Treatment of Comorbid Migraine and Temporomandibular Disorders: A Factorial, Double-Blind, Randomized, Placebo-Controlled Study

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Aims: *To investigate the effectiveness of single and concomitant treatment of migraine and temporomandibular disorders (TMD) in women with the comorbidity.* ***Methods:*** *Eligible female patients met International Classification of Headache Disorders, second edition (ICHD-2) criteria for migraine with or without aura and the Research Diagnostic Criteria for myofascial TMD (Grade ll or lll). After a run-in period (30 days), women with both migraine and TMD were enrolled into a four-arm, double-blind, placebo-controlled, factorial study testing the separate and joint effects of a migraine treatment (propranolol 90 mg) and a TMD treatment (stabilization splint [SS]) in four groups of patients. The four treatment groups were propranolol and SS (n = 22); propranolol placebo and SS (n = 23); propranolol and non-occlusal splint (NOS) (n = 23); and propranolol placebo and NOS (n = 21). The primary endpoint for migraine was change in headache days from baseline to the third month, and the secondary endpoint was change in days with at least moderate headache in the same period. The TMD endpoints included pain threshold and mandibular vertical range of motion. Data were analyzed using analysis of variance (ANOVA, Dunn's post-hoc test) or Kruskal-Wallis test.* ***Results:*** *For the primary endpoint, in intention-to-treat (ITT) analyses (n = 94), propranolol and SS were associated with a nonsignificant reduction in the number of headache days, relative to all other groups. For per-protocol (PP) Completer analyses (n = 89), differences in the number of headache days reached significance (P < .05). The propranolol and SS group was significantly superior to the other groups on all other headache endpoints and in disability, in both ITT and PP analyses. No significant differences among groups were seen for the TMD parameters.* ***Conclusion:*** *In women with TMD and migraine, migraine significantly improved only when both conditions were treated. The best treatment choice for TMD pain in women with migraine is yet to be defined.* J OROFAC PAIN 2013;27:325–335. doi: 10.11607/jop.1096

Key words: clinical trial, migraine, occlusal splint, propranolol, temporomandibular disorders

Migraine and temporomandibular disorders (TMD) are prevalent diseases[1–5] with several similarities. Both conditions can cause headache and facial pain, and they are frequently associated with the development of craniofacial allodynia during painful exacerbations.[6–11] Furthermore, the majority of migraine sufferers have at least one symptom of TMD,[12] and TMD and migraine are comorbid.[13–15] In addition, TMD has been suggested as a risk factor for increased migraine frequency and new onset of chronic migraine.[12,16,17]

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Clinical experience suggests that migraine treatment may be more difficult in patients with TMD, relative to those without the comorbidity.[11,18] The reciprocal influence of migraine on TMD treatment outcomes has not been studied. In clinical practice, when migraine and TMD co-occur, each disorder is separately treated, but it is not clear if combined management approaches improve patient outcomes.

Propranolol is approved for the preventive treatment of migraine and is one of the most widely used migraine preventive medications.[19] Although limited evidence suggests its benefit in preventing pain associated with TMD,[20–22] the drug has not been formally tested in those with TMD and migraine. Similarly, a stabilization splint (SS) is often used for the treatment of TMD and may sometimes be associated with headache improvement,[23–26] although its influence on migraine outcomes in those with comorbidity has not been assessed.

Accordingly, the aim of this study was to investigate the effectiveness of single and concomitant treatment of migraine and TMD in women with the comorbidity. To achieve the aim, a four-arm factorial, double-blind, placebo-controlled study was conducted to assess migraine and TMD outcomes.

Materials and Methods

This was a randomized, placebo-controlled, double-blind, parallel-group study conducted in a tertiary orofacial pain center. Patients were enrolled during the years of 2007 and 2008.

Participants

Since migraine and TMD are more common in women than in men, only women were included in order to decrease heterogeneity. Other inclusion criteria were: *(1)* migraine with or without aura according to the second edition of the International Classification of Headache Disorders (ICHD-2),[27] with the first attack before the age of 50 years; *(2)* from 2 to 14 days of headache per month; *(3)* myofascial TMD with grade II or III of TMD chronic pain, as per the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD), Axis I and II[7]; and *(4)* adequate bilateral occlusal contacts between premolars and molars.

Exclusion criteria were: *(1)* abuse of alcohol or other drugs; *(2)* medication-overuse headache according to the criteria proposed by the ICHD-2[27]; *(3)* use of migraine prophylaxis over the 6 months prior to the study; *(4)* use of antidepressants or antipsychotics in the previous 3 months; *(5)* known sensitivity to the drugs used in this study; *(6)* women of childbearing potential who were not using contraceptives; and *(7)* women with other chronic diseases.

The protocol and study forms were approved by the Research Ethics Committee of Araraquara Dental School (UNESP–Univ Estadual Paulista, São Paulo, Brazil). Written informed consent was obtained from all participants.

Assessment of Temporomandibular Disorders

TMD was assessed using the validated Portuguese version of the RDC/TMD.[7,28,29] The RDC/TMD consists of a dual-axis approach (Axis I and II), established by a 30-item questionnaire and a physical examination. Details of the RDC have been described elsewhere.[7] Axis I is used to stratify TMD into three groups: Group I, TMD with muscular disorders; Group II, TMD with temporomandibular joint (TMJ) disc displacement; and Group III, TMD with *(a)* arthralgia, *(b)* osteoarthritis, or *(c)* osteoarthrosis of the TMJ. Axis II assesses TMD-related chronic pain, depression, nonspecific physical symptoms, and limitations in jaw function. It stratifies TMD pain into five grades: Grade 0, no pain in the prior 6 months; Grade I, low disability and intensity; Grade II, low disability–high intensity; Grade III, high disability–moderately limiting; and Grade IV, high disability–severely limiting.[7] Only women with painful TMD with muscular involvement were included.

In addition to the RDC, pressure pain thresholds (PPT) were established using a pressure algometer applied bilaterally on the lateral pole of the TMJ, the inferior superficial masseter muscles, and the anterior temporalis muscles. The PPT corresponded to the mean of three applications at each of the sites. To ensure reliability of measurements, a template of acetate paper was customized for each patient. References were the line from the tragus to the eye lateral canthus and from the tragus to the labial commissure. The template was used as a guide in the subsequent evaluations.[30,31]

Finally, the mandibular vertical range of motion (mm) during unassisted mouth opening was registered using a digital pachymeter placed between the edges of the right maxillary and mandibular incisors. The vertical range of motion corresponded to the last measurement of three opening movements made by the patient.

Migraine Diagnosis and Evaluation

One of the authors of this study, a neurologist with headache subspecialty training (LTU), evaluated all

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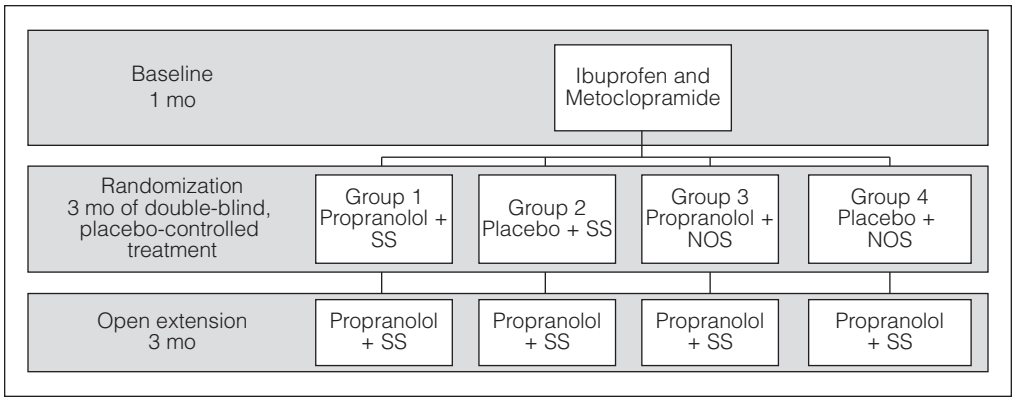

Fig 1 Study protocol. SS, stabilization splint; NOS, non-occlusal splint.

potential participants. Migraine was diagnosed as per the ICHD-2.[27] Migraine-related disability was evaluated using the Migraine Disability Assessment Test (MIDAS),[32] Portuguese version.[33] Frequency and severity of pain were assessed using daily headache calendars. As per the ICHD-2,[27] severity of migraine pain was classified as mild, moderate, or severe. To help ensure the blinding of the study, the author assessing migraine status was not involved in measuring treatment outcomes.

Study Protocol

After agreeing to participate, patients were enrolled in a 1-month, run-in phase, where migraine and TMD characteristics were documented. The protocol of the study is shown in Fig 1. During the run-in phase, participants could use ibuprofen 600 mg and metoclopramide 10 mg for the acute treatment of migraine (these rescue medications could be used throughout the study; no other medications other than the study drugs were allowed). Paper diaries were used to record the headache frequency, duration and intensity of migraine attacks, as well the consumption of acute medication during all phases of the study.

Patients were then randomized to one of the following groups: *(1)* propranolol 30 mg/day (tid) and stabilization splint (SS)[34]; *(2)* placebo and SS; *(3)* propranolol and non-occlusal splint (NOS); or *(4)* placebo and NOS. A blocked randomization method was applied. Since a final sample of 80 patients was needed, one of the authors (DAGG) prepared 25 envelopes (yielding 100 patients and anticipating a dropout rate of 20%) containing 4 numbers linked to each treatment group. Each patient removed one of these numbers until envelope completion.

All splints were made on the maxillary arch with thermosetting resin in casts mounted in a semi-adjustable articulator. The maxillomandibular relationship was registered in maximal intercuspation. A leaf gauge was used for occlusal registration and to define about 2 mm of thickness at the posterior region. All teeth of the opposite arch were in contact with the SS. The NOS (Fig 2) allowed tooth contact between the arches; it had very thin metal clasps that did not interfere with the occlusion. Since all splints partially covered the buccal and palatal surfaces of the maxillary teeth, the patients' perception of treatment was similar, and they could not distinguish between SS and NOS. Patients were instructed to use the NOS and a SS only during the night, and all splints were readjusted monthly. The splints were developed by one investigator (DAGG), who did not participate in further steps of the protocol in order to maintain blinding of the study. Propranolol was started at a dose of 30 mg/day and the dose was increased to 30 mg two times per day in the second week and 30 mg three times per day from the third week.[35–37] Placebo pills were made identical to the propranolol and were given to patients in the same regimen during the blinded phase.

After the blinded phase (3 months), all patients were switched to propranolol and SS (open extension phase).

Outcomes

Patients were assessed monthly, and the TMD and headache assessments were performed as in the run-in phase. Headaches were measured with the use of paper daily calendars. Severity of headache attacks was measured by using the categorical four-point scale defined by the ICHD-2[27] (considered for primary and secondary endpoints) on the daily calendars, and also by using a visual analog scale (VAS) during the monthly consultation. A blinded investigator applied the MIDAS questionnaire at baseline, month 3, and month 6. The TMD evaluation included monthly

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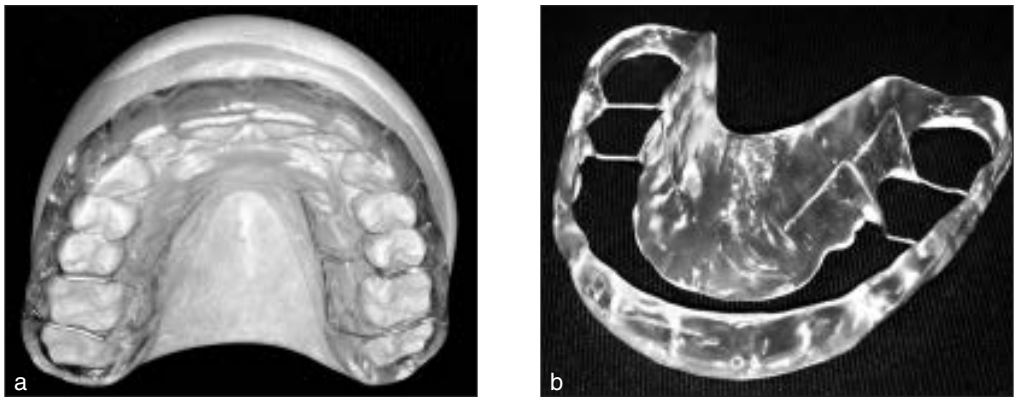

Fig 2 Non-occlusal splint.

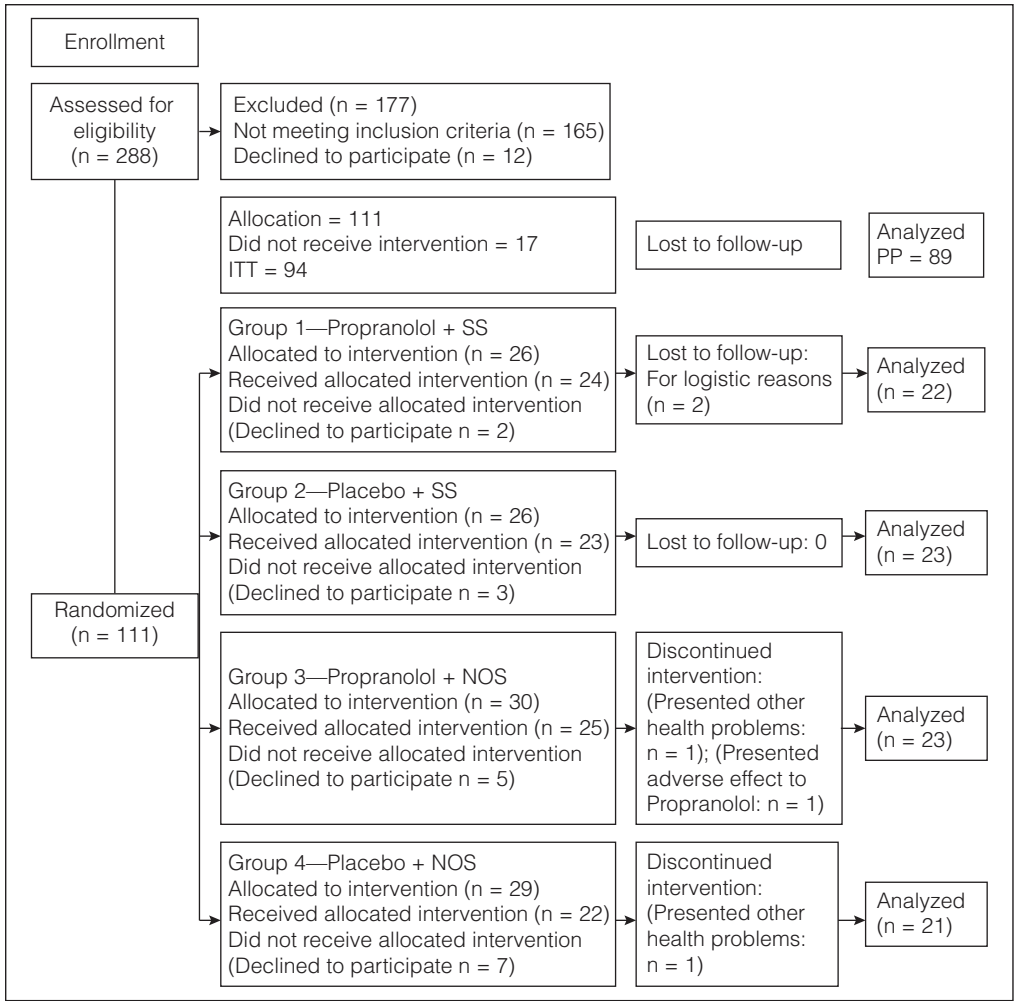

Fig 3 Participants flow diagram. ITT, intention to treat; PP, per protocol; SS, stabilization splint; NOS, non-occlusal splint.

assessment of PPT (muscles and TMJ) and the mandibular vertical range of motion. The RDC/TMD was also reapplied at the end of the open-extension phase (month 6) to capture any TMD changes.

The study was powered for the migraine endpoint, and assessment of TMD endpoints was exploratory. Accordingly, the primary endpoint was change in the number of headache days from baseline

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Table 1 Demographic and Clinical Characteristics of the Intention-to-Treat Sample at Baseline

	Group 1 Propranolol + SS (n = 24)	Group 2 Placebo + SS (n = 23)	Group 3 Propranolol + NOS (n = 25)	Group 4 Placebo + NOS (n = 22)	Total (n = 94)	*P*
Mean age (SD), y	33.4 (10.1)	35.8 (7.3)	33.9 (8.8)	34.1 (9.3)	34.3 (8.8)	.818
Race, n (%)						
White	22 (27.8)	19 (24.1)	19 (24.1)	19 (24.1)	79 (100)	
Black	0	4 (44.4)	3 (33.3)	2 (22.2)	9 (100)	.297
Brown	2 (33.3)	0	3 (50)	1 (16.7)	6 (100)	
Educational level, n (%)						
Low (1–8 y)	6 (33.3)	3 (16.7)	7 (38.9)	2 (11.1)	18 (100)	
Middle (9–11 y)	9 (19.1)	12 (25.5)	11 (23.4)	15 (31.9)	47 (100)	.373
High (12–25 y)	9 (31)	8 (27.6)	7 (24.1)	5 (17.2)	29 (100)	
Marital status, n (%)						
Married	10 (17.5)	17 (29.8)	17 (29.8)	13 (22.8)	57 (100)	
Single	10 (41.7)	5 (20.8)	5 (20.8)	4 (16.7)	24 (100)	.225
Separated/divorced	4 (36.4)	1 (9.1)	2 (18.2)	4 (36.4)	11 (100)	
Grade of TMD Chronic Pain Axis II/RDC-TMD, n (%)						
Grade II	16 (30.7)	12 (23.1)	14 (27)	10 (19.2)	52 (100)	.529
Grade III	8 (19.1)	11 (26.2)	11 (26.2)	12 (28.5)	42 (100)	
Facial pain (average of last 6 mo)	8.5 (1.1)	7.9 (1.5)	8.4 (1.5)	7.8 (1.8)	8.2 (1.5)	.503
PPT (mean of masseter muscle)	1.4 (0.5)	1.3 (0.5)	1.3 (0.5)	1.2 (0.4)	1.3 (0.5)	.669

SS, stabilization splint; NOS, non-occlusal splint; TMD, temporomandibular disorders; RDC/TMD, Research Diagnostic Criteria for Temporomandibular Disorders; PPT, pressure pain threshold.

to month 3, contrasting the several groups. The secondary endpoint was change in the number of moderate and severe headaches. Other endpoints included assessments at other time points, MIDAS scores, and migraine intensity (VAS). For TMD, reduction of TMD grade of chronic facial pain and PPTs were assessed.

Statistical Analysis

This study was planned to generate pilot data as a preliminary step for a large-scale clinical trial. Sample size was calculated to yield a significance level of 5% with 80% power to detect a difference of 20% for the primary endpoint by using one-sided tests. A reduction in headache frequency of approximately 20% for the primary endpoint was assumed, comparing propranolol placebo and NOS with the maximal intervention group. Sample size was defined as being 80 patients.

Normality was tested using the Kolmogorov-Smirnov test. For parameters with normal distribution, variables were contrasted using ANOVA followed by the Dunn's post-hoc test. For nonparametric data, the Kruskal-Wallis test was used. Tests were performed in the intention-to-treat (ITT) sample, with last observation carried forward (LOCF) as well as in those completing all assessment (per-protocol [PP]).

Sample size was calculated for the primary endpoint, but in order to obtain exploratory data to guide decisions on secondary endpoints for future clinical trials, several other endpoints were assessed. Since the only aim was to obtain preliminary data on these exploratory endpoints, tests were not corrected for multiplicity (eg, Bonferroni) and data presented in the results should be interpreted as uncorrected for multiple tests.

Results

Of 288 patients assessed for eligibility, 111 met the inclusion criteria and were randomized. Of these, 17 (15.3%) withdrew during the run-in period. Accordingly, the ITT population consisted of 94 patients. Among the ITT population, 89 participants (94.7%) completed the 3 months of blinded treatment to form the PP analyses group. Sample size was, therefore, sufficient for both the ITT and PP analyses (Fig 3).

Demographic and TMD features of the participant sample are described in Table 1. The randomization yielded four groups that were very similar at baseline. Most participants were white (84%), married (60.6%), and had 9 or more years of education (80.8%). As for TMD features, grade II

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Table 2 Primary and Secondary Endpoints by Treatment Group at Baseline and After the 3 Months of Treatment, on Intention to Treat

	Intention to Treat					
	Group 1 Propranolol + SS (n = 24)	Group 2 Placebo + SS (n = 23)	Group 3 Propranolol + NOS (n = 25)	Group 4 Placebo + NOS (n = 22)	Total (n = 94)	*P*
Primary endpoint						
Headache frequency, mean (SD)						
Baseline	8.2 (3)	9.2 (5. 7)	9.5 (6.2)	8.9 (5.8)	8.9 (5.2)	.916
After 3 mo	3.1 (2.9)	5.9 (3.5)	5.5 (6.3)	5 (3.1)	4.9 (4.3)	.016
Mean of Reduction in 3 mo	–5.1 (3.8)	–3.2 (4.2)	–3.9 (3)	–3.9 (5.4)	–4 (4.1)	.109
Secondary endpoints						
Moderate and severe headache frequency, mean (SD)						
Baseline	6.1 (2.9)	6.0 (4.6)	6.4 (4.1)	6.2 (4)	6.2 (3.9)	.929
After 3 mo	1.5 (1.9)	3.7 (2.7)	4.6 (6)	3.4 (2.8)	3.3 (3.8)	.011
Mean of Reduction in 3 mo	–4.6 (3.2)	–2.3 (3.7)	–1.8 (4.9)	–2.8 (3.9)	–2.9 (4.1)	.022
MIDAS score						
Baseline	59.7 (49)	42.1 (36.3)	56.5 (49.2)	34.4 (31.6)	48.6 (43.1)	.239
After 3 mo	18.7 (20.4)	26.5 (45.5)	38.4 (40.67)	25.5 (26.5)	27.5 (35.1)	.564
Mean of Reduction in 3 mo	–41.0 (46.8)	–15.6 (31.3)	–18.0 (51.2)	–8. 9 (28.9)	–21.2 (42.3)	.025
Headache VAS						
Baseline	7.1 (1.8)	5.2 (2)	5.5 (1.8)	6.2 (1.7)	6.0 (2.0)	.002 (comparing 2 × 1) .007 (comparing 3 × 1)
After 3 mo	3.6 (2.6)	3.5 (1.8)	3.8 (2.3)	4.6 (2.6)	3.9 (2.3)	.380
Mean of Reduction in 3 mo	–3.5 (2.7)	–1.7 (2.7)	–1.6 (3.1)	–1.6 (3.1)	–2.1 (3.0)	.081

SS, stabilization occlusal splint; NOS, non-occlusal splint; VAS, visual analog scale; MIDAS, Migraine Disability Assessment Test.

chronic pain was present in 55.3% and grade III in 44.7% of the patients. Mean intensity of facial pain over the past 6 months was VAS = 8.2 (SD = 1.5). Mean masseter PPT of the total sample was 1.3 KgF (SD = 0.5). Since the mean of PPT of the TMJ, masseter, and temporalis muscles did not differ significantly among groups ($P > .05$), only the data from the masseters are presented.

Headache Outcomes

Table 2 displays the primary and secondary endpoints for the ITT and PP samples. For ITT, mean reduction of headache days from baseline to the third month of blinded treatment (primary endpoint) was numerically but nonsignificantly greater in group 1 (–5.1 days) relative to other groups (group 2: –3.2; groups 3 and 4: –3.9). Differences reached statistical significance for the PP analyses (group 1 = –5.4 days; group 2 = –3.2; group 3 = –4.1; group 4 = –3.5; $P < .05$).

For the secondary endpoint (change in moderate or severe headache days), differences were significant after 3 months of treatment both for ITT ($P = .02$) and PP ($P = .01$) with those in group 1 having additional benefits relative to all other groups (Table 2).

Those in group 1 had a significantly higher reduction in MIDAS scores relative to all other groups (ITT: $P = .025$; completers: $P = .016$) when comparing baseline with the third month.

When severity of headache was measured using the VAS, the groups were imbalanced at baseline (Table 2), and mean severity was higher for group 1. At 3 months versus baseline, mean VAS reduction approached significance for group 1 relative to the others at ITT (–3.5; $P = .081$) and for the completers (–3.5; $P = .074$). There was not enough power to permit adjustments for baseline severity.

Figure 4 illustrates the monthly headache frequency as a function of treatment group, at the blinded and open-extension phase. For both ITT (Fig 4a) and PP (Fig 4b), differences between groups were significant at the 2nd, 3rd, 4th, and 5th months. In both cases, group 1 presented a higher reduction of headache frequency when compared with the other groups.

TMD Outcomes

Treatment groups yielded virtually identical results at 3 and 6 months. No significant differences were seen. Assessments of masseter PPT and mandibular range of motion values at different time points are

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and Completers

Completers					
Group 1 Propranolol + SS (n = 22)	Group 2 Placebo +SS (n = 23)	Group 3 Propranolol + NOS (n = 23)	Group 4 Placebo + NOS (n = 21)	Total (n = 89)	*P*
8.4 (2.8)	9.2 (5.7)	9.5 (6.5)	8.5 (5.6)	8.9 (5.2)	.746
3.1 (3.0)	6.0 (3.5)	5.4 (6.6)	5.0 (3.2)	4.9 (4.4)	.015
–5.4 (3.5)	–3.2 (4.2)	–4.1 (3)	–3.5 (5.1)	–4.0 (4.1)	.043
6.2 (2.9)	6.0 (4.6)	6.4 (4.3)	6.0 (4.0)	6.1 (3.9)	.875
1.4 (1.8)	3.7 (2.7)	4.5 (6.19)	3.5 (2.8)	3.3 (3.8)	.012
–4.8 (2.8)	–2.3 (3.7)	–1.9 (5.1)	–2.4 (3.7)	–2.8 (3.7)	.011
61.9 (50.5)	42.1 (36.2)	55.6 (51.2)	30.8 (27.4)	47.8 (43.6)	.194
17.1 (19.7)	26.5 (45.5)	36.0 (41.4)	21.5 (19.1)	25.5 (34.2)	.716
–44.8 (47.2)	–15.6 (31.3)	–19.6 (53.17)	–9.3 (29.5)	–22.3 (43.1)	.016
7.2 (1.9)	5.2 (2.1)	5.7 (1.7)	6.4 (1.8)	6.1 (2.0)	.003 (comparing 2 × 1) .018 (comparing 3 × 1)
3.6 (2.6)	3.5 (1.8)	3.7 (2.4)	6.4 (7.2)	4.2 (4.1)	.061
–3.5 (2.8)	–1.7 (2.8)	–2.0 (3.1)	0.01 (7.5)	–1.8 (4.5)	.074

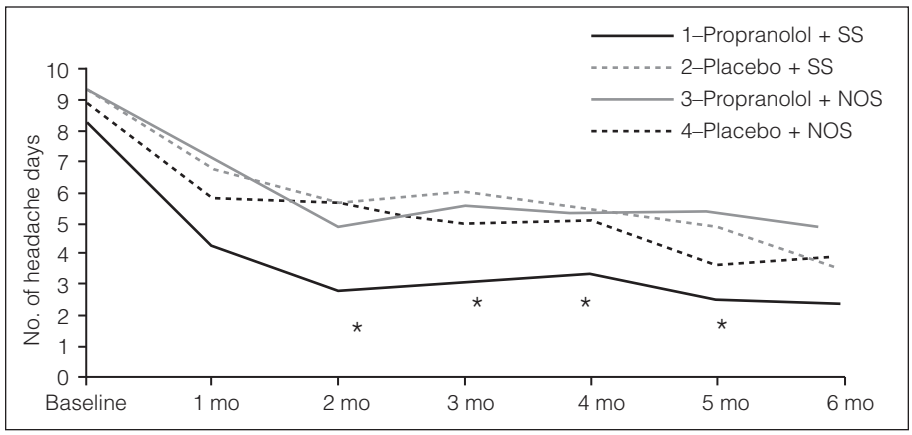

Fig 4a Intention to treat: Average frequency of headache according to the treatment group at baseline and after 1 to 6 months of treatment. *Kruskal Wallis test ($P < .05$). SS, stabilization splint; NOS, non-occlusal splint.

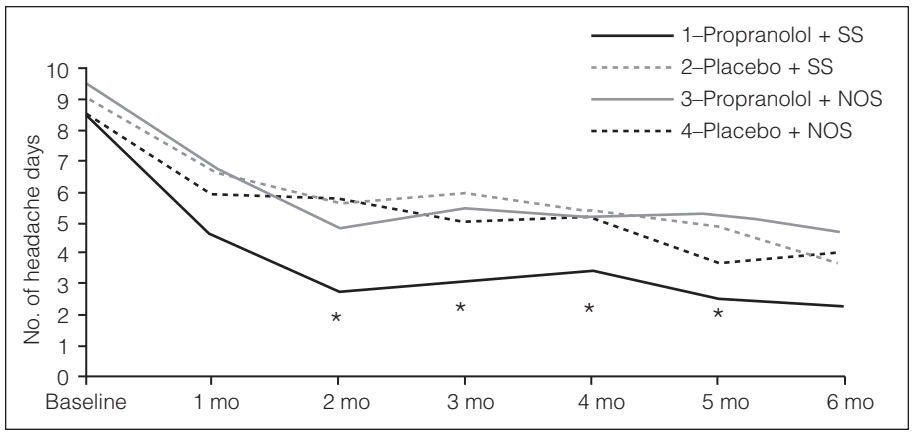

Fig 4b Completers: Average frequency of headache according to the treatment group at baseline and after 1 to 6 months of treatment. *Kruskal Wallis test ($P < .05$). SS, stabilization splint; NOS, non-occlusal splint.

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Table 3 TMD Assessments by Treatment Group at Baseline, After 3 Months, and After 6 Months of Treatment

	Intention to Treat					
	Group 1 Propranolol + SS (n = 24)	Group 2 Placebo + SS (n = 23)	Group 3 Propranolol + NOS (n = 25)	Group 4 Placebo + NOS (n = 22)	Total (n = 94)	*P*
Average of right and left masseter PPT, mean (SD)						
Baseline	1.4 (0.5)	1.3 (0.5)	1.3 (0.5)	1.2 (0.4)	1.3 (0.5)	.669
After 3 mo	1.1 (0.3)	1.2 (0.5)	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	.713
After 6 mo	1.2 (0.2)	1.2 (0.4)	1.1 (0.3)	1.1 (0.2)	1.1 (0.3)	.802
Mandibular vertical range of motion, mm; mean (SD)						
Baseline	42.1 (7.3)	41.8 (6)	42.5 (4.9)	40.7 (4.7)	41.8 (5.8)	.768
After 3 mo	42.1 (8.7)	40.8 (5.8)	42.1 (6.1)	42.5 (6.1)	41.9 (6.7)	.833
After 6 mo	42.6 (7.4)	39.8 (6.7)	40.8 (5.9)	42.8 (6.6)	41.5 (6.7)	.365

SS, stabilization occlusal splint; NOS, nonocclusal splint; PPT, pressure pain threshold.

Table 4 Average Severity of Facial Pain at Baseline and After 6 Months of Treatment

	Group 1 Propranolol + SS		Group 2 Placebo + SS		Group 3 Propranolol + NOS		Group 4 Placebo + NOS		Total		
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	*P*
Baseline	22	8.6 (1)	19	7.9 (1.5)	16	8.5 (1.5)	20	7.7 (1.8)	77	8.2 (1.5)	.269
After 6 mo	22	4.7 (3.4)	21	4.8 (3.6)	18	4.8 (3.4)	20	4.0 (3.5)	81	6.1 (2.6)	.852
Mean of reduction in 6 mo	22	–3.9 (3.2)	19	–3.1 (3.9)	16	–4.1 (3.7)	20	–3.7 (3.4)	77	–3.7 (3.5)	.801

SS, stabilization occlusal splint; NOS, non-occlusal splint.

shown in Table 3. Also, the mean of temporalis and TMJ PPTs did not differ statistically ($P > .05$) between groups at 3 and 6 months.

Table 4 presents the average severity of facial pain during the last 6 months at baseline and at the end of the study (6 months). Although all groups improved from baseline, significant differences were not found. Groups 1 and 3 showed greater reduction in comparison with groups 2 and 4, following a pattern similar to the migraine endpoint.

At baseline, the proportion of individuals with TMD pain classified as grade II or III was similar across groups. Overall improvement was seen at the end of the study relative to baseline, but no differences were seen related to the treatment group. Nonetheless, 46.8% of ITT and 48.3% of completers were classified as grade I or no TMD chronic pain at the end of treatment compared with 55.3% of grade II and 44.7% grade III at baseline.

Discussion

This study assessed the role of combination treatment, propranolol monotherapy, SS monotherapy, and placebo in women with migraine and TMD. The study yielded remarkably consistent results. For the headache primary endpoint, combination treatment approached but did not reach statistical significance versus the other three treatment groups (propranolol alone, SS therapy alone, or placebo) in the ITT sample. It did reach statistical significance in the PP analyses. For other headache endpoints, differences were all significant and favored combination treatment. Furthermore, combination treatment was associated with significant improvement in migraine-related disability relative to other treatment groups. For TMD outcomes, no significant differences were seen.

Disentangling the individual effects of migraine and TMD treatments is a unique contribution of the present study to the current status of knowledge. The results suggest that in women with migraine and TMD, combination therapy is associated with improved migraine outcome. Treating migraine alone (propranolol and NOS) was no better than not treating migraine (placebo and NOS), and treating only TMD pain alone (placebo and SS) was also not effective. Although it was not the aim of this study, the results did not allow for any conclusion on which is the best approach to treat TMD pain in women with migraine.

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Completers					
Group 1 Propranolol + SS (n = 22)	Group 2 Placebo + SS (n = 23)	Group 3 Propranolol + NOS (n = 23)	Group 4 Placebo + NOS (n = 21)	Total (n = 89)	*P*
1.4 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.4)	1.3 (0.5)	.664
1.0 (0.3)	1.2 (0.5)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	.662
1.1 (0.2)	1.2 (0.4)	1.1 (0.3)	1.2 (0.2)	1.1 (0.3)	.756
41.8 (7.6)	41.4 (6)	42.9 (4.6)	40.4 (4.6)	41.7 (5.8)	.590
41.6 (8.9)	40.8 (5.8)	42.3 (6.4)	42.2 (6)	41.7 (6.8)	.873
42.0 (7.6)	39.8 (6.7)	40.9 (6.2)	42.5 (6.6)	41.3 (6.8)	.528

The relationships of migraine and TMD are complex. Migraine and TMD are often comorbid, and TMD is a risk factor for migraine chronification.[11–14,16,17,38] The relationship seems to be biologically specific, since it is not seen for tension-type headache.[12,13] People with migraine and TMD have more allodynia than those with migraine without TMD.[38] Craniofacial allodynia is viewed as the clinical manifestation of sensitization at the level of the first-order neurons and higher-order neurons of the trigeminal–upper cervical complex. These latter neurons integrate nociceptive input from intracranial and extracranial tissues, receive supraspinal facilitatory and inhibitory inputs, and project onto the higher-order neurons in the thalamus.[39–41]

Proinflammatory mediators, usually present in peripheral tissues in those with TMD, may contribute to sensitization.[39,40] High levels of prostaglandin E2 and cytokines, such as interleukin 1β (IL-1β), IL-6, and tumor necrosis factor (TNF-α), have been detected in the synovial fluid of inflamed joints and muscle and are strongly associated with pain; calcitonin gene-related peptide (CGRP), a major contributor to neurogenic inflammation, as well as substance P and serotonin are locally increased in those with TMD.[40–44] These proinflammatory mediators can activate the many peripheral nociceptors located at the peripheral tissues, resulting in sensitization of the nociceptive afferent fibers.[40] These fibers project to the trigeminal–upper cervical complex, where there are widespread distributions of nociceptive neurons responding to the musculoskeletal afferent inputs, and the enhanced afferent inputs to the neurons can lead to an increase in neuronal firing frequency.[39,40,45] Therefore, it can be hypothesized that in women with migraine, nociceptive inputs from the masticatory muscle and/or TMJ may produce central sensitization of the neurons.[40,46,47] Additionally, considering that migraineurs present interictal central neuronal hyperexcitability, descending facilitatory influences may be enhanced, and inhibitory processes may also be suppressed.[46,48]

Previous evidence has shown that propranolol inhibits trigeminal nociceptive processes in thalamocortical neurons[49] and diminishes or even blocks propagation of cortical spread depression, through its serotoninergic and noradrenergic properties.[50] It is conceivable that nociceptive inputs related to TMD pain might counteract the propranolol benefit and decrease the neuronal activation threshold.[39,40]

The lack of improvement in TMD outcomes in those receiving SS[51] is surprising, and three hypotheses may explain the negative findings. First, migraine may have affected responses to therapy for TMD for the same reasons that TMD interfered in the migraine responses to propranolol. Secondly, the study design may have not fully accounted for the substantial clinical response to NOS. Clinical improvement reflects therapeutic response, placebo response,[52] and the natural history of disease (regression to the mean). The route of administration influences the placebo effect, especially in pain studies.[52–55] Interventions directed to the site of pain (eg, intraoral splints for TMD) may generate higher placebo effects. Additionally, it may be that NOS yields pain improvement through non-occlusive mechanism,[56] suggesting that the benefits of SS versus NOS are yet to be determined.[51,57,58] Finally, while clinical experience suggests the benefit of SS in treating TMD signs and symptoms, this modality is rarely used in isolation; it is often associated with physical therapy, and sometimes also education counseling and self-care modalities such as automassage, mandibular exercises, mechanisms for control of parafunctional habits, and breathing techniques.[5,59–61]

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The present study has important limitations. First, as discussed above, the sample may have been underpowered to detect genuine treatment effects in TMD (although TMD endpoints were exploratory and the primary aim was to investigate treatment effects on migraine). Second, the dose of propranolol was in the lower range of the therapeutic range. Third, TMD encompasses a heterogeneous group of related disorders that may differ in their response to treatment. Finally, the method of TMD evaluation may have been insufficiently sensitive to assess TMD pain. The VAS was applied monthly only for headache severity assessment, and it would be better if it were applied monthly also to capture changes in TMD pain levels more accurately.

This study also has several strengths. This was the first study to investigate combined treatment of TMD and migraine in patients with both disorders. It was a randomized, double-blind, placebo-controlled study, well designed to assess the goals. Gold standard diagnostic methods were used and blinding was meticulously pursued.

The results presented support the conclusion that in women with TMD and migraine, migraine improves only when both conditions are treated. The best treatment choice for TMD pain in women with migraine is yet to be defined.

Acknowledgments

This study was sponsored by FAPESP (The State of São Paulo Research Foundation—Brazil), FAPESP 06/00730-5 and 2006/00981-8. The authors reported no conflicts of interest related to this study.

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