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Randomised, double-blind, placebo-controlled clinical trial of a new topical glyceryl trinitrate patch for chronic lateral epicondylitis

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ABSTRACT

Objective: This study aimed to determine whether a new glyceryl trinitrate patch preparation is effective in treating chronic lateral epicondylitis.

Design: Randomised double-blind controlled clinical trial.

Setting: Private practice patients: 154 adult patients with chronic lateral epicondylitis were recruited, with 136 patients completing the trial.

Interventions: 8 weeks of glyceryl trinitrate patch application (dosages of 72 mg/24 h, 1.44 mg/24 h, and 3.6 mg/24 h), or placebo patch application.

Main outcome measures: Subjective global assessment of change in elbow symptoms, patient-rated tennis elbow evaluation, visual analogue pain at rest, visual analogue pain with activity, visual analogue pain intensity, grip strength, and strength testing using the Orthopaedic Research Institute-Tennis Elbow Testing System.

Results: At 8 weeks there was a significant decrease in elbow pain with activity in the glyceryl trinitrate 0.72 mg/24 h group compared with placebo ($p = 0.04$). There were no other significant differences.

Conclusions: Continuous 1.25 mg/24 h topical glyceryl trinitrate treatment, when combined with daily exercise rehabilitation, has previously demonstrated efficacy in treating chronic lateral epicondylitis. There was significantly decreased elbow pain with activity at 8 weeks in the glyceryl trinitrate 0.72 mg/24 h group ($p = 0.04$). This short-term dose-ranging study did not demonstrate a treatment effect of a new topical glyceryl trinitrate patch in dosages of 1.44 mg/24 h or 3.6 mg/24 h, which conflicts with previous studies on topical glyceryl trinitrate treatment.

Trial registration number: NCT00447928.

Lateral epicondylitis, colloquially known as “tennis elbow”, is a degenerative overuse tendinopathy characterised histopathologically by changes of collagen fibre disruption and disorganisation, mucoid degeneration, angiofibroblastic hyperplasia, and the absence of inflammatory cells.¹ It has an incidence of 2%, has an even gender distribution and occurs in all ages, with a peak incidence in the fourth and fifth decades of life, and the dominant arm is involved in 75% of patients.² Despite the colloquial terminology “tennis elbow”, only 5% of cases of lateral epicondylitis are caused by playing a racquet sport.³ However, there is an incidence of 45% in world-class tennis players, and of 47% in average players.^{4, 5} The condition is also associated with fly-fishing, weightlifting, and the leading arm in golfers.⁶⁻⁸ The duration of the average episode is estimated to be between 6 months and 2 years,⁹ with 83% of patients either “completely

recovered” or “much improved” within 12 months with a wait-and-see policy.¹⁰

No treatment is universally successful in treating chronic lateral epicondylitis, which causes considerable morbidity through time lost at work and recreation. Current tendon rehabilitation programmes involve: ice application, relative rest, forearm bracing, and a graduated stretching and strengthening exercise programme. Modification of contributory biomechanical factors prior to return to aggravating activities is an important component of management.^{8, 11}

Topical nitroglycerin, or glyceryl trinitrate, has been used for over 100 years as a therapy for angina pectoris,¹² and it is now accepted that the mechanism of action of the organic nitrates is through production of nitric oxide, the endothelium-derived relaxing factor.^{13, 14} Nitric oxide synthase, the endogenous precursor to nitric oxide (NO), is induced during tendon healing,^{15, 16} and inhibition of nitric oxide synthase results in a significant reduction in healing tendon cross-sectional area and load to failure.¹⁷ Nitric oxide modulates collagen synthesis by human tendon fibroblasts in culture.¹⁸ The mechanism of action of topical glyceryl trinitrate is unknown, but it has been postulated that it may be due to fibroblast stimulation or modulation of the apoptotic pathway.¹⁹

Continuous topical glyceryl trinitrate at a dosage of 1.25 mg/24 h has demonstrated efficacy in treating chronic lateral epicondylitis when combined with exercise rehabilitation.²⁰ This dosage of 1.25 mg/24 h is currently the only dosage of topical glyceryl trinitrate that has been studied for the treatment of tendinopathy.²⁰⁻²²

This dose-ranging study aimed to determine whether a new patch preparation is effective in treating chronic lateral epicondylitis, and whether other doses of topical glyceryl trinitrate are more effective than the dosage of 1.25 mg/24 h.

MATERIALS AND METHODS

The study was conducted by Cure Therapeutics, the manufacturers of the OrthoDerm patch used in this clinical trial, as a Phase II study in the use of topical glyceryl trinitrate treatment in chronic lateral epicondylitis. The OrthoDerm patch was formulated in a very similar way to a currently marketed transdermal nitroglycerin patch, and demonstrated reliable continuous, linear release of nitroglycerin over a 24 h period using standard *in vivo* skin permeation tests. This was a multicentre study.

Ethics approval was obtained, and informed consent given by all study participants. Power analysis determined that, to have an 80% chance of finding a mean 7 kg improvement in painfree grip strength in the topical glyceryl trinitrate group, each group would require 27 patients. The study was designed to recruit 30 patients per group so that even with a 10% dropout rate the power of the study would not be diminished. Painfree grip strength is a commonly used outcome measure in studying lateral epicondylitis and its treatment.^{23–27}

Inclusion criteria were: adult patients between 18 and 70 years of age with a diagnosis of chronic lateral epicondylitis (defined as a symptom duration greater than 3 months) who scored greater than 4 out of 10 on a visual analogue scale with provocative elbow testing (the Orthopaedic Research Institute-Tennis Elbow Testing System, ORI-TETS, was used).²⁸ Exclusion criteria were: body mass index greater than 38, requirement for regular oral or topical analgesia, use of corticosteroid injection within the previous 3 months, worker's compensation cases, previous use of topical glyceryl trinitrate, cardiac disease, pregnant women, bilateral elbow disease, previous upper limb surgery, fracture or dislocation.

Recruited patients were randomised using stratified computer-generated randomisation in the pharmacy, and were randomised to one of four groups: placebo patch, OrthoDerm (Cure Therapeutics, New York, USA) topical glyceryl trinitrate patch 0.03 mg/h (0.72 mg/24 h), OrthoDerm topical glyceryl trinitrate patch 0.06 mg/h (1.44 mg/24 h), or OrthoDerm topical glyceryl trinitrate patch 0.15 mg/h (3.6 mg/24 h). Placebo and active patches were identical in appearance. Patients were instructed to apply the patch daily, wearing each patch for a 24 h period to the area of maximal tenderness, with some rotation of the patch to minimise skin irritation. Patients were also supplied with 500 mg paracetamol tablets for analgesia, if required. Compliance was checked using a diary which recorded headaches and paracetamol use.

At the initial visit (week 0), and at the subsequent visit (week 8), all patients were examined by a medical practitioner at the study centres. Elbow examination was performed to confirm the diagnosis and ensure that inclusion and exclusion criteria were met. Blinded clinical testing included: subjective global assessment of change (SGAC) in overall elbow symptoms, patient-rated tennis elbow evaluation (PRTEV),^{29–30} pain at rest using a visual analogue scale, pain with activity using a visual analogue scale, pain intensity using a visual analogue scale, grip strength measurement using a digital hand-held dynamometer, and strength testing using the ORI-TETS.

All patients were instructed in an elbow rehabilitation programme, which was to be performed three times daily. This programme comprised an isolated contraction of the wrist extensor muscles which was held for 10 seconds, then 2 seconds of muscle relaxation, and then wrist extensor stretching for 15–20 seconds.²³

After the week 8 visit, blinded statistical analysis was performed. Data analysis was performed on an intention to treat basis. Comparison was made between week 0 and week 8 measures using Student's *t* tests to compare between-group and within-group changes. The primary outcome measure used was painfree grip strength. Secondary outcome measures included: ORI-TETS, pain with activity, PRTEV, pain intensity, and SGAC.

It was intended that any statistically significant differences would be tested for durability by continued follow-up of all patients with week 12 and week 20 visits, even though this follow-up would not be blinded.

RESULTS

A total of 154 patients were recruited and there were no significant between-group differences with respect to age, gender, or length of time with lateral epicondylitis. After randomisation, during the course of the study there were 18 discontinued patients (dropouts): three in the placebo group, with two dropouts due to patch or medication non-compliance and one patient lost to follow-up; three in the OrthoDerm 0.72 mg/24 h group, with two dropouts due to patch and medication non-compliance and one due to withdrawal of consent; four in the OrthoDerm 1.44 mg/24 h group with three dropouts due to severe headaches and one due to patch and medication non-compliance; and eight in the OrthoDerm 3.6 mg/24 h group with two dropouts due to patch and medication non-compliance, five due to severe headaches, and one patient with a dermatitis rash.

Thus, there were a total of 136 patients who completed the 8 weeks follow-up. The placebo group had 32 patients, the OrthoDerm 0.72 mg/24 h group had 38 patients, the OrthoDerm 1.44 mg/24 h group had 30 patients, and the OrthoDerm 3.6 mg/24 h group had 36 patients. Intention to treat analysis included all 154 subjects recruited in the clinical trial.

There was significant improvement in elbow pain with activity (carrying heavy loads such as a grocery bag with handles) at week 8 in the OrthoDerm 0.72 mg/24 h group compared with placebo ($p=0.04$). There were no other significant differences found at the week 8 visit (see table 1), although there was a trend towards significant improvements in the OrthoDerm 0.72 mg/24 h group with elbow pain when wringing out a towel ($p=0.08$).

Due to the lack of significant results at week 8 no further follow-up was conducted and the clinical trial was aborted.

DISCUSSION

Continuous topical glyceryl trinitrate treatment at a dose of 1.25 mg/24 h using Nitro-Dur patches (Schering-Plough, Sydney, Australia), when combined with daily exercise rehabilitation, has previously demonstrated efficacy in treating chronic tendinopathies including lateral epicondylitis,²⁰ non-insertional Achilles tendinopathy,²¹ and supraspinatus tendinopathy.²² This current study of continuous topical glyceryl trinitrate treatment using OrthoDerm patches (Cure Therapeutics, New York, USA) assessed dosages of 0.72 mg/24 h, 1.44 mg/24 h, and 3.6 mg/24 h. There was no demonstrated evidence of efficacy of the topical glyceryl trinitrate patches in any dosage.

This study indicates that, in the short term, there is little therapeutic effect of continuous topical glyceryl trinitrate treatment, at any dosage, in chronic lateral epicondylitis when combined with a daily stretching programme only. The apparent rationale for using a stretching-only programme in this clinical trial, rather than a more conventional wrist extensor strengthening exercise programme, was based on the recent study by Martinez-Silvestrini. In this study approximately 30 patients with chronic lateral epicondylitis were assigned to groups performing stretching only, concentric strengthening with stretching, or eccentric exercise only. There were no significant differences between groups at 6 weeks follow-up.

In the only previous randomised controlled trial on continuous topical glyceryl trinitrate treatment of chronic lateral epicondylitis,²⁰ where patch application was combined with concentric-eccentric exercise rehabilitation and stretching, there

Table 1 Table showing baseline data and final data for all outcome measures

	GTN 0.03 mg/24 h (n = 41)	GTN 0.06 mg/24 h (n = 34)	GTN 0.15 mg/24 h (n = 44)	Placebo (n = 35)
Pain with activity	38 (-4) (SD 3.17)	30 (-2.8) (SD 2.38)	36 (-3.9) (SD 2.11)	32 (-3.8) (SD 2.62)
Patient at rest	38 (-3) (SD 2.45)	30 (-1.7) (SD 2.25)	36 (-1.8) (SD 2.23)	32 (-2.6) (SD 1.98)
Pain at night	34 (-3.2) (SD 2.83)	28 (-2.6) (SD 2.2)	32 (-2.1) (SD 1.86)	30 (-2.3) (SD 1.9)
Painfree grip strength (kg)	20.8 (8.2) (SD 9.82)	24.3 (8.8) (SD 12.77)	23.1 (7.4) (SD 12.15)	22.9 (4.5) (SD 8.48)
Maximum force ORI-TETS (kg)	0.5 (0.4) (SD 0.71)	0.7 (0.3) (SD 0.51)	0.7 (0.4) (SD 0.72)	0.5 (0.2) (SD 0.4)
Subjective global assessment of change	38 (-3.5) (SD 3.05)	30 (-2.4) (SD 2.59)	36 (-3.2) (SD 2.38)	32 (-3.1) (SD 2.66)

GTN, glyceryl trinitrate; ORI-TETS, Orthopaedic Research Institute-Tennis Elbow Testing System.

Baseline data is presented above, with change from baseline in brackets below, and standard deviations in parentheses.

were significant improvements in elbow pain with activity at 2 weeks ($p = 0.01$), lateral epicondyle and tendon tenderness at 6 and 12 weeks ($p = 0.02$), wrist extensor peak force and total work with the ORI-TETS at 24 weeks ($p = 0.03$), and asymptomatic patient outcomes at week 24 ($p = 0.005$). The effect size estimate for all outcome measures was 0.12.

Comparing these two studies is difficult due to the use of different drug dosages, different types of glyceryl trinitrate patches, different follow-up periods, single-centre versus multi-centre patient recruitment and clinical testing, and markedly different rehabilitation protocols. The only significant difference noted in the current study was a decrease in elbow pain with activity in the OrthoDerm 0.72 mg/24 h group. Other trends towards significance were noted only in the OrthoDerm 0.72 mg/24 h and 1.44 mg/24 h groups. There were no trends towards significance in the OrthoDerm 3.6 mg/24 h group. The reasons for a lack of demonstrated effect in this study may include too short a treatment period, different patch formulation, or the absence of an exercise programme combined with patch usage. The lack of a formal wrist extensor strengthening programme, as is generally accepted as part of the best practice management of lateral epicondylitis,^{31–34} is a major weakness of this study. It has been postulated that the mechanism of action of topical glyceryl trinitrate treatment is through nitric oxide donation to tendon fibroblasts leading to increased collagen synthesis in tendon.^{35–36} Any increase in collagen synthesis in tendon may still require loading through exercise rehabilitation to form a strong, elastic scar with appropriate biomechanical properties.

Common side-effects of continuous topical glyceryl trinitrate treatment include headache and rash, and it was noted that seven patients were discontinued from the study due to severe headaches. Five of these patients were in the OrthoDerm 3.6 mg/24 h group (11% of group patients), and two patients were in the OrthoDerm 1.44 mg/24 h group (6% of group patients). There was only one patient discontinued due to dermatitis rash and this patient was in the OrthoDerm 3.6 mg/24 h group (2% of group patients). It is interesting to note that in the original Paoloni topical glyceryl trinitrate lateral epicondylitis study where 1.25 mg/24 h patches were used 4.5% of patients were discontinued due to headache, and 4.5% of patients discontinued due to rash. In this current study, as the dose of topical glyceryl trinitrate was increased, so was the incidence of severe headaches. However, the incidence of dermatitis rash was low in all groups using the OrthoDerm patch.

Continuous topical glyceryl trinitrate, at a dosage of 1.25 mg/24 h, has demonstrated efficacy of an early decrease in elbow pain with activity, subsequent reduction in clinical tendon tenderness, a late increase in tendon force measures, and

What is already known on this topic

Topical glyceryl trinitrate has previously demonstrated efficacy in treating chronic lateral epicondylitis.

What this study adds

This short-term dose-ranging study showed no evidence of efficacy in treating lateral epicondylitis with a new glyceryl trinitrate patch. Headache side-effects appeared dose-related. Patch usage combined with an exercise programme may be critical for patch efficacy.

improved patient outcomes at 6 months in patients with chronic lateral epicondylitis.²⁰ This current short-term dose-ranging study showed a significant reduction in elbow pain with activity in the OrthoDerm 0.72 mg/24 h group ($p = 0.04$). The dosages of 1.44 mg/24 h and 3.6 mg/24 h, in particular, showed no significant differences at 8 weeks. The side-effect of headache appeared to be dose-related and resulted in several patients discontinuing the study. The major weakness of this study is the absence of an exercise programme combined with the use of topical glyceryl trinitrate patches, and this may be the reason for the demonstrated lack of efficacy. Further studies need to be performed to determine the mechanism of action of topical glyceryl trinitrate, the definitive role of topical glyceryl trinitrate in treating lateral epicondylitis, and the definitive role of exercise programmes in treating lateral epicondylitis.

Competing interests: None.

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