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Long-term efficacy of dobesilate in chronic patellar tendinopathy.

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ABSTRACT

There is a wide variety of treatment options available for patellar tendinopathy, the majority of which are non-surgical, and no consensus exists on the optimal method of treatment. We report that peritendinous injection of dobesilate in patients with chronic patellar tendinopathy, resulted in significant long-term improvement in knee function and reduced pain.

Keywords:

Patellar tendinopathy. Dobesilate. Peritendinous injection. Fibroblast growth factor

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Introduction

Patellar tendinopathy is a painful knee injury due to overuse, common among jumping athletes. Prevalence of patellar tendinopathy varies from different sports. For example, in young elite soccer players the prevalence of this condition was 13.4% [1], and the duration of symptoms for this condition was 32 ± 25 months [2]. This disease is difficult to treat and there is no treatment of choice, conservative or surgical [3]. In normal, asymptomatic adult tendons, the expression of angiogenic factors is mostly suppressed, while in chronic overused tendons, angiogenic factors are markedly increased in the early and late phases of overuse process [4]. It has been found that cyclic strain applied to tendon cells yields to angiogenic gene expression and synthesis, including fibroblast growth factor (FGF) [5]. Furthermore, it has been reported that neoangiogenesis was associated with an impaired biochemical properties in tendon [6]. Thus targeting angiogenic pathways could represent a new way to treat tendinopathy. Previously, we have reported the short-term efficacy of dobesilate (a FGF inhibitor) injection in patellar tendinopathy [7]. The aim of the present study is to evaluate the long-term effectiveness of dobesilate in patients with chronic patellar tendinopathy.

Patients and Treatment

In the current study, 7 tendons from 7 elite athletes from different sports with chronic patellar tendinopathy were enrolled. Patients referred anterior knee pain and tenderness in patellar enthesis. Conservative therapy did not improve his pain. Pain and hypervascularity were recorded using Visual Analogue Scale (VAS) from 0 to 10, with 10 representing maximal pain, and colour Doppler ultrasound respectively, before and 6 months after treatment. After discussing, the various treatment options with patients, they opted to try a dobesilate injection to the patellar tendon and signed an informed consent. Lidocaine was infiltrated into the skin overlying the patella

enthesis. Patients received thereafter a peritendinous solution of dobesilate (2ml) in the patellar enthesis. Dobesilate was administered as a 12.5% solution of diethylammonium 2,5-dihydroxybenzene sulfonate (etamsylate. Dycinone®. Sanofi-Aventis. Paris. France), under ultrasound-guided procedure into the peritendinous patellar enthesis. The procedure was uneventful. Patients were advised to perform some gentle range of motion exercises the following day.

Results and Discussion

At 6 months follow-up visit, patients showed a significant reduction of their pain (Figure 1), and colour Doppler ultrasound scans depicted no or few remaining neovessels. Furthermore, patients were able to return to previous level of sport without any restriction.

As an example of effectiveness of peritendinous dobesilate injection, we show colour Doppler ultrasound scans of a professional soccer player with patellar tendinopathy, at baseline and after 6 months after treatments. At presentation, pain was rated as 7 out of 10 on VAS. At 6 months follow-up visit, patient reported a dramatic reduction of his pain, and the VAS was rated at 1. Colour Doppler ultrasound scans revealed no neovessels at that time and remodelling of tendon tissue toward a more normal structure (Figure 2)

Normal tendons are no painful and have no visible blood vessels when examined with colour Doppler ultrasound. In contrast, pain has been associated to hypervascularity, and sclerosis of these vessels has been shown to significantly decrease pain [8].

Hypervascularity (angiogenesis or neovascularization) is the hallmark of tendinopathy [7-9]. There is a body of evidence to suggest that neural "sprouting" or neoinnervation accompanies neovessel formation, and that the neoinnervation may be a contributor or even responsible for the pain tendinopathy [10-13]. If the process of

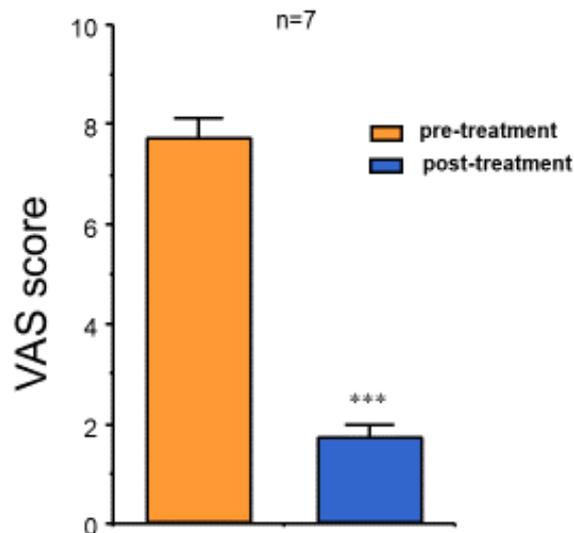


Figure 1. Dobesilate reduces pain associated with chronic patellar tendinopathy. Pain was determined by visual analogue scale (VAS) scores at presentation (pre-treatment) and at six months after intratendinous injection of 250 mg dobesilate (post-treatment). Data are expressed as mean \pm SEM of VAS scores obtained from seven patients (n=7). *** indicates $p < 0.001$ by paired t -test.

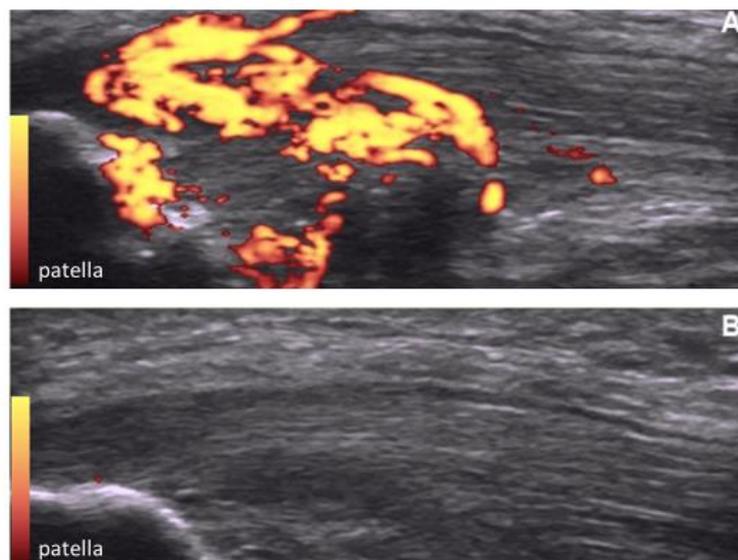


Figure 2. Long-axis colour Doppler ultrasound scans taken at the same plane at baseline (A) and at six months after intratendinous injection of 250mg dobesilate (B). Note the disappearance of hypervascularity after treatment.

neovascularization leads to painful neoinnervation, treatments that stop or hinder the neovascularization may be successful at reducing the pain in chronic tendinopathy. Fibroblast growth factor (FGF) is a pro-angiogenic protein [14] that plays an important role in the pathophysiology of tendinopathy

[15,16]. Potentially, agents that inhibit local expression of FGF, such as dobesilate, [17,18] may inhibit tendon hypervascularity and consequently tendon pain. Since target inhibition of FGF in tissues undergoing pathological angiogenesis is safe without significant off-target effects in normal tissues

[19], dobesilate is an attracting drug for treating tendinopathies.

Experimental evidence suggested a role of FGF in pain modulation [20-22] Furthermore, FGF stimulates substance P that has long been recognized as an important molecule in nociception and pain signalling [23]. Furthermore, substance P has been found in increased levels in chronic tendon pathology [24]. Additionally, substance P also accelerates angiogenesis [25].

Since FGF participates in nociception, injecting dobesilate into the areas of tendon neovascularization could not only decrease the number of pathological neovessels, but also eradicate the pain-generation nerve pathways. Large-scale therapeutic trials are obviously

needed for more solidly establishing the efficacy of dobesilate in the treatment of patellar tendinopathy. The results presented here seem a reasonable support for undertaking these trials.

Conclusion

The large prevalence, the invalidating symptoms, the large time needed to return to activities, and the challenging management of chronic tendinopathy formerly known as “jumper’s knee” constitute all together an important matter for searching an effective and safe treatment for this condition. Dobesilate, an inhibitor of fibroblast growth factor seems to be effective in reducing vascular density and pain in chronic patellar tendinopathy.

Conflict of Interest: None

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