Comparison of Sustained-Release Nifedipine and Temperature Biofeedback for Treatment of Primary Raynaud Phenomenon

Results From a Randomized Clinical Trial With 1-Year Follow-up

Raynaud's Treatment Study Investigators

Background: The efficacy and safety of sustained-release nifedipine for the treatment of primary Raynaud phenomenon (RP) has not previously been demonstrated by a randomized, controlled trial. Temperature biofeedback has been studied in patients with primary RP but not in a large multicenter controlled trial or compared with nifedipine therapy.

Objective: To evaluate and compare the effectiveness of sustained-release nifedipine and temperature biofeedback for the treatment of primary RP.

Participants and Methods: This is a randomized, controlled clinical trial, double-masked for drug and placebo but not masked for temperature and control biofeedback. It included 313 persons with primary RP as defined by medical history, physical examination findings, normal nailfold capillaries, and a history of 2 or more attacks per day during the previous cold season. Participants were randomized to 1 of 4 treatment groups: (1) sustained-release nifedipine, (2) pill placebo, (3) temperature biofeedback, or (4) control (electromyographic) biofeedback. The primary outcome measure was self-reported, color chart–verified RP attacks during 1 winter month approximately 1 year after initiation of treatment. Secondary outcome measures included verified attacks at 2 months, all attacks at 2 months and 1 year, and quality of life.

Results: Nifedipine-treated participants showed a 66% reduction in verified attacks compared with placebo recipients ($P<.001$); temperature biofeedback training did not reduce attacks significantly compared with control biofeedback ($P = .37$). Comparison of nifedipine and temperature biofeedback treatments favored nifedipine use ($P = .08$); similar results were obtained for the secondary end points. Adverse effects resulted in discontinuation of nifedipine treatment in 15% of participants.

Conclusions: Temperature biofeedback is not better than its control treatment and is inferior to sustained-release nifedipine for treating primary RP, whereas sustained-release nifedipine is a safe and effective treatment for this disease.

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EPISODIC ATTACKS of Raynaud phenomenon (RP)[1] occur primarily in the fingers, triggered by cold exposure or emotional stress. Their frequency can vary, and severity can be mild to temporarily disabling. The disorder affects 4% to 20% of the population, with higher prevalence in women.[2] Raynaud phenomenon is customarily divided into 2 categories: primary RP (idiopathic RP) and secondary RP, which is related to connective tissue diseases, arterial occlusive disease, certain neurologic disorders, blood dyscrasias, trauma, drugs and toxins, and other miscellaneous disorders.[3] Raynaud phenomenon is considered primary if underlying causal factors have been ruled out.

Avoidance of cold exposure often provides sufficient protection against attacks. In other cases, administration of vasodilating drugs is necessary. Immediate-release nifedipine therapy has been shown to reduce the frequency and severity of attacks in patients with primary RP.[4-8] However, adverse effects (tachycardia, headache, flushing, dizziness, and edema) occur in 30% to 100% of patients, many of whom discontinue treatment.[4-6,9-11] Although sustained-release nifedipine is being used by many physicians to treat RP, its efficacy and adverse effects have not been demonstrated in this population.

Of the nonpharmacological treatments for RP, temperature biofeedback has been one of the most studied.[12-21] A degree of voluntary control of peripheral

A complete list of the participants in the Raynaud's Treatment Study appears in a box on page 1107.

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PARTICIPANTS AND METHODS

PARTICIPANTS

The 5 participating sites were in different geographic areas and climates. Participants were recruited from local clinics and by advertising. Those who passed a telephone interview were invited for detailed examination. Diagnosis of RP involved a structured interview assisted by color charts[31] to improve the reliability of the diagnosis that is usually based on the patient's history alone and to make a differential diagnosis between RP and acrocyanosis. Only those who reported at least 2 attacks on an average day during the previous cold season were enrolled. The medical evaluation (history, physical examination, and appropriate laboratory tests) focused on ruling out patients with secondary RP. Special attention was given to patients with possible early scleroderma (systemic sclerosis) in whom RP may precede by years the diagnosis of this connective tissue disease. To exclude such patients, nailfold capillary microscopy[32] was performed to detect the scleroderma capillary pattern (an early marker of scleroderma), and antinuclear antibody titers were required to be 1:320 or less. Participants were eligible if they completed at least 75% of the required 1-month baseline record of attacks and had no contraindications to the study treatments. Of 313 participants, 113 were enrolled during the cold season months of November through February in 1993 and 1994 (cohort 1) and 200 were enrolled during the 1994 and 1995 cold season months (cohort 2).

TREATMENTS

Participants were randomly assigned to 1 of 4 treatment groups: sustained-release nifedipine (N) (Procardia XL; Pfizer Labs, New York, NY), matching pill placebo (Np), temperature biofeedback (B), or control (frontalis muscle surface electromyographic [EMG]) biofeedback (Bc). The RTS Coordinating Center generated a set of allocations for each clinical center, with block size varying randomly so that the number of patients allocated to each of the 4 treatment arms could be balanced over time. Whenever a patient became eligible and gave consent, clinical center staff obtained a treatment assignment from the Coordinating Center using the Automated Telephone Randomization System. Treatment was begun immediately after the treatment assignment was received. To safeguard against therapists' expectation effects, staff providing treatment did not collect any outcome data.

Drug Treatment

Nifedipine and placebo were administered in a double-blind manner. Participants were scheduled to be seen weekly for 5 visits by a physician masked to treatment assignment. Treatment began with 30 mg of nifedipine (or matching placebo) daily. If no adverse reactions occurred in the first week, pill use was increased to 2 per day (60 mg). Based on tolerance, dosage was adjusted to 2, 1, or 0 pills per day during the 4 subsequent weekly visits, then continued for 1 year. Adherence was recorded as percentage of pills returned at quarterly clinic visits.

Biofeedback Treatment

For patients and therapists to understand the biofeedback methods and goals, neither temperature biofeedback nor its control could be masked. Participants were asked to attend ten 1-hour sessions over a 5- to 10-week period. Temperature and control feedback sessions were similar. Thermistors and EMG sensors were attached and calibrated with participants seated in a comfortable easy chair in a temperature-controlled room. After resting for 16 minutes to establish a finger temperature or EMG baseline, 16 minutes of feedback training was given during which participants were asked to alter finger temperature (or frontalis muscle EMG) while observing the output of a temperature (or EMG) display device. Progress during the session was discussed with the therapist. Homework included daily 10-minute practice sessions without instrumentation and "applied practice," in which participants were to practice their technique in situations they thought were associated with a high probability of RP attacks. Four booster sessions were scheduled the next fall for individuals who did not meet a predefined criterion of successful learning or who missed at least half of the spring sessions. Minimum biofeedback training was completion of 6 winter and spring sessions or at least 2 assigned fall booster sessions. The RTS temperature biofeedback protocol was tested in about 10 healthy individuals at each RTS clinic (N = 46).

For participants in cohort 1, therapists remained silent during the feedback phase so as not to be distracting. Verbal coaching was limited to the postfeedback phase. For participants in cohort 2, coaching during the feedback phase was allowed because successful learning in the first cohort was less than expected.

Patients were told during informed consent that it was not known whether any of the treatments were superior. During the first therapy session, patients undergoing biofeedback were given the rationale for their assigned treatment and were told that many patients experience a benefit.

END POINTS

End points were assessed 2 months (first winter and spring) and 1 year (second winter) after initiating treatment. Data on adverse effects and symptom severity were collected

blood flow and skin temperature regulation is possible in healthy subjects through temperature biofeedback.[22-24] Individuals with primary RP have been reported to acquire this ability and to reduce the frequency of attacks,[12,15,25-29] especially when exposure to cold stressors is included in training.[27,29,30] This approach might be desirable for patients with primary RP who do not tolerate vasodilators or who prefer nondrug treatments. However, its comparability to nifedipine treatment has not been investigated, and its efficacy has been evaluated only in small, single-center trials with patients likely to be interested in biofeedback. This article presents results of a randomized clinical trial, the Raynaud's Treatment Study (RTS), comparing the effectiveness of sustained-release nifedipine and temperature biofeedback for the treatment of primary RP.

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quarterly. A coordinating center analyzed all data. The study design and informed consent procedures were approved by an independent RTS Data and Safety Monitoring Board and by the institutional review boards of all centers.

Primary End Point

The number of verified attacks (defined below) reported during the 4 weeks immediately after the 1-year assessment constituted the primary end point. All other data collected were secondary end points. Attacks of RP were recorded on attack cards that participants were instructed to keep with them at all times, together with an 8.25 × 13.33-cm (3¼ × 5¼ in) plastic card showing 9 color photographs of hands, some illustrating RP attacks and others showing color changes not characteristic of RP. Each photograph was identified by a letter, without identifying which images illustrated RP attacks. To be counted as a verified attack, an attack card entry had to (1) include a letter code that matched one of the photographs demonstrating true RP and (2) have occurred at least 30 minutes after a previously recorded entry.

Secondary End Points

These included verified attacks reported during the 4 weeks immediately after the 2-month assessment, all attacks (ie, all recorded attacks, whether or not they met verified attack criteria) reported in connection with the 2-month and 1-year assessments, and attacks reported in a daily diary at the 2-month and 1-year assessments. The daily diary was completed every evening for 4 weeks before the baseline, 2-month, and 1-year visits to summarize the number, severity, and duration of attacks and the coping strategies undertaken by the patient. Separate clinical rating assessment forms were completed by participants and physicians at quarterly visits. Participants estimated (1) the number of RP attacks they had during an average week, (2) the severity of their RP on a 4-point scale, (3) the impact of RP on their lives, (4) their improvement compared with baseline, and (5) their general health. Physicians assessed only items 2 through 5.

The Short Form Health Survey,[33] modified slightly to address RP rather than general health, was used as the main quality-of-life measure. Physical symptom reports were obtained using the Cohen-Hoberman Inventory of Physical Symptoms,[34] modified to exclude clearly psychological symptoms (eg, "felt nervous"). Items relevant to RP or potential adverse effects of nifedipine were added. Participants indicated how much each symptom bothered them during the past 4 weeks.

Antinuclear antibody titers, using the Hep-2 cell line in a microscopically interpreted immunofluorescent assay,[35] were determined by a central laboratory. Physicians who performed the nail capillaroscopy were trained and certified to conform to a uniform standard.

STATISTICAL METHODS

The data analysis plan was specified in advance.[36] A global F test determined the simultaneous probability that (1) the outcome for the temperature biofeedback group (B) differed from that of the control biofeedback group (Bc) or (2) the outcome for the nifedipine group (N) differed from that of the placebo group (Np). If this global F test was significant at $P<.05$, individual t tests (ie, B vs Bc and N vs Np) were performed to assess the treatment-control differences in the behavioral and drug treatment arms, respectively. A final test determined whether the treatment vs control group differences for the drug and behavioral treatments (ie, [B – Bc] vs [N – Np]) were significantly different. This contrast was chosen because it compares the effect of each treatment free from nonspecific effects that might arise from unique aspects of the 2 different treatment modalities, one behavioral and the other pharmacological.[36] Attack rates of RP were transformed logarithmically: ln[(No. of attacks + 0.5)/(No. of days)] to stabilize the variance. Summary data for attack rates are presented in the original units, yielding geometric means.[37] The sample size was set at 300 so that with $\alpha = .05$ for the global F test, power would be 0.8 to detect a 42% reduction in attack rate (or a change of 0.545 units on the logarithmic scale, with an SD of 1.00) in the drug or behavioral arm compared with the respective control arms. The percentage reduction corresponds to the noncentrality parameter in the analysis of the log-attack rates. As such, the percentage reduction applies to any starting rate. During design, we anticipated an average baseline attack rate of 2 per day. A 42% reduction would result in 1.16 attacks per day. If the baseline attack rate were 1.0 per day, a 42% reduction would correspond to a final attack rate of 0.58 attacks per day; if the baseline rate were 0.6 per day, a 42% reduction would yield 0.34 attacks per day.

Statistical analyses followed an intention-to-treat principle and corrected for possible bias caused by differences in missing data among groups by using a regression equation based on baseline variables to impute values for the patient with missing data (Bruce Thompson, PhD, Nancy Geller, PhD, and Sally Hunsberger, PhD, et al, unpublished manuscript, September 1999). Estimation proceeds using weighted least squares, but reweighting analyses for missing data variance estimates, are larger than those obtained using standard weighted least squares. Results based on the new reweighting analyses for missing data procedure were almost identical to those based on the more widely used multiple imputation method.[38]

The primary and secondary end point results were adjusted using covariates for baseline attack rate and clinical center. Analyses were performed using SAS routines.[39]

RESULTS

PATIENT CHARACTERISTICS AND COMPLIANCE

Seventy percent of participants were women, 95% were white, and mean age was 45 years (**Table 1**). At baseline, participants assessed their RP symptoms as mild (22%), moderate (50%), or severe (28%). During baseline clinical examinations, physicians assessed participants' RP symptoms as mild (25%), moderate (60%), or severe (15%). The mean attack rate for the previous cold season, reported by participants at the screening visit, was 3.7 per day, with a minimum of 2.0 per day mandated by eligibility criteria. By comparison, the arithmetic mean for all attacks based on attack card entries at baseline was 1.0 per day (Table 1). Self-rated severity of RP symp-

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Table 1. Baseline Characteristics*

	Biofeedback Group		Pharmacological Group		
	Temperature (n = 81)	EMG (n = 74)	Nifedipine (n = 77)	Placebo (n = 81)	*P*
General					
Age, y	44.1 ± 12.5	45.5 ± 11.7	43.6 ± 11.8	44.9 ± 12.0	.77
Age at onset of RP, y	32.0 ± 14.1	30.5 ± 11.7	31.6 ± 12.1	30.3 ± 12.9	.86
Duration of RP, y	12.3 ± 10.4	14.0 ± 11.1	11.1 ± 8.5	13.6 ± 12.0	.44
Body mass index, kg/m^2	23.5 ± 3.7	23.8 ± 3.6	23.2 ± 3.7	22.8 ± 4.0	.34
Attack rates per day (historical)					
In cold weather	3.5 ± 2.0	3.4 ± 2.3	4.0 ± 3.1	4.0 ± 3.4	.42
In warm weather	1.1 ± 1.9	0.6 ± 0.8	0.9 ± 1.8	0.8 ± 1.8	.29
Baseline					
All attacks, arithmetic mean	0.91 ± 0.88	1.12 ± 1.08	0.93 ± 0.74	0.97 ± 0.89	.47
Verified attacks, arithmetic mean	0.58 ± 0.56	0.73 ± 0.85	0.52 ± 0.54	0.60 ± 0.62	.26
All attacks, geometric mean	0.50 ± 0.65	0.60 ± 0.83	0.59 ± 0.65	0.61 ± 0.66	.74
Verified attacks, geometric mean	0.30 ± 0.41	0.34 ± 0.49	0.24 ± 0.36	0.29 ± 0.42	.47

*Data are given as mean ± SD. RP indicates Raynaud phenomenon; EMG, electromyographic feedback.

Table 2. Numbers of Patients Screened, Randomized, Receiving Treatment, and Providing End Point Data*

	Biofeedback Group		Pharmacological Group		
	Temperature	EMG	Nifedipine	Placebo	All
Screened	. . .	. . .	. . .	. . .	**556**
Randomized	81	74	77	81	**313**
Treatment sessions completed					
0	7	1	2	7	**17**
1-4	10	8	19	13	**50**
5	2	3	56†	61†	**122**
6-9	9	3	. . .	. . .	**12**
10	53	59	. . .	. . .	**112**
Dropouts	25	15	19	24	**83**
Attack cards completed					
2 mo	52	53	68	62	**235**
1 y	64	67	67	64	**262**

*EMG indicates electromyographic feedback; ellipses, not applicable.
†Maximum for nifedipine and placebo groups.

toms at baseline had a correlation of 0.43 with baseline log-verified attack rate. At baseline, verified attack rates between the groups were similar (P = .47), as were other attributes listed in Table 1.

The median time from randomization to the "1-year" assessment was 13.5 months. For the primary end point evaluation, 85% of biofeedback and 83% of medication participants completed attack cards (for an average of 26.3 of 28.0 possible days) (**Table 2**). Most patients (93%) completed their attack cards in January or February, the rest in March or April. For the secondary end point evaluation (2-month follow-up), 68% of biofeedback and 82% of medication participants completed attack cards (P = .02) (Table 2). Data from daily diaries were almost identical to "all attack" data collected through attack cards, and will not be presented further.

The amount of follow-up data differs by end point. Of 313 participants, 83 (26%) formally requested to discontinue study participation, 67 within the first 5 weeks of treatment (Table 2). In response to efforts aimed at obtaining as much data as possible, many participants agreed to perform end point assessments even though they were no longer receiving study treatment.

Of 81 participants assigned to the temperature biofeedback group, 53 (65%) completed all 10 training sessions compared with 59 (80%) of those in the EMG biofeedback group (P = .048). All 4 booster sessions were completed by 23 (39%) of 59 temperature and 14 (45%) of 31 EMG biofeedback participants eligible. In all, 80% of temperature and 86% of EMG biofeedback participants completed the minimum number of training sessions as defined in the "Participants and Methods" section.

Of participants assigned to the nifedipine group, 73% completed the 5 required initial treatment visits compared with 75% of those assigned to the placebo group (Table 2). Pill counts of vials returned for refills during clinic visits showed that 82% of nifedipine pills and 83% of placebo pills were taken. After completing 5 initial medication visits, the distribution of pill usage as indicated at the patient's final visit was as follows: 57% of nifedipine participants continued taking the full 60-mg dose, 18% took 30 mg, and 17% took no pills. Corresponding values for placebo participants were 65%, 7%, and 16%, respectively. Data from 8% of nifedipine and 11% of placebo participants were missing. Adverse effects requiring discontinuation of treatment occurred in 14% of participants taking nifedipine and 9% taking placebo.

PRIMARY END POINT

The nifedipine group had the lowest verified attack rate at 1 year, both unadjusted (**Figure**) and adjusted for baseline verified attack and clinical center (**Table 3**). The global F test of the null hypothesis that both of the differences in RP attack rates (ie, between [1] temperature biofeedback and EMG biofeedback and [2] nifedipine and placebo) are zero for the primary end point at 1 year was significant (P = .002). Specifically, the 66% reduction in the number of verified attacks observed in the nifedi-

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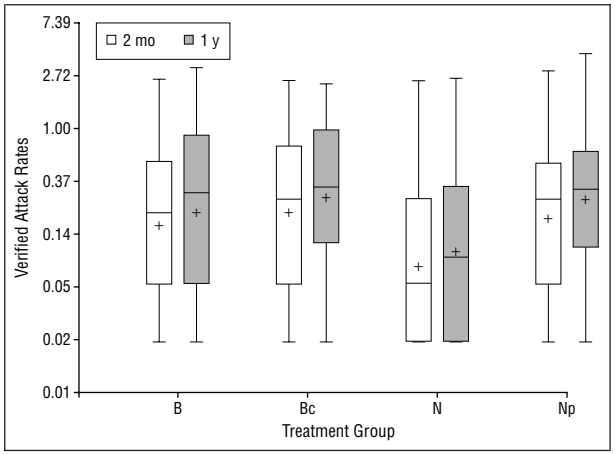
pine group compared with the placebo group was significant ($P<.001$). The 32% reduction in attacks in temperature biofeedback participants compared with EMG biofeedback participants was not significant ($P = .37$). The comparison of temperature biofeedback and nifedipine treatments (ie, [B – Bc] – [N – Np]) showed 56% fewer attacks in the nifedipine group relative to the temperature biofeedback group, a trend toward statistical significance ($P = .08$).

SECONDARY END POINTS

The planned comparison ([B – Bc] – [N – Np]) between temperature biofeedback and nifedipine treatment for all attacks shows an advantage for nifedipine treatment at 1 year ($P = .003$) and a smaller difference at 2 months ($P = .14$). For verified attacks at 2 months, nifedipine treatment showed a 58% reduction relative to temperature biofeedback treatment ($P = .03$). Reductions in attack rates for temperature biofeedback treatment relative to control for the 4 outcomes in Table 3 are from 7% to 32% (smallest $P = .36$). Significantly more participants ($P = .001$) and physicians ($P = .006$) judged that nifedipine treatment had caused improvement than did those judging that biofeedback treatment had done so (**Table 4**). However, this difference might be attributed in part to the substantially higher incidence of reported improvement in the biofeedback control group than in the nifedipine control group.



Box plots of unadjusted daily verified attack rates at 2 months and 1 year. Geometric mean attack rates are indicated near the center of each box (plus sign). Extremes of the box delineate the 25th and 75th percentile values. Error bars represent 95% of the data. B indicates temperature biofeedback; Bc, control (electromyographic) biofeedback; N, nifedipine; and Np, placebo.

ADVERSE EFFECTS AND QUALITY OF LIFE

Participants taking nifedipine had significantly higher incidences of edema (24%) and flushing (8%) than did those in the other 3 groups (0%) ($P<.001$), and 2 participants taking nifedipine reported tachycardia. Thirteen (17%) of 77 participants assigned to nifedipine reported headache compared with 11% of the placebo group ($P = .10$) and only 1 participant undergoing biofeedback treatment. The incidence of dizziness was slightly lower in the nifedipine group (7%) than in the placebo group (8%).

Scores from the RP-specific Short Form Health Survey showed that treatment had little effect on quality of life. The only significant difference was that participants assigned to nifedipine treatment rated their change in RP symptoms as more improved than did participants assigned to the placebo ($P<.001$) or temperature biofeedback ($P = .01$) groups at the 2-month and 1-year

Table 3. Primary and Secondary Raynaud Phenomenon (RP) Attack Frequency Outcome Measures*

Time After Randomization	Daily RP Attack Frequency, Geometric Mean				*P*†			
	B	Bc	N	Np	Global	B–Bc	N–Np	(B–Bc)–(N–Np)
Primary outcome								
Verified attacks at 1 y	0.16	0.23	0.07	0.21	.002	.38	<.001	.08
Secondary outcomes								
Verified attacks at 2 mo	0.12	0.15	0.05	0.13	<.001	.57	<.001	.03
All attacks								
2 mo	0.21	0.31	0.12	0.21	.003	.36	.001	.14
1 y	0.39	0.42	0.20	0.46	<.001	.84	<.001	.003

**B indicates temperature biofeedback; Bc, control (electromyographic feedback) biofeedback; N, nifedipine; and Np, placebo.*
†Adjusted for baseline values and clinical center.

Table 4. Clinical Ratings of Improvement in Raynaud Phenomenon (RP) at 1 Year*

Reported Improvement	Biofeedback Group		Pharmacological Group		*P*		
	B	Bc	N	Np	B vs Bc	N vs Np	B–Bc vs N–Np
Participants	50 (62)	49 (69)	51 (73)	54 (33)	.44	<.001	.001
Physicians	49 (57)	49 (65)	50 (74)	54 (44)	.40	.002	.006

**Data are given as denominator (percentage). B indicates temperature biofeedback; Bc, control (electromyographic feedback) biofeedback; N, nifedipine; and Np, placebo.*

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assessments. There was a trend ($P = .02$) for those taking nifedipine to report less severe changes in RP-related pain than those taking placebo.

SUBGROUP ANALYSES

The outcome for the primary end point was not different between subgroups based on (1) whether randomization was to the preferred treatment, (2) number of baseline attacks, (3) sex, (4) enrollment in the first or second cohort, and (5) whether biofeedback control was learned to criterion. All but the last of these subgroup analyses were specified beforehand in the RTS protocol.

FINGER TEMPERATURE

Only 35% of those in the temperature biofeedback group satisfied the criterion for "successful learning." The results were equivalent for cohort 1 (32%) and cohort 2 (36%). By contrast, 31 (67%) of the 46 healthy individuals taught the temperature biofeedback protocol achieved "successful learning" ($P<.001$).

COMMENT

To our knowledge, this is the first multicenter study comparing pharmacological and behavioral treatments and the first long-term, randomized, controlled trial of a sustained-release calcium channel blocker to treat primary RP. Few therapeutic trials have followed RP for a period spanning 2 winter seasons. We found that participants taking nifedipine reported a greater than 60% reduction in RP attacks at the end of the first and the second winter after beginning treatment compared with those taking placebo. In contrast, participants treated with finger temperature biofeedback did not report a significant reduction in RP attacks compared with the control biofeedback procedure.

Calcium channel blockers are the vasodilating drugs used most often for treating RP. Immediate-release nifedipine has been studied most,[40,41] but others[42-44] have also been investigated. Although studies using immediate-release nifedipine given 3 times daily also reported about 50% fewer RP attacks and significantly reduced severity,[4-6] a trend toward diminished effectiveness over time has been suggested.[4] In our study, sustained-release nifedipine treatment has a comparable initial effect but sustained over 1 year and with a lower incidence of adverse effects than immediate-release nifedipine treatment.[4-6,9-11] Specifically, in our study, 24%, 8%, and 3% of participants taking sustained-release nifedipine reported edema, flushing, and tachycardia, respectively, compared with 56%, 30%, and 23%, respectively, in studies[4,5] of immediate-release nifedipine treatment. Although only 57% of participants taking nifedipine continued taking the full 60-mg dose after 5 initial medication visits, this level of compliance clearly was high enough to produce significant remission of symptoms.

Results of laboratory studies[22,25-27,45-47] of temperature biofeedback in control subjects show that temperature biofeedback with instructions about warming can produce small but significant increases in skin temperature and blood flow, probably by promoting peripheral vasodilation.[12,45] Once learned, hand warming can be produced without feedback,[23,26] generalized to locations outside the laboratory,[23] and retained over time,[12,25,26] suggesting a robust effect that might be used to control RP symptoms. Published studies[20,27,48] provided initial support for this hypothesis.

We considered several possibilities for the lack of benefit from temperature biofeedback observed in the RTS. One is possibly inadequate training or acquisition of the biofeedback response. In this clinical trial, only 35% of participants undergoing biofeedback met study criteria for increasing finger temperature. Increased interaction between biofeedback therapists and patients in cohort 2, as the therapists suggested, did not increase the proportion of patients reaching criterion. However, when we administered the same temperature biofeedback protocol to 46 healthy persons in the RTS clinics, they performed as healthy individuals[22,23] and as RP patients[25,49] in other studies. This indicates that the RTS biofeedback intervention was adequate. The fact that RP patients as diagnosed in the RTS did not acquire the temperature response as healthy individuals do may be relevant for the further study of the nature of primary RP.

Although compliance with treatment was not ideal in this study, it speaks to the question of effectiveness, namely, the extent to which these interventions can be implemented in clinical practice. Comparing those who completed 6 or more of their biofeedback sessions with those completing fewer sessions did not demonstrate any differences in outcome. Another secondary analysis showed that participants who learned to raise finger temperature through biofeedback did not report fewer attacks than did participants who did not learn. Although the number of participants in these subgroups is small, these findings suggest that the outcome is more likely explained by a lack of efficacy than by inadequacy of the biofeedback intervention.

Because the RTS defined and adhered to a rigorous, standardized diagnosis of RP at every site, we might have enrolled participants who differed from those enrolled in previous biofeedback studies, eg, participants with more severe RP or those more difficult to treat using biofeedback. In either case, a relationship should have been seen between successful learning of biofeedback and the number of attacks after treatment. Other factors that could affect treatment outcome also were explored by subgroup analyses, including the potential effect of preference for one or another treatment. No characteristics were found that might identify individuals who benefit from biofeedback treatment.

The disparity between the historical cold weather attack rate reported by RTS participants during screening (3.7/d) and the actual rate for all attacks recorded during baseline data collection (1.0/d) was not surprising. Patients often overestimate symptoms when asked to recall them from memory. The attack rate based on a daily diary or attack card system provides a more accurate estimate of symptom frequency.

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Participants in the Raynaud's Treatment Study (RTS)

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RTS Central Units

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In this study, self-reported symptoms were validated using standard color charts. More than 1 method was used to score attacks and their severity. In addition to the RP attack rate, we obtained subjective indications of treatment outcome through estimates of improvement by study participants and their physicians. These data consistently show significant improvement with nifedipine use but not with temperature biofeedback treatment. The increase in patient- and physician-reported improvement in the biofeedback control group compared with the nifedipine control group, which is not seen in the attack rate data, might be due to a greater subjective expectation of success produced by biofeedback intervention, whether temperature or EMG. This finding supports the importance of separate control groups for behavioral and pharmacological interventions and for the more objective recording of verified attacks to serve as the primary end point.

The efficacy and durability of the temperature biofeedback intervention is suggested by previously published work.[27,49] Because healthy subjects can learn to raise finger temperature by biofeedback, it is conceivable that improved training methods, methods to improve compliance, changes in instrumentation, or more intensive treatment involving daily biofeedback practice as long as symptoms persist might lead to better outcomes. However, this remains a matter for further investigation.

In conclusion, the present clinical trial demonstrates that temperature biofeedback is not better than EMG biofeedback and is inferior to sustained-release nifedipine for treating primary RP. It also demonstrates the effectiveness of sustained-release nifedipine for treating primary RP. Use of this drug was well accepted, had fewer adverse effects than immediate-release formulations, and reduced RP attack frequency by more than half.

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