Q/ Are topical nitrates safe and effective for upper extremity tendinopathies?

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EVIDENCE-BASED ANSWER

A/ **Topical nitrates provide short-term relief** with some side effects, especially headache. Topical nitroglycerin (NTG) patches improve subjective pain scores by about 30% and range of motion over 3 days in patients with acute shoulder tendinopathy (strength of recommendation [SOR]: **C,** small randomized controlled trial [RCT] with no methodologic flaws).

NTG patches, when combined with tendon rehabilitation, improve subjective pain ratings by about 30% and shoulder strength by about 10% in patients with chronic shoulder tendinopathy over 3 to 6 months, but not in the long term (SOR: **C,** RCTs with methodologic flaws). They improve pain and strength 15% to 50% for chronic extensor tendinosis of the elbow over a 6-month period (SOR: **C,** small RCT with methodologic flaws).

NTG patches used without tendon rehabilitation don't improve pain or strength in chronic lateral epicondylitis over 8 weeks (SOR: **C,** RCT).

Topical NTG patches commonly produce headaches and rashes (SOR: **B,** multiple RCTs).

Evidence summary

A small RCT found that NTG therapy improved short-term pain and joint mobility in patients with acute supraspinatus tendinitis.[1] Investigators randomized 10 men and 10 women with acute shoulder tendonitis (fewer than 7 days' duration) to use either 5-mg NTG patches or placebo patches daily for 3 days. Patients rated pain on a 10-point scale, and investigators measured joint mobility on a 4-point scale.

After 48 hours of treatment, NTG patches significantly reduced pain ratings from baseline (from 7 to 2 points; $P<.001$), whereas placebo didn't (6 vs 6 points; P not significant). NTG patches also improved joint mobility from baseline (from 2 points "moderately restricted" to .1 points "not restricted"; $P<.001$), but placebo didn't (1.2 points "mildly restricted" vs 1.2 points; P not significant). The placebo group had less pain and joint restriction than the NTG group at the start of the study. Two patients reported headache 24 hours after starting treatment.

NTG plus rehabilitation improves chronic shoulder pain, range of motion

A double-blind RCT evaluating NTG patches for 53 patients (57 shoulders) with chronic supraspinatus tendinopathy (shoulder pain lasting longer than 3 months) found that they improved pain, strength, and range of motion at 3 to 6 months.[2] Investigators randomized patients to receive one-quarter of a 5-mg 24-hour NTG patch or placebo patch daily and enrolled all patients in a rehabilitation program. They assessed subjective pain (at night and with activity), strength, and external rotation at baseline and at 2, 6, 12, and 24 weeks.

NTG patches improved nighttime pain about 30% (at 12 and 24 weeks), pain with

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activity about 60% (at 24 weeks), strength about 10% (at 12 and 24 weeks), and range of motion about 20% (at 24 weeks; $P<.05$ for all comparisons). The placebo group initially had more pain, less strength, and less mobility than the NTG group. Investigators reported no adverse effects.

NTG and rehab improve elbow pain, but with side effects

Another RCT comparing topical NTG patches in patients with chronic extensor tendinosis of the elbow found that they improved most parameters.[3] Investigators randomized 86 patients with elbow tendonitis (longer than 3 months) to NTG patches (one-quarter of a 5-mg 24-hour patch) or placebo patches and enrolled all patients in a tendon rehabilitation program. They assessed subjective pain, extensor tendon tenderness, and muscle strength at baseline and at 2, 6, 12, and 24 weeks.

NTG patches improved subjective pain, tendon tenderness, and strength significantly more than placebo at all follow-up points, by 15% to 50% ($P<.05$ for all comparisons). The study was flawed because the control group started with more pain, tenderness, and weakness than the NTG group. Five patients discontinued NTG because of adverse effects (headache, dermatitis, and facial flushing).

A follow-up study done 5 years after discontinuation of therapy found equal outcomes with NTG and placebo.[4] Investigators evaluated, by phone or in person, 58 of the 86 patients in the original study. NTG and placebo therapy produced equivalent reductions in subjective 0 to 4 elbow pain scores over baseline (average pain 2.5 initially, 1.5 at 12 weeks, and 1.0 at 5 years; $P<.01$ for all comparisons with baseline, no significant difference between nitrates and placebo).

NTG without rehab works no better than placebo

Another RCT that evaluated 3 different doses of NTG patches for 8 weeks in 154 patients with chronic lateral epicondylosis found NTG treatment was no better than placebo for pain or strength.[5] Investigators randomized patients with more than 3 months of symptoms to 3 NTG patch doses (.72 mg/24 h, 1.44 mg/24 h, or 3.6 mg/24 h) compared with placebo and evaluated subjective pain (at rest, with activity, and at night), grip strength, and force, at baseline and 8 weeks.

The study lacked a formal wrist strengthening rehabilitation program. Patients in the placebo group had lower baseline pain scores than the NTG groups. Seven patients dropped out of the study because of headaches.

Recommendations

We found no authoritative recommendations regarding the use of topical nitrates for upper extremity tendinopathies.

An online reference text doesn't make a recommendation, but references the studies described previously.[6] The authors state that headache is the most common adverse effect of topical nitrates, but it becomes less severe over the course of treatment. They recommend caution in patients with hypotension, pregnancy, or migraines, and those who take diuretics. The authors also note that nitrates are relatively contraindicated in patients with ischemic heart disease, anemia, phosphodiesterase inhibitor therapy (such as sildenafil), angle-closure glaucoma, and allergy to nitrates. JFP

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