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Quinine for Leg Cramps

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Clinical Question

Are quinine-based agents safe and effective in treating muscle cramps?

Evidence-Based Answer

Quinine is moderately effective in decreasing the frequency and intensity of muscle cramps, but it is also associated with an increase in minor adverse effects. In addition, there is a risk of rare but serious adverse effects. (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Muscle cramps affect between 50% and 60% of adults.[1] Little is known about their pathophysiology, so many remedies are used empirically. A crystalline alkaloid powder extracted from the bark of the South American cinchona tree, quinine is well known for its use in treating malaria and providing the bitter flavor for tonic water. Quinine has been used by the Quechua of South America for medicinal purposes for centuries, and has been researched since the 1930s and 1940s as a cure for muscle cramps.[2] However, quinine is not without adverse effects, and the U.S. Food and Drug Administration withdrew the indication for treatment of muscle cramps because of reports of serious adverse effects such as hemolytic uremic syndrome, disseminated intravascular coagulation, and arrhythmias.[3] Despite this, many patients still request quinine and many clinicians continue to use it off label.

This Cochrane review addresses the safety and effectiveness of quinine for muscle cramps and includes 23 studies comparing quinine to various agents: placebo, vitamin E, a combination of quinine and vitamin E, a combination of quinine and theophylline, and xylocaine injection. Dosages of quinine ranged from 200 to 500 mg, divided, once or twice daily. Thirteen studies were pooled to compare quinine vs. placebo with respect to the number of cramps over a two-week period (n = 952). Patients taking quinine had 2.5 fewer cramps than those taking placebo (95% confidence interval [CI], 1.4 to 3.5). Likewise, in seven studies (n = 666), those who took quinine also had decreased cramp intensity (–0.12 units on a three-point scale; 95% CI, –0.20 to –0.05), but this difference does not meet the usual criteria for a minimal clinically important difference. In seven studies (n = 842), quinine also decreased the number of days with cramps in two weeks (–1.2 days; 95% CI, –1.9 to –0.4). There was no difference in duration of muscle cramps. Patients taking quinine had more minor adverse effects, including gastrointestinal distress and tinnitus (risk difference = 0.03; 95% CI, 0 to 0.06). There was no significant difference in major adverse effects.

There was no statistically significant difference between quinine and vitamin E with respect to number of cramps, intensity or duration of cramps, or adverse effects, although patients taking quinine had a reduction in number of days with cramps (–2.8; 95% CI, –3.3 to –2.4) when compared with vitamin E. When quinine was compared with a quinine/vitamin E combination, there was no difference in number of cramps, intensity or duration of cramps, number of days with cramps, or adverse effects. The quinine/theophylline combination was found to be more effective than quinine alone on multiple measures, but these results are based on a single pharmaceutical-sponsored study of 164 patients. In another small study of 24 patients, xylocaine injection was found to provide better relief than quinine four weeks after the cessation of treatment.

Quinine is available for malaria treatment in the United States and is still readily available for leg cramps in many parts of the world. Tonic water is one good source of quinine; 1 L of tonic water contains approximately 60 to 70 mg of quinine.[4] Quinine remains part of the National Health System formulary in Great Britain and is available in brand-name and generic forms in Canada. Physicians should encourage patients to follow the American Academy of Neurology guidelines, which recommend that patients with disabling cramps try nonpharmacologic treatments first and reserve quinine for use only after other agents have failed.[2]

SOURCE: El-Tawil S, Al Musa T, Valli H, et al. Quinine for muscle cramps. *Cochrane Database Syst Rev.* 2015;(4):CD005044.

The practice recommendations in this activity are available at http://summaries.cochrane.org/CD005044.

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REFERENCES

1. Allen RE, Kirby KA. Nocturnal leg cramps. *Am Fam Physician.* 2012; 86(4):350-355.
2. Katzberg HD, Khan AH, So YT. Assessment: symptomatic treatment for muscle cramps (an evidence-based review): report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology.* 2010;74(8):691-696.
3. U.S. Food and Drug Administration. Questions and answers about FDA's enforcement action against unapproved quinine products. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm119653.pdf. Accessed June 16, 2015.
4. Ohira A, Yamaguchi S, Miyagi T, et al. Fixed eruption due to quinine in tonic water: a case report with high-performance liquid chromatography and ultraviolet A analyses. *J Dermatol.* 2013;40(8):629-631.

Electronic Cigarettes for Smoking Cessation

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Clinical Question

Are electronic cigarettes safe and effective in helping smokers to quit or reduce their smoking?

Evidence-Based Answer

Electronic cigarettes with nicotine increase smoking cessation rates compared with placebo, with effectiveness similar to that of nicotine patches. In addition, more patients using electronic cigarettes with nicotine were able to halve their use of cigarettes than those using placebo electronic cigarettes or nicotine patches. Long-term safety is unknown. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Electronic cigarettes have steadily increased in popularity as an alternative to conventional tobacco cigarettes, and 21% of American smokers report having tried them.[1] Although their long-term safety and health effects are not known, the most common reason given for using electronic cigarettes has been to quit or reduce cigarette smoking.[2,3] Although not marketed as smoking cessation devices and therefore not regulated by the U.S. Food and Drug Administration, electronic cigarettes are widely used for this purpose.[1]

This Cochrane review combined data from two randomized controlled trials (RCTs) totaling 957 participants. The first of the RCTs randomized 657 smokers into three groups receiving 16-mg nicotine electronic cigarettes, 21-mg nicotine patches, or placebo electronic cigarettes. The study assessed smoking cessation rates at six months, which were confirmed by exhaled carbon monoxide levels. Between the nicotine electronic cigarette and placebo electronic cigarette groups, there were no statistically significant differences in rates of smoking cessation (7.3% vs. 4.1%; P = not significant). The second trial randomized 300 patients to receive electronic cigarettes containing 7.2 mg of nicotine for 12 weeks; 7.2 mg of nicotine for six weeks followed by 5.2 mg of nicotine for six weeks; or no nicotine for 12 weeks. No statistically significant difference in smoking cessation rates among the groups was found at six and 12 months. The overall quality of the data was considered low because of the small number of trials.

When the results from the two included studies were combined, the authors concluded that electronic cigarettes containing nicotine are more effective than placebo for smoking cessation, with an absolute cessation rate of 9% compared with 4% for placebo (relative risk for quitting = 2.29; 95% confidence interval, 1.05 to 4.96). Further, the authors concluded that participants using nicotine electronic cigarettes were able to cut their cigarette use in half more often than participants using placebo electronic cigarettes (relative risk = 1.31; 95% confidence interval, 1.02 to 1.68).

Clinical trial data did not reveal any immediate severe adverse effects with use of electronic cigarettes. Cohort studies identified in the review revealed some cytotoxic effects as well as short-term increased airway resistance with use of electronic cigarettes. Throat irritation did not seem to abate over time. The clinical significance of these effects, as well as the long-term health effects of using electronic cigarettes, is still unknown.

In a recent recommendation statement, the U.S. Preventive Services Task Force found insufficient evidence to recommend the use of electronic cigarettes for smoking cessation.[4] Although smokers should be supported in any attempt to quit, the American Heart Association does not recommend the use of electronic cigarettes as a

primary smoking cessation aid. Further, it recommends that electronic cigarette users set a quit date rather than use them indefinitely.[5] Clinicians giving advice to their patients seeking to quit smoking with the aid of electronic cigarettes should bear in mind the current large knowledge gaps regarding these devices, in particular their long-term safety.

SOURCE: McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev.* 2014;(12):CD010216.

The practice recommendations in this activity are available at http://summaries.cochrane.org/CD010216.

REFERENCES

1. Ebbert JO, Agunwamba AA, Rutten LJ. Counseling patients on the use of electronic cigarettes. *Mayo Clin Proc.* 2015;90(1):128-134.
2. Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation.* 2014;129(19):1972-1986.
3. Rutten LJ, Blake KD, Agunwamba AA, et al. Use of e-cigarettes among current smokers: associations among reasons for use, quit intentions, and current tobacco use. *Nicotine Tob Res.* 2015;17(10):1228-1234.
4. U.S. Preventive Services Task Force. Final recommendation statement: Tobacco smoking cessation in adults and pregnant women: behavioral and pharmacotherapy interventions. September 2015. http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1. Accessed December 3, 2015.
5. Bhatnagar A, Whitsel LP, Ribisi KM, et al.; American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation.* 2014;130(16):1418-1436. ■