Clinical studies of topical glyceryl trinitrate treatment in chronic overuse tendinopathies

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Abstract

**Background:** Chronic tendinopathies are degenerative in nature, cause considerable morbidity due to pain and lost time at work and recreation, and no treatment is universally effective in their management.

**Hypothesis:** We aimed to assess if topical glyceryl trinitrate therapy coupled with tendon rehabilitation improved patient outcomes in chronic tendinopathies when compared with rehabilitation alone.

**Study Design:** Randomised, double-blind, placebo controlled clinical trials.

**Methods:** Three clinical trials investigated topical glyceryl trinitrate treatment (1.25 mg/24 hour) and tendon rehabilitation versus tendon rehabilitation alone in the treatment of chronic overuse tendinopathies in adults (Achilles tendinopathy, N=84; extensor tendinopathy at the elbow, N=95; supraspinatus tendinopathy, N=57).

**Results:** The glyceryl trinitrate group had significant improvements in patient rated pain, increased tendon force measures, improved functional measures, and improved patient outcomes relative to tendon rehabilitation. Outcomes at week 24 demonstrated that subjects becoming completely asymptomatic were increased in the glyceryl trinitrate groups by 22-29%, effect size estimations ranged from 12-26%, and all clinical trial grouped outcome measures at week 24 improved.

**Conclusions:** Topical glyceryl trinitrate therapy when coupled with tendon rehabilitation can improve patient outcomes in adults with chronic tendinopathies. Glyceryl trinitrate has clinically demonstrated efficacy in modulating pain, force measures, functional measures, and patient outcomes at six months in chronic overuse tendinopathies at multiple sites. Topical glyceryl trinitrate treatment has a role in managing specific chronic overuse tendinopathies.
Key Terms: Tendon, glyceryl trinitrate, shoulder, elbow, Achilles, nitric oxide
**Introduction**

Overuse injuries involving tendon are common and result in considerable morbidity and decreased occupational and recreational participation\(^{19,21}\). Tendinopathies involve collagen degeneration with histopathological features of mucoid degeneration, angiofibroblastic hyperplasia, and a distinct lack of inflammatory cells\(^{4,19,35}\).

Common chronic degenerative tendinopathies include non-insertional Achilles tendinopathy, extensor tendinopathy at the elbow, and rotator cuff tendinopathy\(^1\).

Non-insertional Achilles tendinopathy presents especially among runners\(^9,42\), extensor tendinopathy at the elbow is found in tennis players\(^{31}\) and patients whose work involves repetitive forearm and hand movements\(^{11}\), and rotator cuff tendon injury such as supraspinatus tendinopathy is prevalent in overhead workers and throwing athletes\(^8,15\).

Nitric oxide synthase, the endogenous precursor to nitric oxide (NO) is induced during tendon healing\(^{22,23}\) and fracture repair\(^46\), and inhibition of nitric oxide synthase resulted in a significant reduction in healing tendon cross-sectional area and load to failure\(^{27}\). Nitric oxide modulates collagen synthesis by human tendon fibroblasts in culture\(^43\). Topical glycercyl trinitrate, a prodrug of nitric oxide\(^{12,26}\), has demonstrated efficacy in improving short term pain in acute supraspinatus tendinitis\(^5\).

We aimed to assess if tendon rehabilitation combined with continuous topical glycercyl trinitrate, a nitric oxide donor, altered clinical and functional outcome measures in patients with three common types of chronic degenerative tendinopathies at six months when compared to tendon rehabilitation alone.

There are a variety of non-operative treatments for tendinopathy, many with unproven therapeutic efficacy, and none that are universally effective in the management of chronic tendinopathies\(^7,19,20\). The non-operative management of
tendinopathies involves rehabilitation consisting of relative rest, stretching, and a graduated strengthening exercise program focusing on eccentric tendon loading. Relative rest may be a critical aspect of tendon rehabilitation as suggested by recent research on the role of stress activated protein kinases in apoptosis in degenerative tendinopathies. Tendon unloading with heel-raises has been advocated for treating Achilles tendinopathy, and with a forearm counterforce brace as treatment for extensor tendinopathy at the elbow. Corticosteroid injections remain controversial, and there is little evidence that they produce more than a short term therapeutic effect.

Our current non-operative management of chronic tendinopathy involves a rehabilitation program with an initial period of relative rest and tendon unloading through orthotics or braces, combined with twice daily prolonged static stretching, and a graduated eccentric strengthening exercise program.
Methods

The three clinical trials were approved by our institutional Ethics Committee, and conform to the code of ethics of the World Medical Association. Power analysis determined that to have a 90% probability of finding a 40% difference between groups it was necessary to recruit eighty patients for each clinical trial. Patients with clinical diagnoses of the specific tendinopathies were recruited through newspaper advertisements and private consulting rooms. All subjects were over 18 years of age, and gave written informed consent.

Diagnostic criteria for patient inclusion in the respective trials were: 1) the diagnosis of non-insertional Achilles tendinopathy was based on the insidious onset of Achilles tendon pain, a tender nodule localized to the region 2 to 6 centimeters from the calcaneal insertion, and an ultrasound examination that excluded a frank tendon tear, 2) the diagnosis of extensor tendinopathy at the elbow was based on the insidious onset of lateral elbow pain, tenderness localized to the lateral humeral epicondyle and extensor carpi radialis brevis tendon, pain in the lateral elbow with resisted wrist and third metacarpophalangeal joint extension, and an ultrasound examination that excluded a frank tendon tear, 3) the diagnosis of supraspinatus tendinopathy was based on positive impingement signs (Hawkin’s and Neer’s), pain with supraspinatus muscle testing in the “empty can” position, and magnetic resonance imaging (MRI) high signal intensity without a frank tear in the supraspinatus tendon.

Patients were excluded if they had: tendinopathy of less than three months duration, current pregnancy, previous surgery on the affected limb, dislocation of the ipsilateral limb joints, distal neurological signs, a local corticosteroid injection in the previous three months, cardiac disease, the current use of nitrate medications or
phosphodiesterase inhibitors such as Viagra®, a family history of arthritis other than osteoarthritis, or extra-articular features of seronegative arthropathies.

Patients were randomly allocated into two groups. One group performed tendon rehabilitation and used the active transdermal patch (one quarter of a 5 mg / 24 hour Nitro-Dur glyceryl trinitrate patch, Schering-Plough, Australia), and the other group performed tendon rehabilitation and used a placebo transdermal patch (one quarter of a Nitro-Dur demonstration patch, Schering-Plough, Australia). The active and placebo patches were identical. The randomization was controlled by the senior pharmacist at our institution who also supervised the packaging of transdermal patches and their distribution to patients. Both the patients and the clinical examiner were blinded as to which patches they received.

The transdermal patches were intact when distributed, and patients were required to cut the patches into quarters prior to application. Patients were also given a supply of acetaminophen/ paracetamol tablets (500 mg) and were instructed to use them exclusively for any headaches experienced.

Patients were instructed in the application of the patches at their initial visit. They were informed that the dosing regimen was one quarter of a transdermal patch to be applied daily to the affected tendon. The patches were to be left in situ for 24 hours and then replaced with a new quarter patch. The site of application was demonstrated as over the site of maximal tendon tenderness (region 2 to 6 centimeters from the calcaneal insertion of the Achilles tendon; immediately distal to the lateral humeral epicondyle; and immediately distal to the anteroinferior aspect of the acromion). Patients were instructed to rotate the patch application site around this point with each new patch application for the six month study duration to minimize application site irritation.
At the initial clinical assessment, all patients were instructed in the performance of a tendon specific rehabilitation program. The aim of this program was to encompass the current non-operative management for tendinopathy, and involved: for the Achilles tendon- (1a) rest from aggravating activities in the early stages (particularly repetitive weightbearing activities such as walking, running, and jumping), (1b) the use of 1-1.5 centimeter heel raises, (1c), prolonged daily static stretching of the gastrocnemius and soleus muscles, and (1d) an eccentric calf muscle strengthening program\(^2\): for the extensor carpi radialis brevis tendon- (2a) rest from aggravating activities in the early stages (particularly strong gripping and repetitive forearm and wrist movements), (2b) the early continuous use of a forearm counterforce brace, (2c) prolonged daily static stretching of the wrist extensor musculature, and (2d) a muscle strengthening program initially using isometric exercise and progressing to isotonic exercises of both concentric and eccentric types\(^8,13\): for the supraspinatus and rotator cuff tendons- (3a) early rest from aggravating activities (especially heavy lifting, overhead and behind the back activities), (3b) daily range of motion exercises and stretching of the posterior shoulder capsule and pectoral muscles, and (3c) muscle strengthening with scapular retraction exercises and closed kinetic chain isometric exercises, gradually progressing to dynamic open kinetic chain isotonic resistance exercises\(^20\).

Also at the initial visit and at all subsequent visits, the patient was required to complete a tendon specific symptom assessment sheet using verbal descriptor scales to rate the severity (0 – 4: none, mild, moderate severe, very severe) of their tendon pain with activity, at rest, and at night. This verbal descriptor questionnaire has been validated as a reliable measure of monitoring pain that is responsive to clinical
change\textsuperscript{24}, and these three patient-rated pain scores were used as trial outcome measures.

A single examiner assessed all patients and recorded information on clinical outcome measures. All clinical assessments were repeated at week 0, 2, 6, 12, and 24 with an identical format. Records of headaches, paracetamol use, and compliance with patch application and the tendon rehabilitation program were also made at these scheduled visits. Patients were excluded from the trials for non-compliance at any two visits.

For the Achilles tendinopathy trial the outcome measures were- (1a) the degree of Achilles tendon tenderness using a four point scale (0-3: none, mild, moderate, severe tenderness), (1b) patient rated analogue pain score after the single leg stationary hop test (rated 0-10)\textsuperscript{8,39}, (1c) ankle plantarflexor mean peak force (in Newtons) using a resisted footplate device (The Orthopaedic Research Institute –Ankle Strength Testing System; ORI-ASTS)\textsuperscript{33} and (1d) total ankle plantarflexor work using the ORI-ASTS (in Newtons per 20 seconds). This valid and reliable resisted footplate test involved seating the patient with the foot secured to the footplate, and they were then required to perform a 20 second effort of repeated ankle plantarflexion and dorsiflexion. The footplate was linked to a load cell and the readings were stored directly on computer hard drive using LabView 5.1 biomechanical software (National Instruments, California, U.S.A.).

For the extensor tendinopathy trial the clinical outcome measures were- (2a) the level of local epicondylar and proximal common extensor tendon tenderness using a 4 point scale (0-3: none, mild, moderate, severe tenderness), (2b) hand-held dynamometer measurement of resisted 3\textsuperscript{rd} finger metacarpophalangeal extension with a fully extended elbow (in Newtons), (2c) wrist extensor tendon mean peak force (in
Newtons) using a modified chair pick-up test (The Orthopaedic Research Institute - Tennis Elbow Testing System: ORI-TETS)\textsuperscript{34}, and (2d) total work using the ORI-TETS (in Newtons per 10 seconds). This modified chair pick up test has demonstrated reliability and validity for testing extensor tendinopathy patients, and was performed with the elbow flexed to ninety degrees, and a vertically oriented hand board gripped palm downwards and pulled superiorly for a maximal 10 second effort. The hand board was linked in series with a load cell and the readings stored directly on computer hard drive using LabView 5.1 biomechanical software (National Instruments, California, U.S.A.).

For the supraspinatus tendinopathy trial the clinical outcome measures were- (3a) anteroinferior subacromial tenderness (0-3: no tenderness, mild, moderate, severe), (3b) visually assessed passive shoulder range of motion in abduction, forward flexion, external rotation (in degrees), and internal rotation (hand behind back; in centimeters from vertebra prominens)\textsuperscript{16}, (3c) hand-held dynamometer measurement of muscle force in “empty can” position (90 degrees abduction in scapular plane with full internal rotation)\textsuperscript{41}, adduction, external rotation, internal rotation, and subscapularis push-off (in Newtons)\textsuperscript{17}, (3d) and impingement tests in internal rotation (Hawkin’s sign)\textsuperscript{15} (0-1: negative or positive).

Outcome measures were analyzed with Sigmasstat 2.0 statistical software (Jandel Scientific, California, U.S.A) using Mann-Whitney rank sum tests to compare differences between groups, and using the Wilcoxon sign rank test to compare differences within the groups. The level of significance was defined at $p = 0.05$. A Chi square analysis of patient reported symptom outcomes at week 24 was performed. Effect size estimates were calculated by dividing the mean z-score, calculated from all
outcome measures at week 24, by the square root of the sample size to give a general
measure of the overall effect of the patch on pain, tendon force and function$^{40}$. 
Results

There were 65 patients (84 Achilles tendons) in the non-insertional Achilles tendinopathy trial with 40 men and 25 women, 86 patients (95 elbows) in the extensor tendinopathy trial with 42 males and 44 females, and 53 patients (57 shoulders) in the supraspinatus tendinopathy trial with 24 males and 29 females. The median age of subjects was 49 years (range 24 to 77 years) in the Achilles tendon trial, 46 years (range 30 to 74 years) in the elbow trial, and 52 years (range 25 to 79 years) in the shoulder trial. The median duration of tendon symptoms prior to the study was 16 months (range 4 - 147 months) in the Achilles trial, 17 months (range 4 - 232 months) in the elbow trial, and 14 months (range 4-96) in the shoulder trial. There were no significant differences between groups with respect to age, sex, affected side, symptom severity, or symptom duration.

Analysis of the clinical trial outcome measures for all three trials determined that the data was not normally distributed. Mann-Whitney rank sum analysis compared the glyceryl trinitrate groups with the placebo groups for the individual specific tendinopathies. The significant results are summarized in Table I.

Activity Pain

Significant decreases in tendon pain with activity were noted in the glyceryl trinitrate group compared to the placebo group in the Achilles tendon trial at week 12 (p=0.02) and at week 24 (p=0.03) (Figure 1a), in the extensor tendinopathy trial at week 2 (p=0.01) (Figure 1b), and in the supraspinatus tendinopathy trial at week 24 (p = 0.01) (Figure 1c).
**Night Pain**

Significant decreases in tendon pain at night were noted in the glycercyl trinitrate group compared to the placebo group in the Achilles tendon trial at week 12 (p=0.04), and in the supraspinatus tendinopathy trial at week 12 (p = 0.03) and at week 24 (p = 0.01).

**Rest Pain**

There was a significant decrease in rest pain at week 12 (p = 0.04) and week 24 (p = 0.03) in the supraspinatus tendon trial glycercyl trinitrate group.

**Tendon Tenderness**

In the glycercyl trinitrate group there was significantly less Achilles tendon tenderness at week 12 (p = 0.02), and significantly less lateral epicondylar tenderness at week 6 (p = 0.02) and at week 12 (p = 0.02).

**Tendon Force Measures**

There were significant increases in force measures in the glycercyl trinitrate group compared to the placebo group in the Achilles tendinopathy trial at week 24 (ORI-ASTS measured mean plantarflexion total work increases, p=0.04) (Figure 2a), in the extensor tendinopathy trial at week 24 (ORI-TETS mean total work, p=0.03) (Figure 2b), and in the supraspinatus tendinopathy trial at week 6, 12 and 24 (increased supraspinatus force, p = 0.01, p = 0.001, and p = 0.001 respectively) (see Figure 2c).
Tendon Function

In the glyceryl trinitrate group there were significant improvements in measures of tendon function in the Achilles tendinopathy trial at week 24 (decrease in pain scores after the 10 hop test, \( p = 0.01 \)) (Figure 3a), in the elbow trial at week 24 (ORI-TETS measured mean peak force, \( p = 0.03 \)) (Figure 3b) and in the supraspinatus tendinopathy trial at week 12 (increase in passive shoulder abduction range of motion, \( p = 0.03 \), Figure 3c) and week 24 (decrease in impingement in internal rotation at week 24, \( p = 0.02 \), Figure 3d: increase in passive shoulder abduction range of motion, \( p = 0.02 \), Figure 3c: and an increase in shoulder internal rotation range of motion at week 24, \( p = 0.04 \)).

Patient Reported Outcomes

Across all clinical trials subjects in the glyceryl trinitrate groups reported significantly increased rates of complete symptom resolution with activities of daily living at week 24. In the Achilles tendon trial the active versus placebo group rates were 78% versus 49% (Chi square test \( p = 0.001 \)), in the extensor tendinopathy trial rates were 81% versus 60% (Chi square test \( p = 0.01 \)), and in the supraspinatus tendinopathy trial rates were 46% versus 24% (Chi square test \( p = 0.01 \)). These improvements in excellent self-reported patient outcomes equate to a number needed to treat (NNT) of 3.4 for the Achilles trial, 4.8 for the elbow trial, and 4.5 for the shoulder trial.

Effect Size

At week 24 the effect size estimations for the effect of glyceryl trinitrate treatment on the specific tendinopathies were; Achilles tendinopathy 0.14 (95% CI
0.09 – 0.19), extensor tendinopathy 0.12 (95% CI 0.06 – 0.19), and supraspinatus tendinopathy 0.26 (95% CI 0.19 – 0.32). The between group differences for all mean grouped outcome measures expressed as the percentage improvement from baseline are represented in Figures 4a-c.

**Side-Effects**

The majority of patients in the glyceryl trinitrate groups experienced headache as a side-effect (Table II), however, only in the supraspinatus tendinopathy trial was there a significant increase in the total number of days affected by headache (p = 0.001).

There were significant increases in the total amount of paracetamol required for headache treatment in the glyceryl trinitrate group for the Achilles tendinopathy trial (p = 0.001), and the supraspinatus tendinopathy trial (p = 0.001) (Table II).

**Drop-Outs and Trial Completion Rates**

There were no significant differences between groups in drop-out rates or trial completion rates in any of the clinical trials (Table II). The patients that were discontinued from the clinical trials, mainly for side-effects of headache or application site rash, were all receiving topical glyceryl trinitrate treatment.
Discussion

These three randomized double blind placebo controlled clinical trials demonstrate that continuous 1.25 mg/24 hour topical glyceryl trinitrate treatment for chronic tendinopathies can result in significantly decreased tendon pain with activity, significantly decreased tendon tenderness, significantly improved functional measures, and significantly improved patient outcomes when compared with tendon rehabilitation alone. Whilst the overall outcomes of these three clinical trials are similar the individual outcome measures require closer analysis to determine the likely effects of topical glyceryl trinitrate treatment on specific tendons.

Activity Pain

Within the clinical trials the outcome measure of tendon pain with activity was significantly improved in the glyceryl trinitrate groups in all three trials, although the timing of the improvement varied from early in extensor tendinopathy to late with non-insertional Achilles tendinopathy and supraspinatus tendinopathy. The reason for this is not readily apparent. An analysis of the between group means at week 0 compared with week 24 demonstrated that the glyceryl trinitrate group patient-rated pain scores (with activity, at night, and at rest) for the clinical trials decreased by an average of 65 % (range 64-67%), whilst the placebo group scores for the trials decreased by an average of 30% (range 27-33%) (Figures 4a-c). These results suggest that topical glyceryl trinitrate may have a pain modulation effect in chronic tendinopathies, although the effect appears to differ in timing between specific tendon sites.
**Night Pain and Rest Pain**

Tendon pain at night was significant decreased in the glyceryl trinitrate group in both the Achilles tendon trial and the supraspinatus tendinopathy trial. The effects seen were in the later stages of the trial and this is similar in timing to the decreases in pain with activity. Only late in the supraspinatus tendon trial was there a significant decrease in tendon pain at rest in the glyceryl trinitrate treatment group.

**Tendon Tenderness**

Clinical assessment of tendon tenderness revealed significant decreases in the glyceryl trinitrate groups at week 12 in both the Achilles and elbow tendinopathy clinical trials. There were no significant differences in the supraspinatus tendinopathy trial. These results may be due to the subcutaneous nature of the Achilles and extensor carpi radialis brevis tendons relative to the deeper supraspinatus tendon. The decreased tenderness preceded any significant improvements in force and function measurements.

**Tendon Force Measures**

Across the three clinical trials there were significant increases in force outcome measures in the glyceryl trinitrate groups at the week 24 stage, with the Orthopaedic Research Institute- Ankle Strength Testing System (ORI-ASTS) and Tennis Elbow Testing System (ORI-TETS) demonstrating increased mean total work, and the dynamometer resisted supraspinatus force measurements demonstrating significant increases. These outcome measures have demonstrated excellent intra-rater reliability and validity in testing patients with specific chronic tendinopathies\textsuperscript{17,33,34}. An analysis of the between group means at week 0 compared with week 24 demonstrated that the
glyceryl trinitrate group force outcome measures for the trials increased by an average of 37% (range 33-38%), whilst the placebo group scores for the trials increased by an average of 16% (range 11-20%). These results suggest that topical glyceryl trinitrate may have an effect on tendon that increases force measures in chronic tendinopathies. This may be related to decreased tendon pain and thus decreased functional inhibition, or may be a direct effect on tendon metabolism or fibroblasts possibly increasing collagen organisation in healing tendon\textsuperscript{45}.

**Tendon Function**

In the glyceryl trinitrate groups functional outcome measures were significantly increased at week 24 relative to the placebo group in all three clinical trials. These functional tests included the 10 hop test for non-insertional Achilles tendinopathy (similar to tests in the newly validated VISA-A Achilles tendon scale)\textsuperscript{39}, the ORI-TETS wrist extensor mean peak force for extensor tendinopathy, and shoulder passive range of motion in abduction and in internal rotation, as well as shoulder impingement in internal rotation for supraspinatus tendinopathy. All of these measures reflect important functional characteristics of the tendons involved: hopping involves Achilles tendon loading through push-off and landing as used in running and jumping; wrist extensor tendon peak force measured with a modified chair pick-up test (ORI-TETS) as seen with gripping, or when lifting heavy objects; shoulder range of motion in abduction when utilising supraspinatus function for overhead activities, shoulder range of motion in internal rotation as used with toileting and dressing, and shoulder impingement in internal rotation which is a common cause of shoulder pain in patients with supraspinatus tendinopathy and may perpetuate the “vicious cycle” of rotator cuff tendon injury and dysfunction\textsuperscript{8}. These results indicate that glyceryl trinitrate may
modulate tendon function, and again this may be through direct or indirect effects on
tendon, but correlates with the results of both decreased pain and increased force
suggesting increased control of movement.

Patient Reported Outcomes

Upon completion of the clinical trials 21-29% more patients in the glyceryl trinitrate
treated group than the placebo group were asymptomatic with activities of daily
living. From these results the number of patients needed to treat (NNT) to obtain a
positive outcome can be calculated. For every 3.4 chronic Achilles tendinopathy
patients, every 4.8 extensor tendinopathy patients, and every 4.5 supraspinatus
tendinopathy patients treated with topical glyceryl trinitrate therapy, one patient will
be completely asymptomatic at 24 weeks that would not have occurred with
rehabilitation alone.

Effect Size

The mean estimated effect size at week 24 for the three clinical trials ranged from
0.12-0.26 which is equivalent to a change in patient success rates of 12-26%. This
effect size range is comparable to the 21-29% improvement in patient rated outcomes
noted with topical glyceryl trinitrate therapy. These parallel measures of patient
outcomes are calculated from very different sources (patient rated outcomes versus all
trial outcome measures) and demonstrate a mild to moderate effect of glyceryl
trinitrate treatment in improving outcome measures in three common chronic
tendinopathies.
**Side-Effects**

Headache was the most frequent side-effect and in the glycercyl trinitrate group ranged from 53-76% of patients (Table II). The patient average for number of days with headache was 5-6 days during the 24 week trial. 72% of headaches occurred within the first two weeks of the trial. The percentage of patients experiencing headache in these clinical trials was higher than that reported in the literature of 18-68% for dosages of 5mg/24 hour\textsuperscript{10,25,36}. It is difficult to understand the reasons for this, especially as the dosing regime used in these clinical trials was a continuous low dose of 1.25mg-2.5mg/ 24 hours, but may be due to better patient reporting of side-effects as all subjects had to complete a headache diary which was checked regularly to assess overall compliance. The placebo groups also reported high rates of headache ranging from 33-58% of patients, with an average number of days of headache ranging from 4-7 days. There were significant between group differences in the total number of headaches experienced in the supraspinatus tendinopathy trial, but not in the other clinical trials. The higher rates of headache in the supraspinatus tendinopathy trial may be due to the glycercyl trinitrate patch application site being closer to both the cardiac and cerebral circulation than in either the extensor tendinopathy or Achilles tendinopathy trials, possibly leading to greater systemic absorption. It should be noted that, in general, the glycercyl trinitrate group experienced more severe headaches than the placebo group, as evidenced by the 1-2 patients in each clinical trial discontinued due to this side-effect.

Patients in the clinical trials were supplied with acetaminophen/ paracetamol tablets for exclusive use with the potential side-effect of headache, and in the three glycercyl trinitrate groups the total group paracetamol usage in the 24 weeks ranged from 138-237 tablets, with an average of 7-14 tablets per subject affected by headache. In the
placebo groups the total paracetamol usage ranged from 69-250 tablets, with an average of 3-10 tablets. There were significant between group differences in the total amount of paracetamol used in the Achilles tendinopathy and supraspinatus tendinopathy trials. Despite higher rates of reported headache in the supraspinatus tendinopathy trial the use of paracetamol was lower than in either of the other clinical trials.

Another common side-effect of topical glyceryl trinitrate is application site rash and in the glyceryl trinitrate groups the number of patients experiencing rash ranged from 8-21% compared with rates in the placebo groups ranging from 7-12%. Reports in the literature for glyceryl trinitrate dosages of 5mg/24 hour note rash in 16-38% of patients and these side-effect rates are comparable with those reported in these clinical trials. There was a greater severity of rash in the glyceryl trinitrate groups compared to the placebo groups as evidenced by a total of five patients discontinued due to this side-effect. Other side-effects that were reported included: an increase in pre-existing tinnitus, increased ipsilateral axillary sweating, and a perception of apprehension. None of these were severe, and all were reversible on discontinuation of the patch. The number of patients in the glyceryl trinitrate groups that experienced no side-effects ranged from 30-44% whilst those in the placebo groups ranged from 33-59%.

**Drop-Outs and Trial Completion Rates**

The number of patients discontinued during the course of the clinical trials ranged from 4-6% of clinical trial patients, these patients were all in the glyceryl trinitrate groups, and they were discontinued for recognised side-effects of headache or application site rash. One patient was discontinued for recurrent facial flushing, which
was reversible on discontinuation of the medication. This patient was a type 2 diabetic
and it was felt that this side-effect was caused by arteriolar dilatation.

The trial completion rate for the glyceryl trinitrate group ranged from 81-88% and
the placebo group ranged from 91-94%. There was no significant difference between
groups in regard to completion, or drop-out, rates between groups. The high
completion rate amongst groups may be due to the thorough explanation of
requirements for the clinical trial prior to entry, frequent assessment visits, relatively
low side-effect profile of the medication, or the personalities of patients entering
clinical trials.

Summary

These clinical trials investigating topical glyceryl trinitrate treatment combined
with tendon rehabilitation demonstrated improved patient rated pain scores, increased
tendon force measures, improved functional measures, and improved patient
outcomes relative to tendon rehabilitation alone in the treatment of chronic overuse
teninopathies. Topical nitric oxide donors such as 1.25mg/ 24 hour glyceryl trinitrate
have a long history of therapeutic use in humans\textsuperscript{28}, have a known side-effect profile
with no irreversible effects, and now have clinically demonstrated efficacy in
modulating pain, force measures, functional measures, and patient outcomes at six
months in specific chronic overuse tendinopathies. From these studies it appears
evident that topical glyceryl trinitrate has a role in treating specific chronic overuse
teninopathies and should be used as an adjunct to tendon rehabilitation.
References


Figures and Tables

Figure 1

a) Patient Rated Achilles Tendon Pain with Activity

- GTN Group
- Placebo Group

b) Patient Rated Elbow Pain with Activity

c) Patient Rated Shoulder Pain with Activity

- GTN Group
- Placebo Group
a) Effects of glyceryl trinitrate 1.25 mg / day transdermal patch plus rehabilitation (GTN, n = 41) versus rehabilitation alone (placebo, n=43) on Achilles tendon pain with activity. Statistically significant differences between groups are shown with an asterisk (* p < 0.05).

b) Effects of glyceryl trinitrate 1.25 mg / day transdermal patch plus rehabilitation (GTN, n = 47) versus rehabilitation alone (placebo, n=48) on lateral elbow pain with activity in extensor tendinopathy. Statistically significant differences between groups are shown with an asterisk (* p < 0.05).

c) Effects of glyceryl trinitrate 1.25 mg / day transdermal patch plus rehabilitation (GTN, n = 28) versus rehabilitation alone (placebo, n=29) on shoulder pain with activity in supraspinatus tendinopathy. Statistically significant differences between groups are shown with an asterisk (* p < 0.05).
Figure 2

a) OLI-ASTS Mean Total Work ( Newtons )

- GTN Group
- Placebo Group

b) OLI-TETS Mean Total Work ( Newtons )

- GTN Group
- Placebo Group

c) Supraspinatus Force ( Newtons )

- GTN Group
- Placebo Group
a) Effects of glyceryl trinitrate (GTN, n = 41) 1.25 mg / day transdermal patch plus rehabilitation versus rehabilitation alone (placebo, n=43) on Orthopaedic Research Institute-Ankle Strength Testing System (ORI-ASTS) measured ankle plantarflexor mean total work. Statistically significant differences between groups are shown with an asterisk (* p < 0.05).

b) Effects of glyceryl trinitrate (GTN, n = 47) 1.25 mg / day transdermal patch plus rehabilitation versus rehabilitation alone (placebo, n=48) on Orthopaedic Research Institute-Tennis Elbow Testing System (ORI-TETS) measured mean total work. Statistically significant differences between groups are shown with an asterisk (* p < 0.05).

c) Effects of glyceryl trinitrate (GTN, n = 28) 1.25 mg / day transdermal patch plus rehabilitation versus rehabilitation alone (placebo, n=29) on dynamometer measured supraspinatus force. Statistically significant differences between groups are shown with an asterisk (* p < 0.05, ** p < 0.01).
Figure 3

a) Patient Rated Pain with Hop Test

![Graph showing patient rated pain with hop test for GTN Group and Placebo Group over time.](image)

b) ORI-TETS Mean Peak Force (Newtons)

![Graph showing ORI-TETS mean peak force for GTN Group and Placebo Group over time.](image)

c) Shoulder Abduction Range of Motion (Degrees)

![Graph showing shoulder abduction range of motion for GTN Group and Placebo Group over time.](image)
d) Effects of glyceryl trinitrate (GTN, n = 28) 1.25 mg / day transdermal patch versus rehabilitation alone (placebo, n=29) on shoulder impingement in internal rotation. Statistically significant differences are shown with an asterisk (* p < 0.05).
Figure 4

a)

Achilles- Mean Grouped Outcome Measures

b)

Elbow- Mean Grouped Outcome Measures
Shoulder - Mean Grouped Outcome Measures
a) Percentage differences in mean grouped outcome measures between the glyceryl trinitrate group (GTN 1.25 mg / day patch, n = 41) and the placebo patch group (n=43). A between group comparison of means for grouped outcome measures in the Achilles tendinopathy clinical trial.

b) Percentage differences in mean grouped outcome measures between the glyceryl trinitrate group (GTN 1.25 mg / day patch, n = 47) and the placebo patch group (n=48). A between group comparison of means for grouped outcome measures. A between group comparison of means for grouped outcome measures in the extensor tendinopathy clinical trial.

c) Percentage differences in mean grouped outcome measures between the glyceryl trinitrate group (GTN 1.25 mg / day patch, n = 28) and the placebo patch group (n=29). A between group comparison of means for grouped outcome measures. A between group comparison of means for grouped outcome measures in the supraspinatus tendinopathy clinical trial.
Table I

<table>
<thead>
<tr>
<th>Trial Parameters</th>
<th>Achilles (N=65)</th>
<th>Elbow (N=86)</th>
<th>Shoulder (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Improved Patient Outcomes</strong></td>
<td>29 %</td>
<td>21 %</td>
<td>22 %</td>
</tr>
<tr>
<td><strong>Effect Size</strong></td>
<td>0.14</td>
<td>0.12</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Pain Outcomes</strong></td>
<td><strong>Activity</strong></td>
<td>Decreased Week 12/24</td>
<td>Decreased Week 2</td>
</tr>
<tr>
<td><strong>Night</strong></td>
<td>Decreased Week 12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Rest</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Force Outcomes</strong></td>
<td>Increased mean total work Week 24</td>
<td>Increased mean total work Week 24</td>
<td>Increased supraspinatus, external rotation, internal rotation, adduction, and subscapularis force Week 12/24</td>
</tr>
<tr>
<td><strong>Tenderness Outcomes</strong></td>
<td>Decreased Week 12</td>
<td>Decreased Week 6/12</td>
<td>-</td>
</tr>
<tr>
<td><strong>Functional Outcome Measures</strong></td>
<td>Increased 10 Hop Test Week 24</td>
<td>Increased mean peak force Week 24</td>
<td>Increased abduction, internal rotation range of motion Week 24. Decreased internal rotation impingement Week 24</td>
</tr>
</tbody>
</table>

Table I: Summarised significant results of the topical glyceryl trinitrate groups relative to the placebo groups in clinical trials on Achilles tendinopathy, extensor tendinopathy at the elbow, and supraspinatus tendinopathy.
Table II: Summarised results of the topical glyceryl trinitrate clinical trials on Achilles tendinopathy, extensor tendinopathy at the elbow, and supraspinatus tendinopathy. Significant differences are marked with an asterisk. Includes trial completion rates, discontinuations, drop-outs, and noted side-effects in both the glyceryl trinitrate (GTN) and placebo groups.

<table>
<thead>
<tr>
<th>Trial Parameters</th>
<th>Achilles (N=65)</th>
<th>Elbow (N=86)</th>
<th>Shoulder (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Completion Rate</strong></td>
<td>GTN 84 %</td>
<td>GTN 81 %</td>
<td>GTN 88 %</td>
</tr>
<tr>
<td></td>
<td>Placebo 94 %</td>
<td>Placebo 91 %</td>
<td>Placebo 93 %</td>
</tr>
<tr>
<td><strong>Discontinuations</strong></td>
<td>GTN 81 %</td>
<td>GTN 88 %</td>
<td>GTN 88 %</td>
</tr>
<tr>
<td>(All GTN Group)</td>
<td>Placebo 94 %</td>
<td>Placebo 93 %</td>
<td>Placebo 93 %</td>
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<tr>
<td><strong>Drop-outs</strong></td>
<td>GTN 2</td>
<td>GTN 3</td>
<td>GTN 1</td>
</tr>
<tr>
<td></td>
<td>Placebo 1</td>
<td>Placebo 4</td>
<td>Placebo 2</td>
</tr>
<tr>
<td><strong>Days of Headache</strong></td>
<td>Total</td>
<td>GTN 85 (53%)</td>
<td>GTN 136 (63%)</td>
</tr>
<tr>
<td>(Percentage of patients affected)</td>
<td>Placebo 101 (45%)</td>
<td>Placebo 166 (58%)</td>
<td>GTN 127 (76%) *</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>GTN 5</td>
<td>GTN 5</td>
</tr>
<tr>
<td></td>
<td>Placebo 7</td>
<td>Placebo 7</td>
<td>Placebo 7</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>GTN 4</td>
<td>GTN 3</td>
</tr>
<tr>
<td></td>
<td>Placebo 3</td>
<td>Placebo 1</td>
<td>Placebo 0</td>
</tr>
<tr>
<td><strong>Paracetamol</strong></td>
<td>Total</td>
<td>GTN 237 *</td>
<td>GTN 214</td>
</tr>
<tr>
<td>(Tablets)</td>
<td>Placebo 46</td>
<td>Placebo 250</td>
<td>GTN 138 *</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>GTN 14</td>
<td>GTN 8</td>
</tr>
<tr>
<td></td>
<td>Placebo 3</td>
<td>Placebo 10</td>
<td>Placebo 7</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>GTN 10</td>
<td>GTN 4</td>
</tr>
<tr>
<td></td>
<td>Placebo 0</td>
<td>Placebo 0</td>
<td>Placebo 2</td>
</tr>
<tr>
<td><strong>Other Noted Side-Effects</strong></td>
<td>GTN</td>
<td>Rash 16 %</td>
<td>Rash 21 %</td>
</tr>
<tr>
<td></td>
<td>Placebo 0</td>
<td>Increase Tinnitus 3%</td>
<td>Increase Axillary Sweating 2%</td>
</tr>
<tr>
<td></td>
<td>Placebo 0</td>
<td>Placebo 0</td>
<td>Placebo 0</td>
</tr>
<tr>
<td><strong>No Side-Effects</strong></td>
<td>GTN 44 %</td>
<td>GTN 35 %</td>
<td>GTN 30 %</td>
</tr>
<tr>
<td></td>
<td>Placebo 45 %</td>
<td>Placebo 33 %</td>
<td>Placebo 59 %</td>
</tr>
</tbody>
</table>