FPIN's Clinical Inquiries

Topical Nitroglycerin for Lower Extremity Tendinopathy

Jeremy Loescher, DO; Paul Waclawski, DO; and Richard Guthmann, MD, MPH
Advocate Illinois Masonic Family Medicine Residency, Chicago, Illinois

Clinical Question

Does topical nitroglycerin (NTG) reduce pain from lower extremity tendinopathy and improve function?

Evidence-Based Answer

In non-insertional Achilles tendinopathy, topical NTG patches are minimally better than placebo at 24 weeks. Topical NTG plus physical therapy is not superior for pain relief or functional improvement compared with placebo patches plus physical therapy. (Strength of Recommendation [SOR]: B, inconsistent results in two small randomized controlled trials [RCTs].) In chronic patellar tendinopathy, NTG patches provide no significant pain relief vs. placebo patches at up to 12 weeks. (SOR: B, low-quality RCT.)

Evidence Summary

There are two systematic reviews on the use of topical NTG for tendinopathies. The evidence summary includes four RCTs that were deemed limited, conflicting, or inconsistent.[1,2]

Non-insertional Achilles Tendinopathy. An RCT performed in Australia compared 1.25-mg NTG patches with placebo patches applied daily to the area of maximal tenderness in 65 patients (40 men and 25 women; median age = 49 years).[3] Patients had symptoms for more than three months, no previous surgery on or dislocation of the affected ankle, and no steroid injection in that area in the past three months.

At two- and six-week follow-up, there was no statistical difference in pain at rest, at night, or after activity compared with placebo on a five-point pain severity scale. At 12 weeks, the NTG group's pain scores decreased at rest (mean score = 0.9 vs. 1.6; $P = .02$), at night (0.2 vs. 0.7; $P = .04$), and with activity (0.9 vs. 1.6; $P = .02$). At 24 weeks, the NTG group's pain scores decreased with activity (0.4 vs. 1.0; $P = .03$), but not at rest or at night.

On a mean total work evaluation of ankle plantar flexion assessed with a resisted footplate device, there was no difference between groups from baseline at two, six, and 12 weeks. The NTG group improved more from baseline at 24 weeks (70.3 Newtons vs. 43.0 Newtons; $P = .04$), but the clinical significance of the increase was unclear.

When comparing the NTG group with the placebo group on patient-reported outcomes at 24 weeks, 78% vs. 49% of patients, respectively, reported being asymptomatic (number needed to treat = 3); 22% vs. 44% were unchanged (defined as less than 10% change); and 0% vs. 7% of patient-reported outcomes were worse by more than 10%. At six months, both groups had similar numbers of patients who had completed the study (27 of 32 patients in the NTG group vs. 31 of 33 patients in the placebo group). Adverse effects were

Clinical Inquiries provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations and the level of evidence for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (https://www.cebm.net).

This series is coordinated by John E. Delzell Jr., MD, MSPH, associate medical editor.

A collection of FPIN's Clinical Inquiries published in *AFP* is available at https://www.aafp.org/afp/fpin.

Author disclosure: No relevant financial affiliations.

experienced in both groups, and four patients discontinued treatment because of adverse effects. Headache was the most common (17 patients in the NTG group [53%] vs. 15 patients in the placebo group [45%]), followed by a rash (five patients [16%] vs. four patients [12%]). There was one case of tinnitus in the NTG group.[1,3]

A separate study provided follow-up on these same patients at three years.[4] Most patients were completely or almost completely healed, but those treated with NTG had less Achilles tendon tenderness and improved scores on the Victorian Institute of Sport Assessment–Achilles tendon scale, a quantitative index of pain and function in patients with chronic Achilles tendinopathy. More patients in the NTG group remained asymptomatic at three years compared with rehabilitation alone (88% vs. 67%; $P = .03$).

A second RCT included 40 patients from the United Kingdom (mean age = 41 years).[5] The control group was treated with physical therapy and eccentric stretching, whereas the NTG group received the same therapy plus a daily 2.5-mg 24-hour NTG patch applied to the most tender area. The study used Ankle Osteoarthritis Scale visual analog scores, a self-assessment of pain and disability ranging from 0 to 10, assessed before treatment and at six months after treatment. At the six-month follow-up, both groups had improved, but there were no significant differences in mean pain scores (3.0 vs. 3.1; $P = .42$) or mean disability scores (2.2 vs. 2.3; $P = .38$). Headache was the only adverse effect noted in this study, and all four of the patients who experienced headaches were in the NTG group.[1,2,5]

Patellar Tendinopathy. An RCT from the Netherlands reviewed a group of 40 randomly assigned patients (18 to 40 years of age) with patellar tendinopathy.[6] Seven dropped out (one for a concomitant knee issue, two due to traveling time, and four for unknown reasons), which left 16 patients in the NTG group and 17 in the control group. Patients were treated with a 5-mg topical NTG patch daily to the area of maximal tenderness or a placebo patch in conjunction with an eccentric exercise program. No patient stopped using the NTG patch before the 12-week period ended. The compliance with the eccentric training program was more than 70%. Measurements using the Victorian Institute of Sport Assessment–Patella questionnaire, which assesses knee symptoms, tests of function, and the ability to play sports, were taken at zero, six, 12, and 24 weeks. The maximal score for an asymptomatic, fully performing individual is 100 points, and the minimum is zero points. At 24 weeks, both groups had increases in Victorian Institute of Sport Assessment–Patella scores, but improvement was similar between the groups (12.0 points for the NTG group vs. 12.9 points for the control group). Similarly, visual analog scale scores and patient satisfaction rates improved over time with no difference between the two groups. Three of the patients in the NTG group reported adverse effects (a rash caused by the patches), without other adverse effects noted.[1,6]

Address correspondence to Richard Guthmann, MD, MPH, at RickGuthmann@gmail.com. Reprints are not available from the authors.

References

1. Challoumas D, Kirwan PD, Borysov D, et al. Topical glyceryl trinitrate for the treatment of tendinopathies: a systematic review. *Br J Sports Med*. 2019;53(4):251-262.
2. Gambito ED, Gonzalez-Suarez CB, Oquiñena TI, et al. Evidence on the effectiveness of topical nitroglycerin in the treatment of tendinopathies: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2010;91(8):1291-1305.
3. Paoloni JA, Appleyard RC, Nelson J, et al. Topical glyceryl trinitrate treatment of chronic noninsertional Achilles tendinopathy. A randomized, double-blind, placebo-controlled trial. *J Bone Joint Surg Am*. 2004;86(5):916-922.
4. Paoloni JA, Murrell GAC. Three-year followup study of topical glyceryl trinitrate treatment of chronic noninsertional Achilles tendinopathy. *Foot Ankle Int*. 2007;28(10):1064-1068.
5. Kane TPC, Ismail M, Calder JDF. Topical glyceryl trinitrate and noninsertional Achilles tendinopathy: a clinical and cellular investigation. *Am J Sports Med*. 2008;36(6):1160-1163.
6. Steunebrink M, Zwerver J, Brandsema R, et al. Topical glyceryl trinitrate treatment of chronic patellar tendinopathy: a randomised, double-blind, placebo-controlled clinical trial. *Br J Sports Med*. 2013;47(1):34-39. ■