The efficacy of complementary and alternative medicine in the treatment of Raynaud’s phenomenon: a literature review and meta-analysis

Deanne Malenfant¹, Michelle Catton² and Janet E. Pope¹,³

Objective. Conventional treatment for RP is limited due to side effects, and complementary and alternative medicines (CAM) are widely used by the population. Our objective was to find an effective and well-tolerated CAM for the treatment of RP.

Methods. Using MEDLINE, EMBASE and AMED, 20 randomized controlled trials (RCTs) were found and divided into nine treatment subcategories: acupuncture (n = 2 trials), anti-oxidants (n = 2), biofeedback (n = 5), essential fatty acids (n = 3), Ginkgo biloba (n = 1), L-arginine (n = 2), laser (n = 3), glucosaminoglycans (n = 1) and therapeutic gloves (n = 1). Trials in each subcategory were meta-analysed together.

Results. Several categories did not have enough trials to do a meta-analysis and most trials were negative, of poor quality and done prior to 1990. Biofeedback was negative for a change in frequency, duration and severity of RP attacks, and actually favoured control (sham biofeedback; P < 0.02). The therapeutic glove favoured active treatment (P < 0.00001). Laser resulted in one less RP attack on average over 2 weeks vs sham [weighted mean difference (WMD) 1.18; 95% CI 1.06, 1.29], and a change in severity of attacks (WMD 1.98; 95% CI 1.57, 2.39; P < 0.05). No significant differences were found in the nutritional supplements that were studied.

Conclusions. There is a need for well-designed trials of CAM in RP. The literature is inconclusive except that biofeedback does not work for RP, therapeutic gloves may improve RP (but results may not be generalizable due to single trial site and no intent-to-treat analysis) and laser may be effective but the improvement may not be clinically relevant.

Key words: Raynaud’s phenomenon, Meta-analysis, Complementary and alternative medicine, Laser, Biofeedback, Acupuncture, Anti-oxidants.

Introduction

RP is a condition of the digital arteries that causes the vessels to spasm under conditions of cold or stress. This results in poor circulation in the fingers, toes and uncommonly nose and ears. The condition is remarkable for a tri-phasic colour change; initially the lack of blood flow causes blanching (whitening) followed by cyanosis (blue) and finally reperfusion leading to rubor (redness). There must be well-demarcated pallor and at least one other phase (cyanosis or rubor) in order to make a diagnosis.

There are two classes of RP. Primary Raynaud’s phenomenon is idiopathic, not associated with other pathologies. Secondary Raynaud’s phenomenon appears in patients whose symptoms are secondary to pathology such as scleroderma, SLE or other CTDs, or other causes [1].

RP is generally treated by conservative methods: mittens, keeping out of the cold, etc. In serious cases, vasodilators are used. The calcium channel blocker nifedipine is currently the mainstay treatment [2]. Nifedipine has many associated side effects including headache, dizziness or light-headedness, excessive tiredness, flushing, tachycardia and oedema [3]. Other agents that are also used include PDE5 inhibitors, angiotensin-converting enzyme (ACE) inhibitors, oral and topical nitrates, prostacyclins, α-blockers and even the selective serotonin reuptake inhibitor (SSRI), fluoxetine. The side effects, financial concerns and the need for taking a prescription medication compel many patients with RP to explore complementary and alternative medicines (CAMs). There are trials in the literature for the use of acupuncture, biofeedback and other herbal preparations (Ginkgo biloba and evening primrose oil) in the treatment of RP [4–6]. In addition, standard treatments often yield only modest benefits [2].

CAM usage is more and more common in the general population as well as the chronically ill. Since RP causes intermittent symptoms, CAM may be used frequently in this condition. This meta-analysis examined the published trials in the treatment of RP using CAM treatments.

Materials and methods

A literature search was conducted in the summer of 2007 using Ovid, EMBASE and AMED for all randomized controlled trials that tested an alternative treatment for RP including vitamins, anti-oxidants, herbs, acupuncture, laser and biofeedback. Each type of treatment was analysed separately. We used the National Center for CAM definition to assess if treatments were appropriate for this meta-analysis. The website states: ‘CAM is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine’ [7]. Subjective measures of improvement in RP were used as the outcomes, as RP is usually treated when a patient has increasing symptoms such as more painful, frequent or severe attacks. Side effects were also included and analysed where possible. Inclusion and exclusion criteria were: the trial had to be randomized, RP had to be the condition studied, at least one treatment arm had to contain a CAM, there had to be a comparison (active or placebo), there had to be at least one subjective outcome measurement (such as pain, frequency, duration or severity of attacks of RP), the trial had to have a measure of estimate of effect and a calculable s.d. or range. Included studies also had to use the same definition of RP (well-demarcated pallor and at least one other phase of cyanosis or rubor, or both). The trials were reviewed for quality of methodology and statistics. We used a 5-point scale based on a paper by Altman et al. [8] to score the quality of each trial. This scale uses five categories of randomization, the explanation of the randomization, double blinding, explanation of statistics and intention to treat; each of these is worth 1 point for a score out of 5 for the quality (Table 1). The trials were separated into categories of similar treatment types. The trial characteristics are available in Table 2.

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The results of trials were modified to have similar scales for each outcome measured where possible, such as pain scales. All frequencies were modified to occur over a 2-week period. This was chosen because herbal preparations often need at least this long to show an effect, and to remain consistent across the treatments. For each of the treatment categories, the results of similar outcomes were compiled and weighted mean differences (WMDs) and 95% CI were calculated using RevMan 5.0.11 software.

### Results

The search yielded 29 studies, of which 9 were excluded for: not a trial (four studies), not randomized (one), no control group (one) and unextractable data (three). Twenty trials remained for the analysis. The trials were divided into nine categories: acupuncture (n = 2 trials), anti-oxidants (n = 2), biofeedback (n = 5), essential fatty acids (n = 3), Ginkgo biloba (n = 1), l-arginine (n = 2), laser (n = 3), glucosaminoglycans (n = 1) and therapeutic gloves (n = 1). The trials and their quality are summarized in Table 2.

Three categories only included one trial, which made a meta-analysis impossible. The ‘Ginkgo biloba’ trial [6] was of good quality scoring 4/5 on the Altman scale. It had results for change in frequency, duration and severity of symptoms; these were all non-significant at P = 0.07, 0.75 and 0.23, respectively.

The ‘glucosaminoglycans’ trial [10] was of moderate quality scoring 3/5. It only had one usable outcome, the subjective improvement of symptoms as noted by the patients. The result favoured the treatment group with 10/15 patients noting an improvement. However, this result did not reach statistical significance with an OR of 4.00 (P = 0.07).

The ‘therapeutic glove’ category also had only one trial [11]. It trial [6] was of good quality scoring 4/5 on the Altman scale. It had results for change in frequency, duration and severity of symptoms; these were all non-significant at P = 0.07, 0.75 and 0.23, respectively.

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The ‘therapeutic glove’ category also had only one trial [11]. It had a moderate quality score of 3/5 (details in Table 2). This trial measured the efficacy based on a visual analogue scale (VAS) for pain and the DASH (disability of arm, shoulder and hand) scale. The VAS had a decrease of severity of 0.61/10, which led to a difference from placebo of 0.89 with 95% CI 0.77, 1.01; and P < 0.00001 (<1 cm on a 10-cm VAS). The DASH score decreased...
by 5.3 points, which was a WMD of 7.70 from placebo and again a $P < 0.00001$. However, it was not an intent-to-treat analysis and the drop-out rate was high, so no conclusion can be drawn with respect to the benefits of ceramic-impregnated gloves in the treatment of RP.

The category of 'a-arginine' contained two trials [12, 13]; both were excluded as they used measures that were not directly related to the frequency, severity, duration or pain of RP attacks.

The 'anti-oxidants' category had two trials. These used different products—ascorbic acid in Mavrikakis et al. [14] study and Bio-Antox in Herrick et al. [15] study. The Bio-Antox product contains ascorbic acid and both trials use the same justification for using these products, hence they were combined for the purposes of comparison, but they were not meta-analysed. Mavrikakis et al. [14] published only results in changed dilation as the outcome, not on the effects of RP, hence the data could not be used. The other trial by Herrick et al. [15] was a cross-over study with carry-over effects, hence the data could not be used, except in adverse effects (AEs) where three AEs in the control group and two in the placebo group occurred. The patient preference outcome showed a significant result in favour of the anti-oxidant where 7/11 participants chose the treatment over placebo ($P = 0.04$).

The ‘acupuncture’ category also had two trials; these did not use the same control or the same acupuncture points, hence they could not be meta-analysed. The first trial by Haith et al. [16] compared acupuncture with a sham acupuncture session, and the quality score was 3/5. It had outcomes in frequency and duration of attacks, which favoured the treatment group. The change in severity, as measured by a 5-point scale, favoured the treatment with a WMD of 0.83 on the 5-point scale with 95% CI 0.63, 1.03 and $P < 0.00001$. The second trial by Appiah et al. [4] compared acupuncture with ‘no treatment’ and had a low-quality score of 2/5. It did have a difference in the frequency of attacks over 2 weeks of 5.6 ($P = 0.00001$) in favour of acupuncture, a reduction of almost six attacks over 2 weeks in acupuncture compared with no treatment.

The category of ‘essential fatty acids’ contained three trials. One by DiGiacomo et al. [5] could not be used because the outcomes published were not related to the frequency, severity, pain or duration of RP. The other studies [17, 18] were of poor quality (2/5 each). They had two outcomes that were appropriate for meta-analysis. The subjective improvement favoured the treatment group, but this did not reach statistical significance ($P = 0.21$). Side effects trended towards the control group with an OR of 2.14 ($P = 0.27$), but the heterogeneity ($I^2 = 57.38$) was high. Belch et al. [18] also had some outcomes that were not comparable with Stainforth et al. [17]. This trial showed a decrease in frequency of attacks with a WMD of 20.04 ($P < 0.00001$) or 20 less attacks in active than placebo treatment over 2 weeks, a decrease in duration of attacks (in minutes over 2 weeks) with WMD 1633.80 ($P < 0.0007$) and a non-significant difference in the decrease of the VAS score for severity between treatment and placebo of 0.3 on a 10-point scale (WMD 0.30; $P = 0.21$).

Discussion

This review of the treatment of RP by CAM modalities demonstrates two major flaws of the literature on this subject. First, many trials were published >18 years ago and were neither duplicated to confirm the results nor was trial methodology rigorous. There is a tendency for poor-quality trials, many of which are older trials, to have positive results (Fig. 3). In the ‘biofeedback’ category four out of nine trials could not be analysed. Three trials had to be excluded because the statistics were done using $F$-tests and s.d.s could not be extracted. It was also quite difficult to find...
Many of the controls were treated differently so blinding would have been impossible. For instance, some trials in biofeedback and acupuncture did not have identical shams, including even the frequency and duration of the treatment sessions. Other trials had no treatment as a control.

The ‘low-level laser’ therapy certainly showed the most promising results. All trials were of moderate to good quality; however, since the heterogeneity tests were high, the results are really not comparable. We removed the visual outliers and found that heterogeneity remained.

The ‘biofeedback’ category had by far the largest pool of literature, but the quality of these trials was a major issue and many trials had to be excluded, as statistics used did not allow for a point estimate and s.d. to be determined. Ultimately, only one outcome was meta-analysed and it showed a trend towards the control group, and not the active treatment (biofeedback). This category was dominated by the RTS investigator trial, which was the largest, of highest quality and the most recent trial.

Many trials had to be excluded for methodological reasons. No control treatment, questionable blinding, non-standardized outcome measurements (several of which were not clinically relevant) and statistical heterogeneity were all common. Nearly all trials were conducted before the Raynaud’s Condition Score was published, which may standardize the choice of RP outcome measurements in future RP randomized controlled trials (RCTs) [27].

Due to the limitations discussed, it is impossible to draw a clear conclusion about any CAM studied to date being a proven and relevant treatment for RP. For the trials using treatments that were not herbal, such as biofeedback and acupuncture, perhaps an observation period >2 weeks would yield different results; however, since the main problems with most of the studies were inherent flaws in study design, the quality of the data would not change. Patients are continuing to use CAMs and it is important to design high-quality RCTs in RP using alternative treatments in order to make solid recommendations for or against the use of various complementary and alternative treatments.

### Acknowledgements

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<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>n</th>
<th>Thermal biofeedback, mean (s.d.)</th>
<th>Sham EMG biofeedback, mean (s.d.)</th>
<th>WMD (fixed) 95% CI Weight, % WMD (fixed) [95% CI]</th>
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<tbody>
<tr>
<td>Guglielmii et al. [24]</td>
<td>12</td>
<td>8.95 (6.25)</td>
<td>12</td>
<td>12.83 (7.57)</td>
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<tr>
<td>Freedman et al. [23]</td>
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<td>11.65 (17.32)</td>
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<td>-6.45 (0.14)</td>
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<tr>
<td>Bötter et al. [22]</td>
<td>10</td>
<td>1.80 (1.41)</td>
<td>10</td>
<td>6.60 (0.31)</td>
</tr>
<tr>
<td>RTS investigator [26]</td>
<td>81</td>
<td>8.54 (2.28)</td>
<td>74</td>
<td>16.76 (1.27)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>111</td>
<td>104</td>
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</table>

Test for heterogeneity: $\chi^2 = 47.66, \text{df} = 9 (P<0.00001), F = 9.97, \text{test for overall effect: } Z= 4.94 (P<0.00001)$.

### FIG. 2. Comparison of effects of thermal biofeedback (treatment) vs sham EMG biofeedback (control) on change in frequency of RP attacks over 2 weeks, before and after removing the visual outlier [23].

### FIG. 3. Quality of RP CAM trials over the years of publication.

<table>
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<tr>
<td>Total (95% CI)</td>
<td>103</td>
<td>96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 66.35, \text{df} = 5 (P<0.00001), F = 9.45, \text{test for overall effect: } Z= 5.03 (P<0.00001)$; Note: that the heterogeneity is still significant.
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References