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[Intervention Review]

Calcium channel blockers for primary and secondary Raynaud's phenomenon

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ABSTRACT

Background

Raynaud's phenomenon is a vasospastic disease characterized by digital pallor, cyanosis, and extremity pain. Primary Raynaud's phenomenon is not associated with underlying disease, but secondary Raynaud's phenomenon is associated with connective tissue disorders such as systemic sclerosis, systemic lupus erythematosus, and mixed connective tissue disease. Calcium channel blockers promote vasodilation and are commonly used when drug treatment for Raynaud's phenomenon is required.

Objectives

To assess the benefits and harms of calcium channel blockers (CCBs) versus placebo for treatment of individuals with Raynaud's phenomenon with respect to Raynaud's type (primary vs secondary) and type and dose of CCBs.

Search methods

We searched the Cochrane Central Register of Controlled Trials (May 19, 2017), MEDLINE (1946 to May 19, 2017), Embase (1947 to May 19, 2017), clinicaltrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Portal. We applied no language restrictions. We also searched bibliographies of retrieved articles and contacted key experts for additional and unpublished data.

Selection criteria

All randomized controlled trials (RCTs) comparing calcium channel blockers versus placebo.

Data collection and analysis

Two review authors independently assessed search results and risk of bias and extracted trial data. We used the GRADE approach to assess the quality of evidence.

Main results

This review contains 38 RCTs (33 cross-over RCTs) with an average duration of 7.4 weeks and 982 participants; however, not all trials reported all outcomes of interest. Nine of the identified trials studied patients with primary Raynaud's phenomenon (N = 365), five studied patients with secondary Raynaud's phenomenon (N = 63), and the rest examined a mixture of patients with primary and secondary Raynaud's phenomenon (N = 554). The most frequently encountered risk of bias types were incomplete outcome data and poor reporting of randomization and allocation methods.

When researchers considered both primary and secondary Raynaud's phenomenon, evidence of moderate quality (downgraded for inconsistency) from 23 trials with 528 participants indicates that calcium channel blockers (CCBs) were superior to placebo in reducing the frequency of attacks. CCBs reduced the average number of attacks per week by six (weighted mean difference (WMD) -6.13, 95% confidence interval (CI) -6.60 to - 5.67; I^2 = 98%) compared with 13.7 attacks per week with placebo. When review authors excluded Kahan 1985C, a trial showing a very large reduction in the frequency of attacks, data showed that CCBs reduced attack frequency by 2.93 per week (95% CI -3.44 to -2.43; I^2 = 77%).

Low-quality evidence (downgraded for imprecision and inconsistency) from six trials with 69 participants suggests that the average duration of attacks did not differ in a statistically significant or clinically meaningful way between CCBs and placebo (WMD -1.67 minutes, 95% CI -3.29 to 0); this is equivalent to a -9% difference (95% CI -18% to 0%).

Moderate-quality evidence (downgraded for inconsistency) based on 16 trials and 415 participants showed that CCBs reduced attack severity by 0.62 cm (95% CI -0.72 to - 0.51) on a 10-cm visual analogue scale (lower scores indicate less severity); this was equivalent to absolute and relative percent reductions of 6% (95% CI -11% to -8%) and 9% (95% CI -11% to -8%), respectively, which may not be clinically meaningful.

Improvement in Raynaud's pain (low-quality evidence; downgraded for imprecision and inconsistency) and in disability as measured by a patient global assessment (moderate-quality evidence; downgraded for imprecision) favored CCBs (pain: WMD -1.47 cm, 95% CI -2.21 to -0.74; patient global: WMD -0.37 cm, 95% CI -0.73 to 0, when assessed on a 0 to 10 cm visual analogue scale, with lower scores indicating less pain and less disability). However, these effect estimates were likely underpowered, as they were based on limited numbers of participants, respectively, 62 and 92. For pain assessment, absolute and relative percent improvements were 15% (95% -22% to -7%) and 47% (95% CI -71% to -24%), respectively. For patient global assessment, absolute and relative percent improvements were 4% (95% CI -7% to 0%) and 9% (95% CI -19% to 0%), respectively.

Subgroup analyses by Raynaud's type, CCB class, and CCB dose suggest that dihydropyridine CCBs in higher doses may be more effective for primary Raynaud's than for secondary Raynaud's, and CCBs likely have a greater effect in primary than in secondary Raynaud's. However, differences were small and were not found for all outcomes. Dihydropyridine CCBs were studied as they are the subgroup of CCBs that are not cardioselective and are traditionally used in RP treatment whereas other CCBs such as verapamil are not routinely used and diltiazem is not used as first line subtype of CCBs. Most trial data pertained to nifedipine.

Withdrawals from studies due to adverse effects were inconclusive owing to a wide CI (risk ratio [RR] 1.30, 95% CI 0.51 to 3.33) from two parallel studies with 63 participants (low-quality evidence downgraded owing to imprecision and a high attrition rate); absolute and relative percent differences in withdrawals were 6% (95% CI -14% to 26%) and 30% (95% CI -49% to 233%), respectively. In cross-over trials, although a meta-analysis was not performed, withdrawals were more common with CCBs than with placebo. The most common side effects were headache, dizziness, nausea, palpitations, and ankle edema. However, in all trials, no serious adverse events (death or hospitalization) were reported.

Authors' conclusions

Randomized controlled trials with evidence of low to moderate quality showed that CCBs (especially the dihydropyridine class) may be useful in reducing the frequency, duration, severity of attacks, pain and disability associated with Raynaud's phenomenon. Higher doses may be more effective than lower doses and these CCBs may be more effective in primary RP. Although there were more withdrawals due to adverse events in the treatment groups, no serious adverse events were reported.

PLAIN LANGUAGE SUMMARY

Calcium channel blockers for treatment of patients with Raynaud’s phenomenon

Raynaud's phenomenon (RP) is a disorder that results in decreased blood flow to the fingers and toes as the result of vasospasm. Symptoms include discoloration (such as a fingertip turning white, then blue and/or red), pain, and, in severe cases, open sores of the digits. Cold, stress, and emotional discomfort are the most common triggers of a Raynaud's attack. No underlying disease is associated with primary RP. Secondary RP is associated with underlying conditions such as systemic sclerosis.

This review assessed the benefits and harms of calcium channel blockers (CCBs) compared with placebo (a substance that appears the same as the active drug but has no active ingredient) for treatment of patients with RP, based on studies published up to May 19, 2017. CCBs are drugs that increase blood flow to the digits and usually are used as first-line treatment for patients with RP. The objective of this review was to determine the benefits and harms of CCBs overall, by dose and type of drug and by type of RP (primary vs secondary).

Study characteristics

We identified and included 38 studies with 982 people 18 years old and over with disease of various duration and severity. Nine studies included patients with primary RP, five included patients with secondary RP, and the rest examined patients with both types of RP. Trial duration ranged from 2 to 20 weeks.

What did this review discover about the use of CCBs versus placebo for RP?

Reviewers found that:

• CCBs probably reduce slightly the frequency, severity, and overall patient assessment of Raynaud's attacks (moderate-quality evidence downgraded for concerns of imprecision or inconsistency);

• CCBs may improve slightly the duration and pain of Raynaud's attacks (low-quality evidence downgraded for imprecision and inconsistency);

• because of lack of data and high dropout rates, effects of CCBs on risk of dropout due to treatment side effects remain uncertain;

• the most common side effects were headache, dizziness, nausea, palpitations, and ankle edema; and

• serious adverse events (death or hospitalization) were not reported.

Best estimates of what happens to people with RP who take CCBs for 2 to 20 weeks

When investigators considered both primary and secondary RP, they reported that 528 people who took CCBs experienced six fewer attacks per week than those who took placebo. People who took a CCB had an average of 8 attacks per week, compared with 14 attacks per week among those taking placebo.

Duration of attacks (in minutes) was about the same for people taking CCBs or placebo. However, this finding was based on a small number of people.

Severity of attacks measured on a 10-cm scale (lower scores indicate less severe attacks) was 0.62 cm lower with CCBs; this was equal to a 6% reduction. People who took a CCB rated the severity of an attack as 6.1 cm, compared with 6.7 cm for those taking placebo.

Pain was reduced by 1.5 points on a 0 to 10 scale (15% absolute reduction, lower score means less pain) with CCBs compared with placebo. People who took a CCB reported a pain score of 1.6 points, compared with 3.1 points for those taking placebo.

Overall disability was reduced by 0.4 points on a 0 to 10 scale (4% absolute reduction, lower score means less disability) among people who took CCBs compared with placebo. People who took a CCB reported a disability score of 3.5 points, compared with 3.9 points for those taking placebo.

Six more people out of 100 who took a CCB withdrew from the study owing to adverse events (6% more withdrawals). Out of 100 people taking a CCB, 25 withdrew from the study, compared with 19 out of 100 taking placebo.

This review suggests that CCBs (particularly drugs in the dihydropyridine class such as nifedipine) in higher doses may be beneficial for the management of RP, particularly primary RP. Although slightly more participants taking CCBs withdrew as the result of treatment side effects, no reported side effects were serious.