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Is treatment with topical glyceryl trinitrate effective in reducing elbow pain in patients with lateral epicondylitis?

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A Selective Evidenced Based Medicine Review

In Partial Fulfillment of the Requirements For

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In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not treatment with topical glyceryl trinitrate is effective in reducing elbow pain in patients with lateral epicondylitis.

Study Design: Review of two English language randomized controlled trials and one primary study published 2003, 2009, 2011.

Data Sources: Two double blind randomized controlled and one prospective comparison study comparing the effectiveness of glyceryl trinitrate to placebo in the treatment of pain related to lateral epicondylitis, found using PubMed, EBSCOhost, and CINAHL Plus.

Outcome(s) Measured: The outcome studied was patient self-rated elbow pain at rest, pain with activity, pain at night, and local epicondylar and tendon tenderness, measured with Maudsley's test (newtons) with dynamometer and wrist extension mean peak force, ORI-TESTS.

Results: Paoloni et al (2003) showed pain and tenderness in 81% (35 of 43) patients in the GTN group were asymptomatic with activities of daily living, compared to 60% (26 of 43) in the placebo group. ($p=0.005$). The 2009 trial by Paoloni *et al* was inconclusive due to discontinuation at 8 weeks due to insignificant findings. The prospective study by McCallum *et al* in 2011 was inconclusive, showing no difference between the GTN group and placebo group at 5 years post treatment.

Conclusions:

Key Words: Glyceryl trinitrate, lateral epicondylitis

INTRODUCTION

Lateral epicondylitis, more commonly known as tennis elbow, is a chronic, inflammatory disorder of the extensor carpi radialis muscle attachment to the lateral prominence of the humerus, the epicondyle. It is due to overuse or repetitive movement of the forearm, such as the motion used when playing tennis, or when lifting heavy loads with the forearm pronated, or with grasping. It is characterized by pain and tenderness to palpation over the epicondyle. The muscle attachment over the epicondyle degenerates, causing the pain. It is often described clinically as a dull aching pain, which interferes with activities of daily life due to inability to fully use the affected arm. It commonly occurs in patients 30 – 50 years of age.¹

To physician assistants who practice in general medicine and in musculoskeletal specialties, this is very common injury seen. It is seen between 1-3% of adults (3.2-9.6 million)¹, and leads to many visits and decreased quality of life for patients. The economic burden on the health care system and on the patients was not estimated in any academic sources. However, with an average healing time of 18-24 months, it can be predicted that there are many hours lost from work.

Lateral Epicondylitis is a well-known and studied pathology. The mechanism of injury, as discussed above, is repeated stress to the tendon overlying the epicondyle, leading to degeneration and pain for the patient. Symptoms include morning stiffness, point tenderness, and pain with movement and gripping. It is a chronic condition, meaning that the symptoms last for greater than three months.¹ It decreases quality of life for patients, who have pain with movement of the affected elbow for many months. What is unknown about this condition is the most effective treatment, as there is no agreed upon treatment. There are many options, with

physical therapy being the most prominent. Also unknown, and relevant to this review, is the exact mechanism of action of glyceryl trinitrate.²

Most patients are indeed referred to PT, as this has yielded beneficial results, and is the mainstay treatment. However, many patients continue to complain about the chronic pain, and look for other options, if only for relief. These include NSAIDs, braces, corticosteroid injection, electro-stimulation, surgery, and RICE (rest, ice, compression, elevation.)

The method proposed and studied by this particular review is treatment with topical glyceryl trinitrate (GTN) patches. This transdermal patch is used in conjunction with physical therapy, in hopes of increased nitrous oxide and blood flow to the area, allowing healing of the degenerated tendon. These patches have been shown effective in other tendonopathies. This treatment method is being study due to its non-invasiveness for a very common medical problem.²

OBJECTIVE

The objective of this systematic review is to determine whether or not treatment with glyceryl trinitrate is effective in reducing pain in patients with lateral epicondylitis.

METHODS

Criteria: In order to answer the above question, this review focuses on a population over the age 18, with a diagnosis of lateral epicondylitis. The interventions that were considered include treatment with GTN transdermal patch verses a placebo. The outcomes measured included patient rated pain at rest, with activity, and at night. The studies that are included are two RCT's and one primary study, all of which met above parameters.^{2,3,4}

Data Sources: The sources used for this review came from a search of databases looking at English language articles with the key words “lateral epicondylitis” and “glyceryl

trinitrate.” All articles were published in peer-reviewed articles, and were selected based on relevancy to the question asked, and if they included patient oriented outcomes that matter (POEMS). The search was done via PCOM library access to PubMed, EBSCOhost, and CINAHL Plus. Inclusion criteria for studies included randomization, double blind, and placebo control. A trial was excluded if it was published greater than 15 years in the past, patients who had an acute injury, or if a patient was under 18 years of age. Statistics used in these three trials were Relative Risk Reductions (RRR), Absolute Risk Reduction (ARR) Numbers needed to treat (NNT) and P-values.

Study	Type	#Pts	Age (years)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Paoloni (2003) ⁴	Double blind RCT	86	>18	Patient over the age of 18 who had diagnosis of chronic lateral epicondylitis	Tendonosis < 3 month, pregnancy, Sx or dislocation, distal neuro signs, or steroid injection in last 3 mo	8	¼ of 5mg/24hour Nitro-dur patch
Murrell (2009) ⁵	Double Blind RCT	154	18-70	Adults 18-70 with dx of lateral epicondylitis, who scored > 4 on visual 1-10 pain scale	BMI >38, regular oral/topical analgesia, steroid injection in last 3 mo, work comp cases, pregnancy, previous	18	Orthoderm 0.72mh/24hr Othroderm 1.44mg/24hr Orthoderm 3.6mg/24hr

					GTN use, cardiac dz, upper limb injury hx		
Paoloni et al (2009) ²	Primary	58	>18	Patient over the age of 18 who had diagnosis of chronic lateral epicondylitis	Tendonosis < 3 month, pregnancy, Sx or dislocation, distal neuro signs, or steroid injection in last 3 mo	Follow up of RCT that had 12 W/D	¼ of 5mg/24hour Nitro-dur patch

OUTCOMES MEASURED

All outcomes measure in these three studies reviewed are POEMs. The major outcomes studied included patient rated elbow pain at rest, pain with activity, at night, and local epicondylar/tendon tenderness. The patients, using questionnaires, rated these categories. Data was collected from the surveys and further analyzed. The major measurement used in all three studies was ORI-TETS, or the Orthopedic Research Institute Tennis Elbow Testing System. This test is designed to objectively measure force generated with a simulated chair pickup test.⁵ Results were analyzed by statistical software (Sigmastat 2.0) by way of the Mann-Whitney rank sum test to compare the differences within groups. Significant findings were defined with P values of 0.05 or less. Patients rated safety and tolerability, with headaches and a dermatitis rash being a major side effect. **EDIT**

RESULTS

All of the studies reviewed had patients who were previously diagnosed with lateral

epicondylitis, and had agreed to follow up for the allotted time. Table One shows the demographics for the patients included in all three studies. The data was presented in dichotomous form for the two RCTs studied (Paoloni, Appleyard, Nelson, Murrell 2003; Paoloni Murrell, Burch, Ang 2009), and in continuous form that was converted to dichotomous in the primary study (McCallum, Paoloni, Murrell 2011).

In the RCT by Paoloni et al. (2003, Am Journal of Sports Medicine), 86 patients were selected for the trial, split evenly into 43 GTN and 43 placebo patients. In the GTN group, 5 dropped out due to side effects (headache), 2 dropped out at the 2 week interval with no reason given, and 1 dropped out due to work related injury. This resulted in 35 patients in the GTN group who completed the 6-month trial. The authors reported that 81% (35 of 43) patients in the GTN group were asymptomatic with activities of daily living, compared to 60% (26 of 43) in the placebo group. A chi-square analysis was done comparing outcomes between the groups that showed the GTN group had a significantly increased ($p=0.005$) chance of being asymptomatic by week 24 of the trial. In regards to pain, tenderness, and mean peak force, a Mann-Whitney rank sum test was performed, all showing benefit for the GTN patients.²

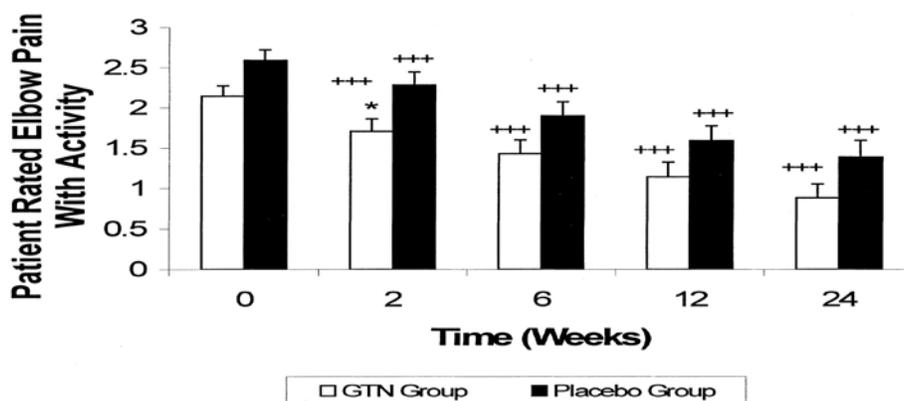


Table 2. Paoloni *et al.* (2003). Effects of Gtn therapy vs placebo on patient rated elbow pain.

Pain was decreased most at week 2 of the study ($p=0.002$), tenderness was measured at week 6 and 12, each with improvement and ($p=0.02$), and peak force at week 24 was increased ($p=0.03$). According to the journal, “at 6 months, 81% of treated patients were asymptomatic during activities of daily living, compared with 60% of patients who had tendon rehabilitation alone.” This gives us the Control event rate (CER) of 60%, for the patients with the placebo patch, and an Experimental event rate (EER) of 81%. Relative risk reduction (RRR) was calculated at 35%, absolute risk reduction at 21%, and numbers needed to treat (NNT) was 5. The NNT shows that a practitioner needs to treat 5 patients who have tennis elbow with GTN in order to have 1 patient show benefit.²

The most clinically significant side effects reported were headache in 63% (27/43), and dermatitis rash in 21% (9/43). The placebo group had 58% (25/43) report headache.²

Paoloni was also involved in an RCT with the British Journal of Sports Medicine. In this RCT (Paoloni *et al.*, 2009), used intention to treat analysis of 154 patients, including 18 discontinued patients (3 dropped from placebo group, 3 from 0.72mg, 4 from 1.44mg, 8 from 3.6mg). They compared different strengths of GTN, namely OrthoDerm 0.72mg/24h (38 patients), 1.44mg/24h (30 patients), and 3.6mg/24h (36 patients) with placebo (32 patients). The study showed significant improvement in elbow pain with activity at week 8 with the 0.72mg/24h versus placebo ($P=0.04$). The authors discontinued the trial after week 8 due to lack of other significant results. This trial had a CER of 88%, EER of 91%, RRR was 3%, ARR was 3% and NNT was 34 in order to improve 1 patient's symptoms.³

The authors mention headache and dermatitis rash as clinically significant side effects for treatment with GTN patches, with effects increasing as the dose was increased. Overall, 7 of the GTN patients were discontinued due to severe headache (17%).³

The third study reviewed for this paper was a five-year prospective comparison. There were 58 patients who had taken part in the original RCT of 6-month duration: 33 men and 25 women, with a mean age of 58 (range 40-78). At 5 years after discontinuation of treatment, the results of treatment with GTN verses that with placebo (both with PT) were compared, and found to be equally effective. Analysis was performed on patient-rated pain, and there were significant improvements in both placebo and GTN groups compared with week 0 of the initial RCT. However there was no significant difference in patient pain between the placebo and GTN groups for activity pain ($p=0.24$), rest pain ($p=0.16$), or night pain ($p=0.16$) at 5 years. Similarly, there was no significant difference in the prevalence of pain with activity ($p=0.43$) at rest ($p=0.24$) or at night ($p=0.26$). There were also no significant differences in the prevalence of lateral epicondylar tenderness ($p=0.52$) or in tenderness severity ($p=0.16$). The P-values here are evident of non-significant data between the groups, showing no benefit of using GTN patches as therapy.⁴

DISCUSSION

After review of the results as presented above, it is important to compare and contrast efficacy, safety, and real life application of the glyceryl trinitrate for tennis elbow. It does not appear that there are many insurance issues, as there were none listed. GTN patches can be gotten generically, and use similar compounds found in nitroglycerin used for cardiac ischemia. Availability in the U.S. would not be a limitation on treatment with GTN.

It is evident that treatment with topical GTN patches has benefit on pain and tenderness for the patient, but only in a short term follow up of six months. The primary study showed that there was no significant benefit 5 years from treatment.

Limitation of each study- primary (2011)- there was a lack of controlled treatment between 6 months and the 5-year study. Also, it is hypothesized that benefit is not seen after 2 years, so the study may have been done too late. The authors state that a power analysis showed they would need 80 patients to have significant data, and although originally recruited, only 58 were used in the final study. The RCT (2003) mentioned that the physical therapy program was not followed closely, as it was done at home. They used verbal patient confirmation that the PT was being performed, giving room for possible non-compliance. The RCT (2009) had many limitations. The authors stated that after week 8 the study was discontinued due to lack of significant results. They stated that there was no exercise program in conjunction with the GTN patches, which is a mainstay of treatment, and thus a major weakness of the study. Further complicating the study was the use of three different dosages of GTN patches, making sample sizes smaller and comparison more difficult.

Glyceryl trinitrate is hypothesized to induce nitric oxide release into tendon fibroblasts leading to increased collagen synthesis in tendon. However, because of this effect, systemic absorption can lead to side effects such as headache, dermatitis rash, and facial flushing. Review of drug safety via Lexi-Comp Online mentions careful use of GTN in patients with cardiovascular conditions. They remind practitioners to only leave patch in place for 10-12 hours and to rotate sites to avoid tolerance.⁶

CONCLUSIONS

The three articles reviewed here point to the conclusion that GTN transdermal patches are efficacious in treating patient rated pain associated with lateral epicondylitis. However, only the study by Paoloni et al (2003) in the American Journal of Sports Medicine showed concrete evidence, as it was the most thorough study. The 2009 Paoloni et al study in the British Journal of Sports Medicine was not followed through past 8 weeks, but pointed to positive results with GTN therapy if combined with PT concurrently. The prospective study by McCallum *et al.* (2011) showed that there are no long term effects of GTN therapy. They did point out that a shorter time may have better results, as a similar study with GTN and Achilles tendonitis had efficacy at 3 years.⁷

Looking at these faults, further studies can be proposed to better answer the question of GTN efficacy with lateral epicondylitis. Because there was only one RCT that was followed through to 6 months, more trials are warranted. Also, rating patient response at 2 years instead of at 5 years may prove that there is less pain and tenderness in the GTN group as compared with placebo.

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