ORIGINAL ARTICLE

Transdermal nitroglycerine treatment of shoulder tendinopathies in patients with spinal cord injuries

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Study design: A clinical blind study was conducted to determine the efficacy of transdermal nitroglycerine treatment on the awareness of shoulder pain.

Objective: This study aims to determine the effects of transdermal nitroglycerine on shoulder pain and on functional shoulder movement in patients with spinal cord injuries and shoulder tendinopathies. A second aim is to establish the side effects of the treatment.

Setting: Hospital “La Fe” in Valencia, Spain.

Methods: A total of 45 spinal cord injury patients, all of whom are wheelchair users with shoulder tendinopathy, were randomly divided into two groups: placebo ($n=12$) and experimental ($n=33$). The experimental group (EG) received transdermal treatment for 6 months in the form of a 1.25 mg nitroglycerine (NT) patch on the greater tubercle. A placebo patch was used with the placebo subjects. Functional shoulder movements were assessed by articular range of motion and pain, using a visual analogical scale.

Results: NT treatment reduced the awareness of shoulder pain and increased the functional movement and range of articular motion in the shoulders of the EG members ($P<0.05$).

Conclusions: We conclude that transdermal NT is an efficient method for treating shoulder tendinopathies in wheelchair users with spinal cord injuries.

Spinal Cord (2011) 49, 1014–1019; doi:10.1038/sc.2011.41; published online 3 May 2011

Keywords: spinal cord injury; shoulder tendinopathy; transdermal nitroglycerine; wheelchair

Introduction

Shoulder pain occurs frequently in patients with spinal injuries, who commonly use the shoulder in a variety of weight-bearing tasks associated with daily activities. The prevalence of pain after 1 year of spinal cord injury evolution is high, between 30 and 59%.^{1,2} Shoulder pain disturbs sleep, increases when propelling a wheelchair and during transfers, and interferes with activities of daily living. As a result, it lowers the level of independence and the quality of life of patients with spinal cord injuries.³

Several factors influence the onset of shoulder pain in spinal cord injury patients. These include: (i) vascular occlusion of the rotator cuff during transfers; (ii) osteoarthritis of the distal portion of the clavicle and osteolysis resulting from repeated trauma to the shoulder while undertaking activities of daily living from a wheelchair; (iii) imbalance between the internal and external rotator

muscles; and (iv) increased dorsal kyphosis in the sitting position, which alters scapula mobility when the humerus is raised.⁴

Shoulder pain has an unfavorable prognosis; only 50% of acute episodes completely recover after 6 months.⁵ Among the structural lesions that cause pain and lessen the degree of functional movement, subacromial impingement is the most common; this is the rotator cuff's incapacity to centre the head of the humerus on the glenoids while the shoulder is moving, thus counteracting the effects of the deltoids.⁶

Among the therapeutic options available for shoulder tendinopathy, we found an innovative line of treatment, the use of transdermal nitric oxide. This treatment stimulates guanylate cyclase, thus increasing the level of cyclic guanine monophosphate (cGMP).⁷ Nitric oxide is a small free radical generated by a family of enzymes known as oxide synthetases; these enzymes have a key role in the physiological process of tendon repair by enhancing fibroblast regeneration. In healthy tendons, very little oxide synthetase activity is observed, but this activity increases in injured tendons. In human Achilles tendon cell cultures, nitric oxide improves the synthesis of the fibroblastic collagen matrix.⁸

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Received 11 September 2010; revised 7 March 2011; accepted 28 March 2011; published online 3 May 2011

Nitroglycerine (NT) is transformed into nitric oxide in the muscle cells of blood vessels and functions independently of the endothelium by imitating the endogenous mediator.⁹ Because of its vasodilating capacity, nitric oxide (NO) is widely used in cases of heart failure; recently, some new indications for its use have appeared.

The first work on treating shoulder tendinopathy with NT was conducted by Berrazueta *et al.* in 1996.¹⁰ This was a double-blind comparative study, in which either 5 mg of NT per day or a placebo was administered over a 3-day period. The study sample comprised 20 patients diagnosed with supraspinatus tendinitis. The treated patients reported significant pain relief, although 10% of them complained of headaches in the first 24 h of treatment.¹⁰ In a separate double-blind study of supraspinatus tendinitis, Paoloni *et al.*¹¹ demonstrated the efficacy of a dose involving a 1.25 mg NT patch/day over a 6-month period. On the other hand, Kane *et al.*¹² recently published a work, in which they report results that do not support the assumed effect of NT on collagen regeneration of damaged tendons. Their study indicates that NT offers no additional benefit to the standard conservative treatment. After a 6-month treatment, no differences on the osteoarthritis scale were seen between the conservatively treated group and the NT-treated group. A histological examination showed no inter-group differences in neovascularization collagen synthesis or in fibroblast stimulation and no differences were found in oxide synthetase modulation as a NO producer in tendons treated with patches.

Because of the controversy regarding the effectiveness of NT treatment of shoulder tendinopathies, further studies are necessary. Also, to date, NT treatment has been applied in populations that, unlike spinal cord patients, do not depend on the shoulder joint to perform everyday life activities.

The main aim of this study is to determine the effects of transdermal NT on pain and on the functional mechanisms of the shoulders of patients with spinal cord injuries and shoulder tendinopathies. A second aim is to establish the side effects of transdermal nitroglycerine treatment.

Materials and methods

Study design

A clinical, double-blind study (examiner and patients) was conducted over a 6-month period with an experimental group (EG) and a placebo group (PG) (controls) to determine the efficacy of NT treatment on the awareness of shoulder pain, shoulder functional movements and the range of shoulder motion in patients with spinal cord injuries and rotator cuff tendinopathies. The patients suffered tendinitis or partial rotator cuff tears diagnosed by magnetic resonance imaging (or ultrasonography when magnetic resonance imaging was contraindicated).

Before starting treatment, awareness of shoulder pain, functional movement and range of motion (ROM) of the shoulders were assessed in the subjects in both groups. After treatment, a second assessment was conducted. Pain was assessed with a visual analogue scale (VAS), pain during

functional movements was assessed with the Wheelchair Users Shoulder Pain Index (WUSPI), functional movements were assessed with the Spinal Cord Injury Measurement (SCIM) and ROM was manually assessed by goniometry. WUSPI was considered to be more specific in patients with spinal cord injury who were wheelchair users.

Patients

Every patient who came to an outpatient annual review between July and December of 2009 and reported shoulder pain during the 3 months before the review was asked to participate in the study. Patients who met the inclusion and exclusion criteria were voluntarily recruited for the study. The 45 qualifying patients were divided into two groups according to the hour and date of their outpatient appointments (considering that the researcher did not know the order of arrival of patients, this can be considered a random selection). To facilitate the objectification of side effects in EG, we assigned twice as many patients to the EG as to the PG. Subjects' characteristics at baseline are shown in Table 1. The inclusion criteria to participate in this study were (i) age greater than 18; (ii) having complete motor paraplegia (that is, grades A and B injury according to the International Standards for Neurological and Functional Classification of Spinal Cord¹³) with a medical or traumatic aetiology; (iii) being a full-time wheelchair user; (iv) presenting tendinitis or proved partial rotator cuff tears (that is, magnetic resonance imaging assessment by a radiologist and ultrasound scans in those cases, in which magnetic resonance imaging was contraindicated); and (v) complaining of shoulder pain in the last 3 months (because it was considered that pain of more than 3 months duration is chronic, thus eliminating self-limiting acute pain). Radiographical studies were not carried out after treatment because such studies had already been conducted to verify tendinitis or the presence of tears.

The exclusion criteria were (i) diagnosis of tetraplegia, paraplegia grades C, D or E, cardiopathy or hypotension with clinical repercussions; (ii) treatment with drugs that release nitric oxide; and (iii) presenting a complete tendon tear or not radiologically presenting a lesion on the tendon.

Table 1 Baseline characteristics of the study participants

	EG (n = 33)	PG (n = 12)
Gender (%)		
Female	30.3	58.3
Male	69.7	41.7
Age (years)	54.3 (2.04)*	42.17 (3.30)
Weight (kg)	84.0 (2.70)	71.75 (3.06)
Height (cm)	170.18 (1.83)	163.08 (3.14)
BMI (kg m ⁻²)	28.91 (0.93)	27.2 (0.99)
Radiologic findings		
Tendinitis (%)	57.57	66.67
Partial tear (%)	18.18	16.67
Tendinitis+partial tear (%)	24.24	16.67

Abbreviations: BMI, body mass index; EG, experimental group; PG, placebo group.

*Indicates the existence of a significant difference ($P < 0.05$) between groups.

Subjects signed an informed consent form before starting the protocol. All the procedures met the requirements listed in the 1975 Declaration of Helsinki and its later amendment in 2008 and were approved by an Ethics Committee.

Treatment

The EG received treatment in the form of NT patches. Each day, patients placed a quarter of a 1.25 mg NT patch (NITRO-DUR, Schering-Plough laboratories, Kenilworth, NJ, USA) on the skin of the lateral aspect of the shoulder (transdermal). This daily patch treatment pattern was followed over a 6-month period, based on studies of Paoloni.^{11,14} The PG received a placebo patch treatment with the same conditions as the treatment received by the EG. To ensure blinding, patches were provided by an independent researcher who did not participate in assessment sessions. Moreover, to ensure patients' compliance, a monthly telephone interview was conducted. Physical therapy or other pharmacotherapy were not used.

Measures

Patients underwent an assessment of shoulder mobility, functional shoulder movements and awareness of shoulder pain before and after the treatment period. Demographical data (age, gender and lateralization) were obtained from the patients' medical records at the start of the study.

WUSPI and SCIM scores

The patients' functional shoulder movements were assessed using the SCIM and the WUSPI. Version III of the SCIM, which is a specific scale to assess the functional movements of patients with spinal cord injuries, was used. The score obtained could vary within a range of 0–100 points,¹⁵ where 0 indicates the lowest functionality and 100 represents full functionality. Shoulder pain during specific functional shoulder movements was assessed using the WUSPI; in this measure, scores vary between 0 and 150, where 0 indicates absence of pain and 150 represents the worst possible pain.¹⁶

Range of motion measures

Articular shoulder ROM was passively assessed while the patient was sitting. For each patient, measurements were manually taken using a goniometer. The positions taken during the ROM measurement of each movement are shown in Figure 1. Abduction was assessed with the shoulder in external rotation,¹¹ whereas antepulsion and retropulsion were examined with the shoulder in neutral rotation position.¹⁴ External and internal rotations were assessed with the elbow fixed at 90° and the shoulder at 90° of abduction.¹⁰ The goniometer was placed over the rotational point for each movement.

Figure 1 Experimental setup for range of motion measurements.

Pain assessment

All the subjects suffered tendinopathy of the shoulder. Therefore, one important outcome of the effect of transdermal NT treatment was the presence and severity of shoulder pain. This outcome was measured through a VAS (ie, scores from 0 to 10).

Statistical analyses

Statistical analyses were carried out using the SPSS software version 17 (SPSS Inc., Chicago, IL, USA). All the data were analyzed according to intention-to-treat. All the dependent variables complied with the assumption of normality (K-S normality test) and homoscedasticity (Levene's test). Standard statistical methods were used to obtain the mean as a measurement of the central trend and the standard error of the mean as a measurement of dispersion. A mixed model MANOVA (group (PG, EG) $\times$ testing time (pre-test, post-test)) was applied to establish the effect of NT treatment on the outcome measures (VAS, WUSPI, SCIM and ROM). The follow-up to the MANOVA was carried out using the univariate contrast method. *Post hoc* analyses were applied using the Bonferroni's correction to avoid an increase in type I error. The level of statistical significance was set at $P < 0.05$.

Results

As described above, the 45 subjects were randomly assigned to two groups. The EG initially included 33 subjects, but nine of them did not finish the treatment. The reason for dropping out was improvement in five of the subjects and not tolerating the treatment in the other four (see Figure 2). Nonetheless, all the subjects except four did the post-test. When the study commenced, the PG included 12 subjects; six of these discontinued the placebo patch treatment. Five did so because they noticed no improvement; the other subject did not tolerate the treatment. However, all the PG subjects did the post-test. In patients who reported improvement in pain, the effect was present 6 months after patch removal.

Multivariate contrasts revealed that there was an interaction effect between the group and testing time on the dependent variables ($F_{8,32} = 17.29$, $P < 0.001$, $\eta_p^2 = 0.81$). Univariate contrasts showed the existence of a group $\times$ testing time interaction effect in abduction ($F_{1,39} = 13.01$, $P = 0.001$, $\eta_p^2 = 0.25$), external rotation ($F_{1,39} = 15.87$, $P < 0.001$, $\eta_p^2 = 0.36$), internal rotation ($F_{1,39} = 20.23$, $P < 0.001$, $\eta_p^2 = 0.34$), anteversion ($F_{1,39} = 29.09$, $P < 0.001$, $\eta_p^2 = 0.43$), retroversion ($F_{1,39} = 21.77$, $P < 0.001$, $\eta_p^2 = 0.29$), SCIM ($F_{1,39} = 5.96$, $P = 0.019$, $\eta_p^2 = 0.13$), WUSPI ($F_{1,39} = 49.28$, $P < 0.001$, $\eta_p^2 = 0.56$) and VAS ($F_{1,39} = 12.95$, $P = 0.001$, $\eta_p^2 = 0.25$).

Pairwise comparisons revealed that the joint range of the experimental group increased in every direction ($P < 0.005$) because of the treatment (see Figure 3), whereas the placebo group worsened ($P < 0.005$). The WUSPI and VAS scores of the experimental group ($P < 0.001$) also improved through treatment (see Table 2). Moreover, there were no inter-group differences observed in the pre-test for any dependent variable. However, in the post-test, the experimental group showed greater anteversion ($P = 0.009$), retroversion ($P = 0.008$) and internal rotation ($P < 0.001$) than the placebo group. The WUSPI score in the post-test was higher in the PG than in the EG ($P < 0.001$).

In all, 10 patients in the EG (33%) reported side effects; seven had headaches (21%), one reported facial reddening (3%), one dizziness (3%) and one tachycardia (3%). These effects were mainly recorded in the first week of treatment. Two PG subjects (16.6%) reported headaches.

Discussion

The results of this study confirm that NT treatment of spinal cord injury patients with shoulder tendinopathy is effective in relieving pain and improving shoulder ROM. Although similar results have been reported previously in other populations, the fact that the treatment was useful in patients who use the shoulder joint to perform most daily

Figure 2 Patients' flow chart.

Figure 3 Comparisons of the range of motion between and within groups. The black columns represent the mean of the experimental group; the gray columns show the mean of the placebo group. The error bars represent the standard error of the mean. *Indicates a significant difference ($P < 0.05$) between or within groups.

life activities is of great importance. Thus, the NT treatment was effective even when the patients did not rest the shoulder.

Paoloni *et al.*¹¹ found a significant pain relief, an increase in ROM of internal shoulder abduction and rotation, and an increase in strength of the external and internal rotator

Table 2 Comparisons between SCIM, WUSPI and VAS scores

	EG (n = 29)		PG (n = 12)	
	Pre-test	Post-test	Pre-test	Post-test
SCIM	55.69 (1.97)	56.79 (1.87)	59.83 (2.81)	57.17 (2.64)
WUSPI	73.09 (4.67)	26.28 (4.71) * [†]	62.87 (8.35)	74.25 (6.27)
VAS	5.42 (3.11)	2.25 (0.41) * [†]	5.33 (0.67)	4.6 (0.68)

Abbreviations: EG, experimental group; PG, placebo group; SCIM, spinal cord injury measurement; VAS, visual analogue scale; WUSPI, wheelchair users shoulder pain index.

Data are expressed as the mean (s.e.m.).

*Significant difference ($P < 0.001$) relative to the pre-test. [†]Significant difference ($P < 0.001$) relative to the PG.

muscles due to a NT treatment. In a double-blind study with 65 patients diagnosed with Achilles tendinitis, NT treatment was used and stretch exercises were carried out, resulting in effective pain relief.¹⁷ Paoloni *et al.* demonstrated the efficiency of one 1.25 mg patch/day over a 6-month period in a double-blind study of supraspinatus tendinopathy¹⁴ and Achilles tendinitis.¹⁸ Moreover, the latter study reports that a lower level of awareness of pain was maintained after a 3-year treatment period, which indicates that the NT function mechanism is not merely analgesic.¹⁸

Nonetheless, one recently published work¹² has aroused controversy because its results oppose the assumed effect of NT on collagen regeneration in damaged tendons. This recent study indicates that NT offers no additional benefit to the standard conservative treatment. In this study, no differences on the osteoarthritis scale were observed between the conservatively treated group and the NT-treated group after a 6-month treatment. A histological examination showed no inter-group differences in neovascularization collagen synthesis or fibroblast stimulation. Finally, no differences were found in nitric oxide synthetase modulation in tendons treated with patches.¹²

In our study, the subjective pain relief achieved in the EG as a result of NT treatment was 58.49%, in contrast to 13.7% in the PG. A drop of 46.81 points in the WUSPI Index score was also noted in the EG, as opposed to an increase of 11.38 points in the PG. In other words, patients in the EG reported pain relief, whereas patients in the PG experienced a slight aggravation of pain. The analgesic effect of NT is objective, with statistically significant inter-group differences in the measurements taken with the WUSPI Index and the VAS. Therefore, the lessening of pain felt by patients with spinal cord injuries justifies the use of NT treatment in these patients.

Despite the observation of improvement in overall functional movements in the EG as measured by the SCIM scale, no significant differences were obtained. This finding is likely because the scale assesses other functional aspects that are not modified with shoulder pain relief. In addition, a larger patient sample is necessary to corroborate the trend observed. Significant improvement was, however, noted between the pre-test and the post-test; in the post-test, the

EG's ROM was better than the PG's articular mobility, which was limited. Inter-group differences were also noted for the post-test in terms of antepulsion, retropulsion and internal rotation. Increased internal rotation mainly occurs because of an antialgic shortening of the antagonist muscles in supraspinatus and infraspinatus tendinitis, consequently leading to restricted internal rotation; this movement becomes freer when the rotator cuff is less inflamed. The fact that the range of the remaining movements increased may be due to relaxation of the muscles in the area and a reduced awareness of pain.

In the study of Berrazueta *et al.*,¹⁰ as in our study, headaches were the most frequent side effect reported. This is not a surprising result because headaches are the most frequently described side effect, when NT is used to treat a variety of pathologies.¹⁹

Despite the fact that headaches were reported by 21.2% of the subjects in the EG, only 12.0% of the treated subjects dropped out because of the occurrence of headaches. Two subjects in the PG also complained of headaches; this was probably due either to a random effect or to suggestion (these patients had previously been informed of the possibility of this particular side effect). The results obtained attribute to a risk of 14% of reporting a side effect in patients receiving NT treatment. It is also noteworthy that only 44.4% of those in the EG who stopped treatment did so because of side effects or because of poor toleration of treatment; the rest of the patients who left treatment did so as a result of experiencing considerable improvement. In contrast, most of the PG subjects who stopped treatment (83.3%) did so because they did not experience any improvement.

One of the main limitations of this work is that it assessed results only after a 6-month period of treatment. Because there are no studies of rotator cuff tendinitis to date that have included long-term follow-up of the results of NT treatment, we will undertake a follow-up of the patients in this study. We might conduct radiological studies after the treatment to determine whether the treatment resulted in compensation for the injury or simply analgesia. Moreover, to check the effect of long-term treatment, it would be interesting to assess pain 1 year after starting treatment. Another limitation is the small sample size, which resulted in loss of statistical power.

Conclusions

The conclusion drawn from this study is that the use of NT patches placed on the greater tubercle at a dose of 1.25 mg per day over a 6-month period is a safe option (ie, without any important side effect) for controlling pain in patients, such as spinal cord injury wheelchair users, who often need to use the shoulder for activities of daily living.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

X GM is a Vali + D researcher in formation and thanks the Generalitat Valenciana.

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