1.

When responder percentages were integrated for clinically meaningful thresholds of 20–70% reduction in FPI, the treatment group difference in cumulative response curves was greater for migraineurs (28 percentage point difference in AUC, 95% CL = 5%, 52%) than for non-migraineurs (6 percentage point difference in AUC, 95% CL = -21%, 33%) ($p = 0.081$) (Figure 2).

Causal mediation of propranolol efficacy

There was negligible correlation between the change in FPI and the change in HIT-6 at week 5 and week 9 with Kendall's tau ranging from 0.09 to 0.27 (Table 3). In the causal mediation analysis with HIT-6 as a potential mediator, the indirect effect of treatment on $\geq 50\%$ reduction in FPI was weak (OR = 1.05; 95% CL = 0.91, 1.19) and only 9% of the total effect was mediated by the reduction in HIT-6 (Figure 3(a)). In contrast, mediation analysis with heart rate as the potential mediator showed a stronger indirect effect (OR = 1.30; 95% CL = 0.86, 1.74) with reduction in heart rate mediating 46% of the total effect (Figure 3(b)).

Discussion

Summary of the main findings

In this RCT of propranolol among patients with chronic TMD pain, half of participants had migraine and the presence of migraine was associated with higher TMD pain-related disability and pain intensity. Across a wide range of clinically meaningful thresholds, propranolol had greater efficacy in reducing TMD pain among migraineurs than non-migraineurs. Intuitively, this finding might be anticipated as an improvement in TMD pain that occurs secondary to the improvement in migraine. However, there was no meaningful correlation between reduction in TMD pain and reduction in headache impact, and the causal mediation analysis revealed only a weak indirect effect of change in HIT-6 on the overall treatment effect. Instead, the overall treatment effect was better explained by reduction in heart rate secondary to propranolol use. The efficacy of propranolol for TMD pain was, therefore, not secondary to the reduction in headache impact but was consequent to the effect on heart rate.

Credibility of the effect modification analysis

Sun et al. (31) proposed 10 study design, analysis, and context criteria for evaluation of credibility of subgroup analyses in RCTs. Our effect modification analysis

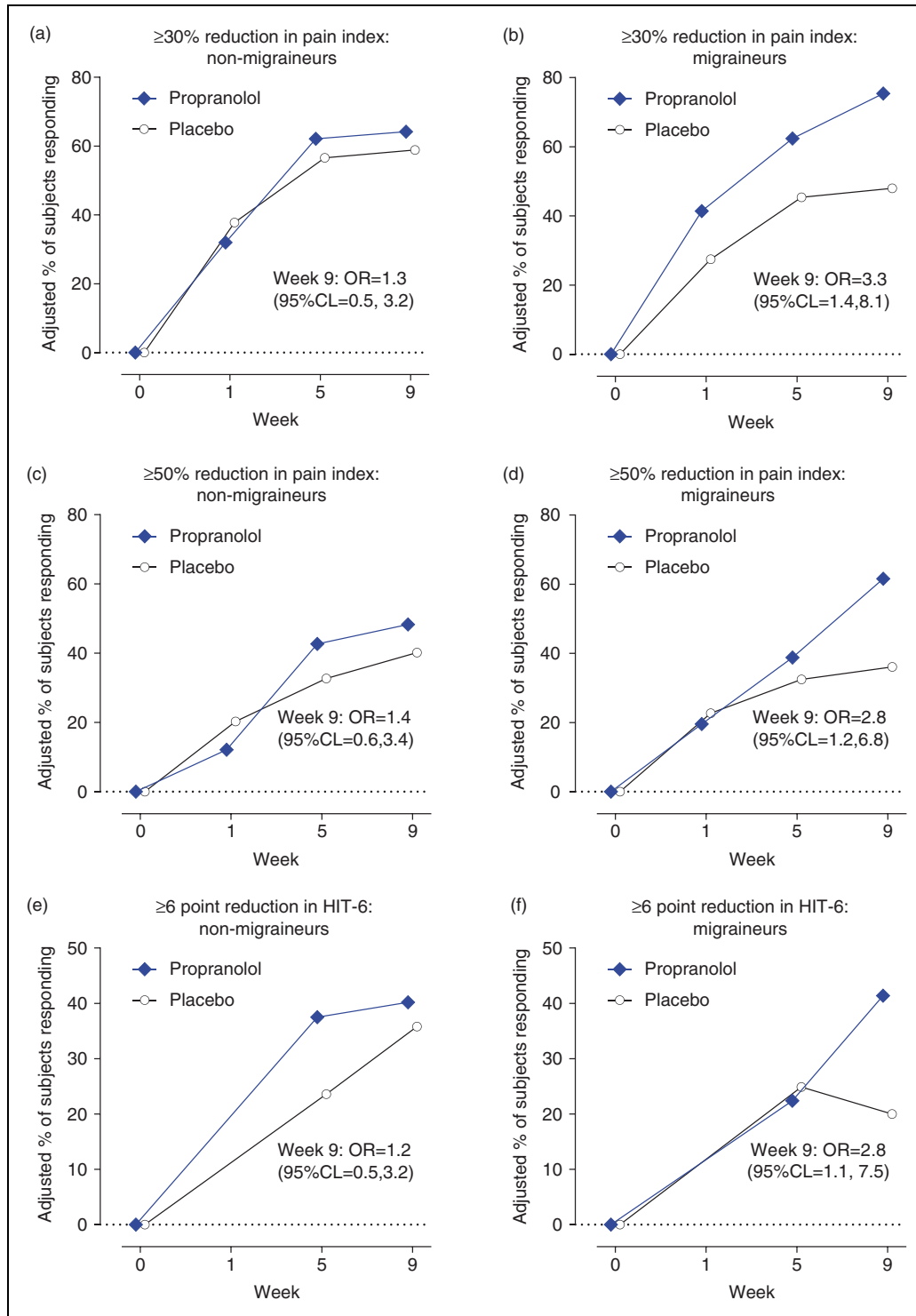


Figure 1. Change in three endpoints at three follow-up visits for participants in two treatment groups stratified according to the baseline migraine status. Endpoints were estimated for propranolol (◆) and placebo (○) groups in regression models (ITT population). Endpoints are: percentage of participants with a $\geq 30\%$ reduction in FPI plotted for (a) non-migraineurs and (b) migraineurs; percentage of participants with a $\geq 50\%$ reduction in FPI plotted for (c) non-migraineurs and (d) migraineurs; and percentage of participants reporting a reduction of ≥ 6 points in the HIT-6 scale plotted for (e) non-migraineurs and (f) migraineurs. FPI endpoints were recorded at up to three follow-up visits that occurred 1, 5 and 9 weeks after initiating treatment. Percentage reductions in FPI were calculated relative to baseline and dichotomized to signify the percentage of participants with $\geq 30\%$ and $\geq 50\%$ reductions. The HIT-6 score was reported at weeks 5 and 9 and dichotomized to signify the percentage of participants with a ≥ 6 -point post-baseline reduction considered a clinically meaningful improvement. Adjusted percentages were estimated from binomial logistic generalized estimating equation models with predictor variables of the baseline migraine status, treatment group, visit, and all two-way and three-way interactions. Covariates were study site, sex, and race/ethnicity (and for the FPI models, the baseline value of FPI). Estimate statements for each model were used to calculate adjusted odds ratios and 95% confidence limits at week 9.

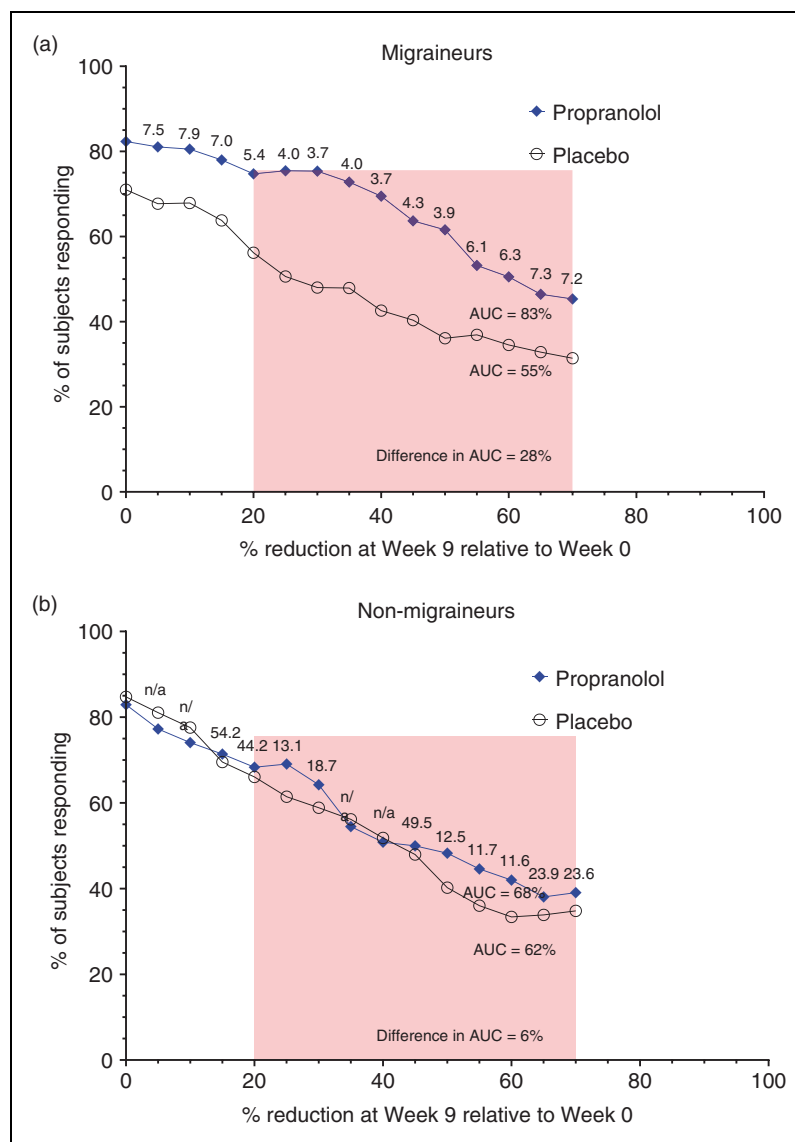


Figure 2. Cumulative proportion of FPI responders at week 9 for two treatment groups analyzed by migraine status (ITT population): (a) migraineurs and (b) non-migraineurs. FPI endpoints were recorded at up to three follow-up visits occurring 1, 5 and 9 weeks after initiating treatment with either propranolol (◆) or placebo (○). Adjusted percentages of participants responding, plotted on the vertical axis, were calculated by dichotomizing relative reductions at week 9 compared to week 0. Thresholds for dichotomization are shown on the horizontal axis. Adjusted percentages were estimated with binary logistic regression models using the generalized estimating equation method allowing for repeated visits by study participants. Numbers above plotted values represent a number needed to treat. Area under the curve (AUC) was calculated using the trapezoid rule and expressed as the percentage of maximum response within the range of 20% to 70% reduction (shaded rectangle).

fulfilled all five study design criteria, namely: i) migraine, the effect modifier, was classified at baseline; ii) efficacy was compared among subgroups within this study; iii) the hypothesis and iv) the direction of the effect modification were specified *a priori*; and v) migraine status was the single effect modifier tested. There was mixed support for two analytic criteria, namely: vi) interaction *p*-values did not reach statistical significance at the 0.05 threshold but, for the analyses of the cumulative response curves and $\geq 30\%$ responders,

p-values were below the 0.2 threshold used for interaction tests in the systematic review of pain treatment modifiers (32); and vii) three out of four subgroup analyses used the FPI and their results were strongly correlated. There was also support for the contextual criteria, namely: viii) subgroup differences in effect estimates were large (e.g. NNTs differed at least four-fold across subgroups); ix) the interaction was consistent across the analyses of the FPI and HIT-6; and x) there was a biological rationale for the hypothesized interaction.

Table 3. Overlap between participants' improvement in facial pain and headache impact (number (%) of participants)*

Pain index reduction	Assessment timepoints					
	5 weeks of treatment			9 weeks of treatment		
	HIT-6 non-responders	HIT-6 responders	τ	HIT-6 non-responders	HIT-6 responders	τ
30% non-responders	57 (33.5)	20 (11.8)		44 (27.0)	22 (13.5)	
30% responders	58 (34.1)	35 (20.6)	0.12	56 (34.4)	41 (25.2)	0.09
50% non-responders	82 (48.2)	24 (14.1)		64 (39.3)	24 (14.7)	
50% responders	33 (19.4)	31 (18.2)	0.27	36 (22.1)	39 (23.9)	0.25

*HIT-6 responders were defined as participants with a ≥ 6 -point reduction in the HIT-6 score.

HIT-6: Headache Impact Test-6; τ : Kendall's tau.

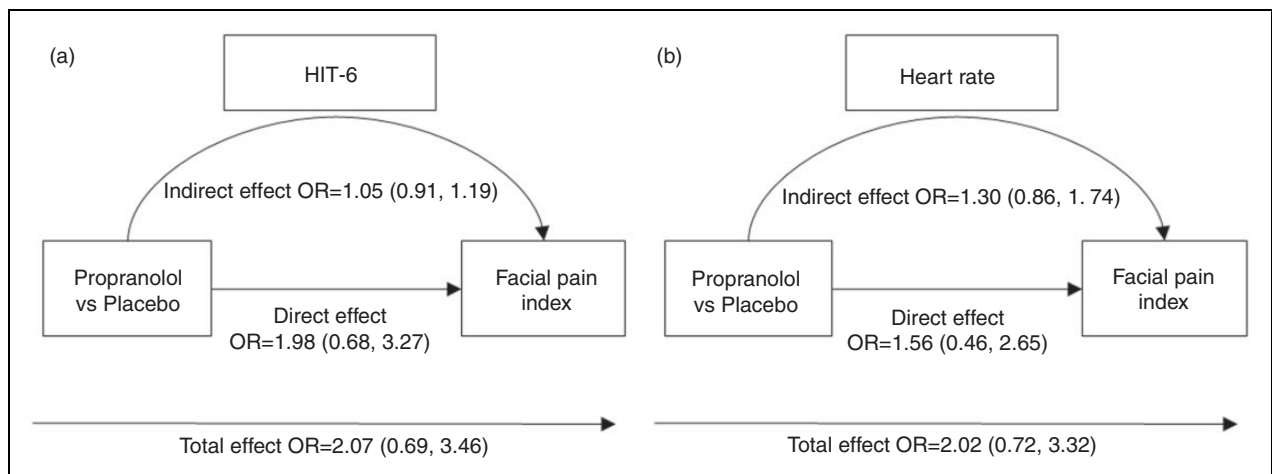


Figure 3. Causal mediation of propranolol effect on proportion of FPI responders at week 9. The mediation model is adjusted for study site, sex, race/ethnicity, and baseline FPI. (a) Mediation model with change in the HIT-6 score (continuous variable) as a potential mediator of the total effect of treatment group on a $\geq 50\%$ reduction in FPI. (b) Mediation model with change in heart rate (continuous variable) as a potential mediator of the total effect of treatment group on a $\geq 50\%$ reduction in FPI. Values are covariate-adjusted odds ratios (ORs) and 95% confidence limits.

Comparison with previously published studies and potential biological mechanisms of propranolol efficacy

Migraine prevalence of 52% in our cohort with myofascial TMD was comparable with prevalence of 56% (6) and 55% (7) reported in other studies. In SOPPRANO, migraine comorbidity was associated with greater severity and disability of TMD pain, similar to what was previously reported (6). While there is no precedent for our finding of greater efficacy of propranolol in reducing TMD pain among migraineurs compared to non-migraineurs, greater TMD severity in migraineurs could be a consequence of a central sensitivity syndrome characterized by augmented mechanisms of central sensitization in patients with multiple painful comorbidities (33). Since propranolol can penetrate the blood-brain barrier and block chronic sensitization of descending pain pathways to the

trigemino-cervical complex (13,14), its greater efficacy among TMD patients with comorbid migraine could be due to propranolol's targeting of abnormal central pain processing.

Interestingly, propranolol's efficacy for TMD pain was independent of its effect on headache impact. As only one third of the study migraineurs met criteria for chronic migraine, perhaps the correlation between relief of TMD pain and headache would have been stronger in the group consisting entirely of patients with chronic migraine. However, our study does not provide statistical power for this analysis. Instead, in our study, propranolol's efficacy was likely mediated by a reduction in heart rate. Propranolol decreases heart rate while increasing HRV and these effects on the cardiovascular and autonomic nervous system may explain the mechanism of pain reduction (18). In a recent RCT investigating the effect of propranolol on HRV and experimental pain, propranolol increased

HRV but did not affect pressure pain sensitivity or other mechanistic pain biomarkers (19). However, the study was conducted in healthy males, and the lack of antinociceptive effect on pain biomarkers may be due to the absence of abnormal pain processing in healthy volunteers and the use of a low single dose of the drug. HRV, which is inversely related to heart rate, was not measured in our study. A recent study concluded that correlation between a change in HRV and altered morbidity can be attributed to the concurrent change in heart rate (34). The mediating effect of heart rate observed in our study suggests that propranolol relieves TMD pain by restoring autonomic dysfunction which, in turn, dampens pain amplification.

Strengths and limitations

An important strength of this study was its randomized and placebo-controlled design with successful masking of participants and staff. In addition, the validated DC/TMD examination (21) was used for the classification of TMD myalgia and arthralgia. The primary outcome was derived from daily symptom diaries, eliminating recall bias. Finally, the excellent retention of study participants and their good compliance with the diaries and study drug added to the rigor of the study.

There are several limitations. First, migraine status was determined via a structured headache interview at the baseline visit. The use of daily headache diaries would be superior, but the focus of the trial was on

TMD. Second, in the absence of daily headache diaries, the effect of propranolol on migraine was assessed via the HIT-6 questionnaire. Nevertheless, the sensitivity of the HIT-6 as a measure of migraine improvement has been proven in previous studies. Third, although this study was not specifically powered for tests of statistical interaction or mediation, the benchmark for a minimum of 20 individuals in the smallest group when conducting subgroup analyses was fulfilled (35). Fourth, while the mediation analysis suggested a greater effect from change in heart rate than in the headache impact, the results did not reach statistical significance and should be interpreted with caution. Finally, as noted above, HRV was not measured in this study, limiting the insight on the pain mechanism underscoring the observed mediating effect of heart rate.

Conclusion

This RCT of patients with chronic myofascial TMD demonstrated that efficacy of propranolol in reducing TMD pain was enhanced in the presence of comorbid migraine. Hence, propranolol appears to be the drug of choice for management of painful TMD in migraineurs. Interestingly, the causal mediation analysis suggested that the reduction in TMD pain was mediated more by reduction in heart rate rather than by reduction in headache impact.

Clinical implications

- TMD patients should be evaluated for the presence of comorbid migraine.
- In patients with myofascial TMD, the presence of comorbid migraine is associated with greater efficacy of propranolol in reducing TMD pain.
- The efficacy of propranolol in reducing TMD pain is not mediated by decreased headache impact, but by propranolol's effect on heart rate.

Acknowledgements

The authors wish to thank patients who participated in the trial, the SOPPRANO research staff, and cardiologists Drs Alan Hinderliter (the University of North Carolina at Chapel Hill), David Sheps (the University of Florida), and Thomas Cimato (the University at Buffalo) for monitoring the participants' safety.


Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Funding for this study was provided by the National Institutes of Health (NIH)/National Institute of Dental and Craniofacial Research (NIDCR) R34-DE022088 and U01-DE024169 grants.

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