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) 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. 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. Raynaud phenomenon is considered primary if underlying causal factors have been ruled out.
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 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 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.

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 3- 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.
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-
The amount of follow-up data differs by end point. The median time from randomization to the “1-year” assessment was 13.5 months. For the primary end point, 85% of biofeedback and 83% of medication participants completed 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 continue 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-
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.

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

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

<table>
<thead>
<tr>
<th>Time After Randomization</th>
<th>Daily RP Attack Frequency, Geometric Mean</th>
<th>( P )†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Bc</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verified attacks at 1 y</td>
<td>0.16</td>
<td>0.23</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verified attacks at 2 mo</td>
<td>0.12</td>
<td>0.15</td>
</tr>
<tr>
<td>All attacks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mo</td>
<td>0.21</td>
<td>0.31</td>
</tr>
<tr>
<td>1 y</td>
<td>0.39</td>
<td>0.42</td>
</tr>
</tbody>
</table>

* \( B \) indicates temperature biofeedback; \( Bc \), control (electromyographic) 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**

<table>
<thead>
<tr>
<th>Reported Improvement</th>
<th>Biofeedback Group</th>
<th>Pharmacological Group</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( B )</td>
<td>( Bc )</td>
<td>( N )</td>
</tr>
<tr>
<td>Participants</td>
<td>50 (62)</td>
<td>49 (69)</td>
<td>51 (73)</td>
</tr>
<tr>
<td>Physicians</td>
<td>49 (57)</td>
<td>49 (65)</td>
<td>50 (74)</td>
</tr>
</tbody>
</table>

* Data are given as denominator (percentage). \( B \) indicates temperature biofeedback; \( Bc \), control (electromyographic feedback) biofeedback; \( N \), nifedipine; and \( Np \), placebo.
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” ($P<.001$).

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, but others 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, a trend toward diminished effectiveness over time has been suggested. 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. 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 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 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. Once learned, hand warming can be produced without feedback, generalized to locations outside the laboratory, and retained over time, suggesting a robust effect that might be used to control RP symptoms. Published studies 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 and as RP patients 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.
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. 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 intervention 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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REFERENCES


