Cochrane for Clinicians

Putting Evidence Into Practice

Cilostazol for Intermittent Claudication Caused by Peripheral Artery Disease

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Clinical Question

Is cilostazol (Pletal) therapy safe and effective for improving walking distance in patients with intermittent claudication due to peripheral artery disease (PAD)?

Evidence-Based Answer

Cilostazol improves initial and absolute walking distances in patients with intermittent claudication secondary to PAD and appears to be equivalent in effect to pentoxifylline (Trental). Adverse effects of cilostazol include headache, diarrhea, dizziness, and palpitations.[1] (Strength of Recommendation: A, meta-analysis with consistent results.)

Practice Pointers

PAD affects up to 12% of people 55 to 69 years of age and 20% of people older than 70 years.[1] A sensation of heaviness and fatigue in the leg muscles, known as vascular claudication, is present in 60% of patients with PAD.[2,3] Intermittent claudication secondary to PAD is an indicator of increased systemic atherosclerosis. Compared with age-matched controls, patients who experience intermittent claudication have a higher risk of amputation and cardiovascular mortality over five years.[4]

Medications used to treat intermittent claudication include pentoxifylline (a hemorheologic agent that helps improve blood flow through narrow arteries), antiplatelet agents, and anticoagulants. Cilostazol is a phosphodiesterase-3 inhibitor with antiplatelet and antithrombotic properties that works on smooth muscle as a vasodilator; it also helps to create a more favorable lipid profile by decreasing triglyceride and increasing high-density lipoprotein levels. The authors of this Cochrane review attempted to determine the effects of cilostazol on initial claudication distance (distance walked before pain onset), absolute claudication distance (total distance walked before needing to stop due to pain), mortality, and vascular events in patients with intermittent claudication.

This Cochrane review included 16 randomized controlled trials with 3,972 participants from five countries (United States, Brazil, Ireland, Russia, and Taiwan).[1] Follow-up ranged from six weeks to 26 weeks. All studies compared cilostazol (50 to 150 mg, twice daily) with placebo; five of these studies also compared cilostazol (100 mg twice daily) with pentoxifylline (400 mg two to three times daily or 600 mg twice daily). Because of differing methods in treadmill protocols between the studies, the authors standardized comparison groups by calculating walking distances for each participant and then determined the mean change from baseline. Initial and absolute claudication distance outcomes were dependent on each participant's perception of calf pain (vascular claudication symptoms) and their ability to communicate the onset of pain or discomfort.

Patients taking cilostazol demonstrated an increased initial claudication distance vs. those taking placebo (mean difference = 26 m; 95% CI, 19 to 34 m; low-certainty evidence). Patients taking cilostazol also had an increased absolute claudication distance compared with placebo (mean difference = 40 m; 95% CI, 22 to 57 m; very low-certainty evidence). There were no significant differences in initial and absolute claudication distance when comparing the use of cilostazol and pentoxifylline.

These are summaries of reviews from the Cochrane Library.

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The evidence was insufficient to draw conclusions about the effect of cilostazol on quality of life or other outcomes such as rates of revascularization, cardiovascular events, or amputation. Patients taking cilostazol had increased odds of experiencing headache compared with those using placebo (number needed to harm = 7; 95% CI, 5 to 10; moderate-certainty evidence) and pentoxifylline (number needed to harm = 10; 95% CI, 4 to 63; low-certainty evidence). Other adverse effects of cilostazol included diarrhea, dizziness, and palpitations.

The 2016 American Heart Association/American College of Cardiology guideline on the management of patients with lower extremity PAD recommends structured exercise therapy, risk factor modification, and smoking cessation as the initial approaches to therapy.[4] More research is needed to assess the impact of pharmacologic treatment of PAD sequelae, including vascular claudication and the subsequent need for surgical intervention. Until then, family physicians may want to offer pharmacotherapy as an option when symptoms persist despite lifestyle interventions for patients with intermittent claudication.

The practice recommendations in this activity are available at https://www.cochrane.org/CD003748.

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Editor's Note: The numbers needed to harm and their corresponding CIs reported in this Cochrane for Clinicians were calculated by the authors based on raw data provided in the original Cochrane review.

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Oral vs. Intravaginal Antifungal Treatments for Uncomplicated Vulvovaginal Candidiasis

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Clinical Question

Are intravaginal antifungals as safe and effective as oral antifungals for the treatment of uncomplicated vulvovaginal candidiasis?

Evidence-Based Answer

Clinical resolution of symptoms is similar for oral and intravaginal antifungal medications at both short-term (five to 15 days) and long-term (two to 12 weeks) follow-up. (Strength of Recommendation [SOR]: A, based on consistent, good-quality patient-oriented evidence.) However, mycological cure rates (fungal spores cleared from vaginal secretions) are higher in patients treated with oral antifungals at both short-term (number needed to treat [NNT] = 30; 95% CI, 17 to 200) and long-term (NNT = 19; 95% CI, 10 to 91) follow-up.[1] (SOR: C, based on disease-oriented evidence.)

Practice Pointers

Vulvovaginal candidiasis, otherwise known as vaginal thrush, is an infection of the vagina or vulva causing inflammation and discharge as well as irritation and pruritus. In the United States, it is the second most common type of vaginal infection after bacterial infections, and estimates suggest that 75% of women experience at least one episode of vaginal thrush before menopause,[2] resulting in an estimated 1.4 million annual outpatient visits for vaginal candidiasis in the United States.[3] The primary objective of this review is to evaluate whether oral antifungal medications are more effective than intravaginal antifungal medications in the treatment of uncomplicated vulvovaginal candidiasis—defined as occurring

in otherwise healthy, nonpregnant women; not associated with severe symptoms; and not recurring more than three times a year.[2]

This review included 26 randomized controlled trials (5,007 patients) that examined the treatment of vulvovaginal candidiasis with eight antifungals.[1] These trials were conducted within varying demographics in the United States, Europe, Thailand, Iran, Japan, and Nigeria. The eight antifungals studied were oral fluconazole (Diflucan) and itraconazole (Sporanox) and intravaginal butoconazole (Gynazole-1), clotrimazole, econazole (Zolpak), miconazole, sertaconazole (Ertaczo), and terconazole. The effectiveness of oral vs. intravaginal antifungals was evaluated for elimination of symptoms (clinical cure), elimination of yeast remnants found in vaginal secretions (mycological cure), and how often medication adverse effects prevented treatment completion.

Clinical cure rates for patients using short-term courses (five to 15 days) of oral vs. intravaginal antifungals were similar. In 13 clinical trials (1,859 patients), the effectiveness of intravaginal treatment (77% cure rate) was comparable to that of oral treatment (79% cure rate; 95% CI, 75% to 83%). When patients were treated with long-term therapy (defined as two to 12 weeks), clinical cure rates were also similar for patients whether they used intravaginal antifungals (84% cure rate) or oral antifungals (85% cure rate; 95% CI, 80% to 89%) based on the results of nine clinical trials (1,042 patients).

Oral antifungals achieved a higher rate of mycological cure vs. intravaginal antifungals over the short term (NNT = 30; 95% CI, 17 to 200) and the long term (NNT = 19; 95% CI, 10 to 91). The evidence suggests that if the rate of mycological cure at short-term follow-up with intravaginal treatment is 80%, then the cure rate with oral treatment would be 83% (95% CI, 80% to 85%; n = 3,057). For long-term follow-up, if the rate of mycological cure with intravaginal treatment is 66%, then the rate with oral treatment would be 72% (95% CI, 67% to 76%; n = 1,661).

The risk of discontinuing therapy because of adverse effects when using oral or intravaginal antifungals was low. Only three studies described patients discontinuing therapy. Reported adverse effects included headache and gastrointestinal symptoms for oral antifungals and irritation or burning sensation for intravaginal antifungals. Due to the low certainty of evidence, it was unclear whether oral treatments reduced the number of adverse effects compared with intravaginal treatments. The likelihood of adverse effects was the same (12%; 95% CI, 10% to 15%) among patients who used either oral or intravaginal treatment.

Guidelines from the Centers for Disease Control and Prevention suggest either oral or topical treatment for uncomplicated vulvovaginal candidiasis, with longer courses (seven to 14 days) of low-dose topical medication or short courses (one to three days) of higher-dose topical medication considered equivalent to oral therapy with one 150-mg tablet of fluconazole. Follow-up is not typically necessary, nor is treatment of the asymptomatic sex partner.[4]

The practice recommendations in this activity are available at https://www.cochrane.org/CD002845.

Editor's Note: The NNTs and their corresponding CIs reported in this Cochrane for Clinicians were calculated by the authors based on raw data provided in the original Cochrane review.

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