

1 **Clinical studies of topical glyceryl trinitrate treatment**
2 **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.

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2 **Key Terms:** Tendon, glyceryl trinitrate, shoulder, elbow, Achilles, nitric oxide

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1 **Introduction**

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

6 Common chronic degenerative tendinopathies include non-insertional Achilles
7 tendinopathy, extensor tendinopathy at the elbow, and rotator cuff tendinopathy¹.

8 Non-insertional Achilles tendinopathy presents especially among runners^{9,42}, extensor
9 tendinopathy at the elbow is found in tennis players³¹ and patients whose work
10 involves repetitive forearm and hand movements¹¹, and rotator cuff tendon injury
11 such as supraspinatus tendinopathy is prevalent in overhead workers and throwing
12 athletes^{8,15}.

13 Nitric oxide synthase, the endogenous precursor to nitric oxide (NO) is induced
14 during tendon healing^{22,23} and fracture repair⁴⁶, and inhibition of nitric oxide synthase
15 resulted in a significant reduction in healing tendon cross-sectional area and load to
16 failure²⁷. Nitric oxide modulates collagen synthesis by human tendon fibroblasts in
17 culture⁴³. Topical glyceryl trinitrate, a prodrug of nitric oxide^{12,26}, has demonstrated
18 efficacy in improving short term pain in acute supraspinatus tendinitis⁵.

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

23 There are a variety of non-operative treatments for tendinopathy, many with
24 unproven therapeutic efficacy, and none that are universally effective in the
25 management of chronic tendinopathies^{7,19,20}. The non-operative management of

1 tendinopathies involves rehabilitation consisting of relative rest, stretching, and a
2 graduated strengthening exercise program focussing on eccentric tendon loading^{2,20,29}.
3 Relative rest may be a critical aspect of tendon rehabilitation as suggested by recent
4 research on the role of stress activated protein kinases in apoptosis in degenerative
5 tendinopathies^{3,44}. Tendon unloading with heel-raises has been advocated for treating
6 Achilles tendinopathy^{1,8}, and with a forearm counterforce brace as treatment for
7 extensor tendinopathy at the elbow^{8,14,38}. Corticosteroid injections remain
8 controversial, and there is little evidence that they produce more than a short term
9 therapeutic effect^{6,30,32}.

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

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1 **Methods**

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

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

21 Patients were excluded if they had: tendinopathy of less than three months duration,
22 current pregnancy, previous surgery on the affected limb, dislocation of the ipsilateral
23 limb joints, distal neurological signs, a local corticosteroid injection in the previous
24 three months, cardiac disease, the current use of nitrate medications or

1 phosphodiesterase inhibitors such as Viagra®, a family history of arthritis other than
2 osteoarthritis, or extra-articular features of seronegative arthropathies.

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

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

16 Patients were instructed in the application of the patches at their initial visit. They
17 were informed that the dosing regimen was one quarter of a transdermal patch to be
18 applied daily to the affected tendon. The patches were to be left in situ for 24 hours
19 and then replaced with a new quarter patch. The site of application was demonstrated
20 as over the site of maximal tendon tenderness (region 2 to 6 centimeters from the
21 calcaneal insertion of the Achilles tendon; immediately distal to the lateral humeral
22 epicondyle; and immediately distal to the anteroinferior aspect of the acromion).
23 Patients were instructed to rotate the patch application site around this point with each
24 new patch application for the six month study duration to minimize application site
25 irritation.

1 At the initial clinical assessment, all patients were instructed in the performance of
2 a tendon specific rehabilitation program. The aim of this program was to encompass
3 the current non-operative management for tendinopathy, and involved: for the
4 Achilles tendon- (1a) rest from aggravating activities in the early stages (particularly
5 repetitive weightbearing activities such as walking, running, and jumping), (1b) the
6 use of 1-1.5 centimeter heel raises, (1c), prolonged daily static stretching of the
7 gastrocnemius and soleus muscles, and (1d) an eccentric calf muscle strengthening
8 program²: for the extensor carpi radialis brevis tendon- (2a) rest from aggravating
9 activities in the early stages (particularly strong gripping and repetitive forearm and
10 wrist movements), (2b) the early continuous use of a forearm counterforce brace, (2c)
11 prolonged daily static stretching of the wrist extensor musculature, and (2d) a muscle
12 strengthening program initially using isometric exercise and progressing to isotonic
13 exercises of both concentric and eccentric types^{8,13}: for the supraspinatus and rotator
14 cuff tendons- (3a) early rest from aggravating activities (especially heavy lifting,
15 overhead and behind the back activities), (3b) daily range of motion exercises and
16 stretching of the posterior shoulder capsule and pectoral muscles, and (3c) muscle
17 strengthening with scapular retraction exercises and closed kinetic chain isometric
18 exercises, gradually progressing to dynamic open kinetic chain isotonic resistance
19 exercises²⁰.

20 Also at the initial visit and at all subsequent visits, the patient was required to
21 complete a tendon specific symptom assessment sheet using verbal descriptor scales
22 to rate the severity (0 – 4: none, mild, moderate severe, very severe) of their tendon
23 pain with activity, at rest, and at night. This verbal descriptor questionnaire has been
24 validated as a reliable measure of monitoring pain that is responsive to clinical

1 change²⁴, and these three patient-rated pain scores were used as trial outcome
2 measures.

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

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

21 For the extensor tendinopathy trial the clinical outcome measures were- (2a) the
22 level of local epicondylar and proximal common extensor tendon tenderness using a 4
23 point scale (0-3: none, mild, moderate, severe tenderness), (2b) hand-held
24 dynamometer measurement of resisted 3rd finger metacarpophalangeal extension with
25 a fully extended elbow (in Newtons), (2c) wrist extensor tendon mean peak force (in

1 Newtons) using a modified chair pick-up test (The Orthopaedic Research Institute -
2 Tennis Elbow Testing System: ORI-TETS)³⁴, and (2d) total work using the ORI-
3 TETS (in Newtons per 10 seconds). This modified chair pick up test has demonstrated
4 reliability and validity for testing extensor tendinopathy patients, and was performed
5 with the elbow flexed to ninety degrees, and a vertically oriented hand board gripped
6 palm downwards and pulled superiorly for a maximal 10 second effort. The hand
7 board was linked in series with a load cell and the readings stored directly on
8 computer hard drive using LabView 5.1 biomechanical software (National
9 Instruments, California, U.S.A.).

10 For the supraspinatus tendinopathy trial the clinical outcome measures were- (3a)
11 anteroinferior subacromial tenderness (0-3: no tenderness, mild, moderate, severe),
12 (3b) visually assessed passive shoulder range of motion in abduction, forward flexion,
13 external rotation (in degrees), and internal rotation (hand behind back; in centimeters
14 from vertebra prominens)¹⁶, (3c) hand-held dynamometer measurement of muscle
15 force in “empty can” position (90 degrees abduction in scapular plane with full
16 internal rotation)⁴¹, adduction, external rotation, internal rotation, and subscapularis
17 push-off (in Newtons)¹⁷, (3d) and impingement tests in internal rotation (Hawkin’s
18 sign)¹⁵ (0-1: negative or positive).

19 Outcome measures were analyzed with Sigmatat 2.0 statistical software (Jandel
20 Scientific, California, U.S.A) using Mann-Whitney rank sum tests to compare
21 differences between groups, and using the Wilcoxon sign rank test to compare
22 differences within the groups. The level of significance was defined at $p = 0.05$. A Chi
23 square analysis of patient reported symptom outcomes at week 24 was performed.
24 Effect size estimates were calculated by dividing the mean z-score, calculated from all

1 outcome measures at week 24, by the square root of the sample size to give a general
2 measure of the overall effect of the patch on pain, tendon force and function⁴⁰.

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1 **Results**

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

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

17

18 **Activity Pain**

19 Significant decreases in tendon pain with activity were noted in the glyceryl
20 trinitrate group compared to the placebo group in the Achilles tendon trial at week 12
21 (p=0.02) and at week 24 (p=0.03) (Figure 1a), in the extensor tendinopathy trial at
22 week 2 (p=0.01) (Figure 1b), and in the supraspinatus tendinopathy trial at week 24 (p
23 = 0.01) (Figure 1c).

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1 **Night Pain**

2 Significant decreases in tendon pain at night were noted in the glyceryl trinitrate
3 group compared to the placebo group in the Achilles tendon trial at week 12 ($p=0.04$),
4 and in the supraspinatus tendinopathy trial at week 12 ($p = 0.03$) and at week 24 ($p =$
5 0.01).

6 7 **Rest Pain**

8 There was a significant decrease in rest pain at week 12 ($p = 0.04$) and week 24 (p
9 $= 0.03$) in the supraspinatus tendon trial glyceryl trinitrate group.

10 11 12 **Tendon Tenderness**

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

16 17 18 **Tendon Force Measures**

19 There were significant increases in force measures in the glyceryl trinitrate group
20 compared to the placebo group in the Achilles tendinopathy trial at week 24 (ORI-
21 ASTS measured mean plantarflexion total work increases, $p=0.04$) (Figure 2a), in the
22 extensor tendinopathy trial at week 24 (ORI-TETS mean total work, $p=0.03$) (Figure
23 2b), and in the supraspinatus tendinopathy trial at week 6, 12 and 24 (increased
24 supraspinatus force, $p = 0.01$, $p = 0.001$, and $p = 0.001$ respectively) (see Figure 2c).

25

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

1 0.09 – 0.19), extensor tendinopathy 0.12 (95% CI 0.06 – 0.19), and supraspinatus
2 tendinopathy 0.26 (95% CI 0.19 – 0.32). The between group differences for all mean
3 grouped outcome measures expressed as the percentage improvement from baseline
4 are represented in Figures 4a-c.

5

6 **Side-Effects**

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

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

13

14 **Drop-Outs and Trial Completion Rates**

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

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1 **Discussion**

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

10

11 **Activity Pain**

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

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1 **Night Pain and Rest Pain**

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

8 **Tendon Tenderness**

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

17 **Tendon Force Measures**

18 Across the three clinical trials there were significant increases in force outcome
19 measures in the glyceryl trinitrate groups at the week 24 stage, with the Orthopaedic
20 Research Institute- Ankle Strength Testing System (ORI-ASTS) and Tennis Elbow
21 Testing System (ORI-TETS) demonstrating increased mean total work, and the
22 dynamometer resisted supraspinatus force measurements demonstrating significant
23 increases. These outcome measures have demonstrated excellent intra-rater reliability
24 and validity in testing patients with specific chronic tendinopathies^{17,33,34}. An analysis
25 of the between group means at week 0 compared with week 24 demonstrated that the

1 glyceryl trinitrate group force outcome measures for the trials increased by an average
2 of 37 % (range 33-38%), whilst the placebo group scores for the trials increased by an
3 average of 16% (range 11-20%). These results suggest that topical glyceryl trinitrate
4 may have an effect on tendon that increases force measures in chronic tendinopathies.
5 This may be related to decreased tendon pain and thus decreased functional inhibition,
6 or may be a direct effect on tendon metabolism or fibroblasts possibly increasing
7 collagen organisation in healing tendon⁴⁵.

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9 **Tendon Function**

10 In the glyceryl trinitrate groups functional outcome measures were significantly
11 increased at week 24 relative to the placebo group in all three clinical trials. These
12 functional tests included the 10 hop test for non-insertional Achilles tendinopathy
13 (similar to tests in the newly validated VISA-A Achilles tendon scale)³⁹, the ORI-
14 TETS wrist extensor mean peak force for extensor tendinopathy, and shoulder passive
15 range of motion in abduction and in internal rotation, as well as shoulder impingement
16 in internal rotation for supraspinatus tendinopathy. All of these measures reflect
17 important functional characteristics of the tendons involved: hopping involves
18 Achilles tendon loading through push-off and landing as used in running and jumping;
19 wrist extensor tendon peak force measured with a modified chair pick-up test (ORI-
20 TETS) as seen with gripping, or when lifting heavy objects; shoulder range of motion
21 in abduction when utilising supraspinatus function for overhead activities, shoulder
22 range of motion in internal rotation as used with toileting and dressing, and shoulder
23 impingement in internal rotation which is a common cause of shoulder pain in patients
24 with supraspinatus tendinopathy and may perpetuate the “vicious cycle” of rotator
25 cuff tendon injury and dysfunction⁸. These results indicate that glyceryl trinitrate may

1 modulate tendon function, and again this may be through direct or indirect effects on
2 tendon, but correlates with the results of both decreased pain and increased force
3 suggesting increased control of movement.

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5 **Patient Reported Outcomes**

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

14

15 **Effect Size**

16 The mean estimated effect size at week 24 for the three clinical trials ranged from
17 0.12-0.26 which is equivalent to a change in patient success rates of 12-26%⁴⁰. This
18 effect size range is comparable to the 21-29% improvement in patient rated outcomes
19 noted with topical glyceryl trinitrate therapy. These parallel measures of patient
20 outcomes are calculated from very different sources (patient rated outcomes versus all
21 trial outcome measures) and demonstrate a mild to moderate effect of glyceryl
22 trinitrate treatment in improving outcome measures in three common chronic
23 tendinopathies.

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1 **Side-Effects**

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

22 Patients in the clinical trials were supplied with acetaminophen/ paracetamol tablets
23 for exclusive use with the potential side-effect of headache, and in the three glyceryl
24 trinitrate groups the total group paracetamol usage in the 24 weeks ranged from 138-
25 237 tablets, with an average of 7-14 tablets per subject affected by headache. In the

1 placebo groups the total paracetamol usage ranged from 69-250 tablets, with an
2 average of 3-10 tablets. There were significant between group differences in the total
3 amount of paracetamol used in the Achilles tendinopathy and supraspinatus
4 tendinopathy trials. Despite higher rates of reported headache in the supraspinatus
5 tendinopathy trial the use of paracetamol was lower than in either of the other clinical
6 trials.

7 Another common side-effect of topical glyceryl trinitrate is application site rash
8 and in the glyceryl trinitrate groups the number of patients experiencing rash ranged
9 from 8-21% compared with rates in the placebo groups ranging from 7-12%. Reports
10 in the literature for glyceryl trinitrate dosages of 5mg/24 hour note rash in 16-38% of
11 patients^{18,36,37} and these side-effect rates are comparable with those reported in these
12 clinical trials. There was a greater severity of rash in the glyceryl trinitrate groups
13 compared to the placebo groups as evidenced by a total of five patients discontinued
14 due to this side-effect. Other side-effects that were reported included: an increase in
15 pre-existing tinnitus, increased ipsilateral axillary sweating, and a perception of
16 apprehension. None of these were severe, and all were reversible on discontinuation
17 of the patch. The number of patients in the glyceryl trinitrate groups that experienced
18 no side-effects ranged from 30-44% whilst those in the placebo groups ranged from
19 33-59%.

20

21 **Drop-Outs and Trial Completion Rates**

22 The number of patients discontinued during the course of the clinical trials ranged
23 from 4-6% of clinical trial patients, these patients were all in the glyceryl trinitrate
24 groups, and they were discontinued for recognised side-effects of headache or
25 application site rash. One patient was discontinued for recurrent facial flushing, which

1 was reversible on discontinuation of the medication. This patient was a type 2 diabetic
2 and it was felt that this side-effect was caused by arteriolar dilatation.

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

10

11 **Summary**

12 These clinical trials investigating topical glyceryl trinitrate treatment combined
13 with tendon rehabilitation demonstrated improved patient rated pain scores, increased
14 tendon force measures, improved functional measures, and improved patient
15 outcomes relative to tendon rehabilitation alone in the treatment of chronic overuse
16 tendinopathies. Topical nitric oxide donors such as 1.25mg/ 24 hour glyceryl trinitrate
17 have a long history of therapeutic use in humans²⁸, have a known side-effect profile
18 with no irreversible effects, and now have clinically demonstrated efficacy in
19 modulating pain, force measures, functional measures, and patient outcomes at six
20 months in specific chronic overuse tendinopathies. From these studies it appears
21 evident that topical glyceryl trinitrate has a role in treating specific chronic overuse
22 tendinopathies and should be used as an adjunct to tendon rehabilitation.

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References

1. Akizuki K, Gartman EJ, Nisonson B et al. The relative stress on the Achilles tendon during ambulation in an ankle immobiliser: implications for rehabilitation after Achilles tendon repair. *Br J Sports Med* 2001;35:329-334.
2. Alfredson H, Pietila T, Jonsson P et al. Heavy load eccentric calf muscle training for the treatment of chronic Achilles tendinosis. *Am J Sports Med* 1998;26(3):360-366.
3. Arnoczky S, Tian T, Lavagnino M et al. Activation of stress-activated protein kinases (SAPK) in tendon cells following cyclic strain: the effects of strain frequency, strain magnitude, and cytosolic calcium. *J Orthop Res* 2002;20:947-952.
4. Astrom M, Rausing A. Chronic Achilles tendinopathy: a survey of surgical and histopathological findings. *Clin Orthop* 1995;316:151-164.
5. Barrazueta J, Losada A, Poveda J et al. Successful treatment of shoulder pain syndrome due to supraspinatus tendinitis with transdermal nitroglycerin. A double blind study. *Pain* 1996;66:63-67.
6. Blair B, Rokito AS, Cuomo F et al. Efficacy of injections of corticosteroids for subacromial impingement syndrome. *J Bone Joint Surg* 1996;78-A(11):1685-1689.
7. Boyer M, Hastings H. Lateral tennis elbow: is there any science out there? *J Shoulder Elbow Surg* 1999;8:481-491.
8. Brukner P, Khan K. *Clinical Sports Medicine* (2nd Edition). Sydney. McGraw-Hill. 2001.
9. Clement D, Taunton JE, Smart GW. A survey of overuse running injuries. *Physician Sportsmed* 1981;9(5):47-58.
10. De Milliano P, Koster RW, Bar FW et al. Long-term efficacy of continuous and intermittent use of transdermal nitroglycerin system. *Am J Cardiol* 1991;68(9):857-862.
11. Dimberg L. The prevalence and causation of tennis elbow (lateral epicondylitis) in a population of workers in an engineering industry. *Ergonomics* 1987;30:573-579.
12. Fung H-L. Clinical pharmacology of organic nitrates. *Am J Cardiol* 1993;72:9C-15C.
13. Gellman H. Tennis elbow (lateral epicondylitis). *Orthop Clin North Amer* 1992;23(1):75-82.
14. Groppe J, Nirschl RP. A biomechanical and electromyographical analysis of the effects of counterforce braces on the tennis player. *Am J Sports Med* 1986;14:712-723.
15. Hawkins RJ, Hobeika PE. Impingement syndrome in the athletic shoulder. *Clinics Sports Med* 1983;2(2):391-405.
16. Hayes K, Walton JR, Szomor ZL et al. Reliability of five methods for assessing shoulder range of motion. *Aust J Physio* 2001;47:289-294.
17. Hayes K, Walton JR, Szomor ZL et al. Reliability of three methods for assessing shoulder strength. *J Shoulder Elbow Surg* 2002; 11(1):33-39.
18. Kapoor A, Dang NS, Reynolds RD. Sustained effects of transdermal nitroglycerin in patients with angina pectoris. *Clin Therapeutics* 1985;7(6):674-679.
19. Khan K, Cook JL, Bonar F et al. Histopathology of common tendinopathies. *Sports Med* 1999; 27(6): 393-408.
20. Krabak B, Sugar R, McFarland EG. Practical non-operative management of rotator cuff injuries. *Am J Sports Med* 2003;13(2):102-105.
21. Labelle H, Guibert R, Joncas J et al. Lack of scientific evidence for the treatment of lateral epicondylitis of the elbow: an attempted meta-analysis. *J Bone Joint Surg [Br]* 1992;74-B: 646-651.
22. Lin J-H, Wang M-X, Wei A et al. Temporal expression of nitric oxide synthase isoforms in healing Achilles tendon. *J Orthop Res* 2001;19:136-142.
23. Lin J-H, Wang M-X, Wei A-Q et al. The cell specific temporal expression of nitric oxide isoforms during Achilles tendon healing. *Inflammation Res* 2001;50:515-522.
24. L'insalata J, Warren RF, Cohen SB et al. A self-administered questionnaire for assessment of symptoms and function of the shoulder. *J Bone Joint Surg* 1997;79-A(5):738-748.
25. Mahapatra R, Mahapatra D, Yaden S. Clinical experience with a transdermal nitroglycerin system. *Angiology* 1987;38(4):277-286.
26. Moncada S, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev* 1991;43:109-142.
27. Murrell GAC, Szabo C, Hannafin JA et al. Modulation of tendon healing by nitric oxide. *Inflammation Res* 1997;46:19-27.
28. Murrell W. Nitroglycerin as a remedy for angina pectoris. *Lancet* 1879;80-81,113-115,151-152,225-227.

- 1 29. Neisen-Vertommen S, Taunton JE, Clement DB. The effect of eccentric versus concentric
2 exercise in the management of Achilles tendinitis. *Clin J Sports Med* 1992;2:109-113.
- 3 30. Newcomer K, Laskowski ER, Idank DM et al. Corticosteroid injection in early treatment of
4 lateral epicondylitis. *Clin J Sports Med* 2001;11:214-222.
- 5 31. Nirschl RP, Pettrone FA. *The upper extremity in sports medicine*. Editor Nicholas J. St Louis.
6 Mosby. 1990.
- 7 32. Nirschl RP, Rodin DM, Ochiai DH et al. Iontophoresis administration of dexamethasone
8 sodium phosphate for acute epicondylitis. *Am J Sports Med* 2003;31(2):189-195.
- 9 33. Paoloni J, Appleyard RA, Murrell GAC. The Orthopaedic Research Institute-Ankle Strength
10 Testing System: inter-rater and intra-rater reliability testing. *Foot Ankle Int* 2002;23(2):312-
11 323.
- 12 34. Paoloni J, Appleyard RA, Murrell GAC. The Orthopaedic Research Institute-Tennis Elbow
13 Testing System: inter-rater and intra-rater reliability testing. *J Shoulder Elbow Surg*
14 2004;13(1):72-77.
- 15 35. Potter H, Hannafin JA, Morwessi RM et al. Lateral epicondylitis: correlation of MR imaging,
16 surgical and histopathological findings. *Radiology* 1991;196:43-46.
- 17 36. Renganathan R, Suranjan B, Kurien T. Comparison of transdermal nitroglycerin and
18 intracavernous injection of papaverine in the treatment of erectile dysfunction in patients with
19 spinal cord lesions. *Spinal cord* 1997;35(2):99-103.
- 20 37. Riley S, Morris B, Walker L et al. Comparison of two transdermal nitroglycerin delivery
21 systems: Transiderm-Nitro and Nitro-Dur. *Clin Therapeutics* 1992;14:438-445.
- 22 38. Rivenburgh D. Physical modalities in the treatment of tendon injuries. *Clinics Sports Med*
23 1992;11:645-659.
- 24 39. Robinson J, Cook JL, Purdam C et al. The VISA-A questionnaire : a valid and reliable index
25 of the clinical severity of Achilles tendinopathy. *Br J Sports Med* 2001;35:335-341.
- 26 40. Rosenthal R, Robin F. *Meta-analytic procedures*. San Francisco. Jossey-Bass. 1979.
- 27 41. Takeda Y, Kashiwaguchi S Endo K et al. The most effective exercise for strengthening the
28 supraspinatus muscle. *Am J Sports Med* 2002;30(3):374-381.
- 29 42. Williams J. Achilles tendon lesions in sport. *Sports Med* 1993;16:216-220.
- 30 43. Xia W, Szomor Z, Wang Y et al. Enhancement of collagen synthesis in human tendon cells
31 via iNOS gene transfection. *Conference proceedings of Australian Conference of Science and*
32 *Medicine in Sport*. Sydney. McGraw-Hill. 2003.
- 33 44. Yuan J, Murrell GAC, Wei A-Q et al. Apoptosis in rotator cuff tendinopathy. *J Orthop Res*
34 2002;20:1372-1379.
- 35 45. Yuan J, Murrell GAC, Wei A-Q et al. Addition of nitric oxide via nitroflurbiprofen enhances
36 the material properties of early tendon healing in young rat Achilles tendons. *Inflammation*
37 *Res* 2003;52:1167-1176.
- 38 46. Zhu W, Diwan AD, Lin J-H et al. Nitric oxide synthase isoforms during fracture healing. *J*
39 *Bone Mineral Res* 2001;16(3):535-540.

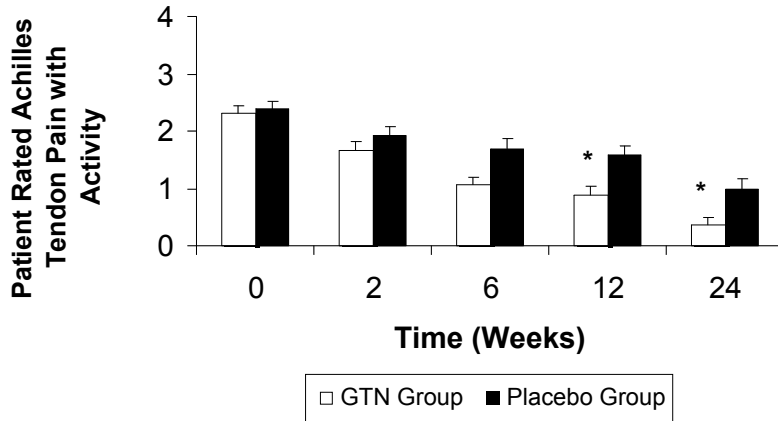
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Figures and Tables

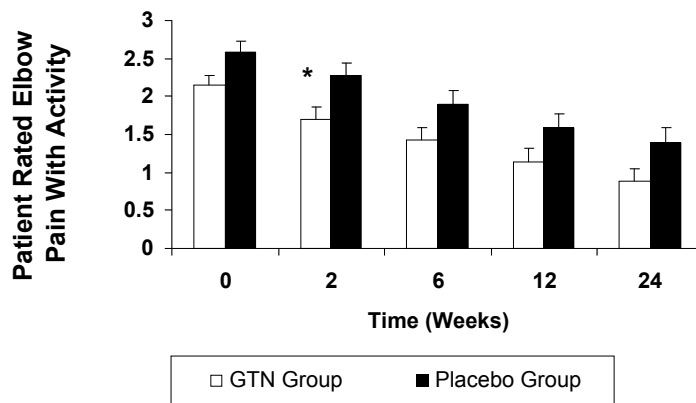
Figure 1

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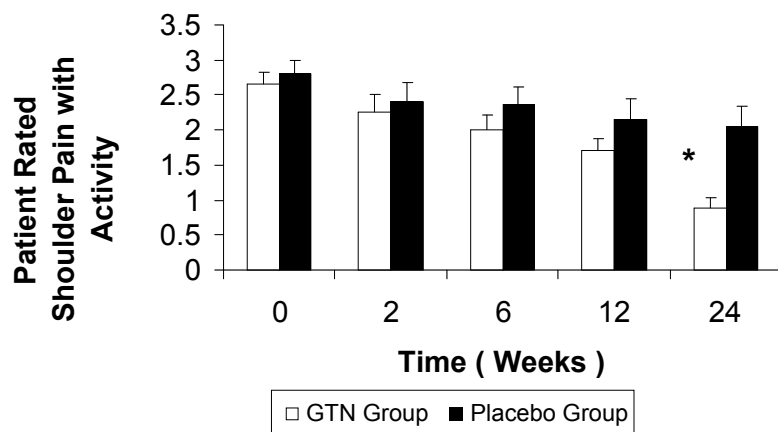
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a) Effects of glyceryl trinitrate 1.25 mg / day transdermal patch plus rehabilitation (GTN, n = 41) versus rehabilitation alone (placebo, n=43) on Achilles tendon pain with activity. Statistically significant differences between groups are shown with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

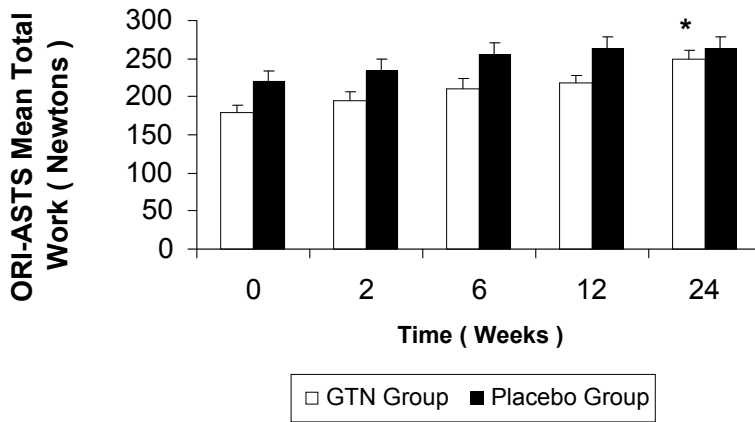
c) Effects of glyceryl trinitrate 1.25 mg / day transdermal patch plus rehabilitation (GTN, n = 28) versus rehabilitation alone (placebo, n=29) on shoulder pain with activity in supraspinatus tendinopathy. Statistically significant differences between groups are shown with an asterisk (* p < 0.05).

1 **Figure 2**

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3 **a)**

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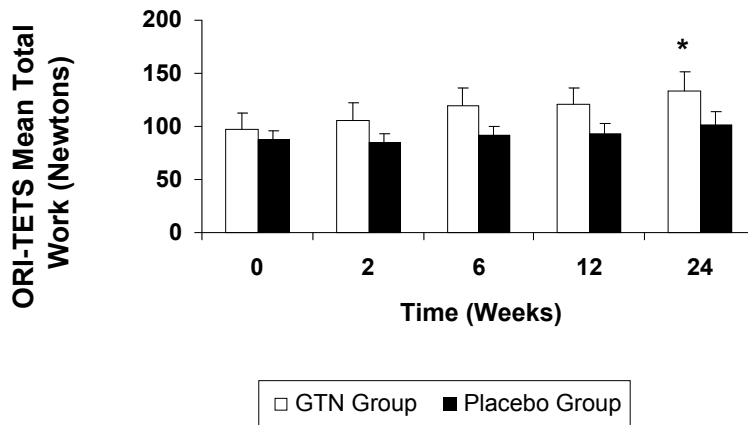
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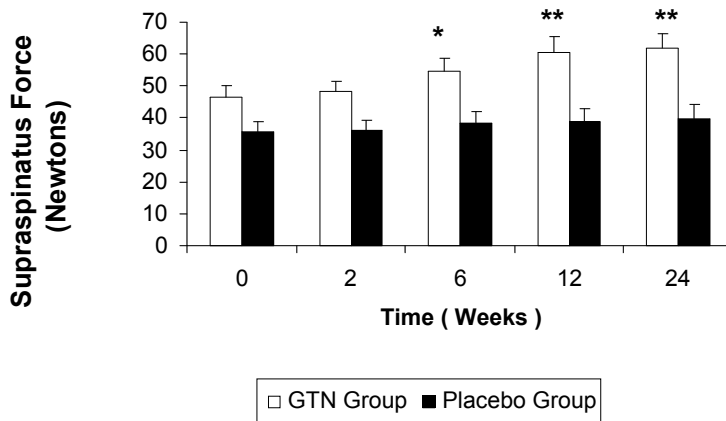
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1 **a) Effects of glyceryl trinitrate (GTN, n = 41) 1.25 mg / day transdermal**
2 **patch plus rehabilitation versus rehabilitation alone (placebo, n=43) on**
3 **Orthopaedic Research Institute-Ankle Strength Testing System (ORI-**
4 **ASTS) measured ankle plantarflexor mean total work. Statistically**
5 **significant differences between groups are shown with an asterisk (* p <**
6 **0.05).**

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

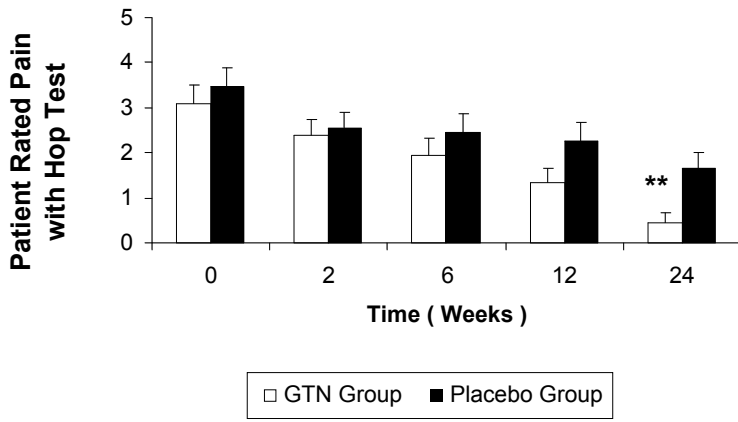
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14 **c) Effects of glyceryl trinitrate (GTN, n = 28) 1.25 mg / day transdermal**
15 **patch plus rehabilitation versus rehabilitation alone (placebo, n=29) on**
16 **dynamometer measured supraspinatus force. Statistically significant**
17 **differences between groups are shown with an asterisk (* p < 0.05, ** p <**
18 **0.01).**

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1 **Figure 3**

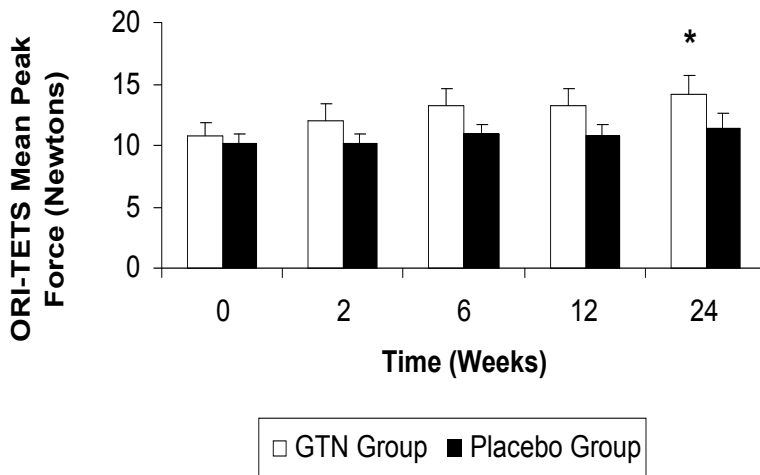
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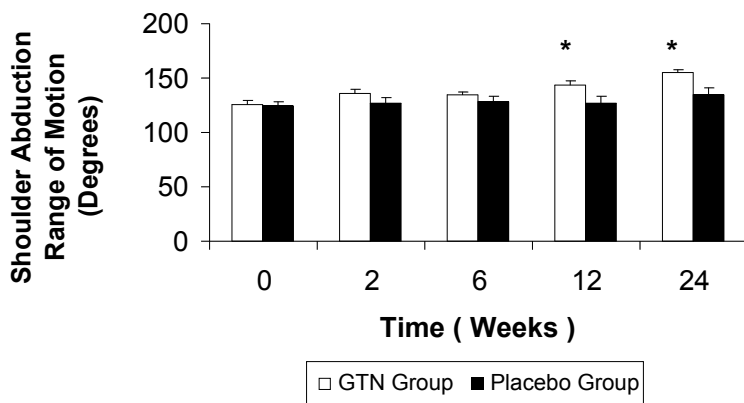
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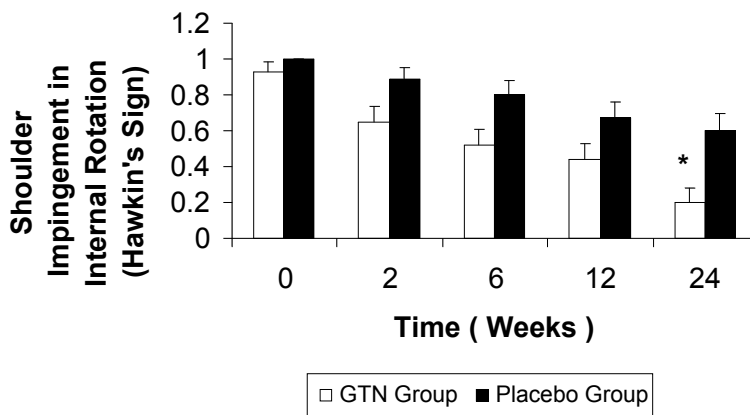
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a) Effects of glyceryl trinitrate (GTN, n = 41) 1.25 mg / day transdermal patch plus rehabilitation versus rehabilitation alone (placebo, n=43) on pain scores after the 10 hop test. Statistically significant differences between groups are shown with an asterisk (* p < 0.05, ** p < 0.01).

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b) Effects of glyceryl trinitrate (GTN, n = 28) 1.25 mg / day transdermal patch versus rehabilitation alone (placebo, n=29) on Orthopaedic Research Institute-Tennis Elbow Testing System (ORI-TETS) mean peak force. Statistically significant differences are shown with an asterisk (* p < 0.05).

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c) Effects of glyceryl trinitrate (GTN, n = 28) 1.25 mg / day transdermal patch versus rehabilitation alone (placebo, n=29) on passive shoulder abduction range of motion. Statistically significant differences are shown with an asterisk (* p < 0.05).

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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).

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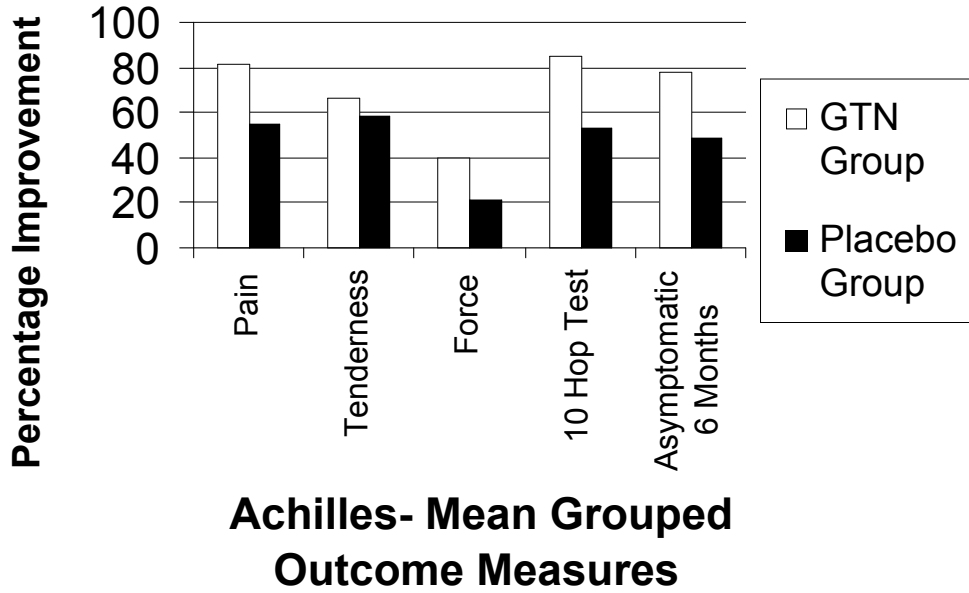
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1 **Figure 4**

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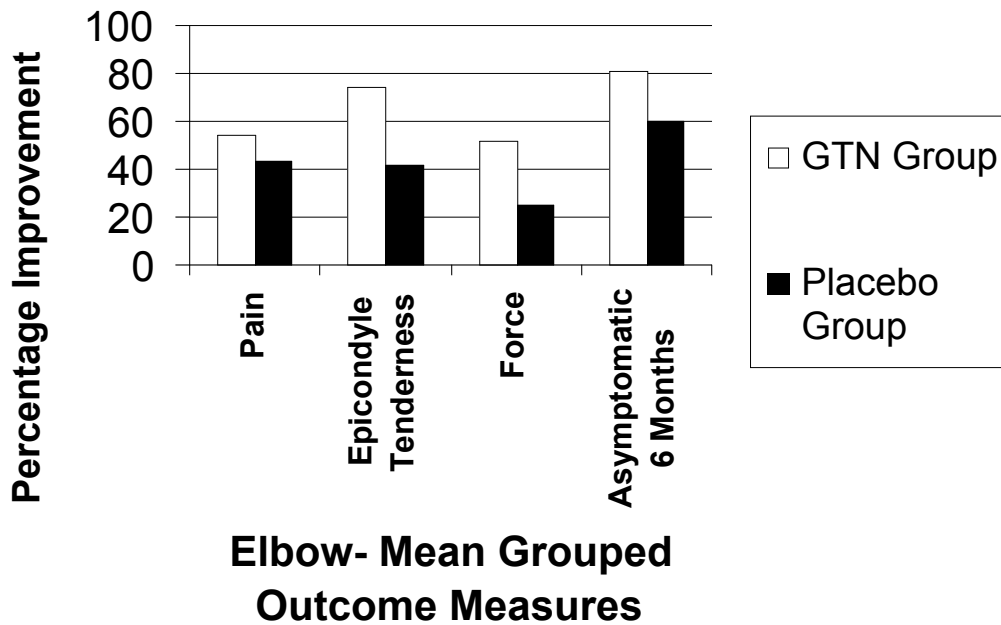
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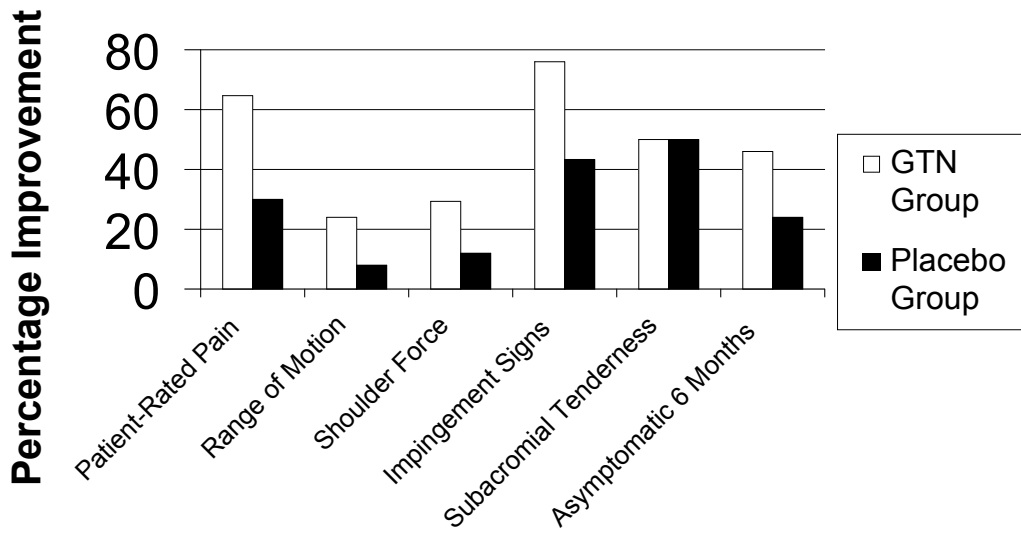
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Shoulder- Mean Grouped Outcome Measures

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- 1 **a) Percentage differences in mean grouped outcome measures between the**
2 **glyceryl trinitrate group (GTN 1.25 mg / day patch, n = 41) and the**
3 **placebo patch group (n=43). A between group comparison of means for**
4 **grouped outcome measures in the Achilles tendinopathy clinical trial.**
- 5 **b) Percentage differences in mean grouped outcome measures between the**
6 **glyceryl trinitrate group (GTN 1.25 mg / day patch, n = 47) and the**
7 **placebo patch group (n=48). A between group comparison of means for**
8 **grouped outcome measures. A between group comparison of means for**
9 **grouped outcome measures in the extensor tendinopathy clinical trial.**
- 10 **c) Percentage differences in mean grouped outcome measures between the**
11 **glyceryl trinitrate group (GTN 1.25 mg / day patch, n = 28) and the**
12 **placebo patch group (n=29). A between group comparison of means for**
13 **grouped outcome measures. A between group comparison of means for**
14 **grouped outcome measures in the supraspinatus tendinopathy clinical**
15 **trial.**

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

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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.

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1 **Table II**

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Trial Parameters		Achilles (N=65)	Elbow (N=86)	Shoulder (N=53)
Trial Completion Rate		GTN 84 % Placebo 94 %	GTN 81 % Placebo 91 %	GTN 88 % Placebo 93 %
Discontinuations (All GTN Group)		Rash 3 (3%) Headache 1 (2%)	Rash 2 (1%) Headache 2 (1%) Facial Flush 1 (1%)	Headache 2 (2%)
Drop-outs		GTN 2 Placebo 1	GTN 3 Placebo 4	GTN 1 Placebo 2
Days of Headache (Percentage of patients affected)	Total	GTN 85 (53%) Placebo 101 (45%)	GTN 136 (63%) Placebo 166 (58%)	GTN 127 (76%) * Placebo 37 (33%)
	Average	GTN 5 Placebo 7	GTN 5 Placebo 7	GTN 6 Placebo 4
	Median	GTN 4 Placebo 3	GTN 3 Placebo 1	GTN 4 Placebo 0
Paracetamol (Tablets)	Total	GTN 237 * Placebo 46	GTN 214 Placebo 250	GTN 138 * Placebo 69
	Average	GTN 14 Placebo 3	GTN 8 Placebo 10	GTN 7 Placebo 8
	Median	GTN 10 Placebo 0	GTN 4 Placebo 0	GTN 2 Placebo 0
Other Noted Side-Effects	GTN	Rash 16 % Increase Tinnitus 3%	Rash 21 % Increase Axillary Sweating 2%	Rash 8 %
	Placebo	Rash 12 %	Rash 9 %	Rash 7 %
No Side-Effects		GTN 44 % Placebo 45 %	GTN 35 % Placebo 33 %	GTN 30 % Placebo 59 %

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