



Glyceryl Trinitrate Patches: A Modern Treatment for Tendinopathies

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Introduction

Tendinopathy encompasses a variety of conditions that develop within tendons in response to overuse, characterized by pain and dysfunction [1,2]. These include disorders of the Achilles tendon, patellar tendon, lateral epicondyle, medial epicondyle and the rotator cuff. Historically, most of these disorders have been attributed to tendinitis or inflammation of the tendon, however recent histopathological work has lent support to tendinosis as the underlying pathology. Changes include collagen degeneration and disorganization, and angiogenesis accompanied by sensitive fresh nerve endings, an entity entitled 'angiofibroplastic hyperplasia' [1]. The currently accepted conservative management for tendinopathies includes rest, progressive loading and stretching, pain mitigation via analgesics and thermal modalities and stabilization via orthotics and braces. Alternative treatments include manipulation, mobilization, friction massage and more invasive corticosteroid injections and surgery [2].

A novel conservative method for tendinopathies is the local application of Glyceryl Trinitrate (GTN) patches over affected areas. GTN patches have been investigated in a spurt of recent clinical trials for the treatment of a range of tendinopathies, due to their ease of application, titration dosage and minimal adverse consequences [3]. The GTN patch elutes Nitric Oxide (NO), postulated to be the source of pain reduction and augmentation of collagen repair [4].

In-vitro and In-vivo experimental studies

Nitric Oxide Synthase (NOS), i.e. the enzyme producing NO, plays a critical role in tendon tissue synthesis during healing in three rat models [4]. Minimal NOS activity was present in uninjured rat Achilles tendons, significantly increasing subsequent to surgical division. In the rotator cuff and overuse models wherein a defect was created in the supraspinatus tendon or subjected to treadmill running and all three isoforms of NOS were expressed [4]. This result was substantiated in a study of excised human tendon cells, which exhibited NOS activity [5]. Furthermore, It was shown that extracellular collagenous matrix organization and tendon stress

performance improved post-operatively, subsequent to exogenous NO administration in surgically divided rat Achilles tendons [3]. These studies paved the way for clinical application.

GTN Clinical Studies

Achilles tendinopathy

Paolini et al. conducted a follow up study on 52 patients with chronic non-insertional Achilles tendinopathy, three years post therapy cessation of GTN therapy or placebo for 6 months. It was reported that the GTN treatment cohort had less tenderness and improved VISA-A scores in comparison to the placebo group at three year follow up (p=0.03 and 0.04 respectively). Thus substantiating GTN therapy has beneficial long-term effects [6]. A noted shortcoming is not controlling for other treatments during the follow-up period, however the results demonstrate that GTN's effect may not merely be analgesic.

Rotator cuff tendinopathies

A recent literature review evaluated the efficacy of four studies investigating GTN patches for the treatment of a rotator cuff tendinopathies. Two studies reported significant improvement in ROM and VAS pain reduction in the GTN cohort when compared with placebo. One described reduced analgesic effect compared to corticosteroids and the remaining study reported improvement in pain duration and joint mobility in GTN compared to placebo. Hence our recommendation for further high-quality trials, maintaining consistent pathology and larger cohorts to substantiate the positive clinical effect demonstrated by GTN patches [3].

Chronic patellar tendinopathy (CPT)

An RCT compared the use of GTN or a placebo patch over 12 weeks concluded that there was no difference in clinical improvement in GTN patches and placebo treatment cohorts (n=40) [7].

Elbow tendinosis

A placebo controlled RCT on 86 patients with extensor tendinosis,

demonstrated that when all patients performed a standard tendon rehabilitation program, the GTN cohort treated patients significantly improved early pain with activity (2 weeks, $p=0.01$) and lateral epicondyle tenderness (6 and 12 weeks, $p=0.02$), though there was no significant difference at later follow up points. The GTN cohort were more likely to be asymptomatic at 24 weeks with activities of daily living ($p<0.005$) [8]. In a comparative five year follow up study of the patients involved in the previous clinical trial, it was reported that the previous GTN therapy did not provide supplementary long-term clinical benefit over the placebo cohort [9].

Complications

The most frequently cited side effects in the literature pertaining to GTN patch administration for tendinopathies are rash over the applied region and headaches. Though seldom severe enough to cause cessation of treatment and always reported to resolve upon discontinuation [3].

Conclusion

Due to our changing understanding of underlying histopathology related to a variety of tendon disorders, our treatment options are evolving. GTN patches are at the forefront; good animal data has stimulated a spurt of clinical studies, some of which aforementioned support their administration as a therapy for differing tendinopathies. However there are other studies, which do not demonstrate a significantly different clinical effect, in comparison to placebo and standard rehabilitation programs. Much work still remains to be done in this field but it is clear that GTN patches hold promise.

References

1. Andres BM, Murrell GA (2008) Treatment of tendinopathy: what works, what does not, and what is on the horizon. *ClinOrthopRelat Res* 466: 1539-1554.
2. Gambito ED, Gonzalez-Suarez CB, Oquiñena TI, Agbayani RB (2010) Evidence on the effectiveness of topical nitroglycerin in the treatment of tendinopathies: a systematic review and meta-analysis. *Arch Phys Med Rehabil* 91: 1291-1305.
3. Assem Y, Arora M (2015) Glyceryl trinitrate patches an alternative treatment for shoulder impingement syndrome. *Journal of Orthopaedic Translation* 3: 12-20.
4. Bokhari AR, Murrell GA (2012) The role of nitric oxide in tendon healing. *J Shoulder Elbow Surg* 21: 238-244.
5. Szomor ZL, Wang MX, Kruller A, Murrell GA, Farmer KM, et al. (2001) Differential expression of cytokines and nitric oxide synthase isoforms in human rotator cuff bursae. *Ann Rheum Dis* 60: 431-432.
6. Paoloni JA, Murrell GA (2007) Three-year followup study of topical glyceryl trinitrate treatment of chronic noninsertional Achilles tendinopathy. *Foot Ankle Int* 28: 1064-1068.
7. Steunebrink M, Zwerver J, Brandsema R, Groenenboom P, van den Akker-Scheek I, et al. (2013) Topical glyceryl trinitrate treatment of chronic patellar tendinopathy: a randomised, double-blind, placebo-controlled clinical trial. *Br J Sports Med* 47: 34-39.
8. Paoloni JA, Appleyard RC, Nelson J, Murrell GA (2003) Topical Nitric Oxide Application in the Treatment of Chronic Extensor Tendinosis at the Elbow A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. *Am J Sports Med* 31: 915-920.
9. McCallum SD, Paoloni JA, Murrell GA (2011) Five-year prospective comparison study of topical glyceryl trinitrate treatment of chronic lateral epicondylitis at the elbow. *Br J Sports Med* 45: 416-420.