Original Article

Acute Achilles tendinopathy: effect of pain control on leg stiffness

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Abstract

Tendinopathies are a major cause of disability in the athletic population; the main purpose of the treatment of these injuries is to reduce pain and improve function. The aim of this study was to evaluate the effect of NSAIDs on leg stiffness of patients suffering acute unilateral Achilles tendinopathy. Twenty-eight eligible male athletes (aged 39.1±10.3 y) suffering acute Achilles tendinopathy were treated with etoricoxib (120 mg oral once daily) during 7 days. Pain (100-mm visual analogue scale-VAS), analgesic effect (percentage of 100-mm VAS reduction), and leg stiffness were evaluated pre- and post- anti-inflammatory treatment. Results of this study showed that over the 7-day treatment period, etoricoxib provided significant relief of Achilles tendon pain (VAS) compared to that experienced at baseline: 54.5±21.6 and 24.5±24.8, respectively ($p<0.001$). Leg stiffness showed a significant improvement after one-week NSAID therapy: LSR 0.89±0.1 vs. 0.97±0.1; ($p=0.02$). In conclusion, findings of this study demonstrated that patients suffering acute unilateral Achilles tendinopathy increased their leg stiffness of the affected side after oral anti-inflammatory therapy. Effective control of tendon pain in the acute phase of such sports-related injuries may contribute to improve capabilities associated with high performance like leg stiffness.

Keywords: Performance, Spring-mass, Etoricoxib, Tendon

Introduction

Achilles tendon problems are a major cause of disability in sports people and those who undertake an active lifestyle[1-6]. Tendinopathy is defined as the clinical syndrome characterized by a combination of pain, diffuse or localized swelling, and impaired performance arising from overuse[7]. Tendinopathy is a difficult problem to treat requiring lengthy management. Most patients with Achilles tendon complaints can be treated conservatively (rest or activity modification, cold, stretching, strengthening, NSAIDs, training correction). However, 25% of patients with persisting symptoms may require surgical treatment[5,8].

The purpose of the treatment of tendinopathies in active individuals is to reduce symptoms and improve function[2,4,5]. In athletes, an additional demand is that the recovery time should be as short as possible[5]; therefore, there seem to be an expanded pharmacological role in the sports medicine practice[9].

Several factors play a role in the cause of pain in patients with Achilles tendinopathy. Mechanical loading is known to increase connective tissue blood flow of human tendons and to cause local release of vasodilatory substances[10,11].

Mechanical stiffness is thought to influence several athletic variables, including rate of force development, elastic energy storage and utilization of sprint kinematics[12]. Stiffness is the resistance of a muscle to an increase in length and is calculated as muscle force/length[13]. Stiffness can be measured at the level of a single muscle fiber to the modeling of the entire body (spring-mass)[13]. Generally, the effect of stiffness on muscular performance is thought important with many changes in strength, power and flexibility being attributed to changes in stiffness[14-16]. For example, the relationship between stiffness and running speed is assumed to be strong as many authors have speculated that a stiff musculo-tendinous unit will enhance the rapid transmission of force[16-18].

Muscle-tendon stiffness seems to be increased by eccentric exercises[19] and reduced by stretching[20]. Calf muscles stiffness variability may play a role in Achilles tendinopathy and in the

positive effects seen of eccentric exercises on that lesion[21]. Farley and coworkers have demonstrated that modulation of ankle stiffness is the primary mechanism for adjusting leg stiffness when humans hop to different heights[22]. Recent studies have shown that leg stiffness is reduced in the involved limb in patients with unilateral Achilles tendinopathy[23]. As ankle stiffness is a function not only of the passive factors associated which each structure (i.e. viscoelasticity) but also of the level of neural influence over each structure[18,24,25], Achilles tendon pain may affect stiffness considerably.

Cyclooxigenase-2 (COX-2) is an enzyme involved in pain and inflammation; its specific mechanism is responsible for the exercise-induced increase in prostaglandin synthesis, and that increase in tissue prostaglandin plays an important role for blood flow in peritendinous connective tissue during physical loading *in vivo*[26]. Etoricoxib is a selective inhibitor of the COX-2; it is a member of the cyclooxignease-2 selective class of non-steroidal anti-inflammatory drugs (NSAIDs)[27] and several clinical trials have confirmed its analgesic and anti-inflammatory efficacy in acute pain conditions.

Objective and hypothesis

The purpose of this study was to evaluate the effect of NSAIDs on leg stiffness of patients suffering acute unilateral Achilles tendinopathy. It was hypothesized that leg stiffness may improve after pain control using etoricoxib (120 mg orally/day/7 days) in subjects suffering acute Achilles tendinopathy.

Materials and methods

General

The study protocol and informed consent form were both approved by the appropriate ethical review committees and institutional review boards. The study was conducted in full accordance with ethical standards for the treatment of patients as laid down in the Declaration of Helsinki. Each patient gave written informed consent prior to undergoing any study procedure.

Eligibility criteria

Patients were eligible if they were male between 18 and 50 years of age and they suffered acute Achilles tendinopathy (<2 weeks). Diagnosis of Achilles tendinopathy was made by means of activity-related achillodynia, morning stiffness or pain, painful one-legged jumping test, tenderness and decreased sports performance[16]. Subjects' age, race, affected tendon (right, left), activity, height and weight were recorded.

Exclusion criteria

Patients were excluded from the study if they had: prior lower limb surgery or major trauma; bilateral Achilles tendinopathy; history of lower limb radiculo-neuropathy or miopathy; hypersensitivity to any NSAIDs; used analgesic agents (NSAIDs, salicilates, narcotics) within 1 week; concurrent medical/arthritic disease (e.g. gout, lupus, rheumatoid arthritis); personal history of gastrointestinal hemorrhage or gastritis; other concurrent medical conditions including diabetes, hypertension, angina or congestive heart failure, ischemic cardiopathy, malabsorption, morbid obesity, bleeding disorders; personal history of renal dysfunction, hepatic dysfunction, anemia, etc.

Efficacy assessment

The pre-defined primary efficacy endpoint of the study was a 100-mm pain visual analog scale (P-VAS), where 0= no pain; 100= extreme pain. The "*Analgesic Effect*" was determined by rating values of P-VAS pre-treatment/P-VAS post-treatment x 100.

Clinical affectation was evaluated by the *VISA-A Questionnaire*[28], the *Achilles Tendinopathy Scoring System (ATSS)*[8].

Baseline visit (visit 1) includes: complete medical history and physical examination; vital signs; informed consent; evaluation (P-VAS, VISA-A, ATSS, leg stiffness); NSAID prescription. Follow-up visit at day 8° includes: complete medical history and physical examination; vital signs; adverse effect/tolerability monitoring; evaluation of pain (P-VAS) and leg stiffness.

Leg stiffness was indirectly determined by modeling the vertical ground reaction force on a portable mat *(Axon Jump 2.0, Axon Bioingeniería Deportiva, Bs. As., Argentina)* measuring flight and contact time during hopping[29,30]:

where m is body mass, CT is contact time, and FT is flight time.

Each subject performed a warm-up for approximately ten minutes (jogging, cycling, skipping, and stretching) and got used to hopping at preferred frequency. The test consisted of hopping in place on one leg, for ten seconds with his hands on his hips while keeping their leg as straight as possible, in three series. Randomization defined which leg was examined first (injured/non affected). A 2-minute rest period was allowed between each series. The stiffness was calculated for each hop and the mean across the hops was estimated. The maximal stiffness mean value was selected for each subject. The test was repeated if the subject did not adhere to the specific jumping protocol. The "*leg stiffness ratio*" (LSR), leg stiffness of the injured leg / leg stiffness of healthy leg, was calculated to determine the relative patient affectation and was used for intra-group comparison and correlation analysis.

Method

Twenty-eight male patients (aged 39.17±10.31 years, range 19-50) were eligible for the study and received etoricoxib 120 mg/day orally for 7 days. Patients' height and weight averaged 172.41±7.78 cm (range 153-180) and 74.58±14.08 kg (range 49-107), respectively.

No additional treatment was prescribed to both groups and the patients must avoid any weight-bearing exercise or sport activity during the anti-inflammatory therapy period.
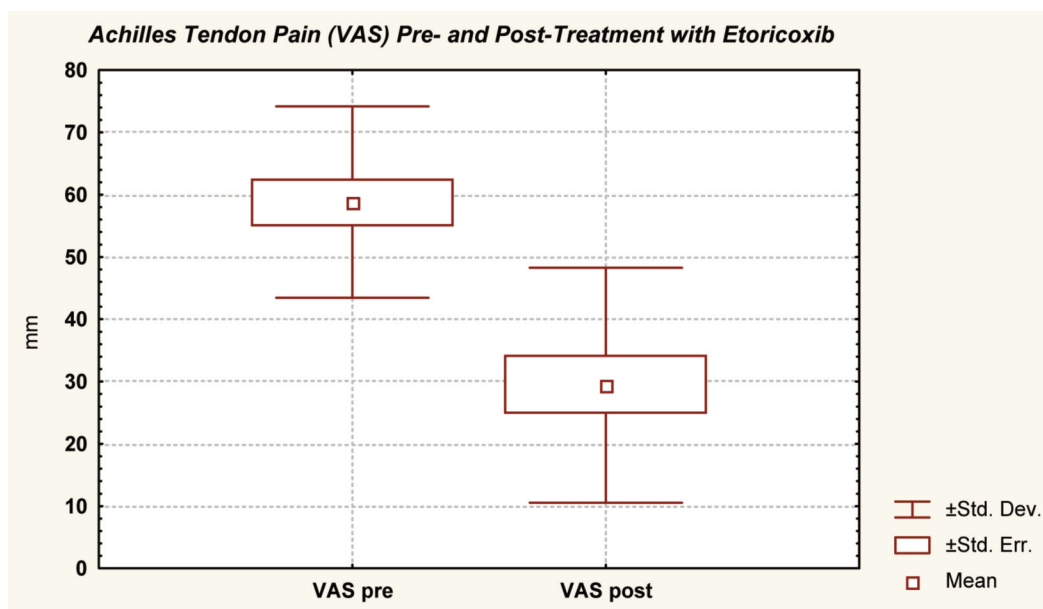
Figure 1. Achillodynia (VAS) pre- and post-treatment with etoricoxib.

At follow-up visit (day 8), the patient was tested in the same manner by an independent blinded examiner.

Safety and tolerability assessments

Throughout the study, patients were carefully monitored for clinical adverse events (AEs). Patients were required to report all adverse events that occurred from the time the patient signed informed consent at visit 1 until 14 days after the drug was discontinued. AEs commonly associated with NSAID or selective COX-2 inhibitor use (for example, elevations in blood pressure, lower extremity edema) and the percentage of patients who discontinued from the study due to adverse experiences were also monitored.

Statistical analysis

A power analysis showed that a sample size of 22 patients, would have 95% power to detect a 10 % difference in leg stiffness pre- and after anti-inflammatory treatment (sd: 0.09) with a 0.05 1-sided significance level. The clinically relevant equivalence range for the primary endpoint was defined as ±10 mm on the VAS pain scale (0-100 mm VAS). This comparability boundary was based upon that used in previous studies with etoricoxib. Statistical analysis was performed using Statistica™ software (*StatSoft Inc, Tulsa, Oklahoma*). Student-t and Wilcoxon tests were used for testing differences between groups or within groups, respectively; $p<0.05$ was considered significant.

Results

Efficacy

Over the 7-day treatment period, etoricoxib provided significant pain relief of Achilles tendon pain measured by the 0-100 mm P-VAS compared to that experienced at the first visit: 54.5±21.6 (CI 95% 44.3-64.6; range 10-80) and 24.5±24.8 (CI 95% 12.8-36.1; range 0-70), respectively ($p=0.0008$, Wilcoxon matched pairs test) (Figure 1).

The *Analgesic Effect* (P-VAS post- /P-VAS pre- treatment x 100) averaged 50.61±31.95% (range 0-100%; CI 95%: 34.1-67.0). After treatment with etoricoxib, the majority of patients reported clinical improvement in achillodynia (89.28%; n=25); a few of them showed no changes (7.14%; n=2), while one patient reported worsening of tendon pain (3.57%) after COX inhibitor therapy.

Leg stiffness

Leg stiffness at baseline averaged 13.04±3.32 kN/m (CI95%: 11.44-14.64) in the injured leg, and 14.64±3.94 kN/m (CI95%: 12.78-16.58) in the uninjured leg. After treatment with etoricoxib, leg stiffness averaged 13.77±4.57 kN/m (CI95%: 11.57-15.98) in the injured leg, and 14.02±3.63 kN/m (CI95%: 12.27-15.78) in the uninjured leg.

Leg stiffness ratio (LSR) showed a significant improvement from baseline values to measurements at day 8°: 0.89±0.11 (CI95%: 0.84-0.95), and 0.97±0.13 (CI95%: 0.91-1.03), respectively (p=0.020, Student test for dependent samples) (Figure 2). Correlation analysis between leg stiffness (LSR) and clinical evaluation tests at baseline (P-VAS, VISA, ATSS) was not significant.

Safety and tolerability

Treatment was well tolerated; the incidence of clinical AEs was 0%. No patient discontinued treatment due to lack of efficacy or AEs. The research protocol did not consider rescue therapy.
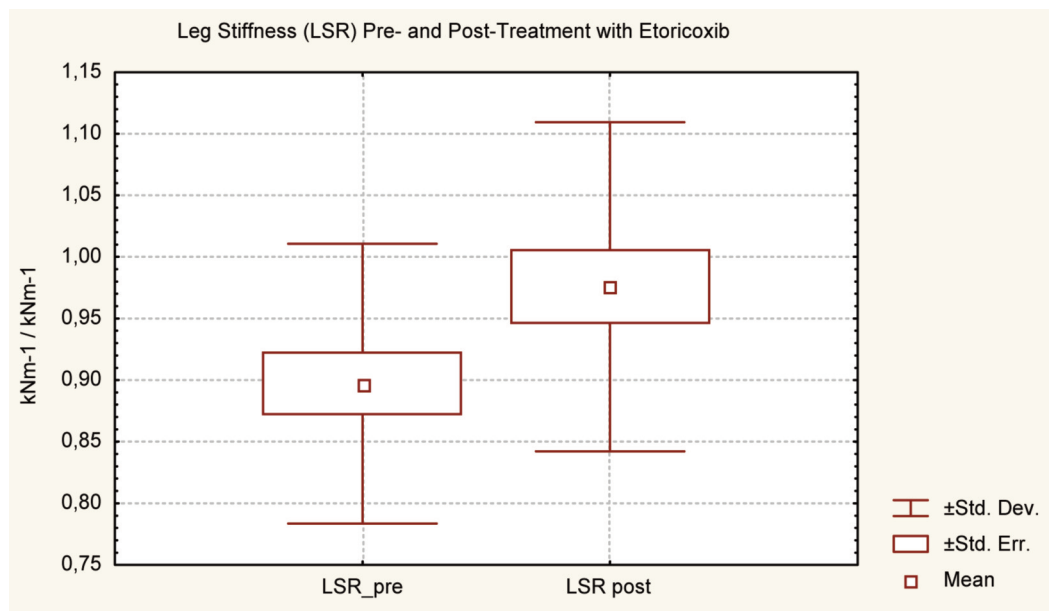
Figure 2. Leg stiffness values pre- and post-treatment with etoricoxib.

Discussion

The main finding of the present study indicated that patients suffering acute unilateral Achilles tendinopathy increased their leg stiffness of the affected side after oral anti-inflammatory therapy. Morevoer, after seven days of COX inhibitor therapy with etoricoxib, achillodynia was reduced in the majority (89%) of this sample of athletes, and they reached a significant relief (50%) of the tendon pain measured by a VAS.

Injuries of the Achilles tendon cause impairment in lower leg muscle tendon function, but the issue of how tendon pain affects leg mechanical abilities and performance is still unknown. Silbernagel et al[31] have found that full-symptomatic recovery in patients with Achilles tendinopathy does not ensure full recovery of muscle tendon function. Only 25% of the patients who were no longer symptomatic had full function as measured by a test battery, including jumps and hopping movements.

Leg stiffness represents the average stiffness of the overall musculoskeletal system during the ground contact phase, and it influences the mechanics and kinematics of the body´s interaction with the ground[22]. In spite of the simplicity of the spring mass model relative to the complexity of the actual neuromuscular system, it describes the mechanics of bouncing gaits remarkably well[22]. Recent studies have shown that leg stiffness is significantly decreased in patients suffering unilateral Achilles tendinopathy[23]. That research showed that mild to moderate Achilles tendon affectation significantly reduced overall leg stiffness[23]. According to Wang et al[32], tendon pain may have the potential to influence the volitional activation of leg muscles and force production. Results of the present research support that leg stiffness is affected by acute Achilles tendon pain. After achieving significant pain relief using oral NSAIDs, leg stiffness increased significantly compared to baseline values.

The source and the background of pain mechanisms associated with Achilles tendinopathy have not yet been clarified. It is hypothesized that the main cause of pain in patients with symptomatic Achilles tendinopathy does not arise from the tendon itself but is generated by its surrounding tissues[33]. The process starts with localized tendon micro-injury and degeneration, which are caused by ageing and repetitive strain below the failure threshold of the tendon. When demands of the tendon are higher than can be managed, micro-injuries develop. Due to the lack of blood vessels within the tendon instead of a chemical, a neurogenic inflammatory process is activated to repair these micro-ruptures. This neurogenic inflammation occurs in the tissue surrounding the Achilles tendon. The transition to symptomatic tendinopathy is marked by nerve proliferation accompanying the vascular ingrowth (neovascularization) to repair the defect, which arises from the paratenon. Therefore, short-term use of etoricoxib and other NSAIDs will be helpful to control pain derived from this neurogenic inflammation in the acute phase of Achilles tendinopathy.

Previous clinical studies have established the efficacy and tolerability of etoricoxib in several chronic musculoskeletal conditions such as osteoarthritis, rheumatoid arthritis, low back pain, and ankylosing spondylitis[34]. Etoricoxib has also been approved for the treatment of a few acute painful conditions, including primary dysmenorrhea, acute gouty arthritis, and postoperative pain[34-36]. To the best of our knowledge, the present study is the first research showing the efficacy of etoricoxib in acute tendon disorders such as Achilles tendinopathy.

Furthermore, it is the first report of a COX-2 inhibitor in sports-related soft tissue injuries, which are the most prevalent lesions among athletes. According to the present data of efficacy and safety, etoricoxib has emerged as a valid alternative for pain control in the initial phase of sport-related soft-tissue disorders like tendinopathies. However, the efficacy of these NSAIDs for the treatment of acute tendinopathies should not be directly extrapolated to other chronic tendon injuries. Most chronic tendinopathies are considered as degenerative processes rather an inflammatory condition[3,37]. Further clinical studies should be carried out to evaluate the efficacy of COX-2 inhibitors in chronic tendinopathies.

In summary, activity-related pain is the primary complaint of athletes suffering acute Achilles tendinopathy. The main goal of initial treatment in these patients is to relieve pain. Results of the present study demonstrated that patients suffering of acute unilateral Achilles tendinopathy increased their leg stiffness of the injured side after oral anti-inflammatory therapy with etoricoxib. Effective control of tendon pain in the acute phase of such sports-related injuries may contribute to reduce morbidity and improve capabilities associated with high performance like leg stiffness.

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