Transdermal nitroglycerin versus corticosteroid infiltration for rotator cuff tendinitis

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**Aims.** To compare transdermal nitroglycerin (NTG) and corticosteroid infiltration in patients with rotator cuff tendinitis (RCT).

**Design.** Experimental, randomized controlled study.

**Setting.** Semirural basic health area in the Garraf region of Barcelona province, Spain, with a population of public health service users of 12,000.

**Patients and methods.** Patients diagnosed as having RCT of less than 6 weeks’ evolution who had not responded to treatment with oral nonsteroid antiinflammatory drugs. The patients were distributed randomly into two groups: a) group A, local infiltration via a posterior approach with a depot corticosteroid and local anesthesia, and b) group B, treated for 3 days with a 5-mg NTC patch.

**Main measures.** Age, sex, pain (measured with an analog visual scale) and adverse events. In patients who showed a partial response, treatment was repeated up to 3 times at 15-day intervals. Pain was tested after 7-10 days of treatment. Complete improvement was considered a reduction in pain of more than 5 points on the analog visual scale; partial improvement was considered a reduction of 3-5 points, and treatment failure was recorded when there was no improvement in pain or when there was a decrease of less than 3 points.

**Results.** A total of 48 patients were included; 33 (69%) were women and 15 (31%) were men. Mean age was 61 years. In group A, complete improvement was seen in 19 patients and partial improvement in 3; treatment failed in 2 patients. In group B complete improvement was seen in 5 patients, partial improvement in 5, and failure of treatment in 14. The difference between groups was statistically significant. Adverse events were mild pain at the injection site in 4 patients from group A, and headache in 15 patients from group B, 8 of whom abandoned treatment for this reason.

**Conclusion.** Treatment with NTG is not a clear alternative to infiltration of corticosteroids in patients with RCT, because of its lack of effectiveness and because of the greater number of patients who had adverse events that lead them to abandon treatment.

**Key words:** Rotator cuff tendinitis. Local infiltration. Transdermal nitroglycerin.
Introduction

Painful shoulder, which can significantly limit the patient’s quality of life, is a frequent complaint in primary health care with an estimated yearly incidence of 11.2/1000 patients. The most frequent cause of this syndrome is rotator cuff tendinitis (RCT), although it can also arise from other disorders such as muscular injury, bursitis, or, less often, from joint problems.

Treatment of this disorder is usually provided by the primary care physician, and the choice of treatment depends on the practitioner’s preference, based mainly on acquired knowledge and personal experience. No clearly established criteria for choosing the most suitable treatment are available; despite the many published studies on this topic, there is little scientific evidence to support one option over another.

The three potential pharmacological treatments consist of transdermal nitroglycerin, infiltration with corticosteroids and local anesthesia, and nonsteroid antiinflammatory drugs. Transdermal nitroglycerin has been shown to be effective as an antiinflammatory and analgesic for different indications such as thrombophlebitis, dysmenorrhea and RCT. Advocates of this approach explain these effects on the basis of the fact that nitroglycerin is transformed into nitric oxide in the vascular smooth muscle, and thus imitates the action of endogenous nitric oxide (produced in the endothelium) on the peripheral nervous system, and on the modulation of the inflammatory process. On the other hand, infiltration of corticosteroids with local anesthesia has been found more effective than oral nonsteroid antiinflammatory drugs for RCT.

Given the high prevalence of RCT in our setting and the contraindications, the potential adverse effects of some treatments (i.e., oral antiinflammatory drugs) and the invasive nature of other treatments (i.e., local infiltration), we believed it worthwhile to investigate the efficacy of transdermal nitroglycerin for the treatment of pain in RCT. If this treatment were found to be at least as effective as conventional treatments, it might offer advantages (ease of application, low cost, nonaggressive nature) that would make nitroglycerin an attractive alternative.

The aim of this study was to compare the effects of transdermal nitroglycerin and local infiltration of corticosteroids in controlling the pain of RCT in patients who had not responded to oral nonsteroid antiinflammatory drugs.

Material and methods

This experimental study, in which patients were assigned randomly to receive one treatment or the other, was done at the primary health care center of a semirural basic health care area in the Garraf region, Barcelona province, Spain. The health care center serves a population of approximately 12000 inhabitants, most of whom have received a moderate to low level of formal schooling. About 60% of the population are of legal working age, and the main types of employment are construction work (men) and cleaning work (women).

The participants were selected during a visit to the health center at which they were seen by members of one of three different primary care teams. The inclusion criteria were: a) clinical diagnosis of RCT, defined as pain on moving the arm through a 60–120° arc, positive impingement test and positive Jove (supraspinatus), Gerbe (subscapularis) or Paté (infraspinatus and teres minor) test; b) symptoms present for less than 6 weeks at the time of diagnosis; and c) no response to previous treatment for one week with oral nonsteroid antiinflammatory. Patients were excluded if they had adhesive capsulitis (limited or painful passive mobility of the shoulder), biceps tendinitis (positive palm up test or Yergason test), allergy or intolerance of any of the drugs used in the study, or if they were receiving treatment with nitroglycerin patches for heart disease.

Sample size was calculated at 24 patients per group according to a comparison of proportions test for a unilateral hypothesis. Alpha error was set at 0.05, and beta error at 0.20. Keeping in mind that the efficacy of infiltration is 70–90%, we assumed that a difference of 30% or less would be clinically relevant. The main variable in the study was pain, measured with a visual analog scale (VAS) at the time of inclusion in the study and after 7 days of treatment. Other variables studied were age, sex and adverse effects of both treatments.

From May 1999 to April 2000 all patients who came to the center and fulfilled the inclusion criteria were assigned to one of two

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Material y métodos

Introducción

El dolor del hombro, que puede significativamente limitar la calidad de vida del paciente, es un reclamo frecuente en la atención primaria de salud con una incidencia estimada anual de 11,2/1000 pacientes. El más frecuente de estos síndromes es la tendinitis del cuello del hombro (RCT), aunque también puede surgir de otras condiciones como lesiones musculares, bursitis, o menos a menudo por problemas articulares.

El tratamiento de esta condición se realiza usualmente por el profesional de salud primario, y la elección del tratamiento dependerá de la preferencia del practicante, basándose principalmente en el conocimiento adquirido y la experiencia personal. No existen criterios establecidos para elegir el tratamiento más adecuado.

Los tres tratamientos potenciales son el uso de nitroglicerina transdérmica, la inyección de corticosteroides y anestesia local, y los antiinflamatorios no esteroidales. El nitroglicerina transdérmica ha sido demostrada como efectiva como antiinflamatoria y analgésica para diferentes indicaciones como trombophlebitis, dismenorrea y RCT. Los partidarios de esta forma de tratamiento explican estos efectos sobre la base de la transformación del nitroglicerina en óxido nítrico en el músculo de la pared arterial, y así imita la acción del óxido nítrico endógeno (producido en la endotelio) en el sistema nervioso periférico, y en la modulación del proceso inflamatorio. Por otro lado, la inyección de corticosteroides con anestesia local ha demostrado ser más efectiva que los antiinflamatorios no esteroidales orales en el tratamiento de RCT.

Dado el alto porcentaje de RCT en nuestro entorno y las contraindicaciones, los posibles efectos adversos de algunos tratamientos (i.e., los antiinflamatorios no esteroidales orales) y la invasividad de otros tratamientos (i.e., la infiltración local), creímos que era apropiado investigar la eficacia del nitroglicerina transdérmica para el tratamiento del dolor de RCT. Si este tratamiento resultara al menos tan eficaz como los tratamientos convencionales, podría ofrecer ventajas (fácil de aplicar, bajo costo, naturaleza no invasiva) que lo convertirían en un tratamiento atractivo.

El objetivo de este estudio fue comparar los efectos del nitroglicerina transdérmica y la infiltración local de corticosteroides en el control del dolor de RCT en pacientes que no habían respondido a los antiinflamatorios no esteroidales orales.

Material y métodos

Este estudio experimental, en el que los pacientes fueron asignados de forma aleatoria a recibir uno de los tratamientos, se realizó en el centro de atención primaria de salud de un área básica semirural de la comunidad de Garraf en la provincia de Barcelona, España. El centro de atención primaria atiende a una población de alrededor de 12000 habitantes, la mayoría de los cuales han recibido un nivel medio a bajo de formación escolar. Cerca de 60% de la población es de edad laboral, y los principales tipos de empleo son el trabajo de construcción (hombres) y limpieza (mujeres).

Los participantes fueron seleccionados durante una visita al centro de salud en la que se los vio por miembros de uno de los tres equipos de atención primaria disponibles. Los criterios de inclusión eran: a) diagnóstico clínico de RCT, definido como dolor al desplazar el brazo a un ángulo de 60–120°, pruebas de impinjición positivas y pruebas de Jove (supraspinatus), Gerbe (subscapularis) o Paté (infraspinatus y teres minor); b) síntomas presentes durante menos de 6 semanas a la fecha del diagnóstico; y c) falta de respuesta a un tratamiento previo durante una semana con antiinflamatorios no esteroidales orales. Los pacientes fueron excluidos si tenían capsulitis adhesiva (limitación o dolor pasivo de movimiento del hombro), tendinitis del biceps (prueba de palmar recta positiva o prueba de Yergason), alergia o intolerancia a alguno de los medicamentos usados en el estudio, o si estaban recibiendo tratamiento con parches de nitroglicerina para enfermedades cardíacas.

El tamaño de muestra se calculó a 24 pacientes por grupo según una comparación de proporciones test para una hipótesis unilateral. El error alfa se fijó en 0.05, y el error beta en 0.20. Teniendo en cuenta que la eficacia de la infiltración es de 70–90%, se supuso que una diferencia de 30% o menos sería clínicamente relevante. La variable principal del estudio fue el dolor, medido con una escala analógica visual (VAS) al momento de inclusión en el estudio y después de 7 días de tratamiento. Otros variables estudiados fueron la edad, el sexo y los efectos adversos de ambos tratamientos.

Desde mayo de 1999 hasta abril de 2000 todos los pacientes que llegaron al centro y cumplían los criterios de inclusión fueron asignados a uno de los dos

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Scheme of the study design

Experimental study with randomized distribution of participants.

Rotador cuff tendinitis

Oral NSAIDS (7 days)

No improvement: 48 patients

Randomization

Local infiltration: 24 patients

Transdermal nitroglycerin: 24 patients

Efficacy evaluated after 7 days

Complete improvement: 19 patients

Complete improvement: 5 patients

| Local infiltration: 24 patients

Efficacy evaluated 7 days

Complete improvement: 19 patients

Complete improvement: 5 patients

| Transdermal nitroglycerin: 24 patients

Efficacy evaluated after 7 days

Complete improvement: 5 patients

Complete improvement: 5 patients

Experimental study with randomized distribution of participants.
groups (A or B) according to a random number table, if they gave their consent to take part after receiving verbal information about the study. Group A patients received infiltration via a posterior approach (1 cm below the outer edge of the posterior spine of the scapula) of 1 mL triamcinolone acetonide and 1 mL 2% mepivacaine delivered with a 21 G intramuscular needle. Group B patients were given a set of 5-mg nitroglycerin patches to be placed over the area of worse pain (lateral face of the shoulder) for 3 days. Each patient was trained in the proper way to apply the patch daily. During the treatment period no oral analgesics or antiinflammatories were allowed.

After 7 days of treatment we evaluated the dependent variables pain and adverse events. Complete improvement was considered a reduction in pain of more than 5 points on the VAS; partial improvement was considered a reduction of 3–5 points, and treatment failure was recorded when there was no improvement in pain or when the decrease was less than 3 points. Adverse effects were also recorded. Patients whose pain did not show complete improvement were given an appointment 15 days after treatment to receive nitroglycerin or infiltration depending on their initially assigned treatment, and pain and adverse events were again recorded one week later. This procedure was repeated up to 3 times. Scheme illustrates the overall design of the study.

The results were analyzed statistically by comparison of proportions with the SPSS. The results were expressed together with 95% confidence intervals (CI).

**Results**

A total of 48 patients (33 women, 69%, and 15 men, 31%) were studied. Mean age was 61 years. There were no significant differences between the groups in age or sex. In group A complete improvement was seen in 19 patients (79%), partial improvement in 3 (12%) and treatment failure in 2 (8%). Of the 19 patients with complete improvement, this result was obtained with one infiltration in 10 participants, 2 infiltrations in 3, and 3 infiltrations in 6. In group B complete improvement was seen in 5 patients (21%), partial improvement in 5 (21%) and treatment failure in 14 (58%). Of the 5 patients with complete improvement, this result was obtained with one 3-day set of patches in 3, and with 3 sets of patches in 2 (fig. 1).

With regard to adverse effects, 4 patients (16%) in group A reported mild pain at the injection site, whereas in group B 15 patients (62%) reported headaches, which led 8 of them to abandon treatment (fig. 2).

When we compared patients who showed complete improvement with the other two outcome groups (partial improvement and treatment failure), we found a difference in the proportion of each treatment group of 0.58 (95%
The available treatments are oral nonsteroid antiinflammatory drugs, local corticosteroid infiltration and transdermal nitroglycerin. Different treatments are often needed to attain improvement in symptoms and function. However, some limitations should be noted. The variable side effects was higher with the latter treatment. The adverse effects of nitroglycerin and a placebo for RCT found significant differences in favor of nitroglycerin. It should nonetheless be noted that the statistical power and design of their study were problematic: only 10 patients were included in each group, and the response was evaluated after a very short treatment period (24 and 48 h).

In the present study, randomization bias was significantly reduced by a controlled, random process of assignation; thus our groups were comparable for prognostic factors. We compared the proportions of patients with complete and partial improvement, the difference in proportion between the two treatment groups was 0.500 (95% CI: 0.27–0.72), which was also statistically significant.

The efficacy of treatment with local corticosteroid infiltration was compared with that of transdermal nitroglycerin. Local infiltration led to greater improvements that did nitroglycerin. The use of transdermal nitroglycerin led to more side effects.

References


ORIGINAL ARTICLE

Pons S, Gallardo C, Caballero JC y Martínez T.–
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COMMENTARY

Transdermal nitroglycerine versus corticosteroid infiltration for rotator cuff tendinitis

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The painful shoulder syndrome is a frequent cause of visits to primary care physicians. Between 10% and 20% of the population can expect to have at least one episode of this disorder. The etiopathogenic mechanisms of painful shoulder have not been adequately established. In some cases there are clear antecedents of mechanical overload or traumatic injury, but in others these antecedents are lacking, or the patient has no recollection of any cause that might account for the pain. In addition, the disorder is more common against a background of certain clinical entities such as diabetes, although the causes of this relationship are unknown.

Conservative approaches to treatment offers several options. Pharmacological treatment is based mainly on non-steroid antiinflammatories and analgesics, and on the infiltration of depot corticosteroids and anesthetics. Physiotherapy is another available option. As yet there are no clear clinical criteria for choosing one option over another, for combining different treatments, or for deciding in which order to use different options. None of the treatments individually is infallible, and practitioners must rely on their own training and experience in deciding which option to use. Because of these uncertainties, new lines of research are being tried (and further possibilities also merit study) with the aim of developing appropriate treatments with lower risks.

Surprisingly, despite the high incidence of this disorder there are few well-structured studies that compare treatment alternatives. The article in this issue by Pons et al. compares one treatment previously found to be superior to a placebo, i.e., local infiltration of corticosteroids, with a newer option: nitroglycerin patches placed over the painful area. The results of their study show that nitroglycerin patches cannot be considered an additional treatment option: the hoped-for clinical benefits were not obtained, and moreover many patients abandoned treatment because of adverse effects.

Infiltration in Primary Care

- Painful shoulder is a highly prevalent disorder in our setting. Most patients are treated by their family doctor.
- Additional epidemiologic research is needed to evaluate the actual status of this disorder in primary care.
- Family physicians should have adequate skills to treat the disorder, including knowledge of local infiltration and physiotherapy, with the aim of reducing the patient’s pain and functional limitations as promptly as possible.
- New approaches to treatment aimed at enhancing the results without increasing risks or side effects should be explored.

Bibliografía