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Topical glyceryl trinitrate (GTN) and eccentric exercises in the treatment of mid-portion achilles tendinopathy (the NEAT trial): a randomised double-blind placebo-controlled trial

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ABSTRACT

Objectives To investigate if daily treatment with glyceryl trinitrate (GTN) ointment, over 24 weeks combined with a 12-week eccentric exercise programme is more effective for chronic mid-portion Achilles tendinopathy than placebo ointment and eccentric exercise.

Methods This was a single-site randomised double-blind placebo-controlled trial at an acute hospital, Dublin, Ireland. Patients with chronic mid-portion Achilles tendinopathy were randomised to either 24 weeks of daily GTN ointment or placebo ointment. Both groups received an identical 12-week eccentric exercise programme. The primary outcome measure was the Victorian Institute of Sport Assessment–Achilles (VISA-A) questionnaire at 24 weeks, which measures pain, function and activity. Secondary outcomes included pain severity, self-reported physical function, calf muscle function, pressure pain thresholds and ultrasound changes. Statistical analyses were performed according to intention-to-treat principles.

Results 76 patients (30 women; 46 men, mean age±SD, 45.6±8.2 years) were recruited for the trial. Significant improvements in VISA-A scores occurred in both groups at 6-week, 12-week and 24-week follow-up. The increase was not significantly different between groups, adjusted mean between-group difference from baseline to week 6, −1.33 (95% CI −6.96 to 4.31); week 12, −1.25 (95% CI −8.0 to 5.49) and week 24, −3.8 (95% CI −10.6 to 3.0); negative values favour GTN. There was no significant between-group difference in any of the secondary outcome measures at 6, 12 and 24 weeks.

Conclusions Adding daily GTN ointment over 24 weeks to a 12-week eccentric exercise programme did not improve pain, function and activity level in patients with chronic mid-portion Achilles tendinopathy when compared with placebo ointment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Glyceryl trinitrate (GTN) is a drug which delivers nitric oxide (NO). Inhibition of NO has been shown to impair tendon healing, whereas the addition of NO has been shown to enhance tendon healing. Only two studies have specifically assessed the use of GTN to deliver NO in Achilles tendinopathy, yielding conflicting results.

⇒ This study was conducted using tendon-specific primary and secondary outcome measures to investigate if topical GTN in addition to an eccentric exercise programme could improve outcomes for patients with Achilles tendinopathy.

WHAT THIS STUDY ADDS

⇒ This is the first study to investigate GTN ointment in tendinopathy and the largest to date to investigate GTN in Achilles tendinopathy. Findings indicate that adding topical GTN ointment to an eccentric exercise programme does not yield any additional benefits in the treatment of Achilles tendinopathy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on this study's findings, topical GTN ointment is not recommended for patients with Achilles tendinopathy. Despite the robust study findings, there is still uncertainty surrounding the treatment effects. Currently, no optimal dosage of GTN in treating tendon pain has been established and future research could explore optimal GTN dosage and delivery methods for treatment of tendon pain.

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BACKGROUND

Achilles tendinopathy is persistent Achilles tendon pain associated with mechanical loading[1] and affects sporting and sedentary populations.[2] A spectrum of changes to the tendon including disorganised collagen bundles with fragmented collagen fibres, accumulation of glycosaminoglycans and increase in tendon microvasculature with associated neoinnervation are characteristic of tendinopathy.[3–5] In addition to the pain with activity, it is associated with significant psychosocial impact.[6] Tendon loading programmes are the primary treatment method for Achilles tendinopathy. However, success rates are variable,[7] and a high proportion of patients fail to respond adequately to loading, with one in three patients experiencing persistent long-term symptoms and functional deficits.[8] Consequently, exploring pharmacological adjuncts to bolster the response to loading is justified.

The benefits of nitric oxide (NO) in tendon healing have been clearly demonstrated in laboratory and animal studies.[9] Proposed mechanisms include vasodilation, increased local blood flow,

enhanced collagen synthesis and stimulation of tenocytes and extracellular matrix genes.[9] Glyceryl trinitrate (GTN) has been used as an NO donor for decades as a mainstay treatment for angina pectoris.[10] Despite the biological plausibility behind treating tendinopathy with NO via GTN, its exact role in treatment of tendon pain in human populations is somewhat unclear. A recent systematic review concluded there is good evidence for the effectiveness of GTN in the treatment of tendinopathies and suggested GTN should be considered, as an adjunct to loading programmes when less than satisfactory results are produced with exercise alone.[11] However, only two randomised controlled trials (RCTs) have investigated GTN for Achilles tendinopathy, reporting conflicting results.[12 13] All tendinopathy studies that investigated GTN thus far have used transdermal patches to administer GTN, cutting them to deliver the desired dosage. During the design phase of this trial, several issues surrounding the process of cutting patches were identified, cutting transdermal patches may result in dosage dumping, overdosage and decay of the drug contained within the patch.[14] In addition, there are concerns surrounding the storage of cut patches once removed from the foil container. Therefore, the exact dosage delivered in previous tendinopathy trials that used cut GTN patches is questionable. In addition, studies to date have used a 24-hour application of GTN, however, the effect of GTN can be attenuated or negated when used continuously, a phenomenon known as nitrate tolerance.[15]

Due to the variable success rates with Achilles loading programmes and conflicting results from GTN trials in Achilles tendinopathy to date, we aimed to determine the role of GTN as an adjunct to eccentric exercise, delivered by a topical ointment, rather than a transdermal patch, using intermittent (12–14 hours) exposure to minimise tolerance. In addition, we used a validated tendon-specific outcome measure alongside secondary outcomes to measure treatment response. The overall aim of this placebo-controlled RCT was to evaluate the effectiveness of daily treatment with GTN, delivered by topical ointment over 24 weeks, in addition to a 12-week eccentric exercise programme compared with a placebo topical ointment and 12-week exercise for individuals with chronic mid-portion Achilles tendinopathy.

METHODS

Study design

This single-centre placebo-controlled double-blind RCT study was conducted between September 2014 and October 2018 at the physiotherapy department in a large public hospital (Connolly Hospital), Dublin, Ireland. The study is reported in accordance with the Consolidated Standards of Reporting Trials guidelines[16] and the Template for Intervention Description and Replication checklist.[17] The study protocol was prospectively registered on ClinicalTrials.gov (ID: NCT02499484). There was no public or patient involvement in the design of this trial.

Participants

Inclusion criteria were current diagnosis of mid-portion Achilles tendinopathy, able and willing to give written informed consent and comply with study protocol requirements, aged ≥18 years, Achilles pain >3 months, palpable thickening and tenderness of the Achilles 2–6 cm proximal to the Achilles insertion and an ultrasound scan demonstrating hypoechogenic areas and a thickened tendon to confirm the diagnosis and to rule out a tear. Participants were excluded if they had a corticosteroid injection to the affected tendon in the past 3 months, symptoms <3 months, previous use of topical GTN therapy, contraindications to GTN therapy, current pregnancy, Victorian Institute of Sport Assessment (VISA) score >80 points, insertional Achilles tendinopathy, previous surgery to the affected Achilles tendon, seronegative spondyloarthropathy with Achilles enthesitis, performance of a heavy load Achilles eccentric exercise programme in the previous 3 months and inability to perform the exercise programme. Further eligibility criteria are in online supplemental file 1S. The principal investigator (PI, PDK) screened all participants for trial eligibility and enrolled participants following receipt of written informed consent.

Equity, diversity and inclusion statement

Our clinical trial was offered to all identified cases of chronic mid-portion Achilles tendinopathy who presented to a general public hospital in Dublin, Ireland. The trial participants included a spectrum of ages, genders, demographics and comorbidities and reflect the typical cohort of patients who suffer from Achilles tendinopathy in Ireland. The research team include one woman (academic supervisor) and two men (early career researcher/PhD student and clinical supervisor) all from Ireland. Authors' disciplines are physiotherapist and rheumatologist.

Randomisation and blinding

A computer-based randomisation list was prepared in advance of trial recruitment and conducted off-site by one of the study team (HPF), who was not involved in participant recruitment, assessment or treatment. Participants were randomly assigned to either GTN or placebo groups using 1:1 allocation, in block sizes of 6. Group allocation was communicated by the randomiser to a member of the research team (TD), a consultant rheumatologist, who prescribed and distributed the medication (GTN or placebo ointment). The PI and participants were blinded to the allocation of GTN or placebo ointment.

Medication tubes were prepared to blind participants by completely obscuring any details of the medication tube contents. Participants were advised not to bring the medication tubes to any appointments, with the exception of the final assessment when the tubes were returned. The medication tubes were inspected by the PI (PDK) on trial completion, to verify no tubes were tampered with, to assess participant blinding.

Interventions

Exercise intervention: Alfredson protocol

All participants received a 12-week home-based eccentric calf muscle exercise programme.[18] This eccentric programme was selected over others as it allowed for all participants to perform the same standardised Achilles rehabilitation routine, the heavy slow resistance programme was not considered as evidence of effectiveness was published after this trial was designed.[19] A written manual was provided, outlining the details of the exercise protocol. The exercise programme consisted of two exercises that loaded the calf muscle eccentrically, one exercise performed with a straight knee and one with bent knee. Both were to be performed twice per day, 7 days a week, for 12 consecutive weeks. Participants were instructed to perform three sets of 15 repetitions of each exercise, maintaining the eccentric contraction for at least 3 s, returning to full plantarflexion using the uninvolved limb. Participants who were unable to complete 15 repetitions were advised to do 3 sets of as many as possible and to build up to performing 15 repetitions and 3 sets. Those who could not perform single-leg eccentric exercise were advised to start with bilateral exercise and transition to unilateral exercise when able. From week 12 onwards, participants were advised to

continue the same exercise programme, 2–3 times per week as a maintenance routine. The pain monitoring guidelines described by Silbernagel *et al*[20] were followed.

Once the full set of exercises could be performed with no pain, participants were advised to add load by wearing a backpack and adding 5 kg to the pack. The goal was to add weight in 5 kg increments to keep the exercises challenging while maintaining pain within acceptable limits (≤5/10).[21] Continued participation in sports was allowed once pain did not increase >5/10, settled promptly on exercise cessation, with no increase in Achilles morning pain and/or stiffness. Participants not involved in sports at baseline were advised to refrain from tendon loading sporting activity in the initial 4–6 weeks to allow time to adapt to the increase in load from the exercise programme, after which time a gradual return to sports was encouraged. They could continue to perform other sporting activity in the initial 4–6 weeks such as swimming, cycling or gym-based exercises but to avoid running/jumping sports. An increase in either exercise session time or intensity by 10%–15%, but not both, was permissible.[22] Participants were advised not to change their typical daily footwear until their Achilles pain improved and to avoid barefoot walking or flat footwear.

Application of GTN and placebo ointment

Participants randomised to the GTN group received topical GTN ointment (Percutol, Aspire Pharma, UK). It was not possible to use altered or cut transdermal GTN patches for the purpose of this trial, in line with European Union regulations. Local application of GTN ointment has been shown to be as effective as patches for NO delivery.[23] The placebo ointment was a tube of aqueous cream, which contained no ingredients that would aid in tendon recovery. Application of both ointments was identical. Participants were provided with a medication pack, which included a tube of ointment, paper applicator sheets, adhesive tape (figure 1) and instructions on how to apply the ointment. They were instructed to squeeze the ointment from the tube so that the shaded circular area, measuring 0.5 cm in diameter, on the paper applicator was covered with ointment (figure 1A, B), approximately the size of a pea. This was the smallest measurable dose and corresponded to one daily dose of GTN (2.8–3.4 mg) or placebo ointment. Participants placed the paper onto the painful area of the affected Achilles tendon with the ointment contacting the skin, using the paper to lightly spread the ointment to cover the painful area of the tendon, but not to rub it into the skin. Participants were advised to apply the ointment within 1–2 cm of the site of maximal tenderness of the Achilles tendon and to rotate the ointment about this site over the 24-week treatment duration to minimise skin irritation. The paper applicator was then covered with adhesive tape to secure the ointment and paper applicator in place (figure 1C).

To minimise the likelihood of participants developing nitrate tolerance, the ointment was to be applied in the morning after wakening and/or showering and left in situ for daytime hours (12–14 hours). After 12–14 hours, participants discarded the adhesive tape and the attached applicator strip. It was emphasised to place the ointment onto the affected Achilles during waking hours and in particular to have the ointment on the skin for the home exercise programme sessions, which were performed twice per day. Participants who had bilateral Achilles tendinopathy applied the ointment only to the most painful side and completed the exercises on both sides.

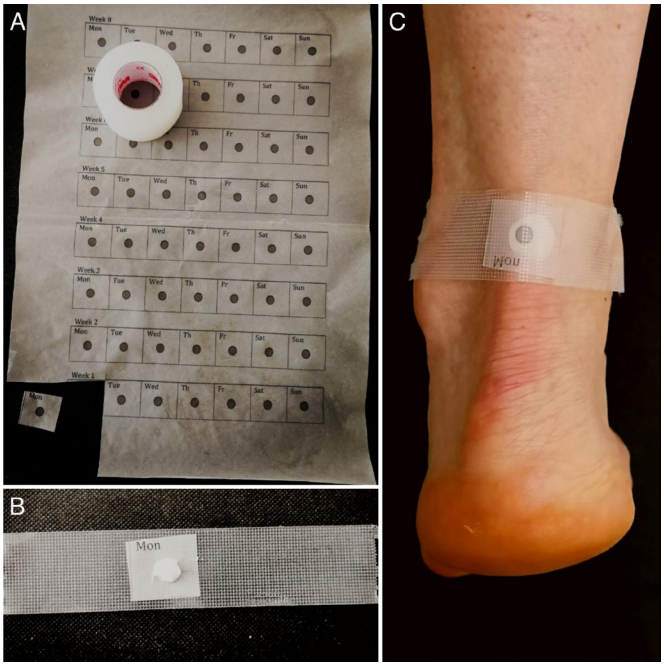

Figure 1 Measurement and application of ointment.

Outcomes

The primary outcome was the Victorian Institute of Sport Assessment–Achilles (VISA-A) questionnaire. This valid, reliable self-administered questionnaire evaluates pain, function and activity on a scale of 0–100, with lower scores representing greater clinical severity.[24] It is the gold standard for assessing pain and function in Achilles tendinopathy.[25]

Secondary outcomes included the following.

1. Severity of pain, measured on the Quadruple Visual Analogue Scale (VAS), which includes four components: pain right now, average pain, pain at its best and pain at its worst, scored on a 0–10 scale. Pain at its worst was used for analysis.
2. Lower Extremity Functional Scale (LEFS) is a self-report valid and reliable measure of functional ability suitable for use in lower extremity musculoskeletal conditions.[26] Scores range from 0 to 80, with higher scores indicating better function.
3. Pressure pain threshold (PPT), the first point at which pressure applied to the tendon becomes pain,[27] was measured using a pressure algometer with a 1 cm^2 rubber tip (Wagner Instruments, Greenwich, Connecticut, USA). The mean of three readings was used for analysis.
4. Calf muscle function was assessed using two tests
   a. The standing heel raise to endurance test is performed in a single-leg-stance position, rising into plantarflexion with the knee straight at a set pace of one complete repetition every 2 s, for as many repetitions as possible.[28] The number of heel raises completed and any pain associated with the test were recorded.
   b. Calf muscle function was also assessed with a hopping test.[28] This entails hopping on one leg for as many repetitions as possible, with termination of the test if there was an increase in pain severity or until fatigue. The number of hops completed and any pain associated with the test was recorded.
5. The Y balance test (YBT) was used to assess dynamic balance and postural control.[29] The reach distance in centimetres was divided by the participant's limb length to give a score ex-

pressed as a percentage of lower limb length. The mean of three trials was used for analysis.

6. Ultrasound anteroposterior thickness measures: The thickest point (anterior to posterior (A-P) distance), of the tendon was measured. The mean score of three thickness measures was used for analysis. (online supplemental file 2S).

All outcome measures were collected at baseline, 6, 12 and 24 weeks by a blinded outcome assessor (PDK). For those with bilateral tendinopathy, the most affected side was assessed and used in statistical analysis.

Intervention adherence

Adherence to the exercise programme and daily ointment application was monitored using a self-report exercise diary over 12 weeks and self-report drug diary over 24 weeks. Diaries were completed by participants in paper format and returned to the blinded outcome assessor (PDK) at 12 weeks for the exercise diary and at 24 weeks for the drug diary. Exercise adherence was reported as a percentage of the total number of prescribed exercise sessions completed. Drug adherence was reported as a percentage of the total number of daily applications of ointment completed.

Adverse events

Adverse events were classified as serious or non-serious and recorded on a standardised adverse events form, completed at 6, 12 and 24 weeks, by the blinded assessor (PDK).

Sample size

The sample size was based on the primary outcome (VISA-A).[24] We estimated, based on previous research,[30] that those in the GTN group would score 9 points higher at 24 weeks compared with the placebo group. The SD was estimated at 11 points. Therefore, a sample of 33 per group was required, with 90% power and an alpha of 0.05 (two tailed). To account for a 15% loss to follow-up at 24 weeks, this increased the sample size to 38 per group, thus requiring a total sample size of 76 participants.

Statistical analysis

All statistical analyses were performed on an intention-to-treat basis, using IBM SPSS V.26. Missing data were replaced using the last observation carried forward.[31] All continuous data were explored for normality. Data were presented as means, SD or 95% CIs for normally distributed continuous variables, median and IQR for non-normal continuous data and as frequency and percentages for ordinal and categorical data. For continuous variables, linear regression was used to analyse between-group differences at 6, 12 and 24 weeks, adjusting for any baseline between-group differences. General linear repeated measures analysis was used to assess changes over time within each group. Within-subject variables selected were the outcome measure at each time point, and the between-subject factor was group allocation (GTN or placebo). Pairwise comparisons were conducted using Bonferroni adjustment to determine any significant improvement in the mean outcome measure scores at each time point in the GTN group and the placebo group. P values <0.05 were considered statistically significant.

Protocol deviations

There were several protocol deviations from the trial registration. Exercise and drug diaries were included to monitor adherence. Quadruple VAS was selected over NRS to capture the variable nature of Achilles tendon pain. The sample size reverted from a larger sample size of 240 participants to the original smaller sample size of 76. This was due to delays launching the trial, due to the aforementioned concerns surrounding cutting transdermal patches. The trial was only allowed to proceed with the use of GTN ointment in lieu of transdermal patches.

Table 1 Baseline characteristics of the GTN, placebo group and all trial participants

	GTN (n=37) Mean±SD	Placebo (n=39) Mean±SD	All participants (n=76) Mean±SD
Age (mean±SD years)	44.4±9.18	46.7±7.19	45.6±8.2
Number of females (%)	16 (43)	14 (36)	30 (39)
Height (mean±SD cm)	170.5±17.4	174.4±9.86	172.5±14.1
Body mass (mean±SD kg)	81.4±13.97	82.2±14.84	81.78±14.3
BMI (mean±SD kg/m^2)	27.2±3.98	27.0±4.29	27.1±4.1
Duration of symptoms (mean±SD months)	37±51.9	29±41.58	33±46.8
Number with unilateral symptoms (bilateral symptoms)	29 (8)	25 (14)	54 (22)
Activity per week, before injury (mean±SD days/week)	5.5±2.21	5.3±1.94	5.4±2.1
Activity per week, before injury (mean±SD min/week)	330±165.84	349±168.87	340±166.5
Comorbidities, number of participants (%)			
HTN	5 (14)	2 (5)	7 (9)
Hypercholesterolaemia	4 (11)	2 (5)	6 (8)
Type II DM	0 (0)	1 (3)	1 (1)
Smoking	1 (3)	0 (0)	1 (1)
Ethnicity, number of participants (%)			
Caucasian	36 (97)	39 (100)	75 (99)
Afro-Caribbean	1 (3)	0 (0)	1 (1)
Asian	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)
Previous treatment, no. of participants (%)			
CSI>3 months before recruitment	1 (3)	2 (5)	3 (4)
HVI	0 (0)	1 (3)	1 (1)
Night splint	0 (0)	1 (3)	1 (1)
PRP	0 (0)	1 (3)	1 (1)

BMI, body mass index; CSI, corticosteroid injection; DM, diabetes mellitus; GTN, glyceryl trinitrate; HTN, hypertension; HVI, high-volume injection; PRP, platelet rich plasma injection.

RESULTS

Participants

Between September 2016 and May 2018, 76 participants (30 women, 46 men; mean age±SD, 45.6±8.2 years; mean BMI±SD, 27.1±4.1 kg/m^2; mean duration of symptoms±SD, 27.1±4.1 months) were recruited to the trial, 37 participants to the intervention group and 39 to the placebo group. Baseline characteristics were similar in both groups (table 1). Retention was 95% at week 6 and 12 (n=72) and 87% at week 24 (n=66). Figure 2 shows the participant flow through the trial and reasons for drop-out. 10 participants were lost to follow-up, 4 in the GTN group and 6 in the placebo group.

Primary outcome measure

At 24 weeks, there was no between-group difference in VISA-A scores. Both groups displayed significant improvements in VISA-A scores at each time point (figure 3), with no statistically significant difference between groups at any time point

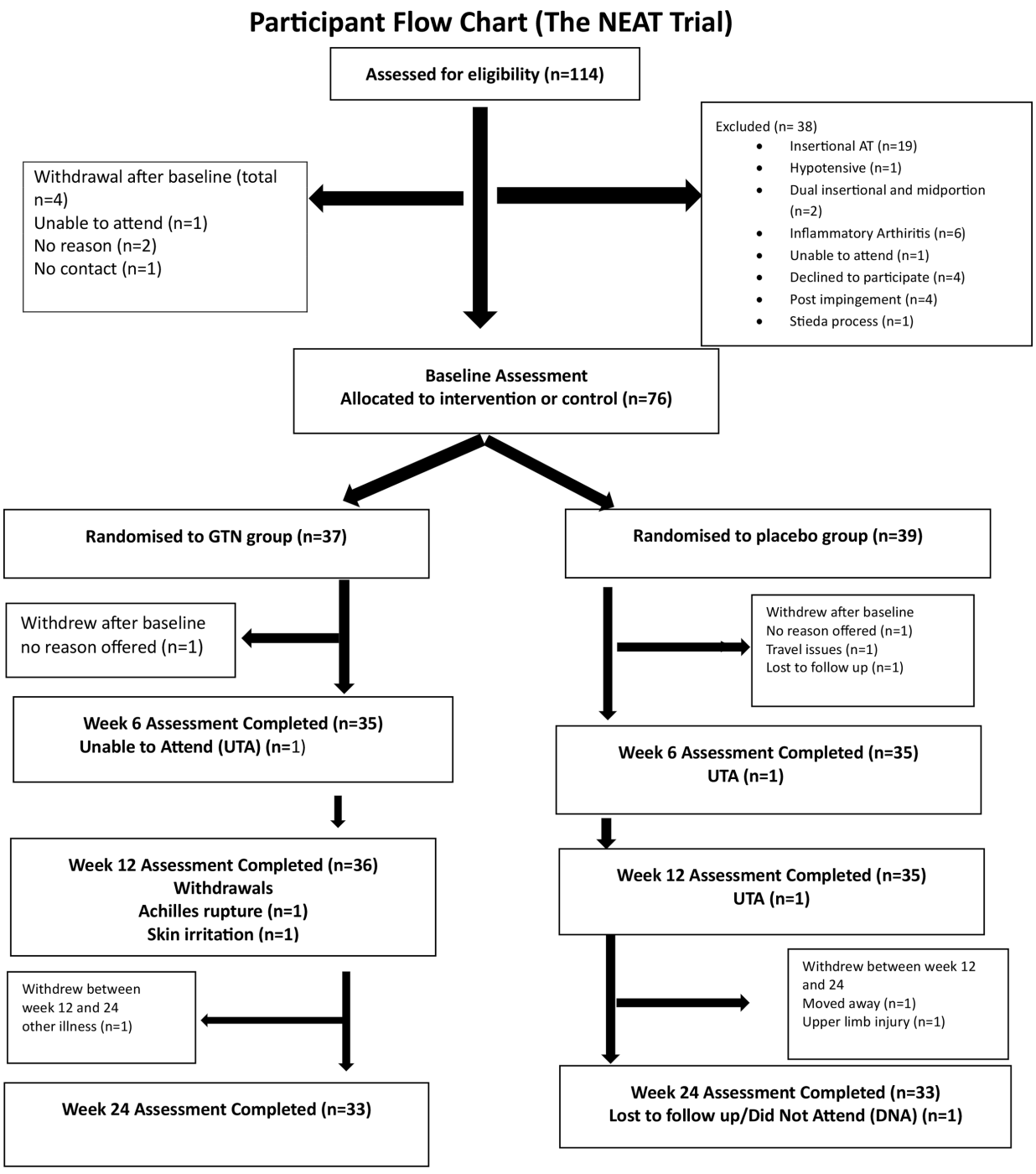

Figure 2 Flow of participants through the NEAT RCT. GTN, glyceryl trinitrate; RCT, randomised controlled trial.

(tables 2 and 3). Mean VISA-A scores improved by 20.6 points (95% CI 13.63 to 27.61) in the GTN group at 6 weeks and by 17.62 points (95% CI 12.94 to 22.92) in the placebo group. At 12 weeks, there was a further 11.19 point mean improvement (95% CI 6.27 to 16.1) in the GTN group and a further 10.41 point mean improvement (95% CI 4.84 to 15.98) in the placebo group. At week 24, the GTN group improved further by a mean of 8.16 points (95% CI 3.77 to 12.55) and the placebo group further improved by 4.95 points (95% CI 1.14 to 8.75).

Secondary outcomes

There was no statistically significant difference between groups in the LEFS, heel raises to endurance, hopping test, PPT, ultrasound measure or YBT at any time point (table 3). At week 6, there was a statistically significant improvement in VAS of 1.15 points (95% CI −2.23 to −0.07, p=0.037) in favour of the placebo group.

Adherence

Exercise diaries were returned by 59 (82%) of the 72 participants who attended for 12-week assessment. Full adherence to the exercise protocol amounted to 84 consecutive days of eccentric exercise completed, and 168 total sessions completed. The mean exercise adherence rate was 87% for the GTN group, and 89% for the placebo group, only five participants completed less than 75% of the exercise protocol.

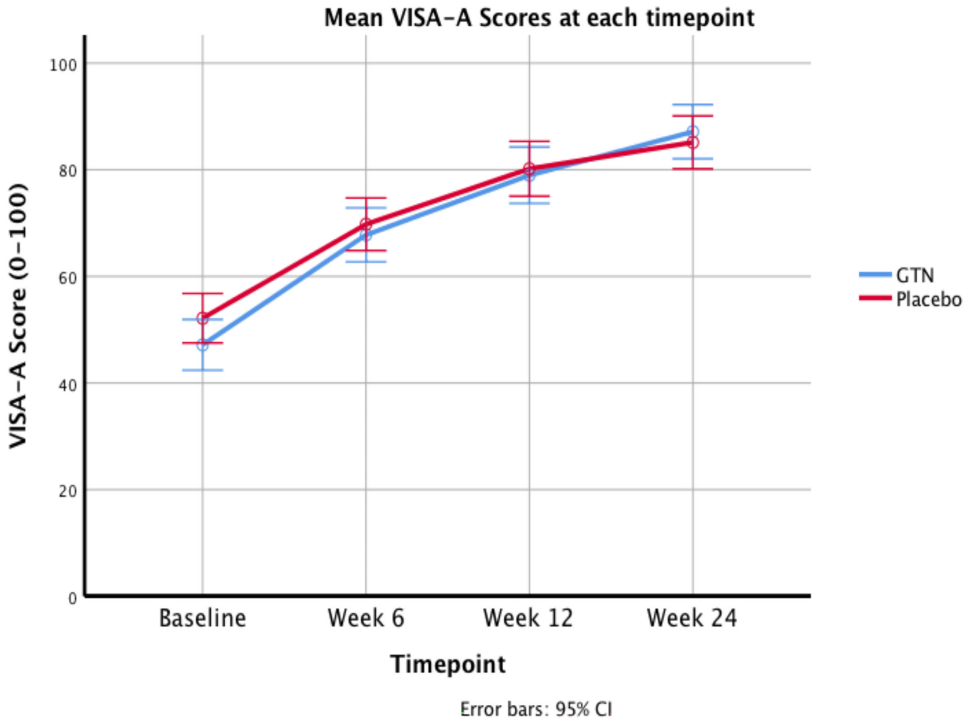

Figure 3 Mean VISA-A scores between the two groups over the four time points. VISA-A, Victorian Institute of Sport Assessment–Achilles.

Drug diaries were returned by 54 (82%) of the 66 participants who attended for 24-week assessment. The mean drug adherence rate was 91% for all participants (93% for the GTN group and 90% for the placebo group).

Adverse events

A total of eight adverse reactions were reported, six in the GTN group and two in the placebo group (online supplemental file 3S,4S). Headache was reported by two participants (5%) in the GTN group and two (5%) in the placebo group. The duration of headaches ranged from 1 day to 1 week, all headaches resolved and none required treatment or trial withdrawal. Skin irritation was reported by three participants in the GTN group. Two of these were of short duration, ranging from 5 days to 2 weeks and resolved. One participant was withdrawn from the trial following the week 12 assessment due to persistent skin irritation. No cases of skin irritation were reported in the placebo group. Adverse events unrelated to the drug/medication occurred in six participants. One serious adverse event unrelated to the trial intervention occurred, a patient ruptured their Achilles in a fall (online supplemental file 3S–5S).

Table 2 Mean changes in VISA-A from baseline to all follow-up time points

VISA-A score improvement from baseline, mean (SD)	Week 6	Week 12	Week 24
GTN group	20.62 (15.23)	31.81 (16.94)	39.97 (18.35)
Placebo group	17.62 (10.5)	28.03 (15.47)	32.97 (16.27)
Adjusted between-group mean differences (95% CI)*	−1.33 (−6.96 to 4.31)	−1.25 (−8.0 to 5.49)	−3.80 (−10.63 to 3.02)
Significance†	P=0.64	P=0.71	P=0.27

*Adjusted for baseline VISA-A scores.
†Statistically significant between-group at p<0.05.
GTN, glyceryl trinitrate; VISA-A, Victorian Institute of Sports Assessment-Achilles.

DISCUSSION

The results of this trial showed no benefit from adding topical GTN to an eccentric programme for adults with mid-portion Achilles tendinopathy. This is the first double-blinded randomised placebo-controlled trial to investigate GTN ointment in the treatment of AT. The primary outcome measure, the VISA-A score, improved significantly in both groups at all time points, with no significant between-group difference at any of the three follow-ups. At week 24, the change in VISA-A from baseline differed between groups by 7 points (table 2) which has been reported as the minimally clinically important difference[32] but after adjusting for baseline differences this was not significant. This finding was supported by the results from secondary outcomes, which also showed no significant between-group differences, although both groups displayed significant improvements in VAS, LEFS, calf muscle endurance, hopping capacity, PPT and YBT.

Direct comparison of the results from the NEAT trial with the two previous trials of GTN is limited as no previous trial used the VISA-A to measure intervention effects. The two previous RCTs that have investigated the effect of GTN in AT found conflicting results.[12 13] Our trial results are in agreement with the findings reported by Kane *et al*.[12] Comparison with their study is limited as they used a different outcome measure, assessed participants at one time point (24 weeks) and used a cut patch to apply daily GTN. In addition, their trial did not include a placebo control, assessment of physical outcomes or adherence monitoring.

The only other trial to investigate GTN in AT found results in support of GTN[13] thus contradicting our results. This well-designed, randomised, double-blind placebo-controlled trial[13] with a low risk of bias[11] had similar eligibility criteria, age profile and exercise programmes to ours. It is not clear why the two trials yielded different results, but the different outcome measures selected is one possibility. The verbal rating scale of pain used by Paoloni *et al*[13] is a 5-point verbal descriptor of pain severity at rest, at night and with activity. While it has been validated as

Table 3 Results of primary and secondary outcomes for GTN and Placebo groups at baseline, weeks, 6, 12 and 24

	Baseline		Week 6		Week 12		Week 24	
	GTN	Placebo	GTN	Placebo	GTN	Placebo	GTN	Placebo
	(n=37)	(n=39)	(n=37)	(n=39)	(n=37)	(n=39)	(n=37)	(n=39)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
VISA-A (0–100)*	47.16±14.54	52.15±14.51	67.78±14.99	69.77±15.89	78.97±14.43	80.18±17.55	87.14±13.99	85.14±16.82
LEFS (0–80)*	53.7±15.37	58.18±14.03	61.7±12.49	65.03±12.13	68.65±9.05	68.54±13.02	72.89±9.96	71.95±10.25
VAS (worst) (0–10)†	7.62±1.769	7.54±2.4	5.51±2.51	4.33±2.39	4.11±2.44	3.62±2.83	3.22±2.88	2.90±2.88
Heel raises, number performed*								
Affected side	16.68±8.625	18.23±9.4	23.84±8.22	28.67±14.9	26.38±9.36	29.77±10.3	28.19±10.3	31.64±13.6
Unaffected side	22.78±8.45	24.51±8.8	26.11±6.89	31.0±11.71	26.84±8.12	29.9±12.04	28.73±8.81	33.28±15.58
Hops, number performed*								
Affected side	15.14±16.01	25.26±22.56	46.11±32.37	63.28±40.08	66.68±40.75	73.49±48.07	77.65±42.85	79.85±42.2
Unaffected side	49.62±32.53	63.69±40.417	63.38±34.16	76.18±40.88	66.62±36.78	88.39±47.27	75.35±42.02	85.85±42.27
US thickness, mm								
Affected side	7.97±2.66	7.90±1.93	7.80±2.52	7.84±2.55	7.85±2.55	8.02±2.22	7.78±2.44	7.92±2.21
Unaffected side	5.98±1.56	6.22±1.48	6.12±1.52	6.23±1.42	6.15±1.58	6.25±1.43	6.18±1.55	6.22±1.31
PPT, kgf*								
Affected side	3.27±1.63	3.18±1.638	4.61±2.21	4.49±2.56	5.73±2.83	5.27±2.82	6.31±2.98	5.94±2.92
Unaffected side	6.22±3.03	6.55±2.87	6.72±2.78	7.11±2.58	7.43±2.97	7.66±2.51	7.82±2.67	8.15±2.36
YBT anterior reach *								
Anterior reach affected side	58.7±8.5	61.8±6.3	61.6±7	63.4±5.8	62.3±8.4	63.7±6.8	62.6±8.4	64.2±6.6
Anterior reach unaffected side	59.7±8	62.82±5.89	61.8±7	63.7±5.5	62.24±8.7	64.13±5.4	62.32±9	63.8±6.77
YBT posteromedial reach*								
Affected side	89.4±11.1	93.9±9.6	94.6±9.5	96.3±10.4	94.1±8.7	97.7±10.9	98.7±10.7	98.7±10.2
Unaffected side	90±9	94±9.7	94±8.3	97±9.9	95±9.7	98±10.2	97±10	99±9.9
YBT posterolateral reach*								
Affected side	78.2±13.2	84.1±12.5	85.1±10	87.9±12.3	86.3±9.1	89.1±12.1	88.7±9.2	90.2±12.7
Unaffected side	80±13	85±12.8	85±10.5	89±12.4	86±8.6	89±11.8	88±9	90±12

Data are presented as mean±SD unless otherwise specified.
*A higher score as better/improvement.
†A lower score as better/improvement.
LEFS, Lower Extremity Functional Scale; PPT, pressure pain threshold ; US, ultrasound; VAS, Visual Analogue Scale; VISA-A, Victorian Institute of Sports Assessment-Achilles questionnaire; YBT, Y balance test.

a pain scale it is not tendon-specific. They also measured the degree of tenderness, pain severity after completing ten single-leg hops and ankle plantar flexor peak and maximum torque. Their study found improvements in the GTN group with decreased pain with activity at 12 and 24 weeks, decreased night pain at 12 weeks, reduced tenderness at 12 weeks, decreased pain after the hop test at 24 weeks and increased ankle plantar flexor mean total work at 24 weeks. Our trial found no difference between groups at any time point using a selection of outcome measures. The different outcomes used in the two studies limits direct comparisons of results.

The different dosage and delivery method of GTN used in the NEAT trial may also account for these conflicting results. It is possible that intermittent GTN ointment delivered over 12–14 hours may have resulted in subtherapeutic dosage and might offer a possible explanation for the different results obtained when compared with the successful response to GTN with 24-hour exposure. Common side effects of GTN include headache and skin irritation. Paoloni *et al*[13] reported higher numbers of side effects, with 53% of the GTN group and 45% of the placebo group reporting headache resulting in 5%–8% of participants stopping treatment due to either rash or headache, whereas fewer side effects were reported in the NEAT trial, with 5% reporting headache. This smaller number of side effects in our trial may indicate that NO levels were too low to provide a therapeutic effect.

Approximately one in five of the NEAT trial participants failed to return their exercise and drug diaries and therefore their adherence with the ointment and exercise is unknown. Drawing conclusions on the effect of treatment with no measure of adherence is challenging. Adherence to the trial medication and exercise was reported as excellent by Paoloni *et al*,[13] although no specific adherence results were provided, limiting comparisons to our trial.

Adding the findings from the NEAT trial to the existing evidence, three studies of lower limb tendinopathy do not support GTN,[12 30] compared with one trial, which found GTN beneficial for lower limb tendinopathy.[13] To date, five RCTs, which investigated GTN in upper limb tendinopathy, found favourable results in support of using GTN.[33–37] This indicates that upper limb tendons may respond favourably to GTN compared with lower limb tendons. A definitive explanation for why lower limb tendinopathy appears more recalcitrant to GTN is not currently available but varied methodologies, outcome measures and GTN dosage and delivery methods may explain the different responses.

While we found no between-group differences, improvements at weeks 6, 12 and 24 occurred across all outcomes in both groups. These favourable clinical outcomes are likely in response to eccentric exercise, advice and education, and further add to the evidence in support of loading in the treatment of Achilles tendinopathy. Recent studies have demonstrated benefits from

other modes of contraction, and it is no longer suggested that isolating the eccentric component is integral to treatment success.[19 21 38–40] Consequently, clinicians can continue to recommend and prescribe loading programmes, including eccentric exercise, for Achilles tendinopathy.

The beneficial effect of exercise in treating tendinopathy is recognised, yet the underlying mechanisms are not fully understood.[41] The release of NO as a result of exercise might provide an explanation for the mechanism underpinning how exercise improves symptoms of tendinopathy that as of yet has not been explored. Exercise can elicit an increase in NO formation[42] in humans[43] that can remain elevated for several weeks.[44] It is possible that the eccentric exercise protocol performed by all NEAT trial participants provided an increase in plasma NO that was adequate for improvement of tendinopathy symptoms, and the supplementation with GTN provided additional, but unnecessary, levels of NO. While this is speculative, it merits investigation and would explain similar results in both placebo and GTN groups.

The lack of change in tendon structure, as measured by ultrasound AP diameter, at all time points, adds further evidence in support of findings from previous systematic reviews[45 46] that clinical improvements in Achilles tendinopathy are not associated with a change in tendon structure up to 24 weeks.

In light of our incomplete understanding of tendon pathophysiology, the study of GTN is warranted, as basic science, animal and human studies have confirmed NO as an important chemical messenger in tendon pathology and repair.[9] Research findings suggest NO can enhance extracellular matrix synthesis with the potential to improve tendon material and mechanical properties,[47] yet the effectiveness of GTN in tendinopathy remains unclear.

Clinical implications

Although three systematic reviews have concluded that GTN is potentially beneficial in treating tendinopathy,[11 48 49] our results do not support the use of topical GTN ointment in treating Achilles tendinopathy. Our findings are important and clinically relevant, as a large portion of patients who present with Achilles tendinopathy fail to make an adequate recovery with exercise interventions alone and symptoms persist in up to a quarter of patients 10 years after treatment.[50]

Study strengths and limitations

This is the largest trial to investigate GTN in Achilles tendinopathy to date. The primary outcome (VISA-A) is recognised as the only validated and reliable measure to assess pain and function in mid-portion Achilles tendinopathy.[28] This is also the first known RCT to investigate the delivery of GTN in tendinopathy using an ointment, rather than patches. It is also the first trial of GTN in Achilles tendinopathy to monitor and report adherence to the drug and exercise programme and to assess a range of health-related domains, which align with the core domains recommended for use in tendinopathy.[51] The trial used rigorous methodology including independent off-site randomisation, allocation concealment, blinding of participants and assessor, validated outcome measures and intention-to-treat analysis. The PI was an experienced musculoskeletal physiotherapist who was able to effectively screen patients for eligibility.

Some issues surrounding the application of GTN with cut transdermal patches were identified in our trial planning, which had not been discussed in previous RCTs. These related to GTN delivery, particularly the safety, storage, dosage and mode of GTN used in previous trials. We chose to use GTN ointment as a stable medium to store and deliver GTN, thereby avoiding the numerous issues surrounding the process of cutting patches. The NEAT trial attempted to minimise nitrate tolerance by recommending a 'nitrate holiday', whereby patients were recommended to remove the medication at night.[52] This differs from previous trials of GTN to date that have recommended daily 24-hour GTN.

There were some limitations in this study. First, optimal dosage of GTN in treatment of tendinopathy has not been established. The current dosage was selected to minimise possible side effects, future research should take this into consideration prior to further clinical trials being conducted. Also, no histological examination or tissue sampling was performed to analyse for the presence of increased NO levels or surrogate markers of NO activity. No statistical analysis plan was outlined in the trial protocol. No measure of participant general well-being, or psychological health was included in this trial, as recommended in the recently published guidelines for conducting clinical trials in tendinopathy[51] published after NEAT trial recruitment commenced. Exercise and drug diaries were not included in the original protocol but were used to capture adherence data. We reverted to the original sample size of 76 participants from a larger sample size. This should be kept in consideration when interpreting the results as there is a possibility of a type 2 error where an effect may have been missed.

CONCLUSION

The results of this placebo RCT do not support the use of topical GTN ointment in the treatment of chronic mid-portion Achilles tendinopathy. While improvements were obtained at 6 weeks and further improvements occurred at 12 and 24 weeks, the addition of GTN did not result in further improvements in clinical outcomes.

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