Topical Nitroglycerin in Treatment of Plantar Fasciitis

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ABSTRACT:

BACKGROUND:

Planter fasciitis is the most common cause of inferior heel pain in adults; it is a degenerative process of the planter fascia at its origin on the calcaneus. Many treatment modalities are used including $NSAID_s$, orthotics, local steroid injection, extracorporeal shock wave therapy and others. Recent studies have shown that topical nitroglycerin has a healing and analgesic effect in other tendinopathies like: tennis elbow, suraspinatus tendinitis and Achilles tendinitis.

OBJECTIVE:

We want to establish the role of topical nitroglycerin in treatment of plantar fasciitis.

PATIENTS AND METHODS:

A double blind placebo controlled study included 54 patients, after taking medical history they were subjected to physical examination. Nitroderm TTS^R 5 patches were used in the treatment group, similar placebo patches were used in the placebo group. The severity of the symptoms was quantified initially for each patient using the visual analogue scale (VAS). By using SPSS (statistical package for social sciences) software for windows, data of all patients were entered and analyzed with appropriate statistical tests according to the types and distribution of variables (Chi square test and Students't test).

RESULTS:

Response to topical treatment was (76.7%) in the GTN group most of them with moderate and good response compared to (41.7%) in placebo group most of them with mild response.

CONCLUSION:

It was clear that NGT patches were superior to placebo patches in improving the symptoms of patients, so that topical NGT can enhance healing of planter fasciitis. This may be a useful alternative to the current modalities of treatment used for this common

KEY WORDS: topical nitroglycerin, plantar fasciitis, calcaneal spur condition.

INTRODUCTION:

Plantar fasciitis (PF) is a degenerative syndromeof the plantar fascia resulting from repeated trauma at its origin on the calcaneus.[(1)] PF is reported to be the most common cause of inferior heel pain in adults[(2)]. The word "fasciitis" assumes inflammation is an inherent component of this condition. However, recent research suggests that some presentations of PF manifest non-inflammatory, degenerative processes and should more aptly be termed "plantar fasciosis."[(3,4)]PF affects individuals regardless of sex, age, ethnicity, or activity level. It is seen in physically active individuals such as runners and military personnel, but is also prevalent in the general population, particularly in women ages 40-60years.[(2,5,6)] Planter fascia provides support of the longitudinal arch and serves as a dynamic shock absorber for the foot and entire leg.[(7)] While this condition can occur in association with various arthritides, the etiology is unknown in approximately 85 percent of cases.[(8)] Risk factors include: obesity,[(8)] sportings,[(9)] alterationsin gait and anatomy of foot[(1,6,8,10,11,12,13)] and heel spurs [(14)]. Diagnosis of PF is usually made on the basis of history and physical examination. Pain on first rising in the morning is typical of PF, and may be helpful in distinguishing it from other forms of heel pain. For example, in the case of a calcaneal stress fracture or nerve entrapment, pain would actually increase with more walking, rather than diminish after the first few steps.[(2,9)] Associated paresthesia is not a common characteristic of PF.[(6)] Nocturnal pain should raise suspicion of other causes of heel pain, such as tumors, infections, and neuralgia (including tarsal

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tunnel syndrome).[2] PF is usually unilateral, but up to 30 percent of cases have a bilateral presentation.[6] Bilateral disease in young patients may indicate Reiter's syndrome, so this group of patients should also be questioned about other features of seronegative arthritides.[2] Physical examination presents with localized tenderness at the antero-medial aspect of the calcaneus. Pain may be exacerbated by passive dorsiflexion of the toes or having the patient stand on the tips of the toes.[9] Tightness of the Achilles tendon (with dorsiflexion at the ankle limited by 5^{o} or more) is found in almost 80 percent of patients.[2] Diagnostic imaging is rarely indicated for initial evaluation and treatment, but may be helpful in certain cases to rule out other causes of heel pain. Plain radiographs can rule out calcaneal stress fracture and may detect an underlying spondyloarthropathy. [6] Bone scans, magnetic resonance imaging (MRI), and ultrasonography may also serve useful, but are not routinely used.[6,15] Treatment of PF may include: rest and avoidance of aggravating factors,[2,6,9,38] proper shoe,[9,38] arch support and orthotics,[39,40,41,42] stretching and strengthening exercies,[9, 38] splinting and walking casts,[6,9] anti-inflammatory agents,[11, 43,44] extracorporeal shock wave therapy[45- 48] and finally surgical treatment should be considered only after all other forms of treatment have failed.[1,9,49] Nitric oxide (NO) is a small soluble gas synthesized by a family of enzymes, the nitric oxide synthases (NOSs). Like other free radicals, in large doses NO is toxic. In smaller, physiological doses, however, it acts as a messenger molecule. The family of NOSs consists of three isoforms regulated by a number of cofactors. eNOS (originally found in endothelial cells[16]) and bNOS (originally identified in brain and neuronal tissue[17]) are constitutive, low-output isoforms important in blood pressure regulation and memory. Inducible NOS (iNOS) is a high-output isoform important in host defence.[18,19] Experimental studies have shown up-regulation in production of NO in damaged tendon.[20.21,22,23,24,25,26] Similar NOS_s up regulation occurred after human rotator cuff tendon injury[27].

It was found that iNOS alone is not responsible for the beneficial effects on tendon healing.[28] Experiments identified NO to be important in collagen synthesis,[29] cellular adhesion in tenocytes[30] and on collagen organization and tendon healing[31,32].

AIM OF THE STUDY:

To study the potential therapeutic effects of Nitroglycerin patches in the treatment of Plantar fasciitis.

MATERIALS AND METHODS:

The double blinded placebo controlled study included 54 patients, 30 in the treatment group (20 females and 10 males) and 24 in the control group (18 females and 6 males), Nitroderm TTS^{R} 5 patches were used in the treatment group, a multiple layers patch with a reservoir of about 25 mg nitroglycerin (NTG) as liquid creamy material, that supplies the patient percutaneously 5 mg NTG through a permeable membrane over 24 hours. The same patches were used in the placebo group, after removing the active ingredient. A medical history taken from and physical examination done for each patient, patients with allergy to nitrates, hypertension, anemia, coronary artery disease, dehydration, pregnancy, breast-feeding were excluded.

Patients were instructed to use the patches daily, for 24 hours a day, for 2 weeks, putting the patches at the area of maximum tenderness. Male patients were warned not to use drugs that enhance penile erection during the 2 weeks of treatment.

The severity of the symptoms was quantified initially for each patient using the visual analogue scale (VAS), this helped us to determine degree of decrement in severity of pain at the early morning after two weeks of treatment, those with less than 25% in reduction of pain severity were considered to have mild response, while those with 25% to less than 50% and patients with 50% or more were considered to have moderate and good response respectively. An X- ray film (lateral view) for each foot was taken to look for a calcaneal spur.

By using SPSS (statistical package for social sciences) software for windows, data of all patients were entered and analyzed with appropriate statistical tests according to the types and distribution of variables.Chi square test was used to compare in between groups in nominal and ordinal variables (Sex, age groups, presence of spur and previous treatment). Students't test (independent 2 sample test) was used to compare in between both groups in means of continuous variable (age, BMI, length of spur, duration of symptoms). Level of significance P. value ≤ 0.05 considered as significant difference and $P \leq 0.01$ considered as highly significant. Finally data and results were summarized and presented in tables and figures and a valuable interpretation and explanation had been written.

RESULTS:

There were 54 patients all with plantar fasciitis; they were divided into two groups: Treatment group (30) patients and Placebo group (24) patients.

The mean age was (43.6 ± 9.6) years in treatment group and (43.2 ± 9.2) years in placebo group. The distribution of age groups among study groups is shown in table1.

Female patients were 20 (66.7%) versus 10 (33.3%) males among treatment group compared to 18 (75%) females and 6 (25%) males in placebo group.

The mean BMI for treatment and placebo groups was (31.7 ± 6.6) kg\m^2 and (33.3 ± 6.7) kg\m^2 respectively.

No significant differences had been found regarding mean age, age groups, sex and mean BMI, in all comparison between groups (P>0.05), table 1.

Table 1: Age and BMI distribution of studied groups.

Variable		Treatment group (N=30)	Placebo group (N=24)	P. value**
Age (year)	Mean ± SD*	43.6 ± 9.6	43.2 ± 9.2	0.88 not significant
	Age groups n (n %)			0.88
	20 – 29	3 (10%)	1 (4.2%)	
	30 – 39	6 (20%)	7 (29.2%)	
	40 – 49	12 (40%)	11 (45.8%)	
	≥ 50	9 (30%)	5 (20.8)	
	Total	30 (100%)	24 (100%)	
Sex n (n %)	Male	10 (33.3%)	6 (25%)	0.51
	Female	20 (66.7%)	18 (75%)	
BMI (kg\m^2)	Mean ± SD*	31.7 ± 6.6	33.3 ± 6.7	0.40

** SD standard deviation**significant P value < 0.05*

As it shown in table 2, spur was present in 17 (56.7%) patients of treatment group and in 10 (41.7%) of placebo group, for those patients whom had spur, the mean length of spur was (4 ± 1.5) mm in treatment group versus (4.3 ± 1.2) mm in placebo group.

The mean duration of symptoms in months was (7.5 ± 2) in treatment group compared to (11.7 ± 3) in placebo group.No significant differences had been found in between groups in the presence of spur, mean length of spur or duration of symptoms,(P>0.05), table 2.

Table 2: Comparison of Length of spur and duration of symptoms in between study groups.

Variable		Treatment group (N=30)	Placebo group (N=24)	Total	P.value**
Presence of Spur n (n%)	No	13 (43.3%)	14 (58.3%)	27 (50%)	0.27
	Yes	17 (56.7%)	10 (41.7%)	27 (50%)	
	Total	30 (100%)	24 (100%)	54 (100%)	
Length of spur (mm)	Mean ± SD	4 ± 1.5	4.3 ± 1.2	4.1 ± 1.4	0.6
	Range	2 - 7	3 - 6	2 - 7	
Duration of symptoms (months)	Mean ± SD	7.5 ± 2	11.7 ± 3	9.4 ± 1.8	0.27
	Range	1 - 48	2 - 48	1 - 48	

***significant P value < 0.05*

The previous treatment that consumed by patients in both groups are summarized in table 3, NSAIDs were the most frequent (46.3%) medication that consumed by patients in both groups, while 18 patients (33.3%) did not used any medication, and 6 patients (11.1%) had used more than one treatment, no significant variation in the usage of medication had been found in between the study groups, P>0.05.

Table 3: Previous treatment distribution among study groups.

Previous treatment	Group		Total
	Treatment group	Placebo group	
Non	12	6	18
	40.0%	25.0%	33.3%
NSAIDs	11	14	25
	36.7%	58.3%	46.3%
Local steroid injection	1	2	3
	3.3%	8.3%	5.6%
NSAID and steroid injection	1	0	1
	3.3%	.0%	1.9%
Physiotherapy	1	0	1
	3.3%	.0%	1.9%
Many	4	2	6
	13.3%	8.3%	11.1%
Total	30	24	54
	100.0%	100.0%	100.0%
P. value = 0.73 not significant			

significant P value < 0.05

Regarding the response to the NGT patches as treatment showed a highly significant difference in between groups; patients in treatment group had higher response rate rather than those in placebo group, from other point of view when response to NGT categorized into 4 categories (No response, mild, moderate and good response) it had been noticed that patients in treatment group were significantly had 2.5 folds moderate response (50% *vs*. 20.8%) and about 5 folds good response rate (20% *vs*. 4.2%) while patients in placebo group had experienced about 2 folds non response (58.3%

vs. 23.3%) and about more than 2 folds mild response than treatment group (16.7% vs. 6.7%) .
In general the overall response rate was (76.7%) in treatment group most of them with moderate and good response compared to (41.7%) in placebo group most of them with mild response, tables (4 and 5) .

Table 4: Comparison of degree of response to NGT patches in between study groups.

Response to NGT patches	Group		Total
	Treatment group	Placebo group	
Non	7	14	21
	23.3%	58.3%	38.9%
Mild	2	4	6
	6.7%	16.7%	11.1%
Moderate	15	5	20
	50.0%	20.8%	37.0%
Good	6	1	7
	20.0%	4.2%	13.0%
Total	30	24	54
	100.0%	100.0%	100.0%
P. value = 0.002 highly significant			

significant P value < 0.05

Table 5: Comparison of response and non response to NGT patches in between study groups.

Response to NGT patches	Group		Total
	Treatment group	Placebo group	
Yes	23	10	33
	76.7%	41.7%	61.1%
No	7	14	21
	23.3%	58.3%	38.9%
Total	30	24	54
	100.0%	100.0%	100.0%
Odds ratio = 2.1 P. value = 0.002 highly significant			

significant P value < 0.05

DISCUSSION:

The demographic data regarding our study populations (treatment group versus placebo group) had shown; mean age of (43.6 ± 9.6) versus (43.2 ± 9.2) years respectively, female: male ratio was 2:1 versus3:1, these findings are consistent with the studies by Singh D, *et al*[2], Riddle DL, *et al*[5] and Buchbinder[6]. Planter fasciitis was most prevalent in age group of 40-49 years, fortunately no significant difference had been found between the treatment group and the placebo group with regard to age and sex distribution, using the Students't test and chi- square test.
Calcaneal spur was present in 56.7% of patients in the treatment group with a range of 2-7 mm length compared to 41.7% in the placebo group with a range of 3-6 mm, showing statically no significant

difference, between the two groups. DeMaio M. *et al*found that approximately one-half of patients diagnosed with PF have heel spurs, other study by Cornwall MW and McPoil TG reviewed the radiographs of 1,000 patients found 13.2 percent had heel spurs; of these, only 39 percent (5.2% of the total sample) reported any history of subcalcaneal pain[1].

The mean BMI for the treatment and the placebo groups was (31.7 ± 6.6) kg\m^2 and (33.3 ± 6.7) kg\m^2 respectively. Riddle DL, *et, al* found that individuals with a body mass index (BMI) > 30 kg/m2 (the cutoff for grade-II obesity) had an odds ratio of 5.6 for PF compared to those with a BMI ≤ 25 kg/m2[8]. This is quit consistent with our results, because most of our patients are obese, so obesity is an important risk factor for planter fasciitis.

The mean duration of symptoms in months was (7.5 ± 2) in the treatment group compared to (11.7 ± 3) in the placebo group. Regarding previous treatment modalities, NSAIDs were the most frequent (46.3%) medication that consumed by patients in both groups, while 18 patients (33.3%) did not used any medication, and 6 patients (11.1%) had used more than one treatment, again there were statistically no significant differences regarding the duration of symptoms and the previous treatments. Similarity between the study groups regarding all the above demographic features makes the difference in response to GTN patches from that to placebo patches to be most likely a genuine response.

Patients in the treatment group had higher response rate than those in the placebo group. From other point of view, when response to NGT was categorized into 4 categories (No response, mild, moderate and good) it had been noticed that patients in the treatment group significantly had 2.5 folds moderate response (50% *vs*. 20.8%) and about 5 folds good response rate (20% *vs*. 4.2%). Patients in placebo group had experienced about 2 folds non response (58.3% vs. 23.3%) and about more than 2 folds mild response than treatment group (16.7% vs. 6.7%), mild response among placebo group might be attributed to other factors rather than real response to treatment.

In general the overall response rate was (76.7%) in treatment group most of them with moderate and good response compared to (41.7%) in placebo group most of them with mild response. These results imply that NGT patches can be effective treatment modality in planter fasciitis. To our knowledge we are the first who used this treatment in planter fasciitis. Paoloni JA, *et al* used GTN patches in treatment of tennis elbow[33], Achilles tendinopathy[34] and supraspinatus tendinopathy[35]. This study has used GTN patches of 5mg strength, which is higher than that used by the previous studies, taking into consideration the thicker skin and the less absorption at the sole.

In all of the three studies mentioned above, 53 to 86 patients were randomly assigned to the treatment group or control group. The treatment group received GTN patches that delivered 1.25 mg GTN every 24 hours. The control group received a placebo patch. In the tennis elbow study[33], 81% of the treatment group was asymptomatic compared with 60% of the control group at 6 months of treatment. The Achilles and supraspinatus tendinopathies studies[34,35] showed comparable results of 78% versus 49% and 46% versus 24% respectively. There is some question whether nitric oxide simply has an analgesic effect or a healing effect in the treatment tendinopathies. A 3-year follow up of the Achilles tendinopathy study described above has recently been published [36]. It showed persistent improvement in the group treated with the GTN patches for 6 months compared to the control group. At 3 years, 88% of the treatment group was completely asymptomatic compared to 67% of the control group. This study suggests treatment with transdermal GTN had a healing effect rather than an analgesic effect in Achilles tendinopathy. In contrast to this, another randomized clinical trial was previously published comparing a 3-day course of transdermal nitroglycerin patches to placebo in 20 patients with rotator cuff tendinopathy [37]. This study reported an improvement in pain scores in the treatment group compared to the control group as early as 24 hours after starting the patch. The improvement in pain was seen at all three time points: 1, 2, and 15 days. This suggests topical nitric oxide may have an analgesic effect as well. As a whole, these studies provide convincing evidence, that administration of NO directly over an area of tendinopathy through a GTN patch enhances healing and provides some pain relief in the treatment of tendinopathy. In these studies the response rate was highest among tennis elbow

patients, also the response rate to placebo patches in these studies in general was relatively high, and it may be attributed to the long duration of treatment, giving the rise to false good response to placebo patches, this also may be applicable to the NGT patches (taking in consideration the natural history of disease, where the typical resolution time is anywhere from 6-18 months, sometimes longer[9]) so in the future studies higher doses patches (2-3 mg) and shorter duration of treatment may be more appropriate.

CONCLUSION:

It was clear that NGT patches were superior to placebo patches in improving the symptoms of patients, so that topical NGT can enhance healing of planter fasciitis. This may be a useful alternative to the current modalities of treatment used for this common condition.

Recommendations

Follow up study of our patients may be required to see rate of symptoms relapse. Larger scale studies with longer duration of treatment are required to consolidate our results.

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