Calcium channel blockers for primary Raynaud’s phenomenon: a meta-analysis

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Background. To determine the efficacy of calcium channel blockers (CCBs) for primary Raynaud’s phenomenon (RP). Primary outcomes were frequency and severity of RP attacks.

Methods. A meta-analysis was conducted using primary data sources: Medline, Current Contents and the Cochrane Controlled Trials Register. Inclusion criteria were randomized controlled trials (RCTs) of >2 days’ duration with <35% dropouts. Eighteen of 31 trials were eligible for inclusion [13 nifedipine vs placebo; five other CCBs vs placebo (n = 361)]. The main reasons for trial exclusion were: subset data (primary RP) not provided (n = 10); data published more than once (n = 1); lack of control group (n = 1); and lack of randomization (n = 1). Data were abstracted independently and a weighted mean difference (WMD) was calculated for the outcomes.

Results. The WMD (95% confidence interval) of all CCBs vs placebo for reduction in the frequency of attacks (n = 17) over 1 week was −5.00 (−9.02, −0.99) (P = 0.01) or −2.80 (−3.90, −1.70) when heterogeneity was considered, and −6.05 (−11.19, −0.19) (P = 0.04) for nifedipine alone (n = 10). The WMD of all CCBs vs placebo (n = 8) for reduction in severity of attacks (assessed with a 10-cm visual analogue scale) was −1.39 (−2.20, −0.58) (P = 0.0007) and −1.81 (−3.08, −0.54) (P = 0.005) for nifedipine alone (n = 5).

Conclusions. Several small RCTs of CCBs for primary RP have been conducted and have yielded clinical improvement in the frequency and severity of ischaemic attacks. Most trials were crossover trials in which order effect was not studied; this may have introduced bias. The effect size may have been small because of low dosing in studies. The efficacy of CCBs for reducing severity and frequency of ischaemic attacks in primary RP is small (average of 2.8 to 5.0 fewer attacks per week and a 33% reduction in severity).

Raynaud’s phenomenon (RP) is defined as vasospasm of arteries or arterioles causing pallor and at least one other colour change upon reperfusion, such as cyanosis or redness. Primary or idiopathic RP occurs without an underlying disease, whereas secondary RP occurs in association with an underlying disease—usually a connective tissue disorder, such as scleroderma, systemic lupus erythematosus, rheumatoid arthritis or polymyositis. The aetiology of primary RP is unknown [1]. There is evidence for genetic predisposition [2, 3], which is most likely in people with early-onset RP (age <40 yr) [4]. Women are at increased risk compared with men [5]; the other known risk factor is occupational exposure to vibration from tools (8 vs 2.7% in two cohorts from Japan) [6, 7]. People who are obese may be at less risk.

The prevalence of RP varies by gender, country and exposure to workplace vibration. One large US cohort study (4182 people) found symptoms in 9.6% of women and 8.1% of men, of whom 81% had primary RP [8]. In smaller cohorts in Spain the prevalence of RP was estimated to be 3.7–4.0%, of whom 90% had primary RP [9, 10]. One cohort study in Japan (332 men, 731 women) found symptoms of primary RP in 3.4% of women and 3.0% of men [11].

There have been many randomized controlled trials of the treatment of idiopathic or primary RP and secondary RP accompanied by scleroderma and other connective tissue diseases. Over the last two decades drugs have been developed, including calcium channel blockers and prostacyclin analogues, which are better tolerated than medications used in the past (i.e. ganglion blockers and α blockers).

This meta-analysis was performed to determine the efficacy of calcium channel blockers for the treatment of primary RP.

The specific hypotheses tested in this meta-analysis were: (i) calcium channel blockers reduce the frequency of ischaemic attacks; and (ii) calcium channel blockers reduce the severity of ischaemic attacks.

Methods

Randomized controlled trials (RCTs) in which calcium channel blockers were compared with either placebo or another treatment were found by a computerized search of Medline (from 1966 to April 2003) using the Cochrane search strategy developed by Dickersin et al. [12]. The keywords used were ‘Raynaud’s’ or ‘vasospasm’ and ‘calcium channel blockers’, ‘nifedipine’, ‘nicardipine’, ‘felodipine’, ‘nisoldipine’, ‘amlodipine’, ‘diltiazem’ and ‘verapamil’. References of any review articles were scrutinized.

Each trial was assessed independently using a validated quality assessment tool (consisting of items pertaining to descriptions of...
randomization, double-blinding, dropouts and withdrawals) [13]. Only randomized trials were eligible, whether or not they were double-blinded. Both parallel and crossover trials were included. All non-English trials were translated. Some trials included RP patients with a number of diagnoses other than primary RP and were included if a subset of patients with primary RP could be identified separately and their outcome assessed independently; or if more than 75% of the patients had primary RP. Trials with a dropout rate greater than 35% were excluded.

The major outcomes of the meta-analysis were differences between treatment groups in the severity and frequency of RP at the end of intervention. Where possible, these data were calculated for attacks over a 1-week period. We used a weighted mean difference (WMD) of the effect of placebo minus the effect of active drug. A fixed effects model approach was used to calculate a weighted estimate appropriate for continuous variables [14]. When heterogeneity existed among trials, a random effects model was used for the analysis or the outlying trials were removed. Heterogeneity was determined using the $\chi^2$ test. All tests and confidence intervals were two-sided with $P < 0.05$. Calculations were done using Revman software, developed by the Cochrane Collaboration. Arbitrarily, we decided that a decrease of 30% in the frequency and/or severity of Raynaud’s attacks was clinically significant and a moderate effect size.

**Results**

Thirty-one studies published between 1983 and 2000 were found, of which 10 were excluded because a subset analysis for patients with primary RP was not available [15–24]. One other study was excluded because it had been published previously [11]. Another study was excluded as no control group was used [25] and another because it was not blinded or randomized [26]. Eighteen trials were suitable for use in the meta-analysis [1–8, 27–31, 32–36], and were published between 1983 and 2000. The overall (unweighted) mean frequency of attacks per week in the control populations studied was 10.8±1.4 [95% confidence interval (CI) 7.8, 13.8]. The duration of the treatment arm ranged from 1 to 10 weeks. All trials were randomized, double-blinded and placebo-controlled; 16 of them were crossovers and two were parallel in design. One trial also compared calcium channel blockers with dazoxiben and placebo; however, the dazoxiben data were not utilized [30]. Most trials used symptom diaries to record the frequency and severity of attacks. An order effect was not analysed in any of the crossover trials, so it is unknown if a significant carryover effect between the first and second treatments occurred. Table 1 summarizes the trials that were included.

**Calcium channel blockers compared with placebo**

Seventeen trials (15 of which were crossover trials) involving 348 patients comparing the frequency of ischaemic attacks in those taking calcium channel blockers vs. placebo were included in this meta-analysis. The other trial did not report on the frequency of ischaemic attacks and could not be included [6]. Twelve of these trials compared nifedipine, at doses of 10–20 mg three times daily, with placebo, the duration of treatment ranging from 1 to 10 weeks. Two more trials compared nicardipine with placebo, at doses of 20 mg three times daily and 50 mg extended release (XL), once a day (OD), with the duration of treatment 2 weeks in each trial. Two trials compared nisoldipine with placebo, at doses of 10 and 20 mg OD for 2 and 4 weeks’ duration, respectively. A final trial compared diltiazem 120 mg three times daily with placebo for 2 weeks. Two trials used primary and secondary RP patients where the subgroup data were unavailable but most contained primary RP subjects [5, 27]. All study participants were included in the analysis, with the exception of two studies, in which 5 of 34 and 2 of 24 subjects, respectively, were not included in the analysis.

The analysis was performed on 17 trials containing 348 patients.

Using a random effects model, the meta-analysis showed that calcium channel blockers provided a significant reduction, compared with placebo, in the frequency of ischaemic attacks over a 1-week period, with a WMD (95% confidence interval) of $-5.00 \text{ (} -9.02, -0.99 \text{)} (P = 0.01)$ (Fig. 1), which means a reduction of about five attacks in a 1-week period. A random effects model was used because the trials in this analysis showed significant heterogeneity. When the two trials ($n = 16$ patients) of nifedipine 20 mg three times daily vs placebo with the most extreme positive and negative point estimates were removed from the analysis, the heterogeneity was eliminated and the results remained significant, with a WMD of $-2.80 \text{ (} -3.9, -1.7 \text{)} (P = 0.0007)$ (Fig. 2).

A significant reduction in the severity of ischaemic attacks, as measured on a 10 cm visual analogue scale, was demonstrated with a WMD of $-1.39 \text{ (} -2.20, -0.58 \text{)} (P = 0.00001)$ (Fig. 3). With an average mean severity in the placebo group of 4.25, this can be thought of as a 33% reduction in the severity of attacks. Patients also reported a significant improvement in ischaemic attacks,

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Total no. of patients</th>
<th>Number with primary RP</th>
<th>Treatment duration (weeks)</th>
<th>Daily dose</th>
<th>Design</th>
<th>Treatment comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahan [28]</td>
<td>1983</td>
<td>30</td>
<td>12</td>
<td>2</td>
<td>20 mg t.i.d.</td>
<td>Crossover</td>
<td>Nifedipine vs placebo</td>
</tr>
<tr>
<td>Ettinger [30]</td>
<td>1984</td>
<td>22</td>
<td>3</td>
<td>3</td>
<td>20 mg t.i.d. (N)</td>
<td>Crossover</td>
<td>Nifedipine vs Dazoxiben</td>
</tr>
<tr>
<td>Kahan [31]</td>
<td>1985</td>
<td>15</td>
<td>5</td>
<td>1</td>
<td>20 mg t.i.d.</td>
<td>Crossover</td>
<td>Nifedipine vs placebo</td>
</tr>
<tr>
<td>Kahan (diltiazem) [32]</td>
<td>1985</td>
<td>16</td>
<td>6</td>
<td>1</td>
<td>120 mg t.i.d.</td>
<td>Crossover</td>
<td>Diltiazem vs placebo</td>
</tr>
<tr>
<td>Aldoori [27]</td>
<td>1986</td>
<td>9</td>
<td>7</td>
<td>3</td>
<td>10 mg 8-hourly</td>
<td>Crossover</td>
<td>Nifedipine vs placebo</td>
</tr>
<tr>
<td>Gjorup [34]</td>
<td>1986</td>
<td>19</td>
<td>19</td>
<td>2</td>
<td>20 mg b.i.d.</td>
<td>Crossover</td>
<td>Nifedipine vs placebo</td>
</tr>
<tr>
<td>Redondo [29]</td>
<td>1986</td>
<td>17</td>
<td>4</td>
<td>2</td>
<td>20 mg 8-hourly</td>
<td>Crossover</td>
<td>Nifedipine vs placebo</td>
</tr>
<tr>
<td>Challener [33]</td>
<td>1987</td>
<td>36</td>
<td>36</td>
<td>6</td>
<td>5–10 mg</td>
<td>Crossover</td>
<td>Nifedipine vs placebo</td>
</tr>
<tr>
<td>Kahan [35]</td>
<td>1987</td>
<td>20</td>
<td>3</td>
<td>2</td>
<td>20 mg t.i.d.</td>
<td>Crossover</td>
<td>Nifedipine vs placebo</td>
</tr>
<tr>
<td>French group [36]</td>
<td>1991</td>
<td>69</td>
<td>69</td>
<td>2</td>
<td>50 mg b.i.d.</td>
<td>Crossover</td>
<td>Nifedipine vs placebo</td>
</tr>
<tr>
<td>RTSI [7]</td>
<td>2000</td>
<td>130</td>
<td>130</td>
<td>8</td>
<td>30 mg 30 mg b.i.d.</td>
<td>Parallel</td>
<td>Nifedipine vs placebo</td>
</tr>
</tbody>
</table>

RTSI, Raynaud’s Treatment Study Investigators; b.i.d., twice daily; t.i.d., three times daily; N, nifedipine; D, dazoxiben.
indicated on a 5-point scale, with a WMD of \(-1.04 [-1.51, -0.56]\), \(P = 0.0015\) (Fig. 4). Clinically this can again be viewed approximately as a 33% reported improvement in ischaemic attacks. A random effects model was used for both comparisons of severity and improvement due to significant heterogeneity among included trials.

**Nifedipine compared with placebo**

The results obtained in the large subset of trials comparing nifedipine with placebo do not significantly differ from those comparing all calcium channel blockers with placebo. This analysis consisted of 12 trials containing 215 patients. Nifedipine was used...
in doses ranging from 5 to 20 mg three times daily, one trial using 30 mg XL OD with treatment duration ranging from 2 to 10 weeks.

Nifedipine significantly reduced the frequency of ischaemic attacks, WMD $-6.05 (-11.19, -0.19)$ ($P = 0.04$) and the severity of attacks on a 10-cm visual analogue scale [WMD $-1.81 (-3.08, -0.54)$, $P = 0.005$]. Nifedipine also improved ischaemic attacks, on a five-point scale [WMD $1.11 (-1.38, -0.85)$, $P < 0.00001$].

Other calcium channel blockers compared with placebo

Two trials compared nicardipine with placebo using doses of 20 mg three times daily and 50 mg XL OD, with treatment duration of 2 weeks in each trial. The analysis favoured nicardipine, but this drug did not significantly reduce the frequency or severity of ischaemic attacks.

Two trials compared nisoldipine with placebo using doses of 10–20 mg OD with treatment durations of 2 and 4 weeks. Although the analysis favoured nisoldipine, this drug did not significantly reduce the frequency or severity of ischaemic attacks.

Discussion

Primary RP is common in the general population and can be quite disabling. The mean frequency of attacks per week in the general population may be approximately 10.8. It is standard practice to use calcium channel blockers to alleviate symptoms. This meta-analysis found a reduction in the frequency and severity of ischaemic attacks which was significant, translating into a 33% reduction in the severity of attacks and an average decrease of 2.8–5.0 attacks over a 1-week period. A recent meta-analysis of calcium channel blockers in RP secondary to systemic sclerosis found a moderate reduction in the frequency and severity of ischaemic attacks which was significant, translating into a 35% reduction in the severity of attacks and a decrease of four attacks over a 1-week period, which is a similar absolute reduction compared with nifedipine in this meta-analysis [38]. However, the absolute number of attacks in the scleroderma-associated meta-analysis was higher, so the reduction in scleroderma-associated RP attacks is slightly less.

The results of this meta-analysis indicate that the risk/benefit ratio of these agents must be considered when deciding how to treat RP. These trials did not routinely examine the side-effects of calcium channel blockers in primary RP. The side-effects of hypotension, dizziness, flushing, dependent oedema, and headaches seen with these agents are believed to be fairly common [2, 39].

There are several limitations to a meta-analysis. Our search from Medline and the references of the key review articles may reveal only some of the published articles. Therefore, at this point in time, some articles could be missing; and because of small
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The authors have declared no conflicts of interest.


