Intratendinous Injection of Platelet-Rich Plasma under US Guidance to Treat Tendinopathy: A Long-Term Pilot Study

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ABSTRACT

Purpose: To assess the potential therapeutic effect of intratendinous injection of platelet-rich plasma (PRP) under ultrasound (US) guidance to treat tendon tears and tendinosis in a pilot study with long-term follow-up.

Materials and Methods: The study included 408 consecutive patients referred for treatment by PRP injection of tendinopathy in the upper (medial and lateral epicondylar tendons) and the lower (patellar, Achilles, hamstring and adductor longus, and peroneal tendons) limb who received a single intratendinous injection of PRP under US guidance. Clinical and US data were retrospectively collected for each anatomic compartment for upper and lower limbs before treatment (baseline) and 6 weeks after treatment. Late clinical data without US were collected until 32 months after the procedure (mean, 20.2 months). The McNemar test and regression model were used to compare clinical and US data.

Results: QuickDASH score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and residual US size of lesions were significantly lower after intratendinous injection of PRP under US guidance at 6 weeks and during long-term follow-up compared with baseline (P < .001 in upper and lower limb) independent of age, gender, and type of tendinopathy (P > .29). No clinical complication was reported during follow-up.

Conclusions: Intratendinous injection of PRP under US guidance appears to allow rapid tendon healing and is well tolerated.

ABBREVIATIONS

D0 = day 0, PRP = platelet-rich plasma, VAS = visual analogue scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, W6 = week 6

Tendon tear and tendinosis are common disorders that usually result in cessation of relevant activities (1). Although histology of tendinopathy shows no signs of inflammation, early anarchic misalignment of collagen fibers is seen, which results in significant fibrillar disorganization. Regarding neoangiogenesis, it has been shown in the literature that neovessels, even early after the beginning of tendinosis, carry proteolytic enzymes, nitric oxide, and deleterious prostaglandins that may be responsible for tendon degeneration. Conversely, later in the healing process, these neovessels provide active growth factors that stimulate scarring, promote stem cells, and directly stimulate fibroblast-mediated collagen production (2).

Several lines of research have been explored for non-operative treatments of tendinopathy, including ultrasound (US)-guided intratendinous injection of polidocanol, or hyperosmolar solutions, and autologous blood or platelet-rich plasma (PRP), with variable results (3,4).
Peritendinous injection of corticosteroid is widely used to treat tendinopathy, despite the absence of inflammation in this condition and the risk of tendon atrophy or secondary rupture (5, 6). PRP is plasma with a platelet concentration three to eight times higher than in blood, which permits the availability of higher concentrations of active growth factors (ie, platelet-derived growth factor, transforming growth factor-β, vascular endothelial growth factor), and might promote stem cell recruitment and fibroblast collagen production; stimulate tendon repair; and, as suggested in animal models, improve the quality of tendon repair (7).

Although platelet and leukocyte counts in PRP treatment are often not reported in the literature, which makes the results difficult to interpret, many institutions use PRP injections in various conditions (8, 9–11). The aim of our pilot study was to assess the efficacy and tolerance of intratendinous injection of PRP (with controlled platelet and leukocyte number) under US guidance to treat tendinosis and tendon tear in a large group of patients with clinical and US follow-up.

**MATERIALS AND METHODS**

**Patients**

This single-center descriptive retrospective pilot study was conducted from January 2010 to September 2012 in 408 consecutive patients with persistent tendinopathy referred to our institution for PRP treatment after initial conservative treatment failure. Previous conservative treatments consisted of rehabilitation using analgesic physiotherapy and eccentric work. Exclusion criteria were pregnancy, infections, previous corticosteroid injection, and immunodeficiency. Patients who received additional treatment after PRP injection during follow-up (either medical or surgical) were also excluded from long-term follow-up assessment.

Clinical data assessment at day 0 (D0), before PRP treatment, was performed for functional tests using the *QuickDASH* (12) for upper limbs and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (13) for lower limbs. A visual analogue scale (VAS) score (pain intensity ranging from 0–10) was used for pain scoring.

*QuickDASH* is a shortened form of the DASH [Disabilities of the Arm, Shoulder and Hand] Outcome Measure developed in 2005 comprising 11 items. It is designed to measure physical function and symptoms in people with any of several musculoskeletal disorders of the upper limb.

WOMAC is the one of the most widely used self-report measures of lower extremity symptoms and function. Initially developed for use among patients with hip and knee osteoarthritis, it has been used extensively to examine changes after treatments. Used to assess pain, stiffness, and physical function in patients, this test comprises 24 items divided into three subscales: pain (5 items), stiffness (2 items), and physical functions (17 items).

The study included 268 men and 140 women (mean age, 44.4 ± 12.4; median age, 45 y) for early US and clinical follow-up and 393 consecutive patients (260 men and 133 women) were finally included for clinical long-term follow-up from January 2010 to September 2012 with an average follow-up time of 20.2 months. Excluded from long-term clinical follow-up were 15 patients (3.7%) who received five additional corticosteroid injections and 7 patients who underwent surgery after week 6 (W6) because of persistent pain and functional impairment. Before PRP injection, the average duration of symptoms was 6.4 months ± 1.3.

Among the 408 included patients, 250 patients (146 men and 104 women) had tendinopathy involving the upper limb (lateral epicondylar tendons, n = 220 [88%]; medial epicondylar tendons, n = 30 [12%]), and 158 (122 men and 36 women) had tendinopathy involving the lower limb (Achilles tendon, n = 54 [34.2%]; patellar tendon, n = 41 [25.9%]; hamstring and adductor longus tendons, n = 40 [25.3%]; peroneal tendons, n = 23 [14.6%]).

There were 25 cases of tendinosis (15 in lower limb and 10 in upper limb) and 383 cases of tendon tear (239 in upper limb and 144 in lower limb) diagnosed. Among the 15 excluded patients from long-term assessment (13 for corticosteroid injection treatment and 2 for surgery between W6 and long-term follow-up), 14 had a lateral epicondylar cleft tear, and 1 had Achilles tendinosis that was treated by surgery. No comorbidity was noted in these 15 patients.

**US Data before PRP Treatment and PRP Preparation with Intratendinous Injection**

Before PRP injection, all patients had US evaluation by a senior musculoskeletal radiologist with at least 5 years of musculoskeletal imaging experience (L.P., P.M., A.S.) at D0 with a 17-MHz linear probe using B mode and color Doppler (IU-22; Philips Healthcare, Amsterdam, the Netherlands). Axial and longitudinal sonograms enable the diagnosis of the specific type of tendinopathy (ie, tendon cleft tear, defined as an intratendon anechoic liquid gap, or tendinosis, defined as a heterogeneous, generally hypoechoic area with less fibrillar aspect). The tendinopathy area was measured on its long axis. Hyperemia on color Doppler was also noted (stage 0, absence; stage 1, slight; stage 2, moderate; stage 3, important) to measure vascular activity.

The patient was referred to a clinical pathologist (A.P.) for PRP preparation; 27 mL of venous blood was collected in a syringe containing 3 mL of Acid Citrate Dextrose A anticoagulant. Blood was centrifuged at 620g for 15 minutes, and a final volume of 3 mL of PRP was recovered in the lower plasma layer.
The obtained PRP had a platelet concentration equal to about three times the concentration measured in the blood as verified by counting platelets under an optical microscope for 40 patients. PRP contained a controlled platelet number (900,000 per mm$^3$ ± 25,000) and a controlled leukocyte number (200 per mm$^3$ ± 35).

Intratendinous injection of PRP in the tear or tendinosis area under US guidance (with the same ultrasound scan) was performed (L.P., P.M., A.S., B.D.) < 30 minutes after the end of centrifugation in the musculoskeletal interventional department. The transducer was positioned in the visually thickened segment of the tendon. Locoregional anesthesia in fat tissues was performed using 10 mL of lidocaine 1% (Xylocaine; AstraZeneca, London, United Kingdom). An intramuscular 21-gauge needle was inserted in the tendon with at a 45-degree angle, and the PRP injection was performed when the needle reached the tendinosis or tear area of the tendon under US guidance (Fig 1a–d). We tracked the needle under real-time US guidance (without a needle guide) to optimize the precision of the PRP injection in the tendinosis or tear areas, which can be very small. US guidance helped us to identify precisely the entry point for the needle, follow the needle toward the target, and control the quality of PRP injection (adequate location and stability of the needle during the injection).

### Early Clinical US Follow-up and Long-Term Clinical Follow-up

All patients were seen in consultation 6 weeks later by a senior musculoskeletal radiologist with at least 5 years musculoskeletal imaging experience (L.P., P.M., A.S., B.D.). For clinical assessment, QuickDASH for upper limbs and WOMAC for lower limbs were used to assess functional outcome. VAS ranging pain intensity from 0–10 was used to assess pain. Pain level during and immediately after PRP injection was also assessed using VAS.

All US (with the same ultrasound scan) early after therapy was performed in the same time by the same senior musculoskeletal radiologist. For each anatomic compartment, we recorded lesion type (tear or tendinosis), size of the lesion on its long axis, and hyperemia (as activity) using the same US protocol (see data for US performed before PRP injection) at W6 (Fig 2a,b).

Final clinical assessment by QuickDASH, WOMAC, and VAS was performed by a single senior musculoskeletal radiologist (B.D.) in September 2012, 32 months after the procedure (mean, 20.2 mo). We used a binary (yes or no) subjective satisfaction index to assess patient satisfaction and asked about any local complications (at the site of tendinitis) that might have occurred after PRP injection to assess tolerance. The long-term clinical follow-up was performed using a telephone survey.

### Image Analysis and Statistical Methods

US data acquired before and after the procedure were centralized on the picture archiving and communication system. A single reader (B.D.) measured the tendinopathy (tear or tendinosis) area on the long-axis view. Hyperemia on color Doppler was also noted. Image analysis was performed randomly regarding patient selection and US study date.

Statistical analysis was performed using SAS software (SAS Institute, Inc, Cary, North Carolina). Binary variables were tested with the McNemar test. Differences
in lesion size (tear or tendinosis) were compared using the Wilcoxon test. The evolution of intratendinous injection of PRP under US guidance was assessed using a Friedman test. A $P$ value < .05 was considered significant.

**RESULTS**

**Early W6 Clinical and US Follow-up**

No patients were lost to follow-up at W6 for clinical and US evaluation. Patients achieved a significant clinical improvement when comparing functional tests at D0 and W6 follow-up ($P < .001$ for upper and lower limb [$n = 408$] and for each anatomic area with either tendinosis or tendon tear).

In the upper limb, *QuickDASH* scores were $38.5 \pm 9$ at D0 and $15.5 \pm 6.3$ at W6 follow-up. In the lower limb, WOMAC scores were $35.9 \pm 18.8$ at D0 and $12.9 \pm 10.3$ at W6 follow-up (Table 1). All these results were independent of age ($P = .45$), gender ($P = .32$), and the type of tendinopathy (tendinosis or tear) ($P = .38$) at W6 follow-up. VAS scores were also significantly improved ($P < .01$): $5.8 \pm 1.6$ at D0, with residual pain, and $2.3 \pm 1.9$ at W6 follow-up.

Regarding pain during and immediately after PRP injection, VAS mean scores were $1.6 \pm 0.3$ and $0.8 \pm 0.2$, respectively. Aside from transitory local pain that required analgesic oral treatment (4 g paracetamol per day $\times$ 2 days) in nine patients, no major side effects or complications after PRP injection were encountered. No clinical complications were reported during early follow-up.

The residual mean size of lesions for upper and lower limbs, as evaluated by US, was significantly lower at W6 after intratendinous injection of PRP under US guidance compared with baseline ($P < .001$ in upper and lower limb, $P < .001$ for lateral and medial epicondylar tendon lesions, and $P < .001$ for all anatomic compartments in the lower limb). Hyperemia was $2 \pm 1$ at D0 and $3 \pm 0$ at W6 (Figs 3a,b, 4a,b). All these results were independent of age ($P = .86$), gender ($P = .43$) and type of tendinopathy (tendinosis or torn tendon; $P = .56$) (Table 2).

**Table 1. Mean and SD Values of Functional Clinical Data in Upper and Lower Limb at Day 0, Week 6, and Long-Term Follow-up**

<table>
<thead>
<tr>
<th>Upper Limb QuickDASH</th>
<th>Lower Limb WOMAC</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>D0</td>
</tr>
<tr>
<td>Lateral epicondylar tendons</td>
<td>37.9 ± 9.3</td>
</tr>
<tr>
<td>Medial epicondylar tendons</td>
<td>40.5 ± 7.8</td>
</tr>
<tr>
<td>Hip tendons</td>
<td>32.9 ± 18.8*</td>
</tr>
</tbody>
</table>

$D0 = \text{day 0; } LTF = \text{long-term follow-up; } W6 = \text{week 6; WOMAC} = \text{Western Ontario and McMaster Universities Osteoarthritis Index.}$

* $P < .001.$
(P = .29), and type of tendinopathy (tendinosis or tear; P = .38) on long-term follow-up. VAS scores were also significantly improved (P < .01): 1 / 1006 at 1.5 at long-term follow-up.

On long-term follow-up, 349 patients (88.8%) were satisfied with the procedure. No clinical complications were reported during long-term follow-up.

DISCUSSION

Our study strongly suggests that a single intratendinous US-guided injection of PRP allows rapid healing of tendinopathy with good tolerance. To our knowledge, few studies have been published evaluating the clinical efficacy of intratendinous or peritendinous PRP injections in a clinical setting with a long-term follow-up. These studies have shown discordant results regarding the efficacy of PRP injection (4,14,15). Mishra and Pavelko (16) assessed 140 patients with elbow epicondylar pain (mean follow-up, 25.6 mo) and obtained a pain reduction of 93% after PRP intratendinous injection (P < .0001). In the study by Gosens et al (17), injection of PRP reduced pain and increased function significantly in patients with chronic lateral epicondylitis, exceeding the effect of corticosteroid injection after a follow-up of 2 years.

Conversely, Krogh et al (18) showed in a randomized, double-blind, placebo-controlled trial (n = 60) that neither PRP nor glucocorticoid injection was superior to saline intratendinous injection with regard to pain reduction in lateral epicondylitis at 3-month follow-up. However, injection of glucocorticoid had a short-term pain-reducing effect at 1 month and reduced both color

Table 2. Values of US Lesions in Each Anatomic Compartment in Upper and Lower Limb at Day 0 and Week 6

<table>
<thead>
<tr>
<th>Upper Limb</th>
<th>Lower Limb</th>
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<tbody>
<tr>
<td></td>
<td>D0</td>
</tr>
<tr>
<td>Lateral epicondylar tendons</td>
<td>7.5 ± 3</td>
</tr>
<tr>
<td>Medial epicondylar tendons</td>
<td>7.5 ± 2.9</td>
</tr>
<tr>
<td>Patellar tendons</td>
<td>21.2 ± 18.5</td>
</tr>
<tr>
<td>Ankle tendons</td>
<td>10.2 ± 3.9</td>
</tr>
</tbody>
</table>

Note. Values are mean ± SD (mm).
*P < .001.

Figure 3. A 17-mm tear (arrows, a,b) at D0 (a) in the lateral epicondylar tendon with complete filling at W6 (b). (Available in color online at www.jvir.org.)

Figure 4. A 15-mm tendinosis area (arrow, a,b) at D0 (a) in the proximal Achilles tendon with US improvement and hyperemia stage 2 at W6 (b). (Available in color online at www.jvir.org.)

Table 2. Values of US Lesions in Each Anatomic Compartment in Upper and Lower Limb at Day 0 and Week 6
Doppler activity and tendon thickness compared with PRP and saline. Finally, in a systematic review and network meta-analysis (17 trials, 1,381 participants) of randomized controlled trials assessing the effectiveness of injection therapies in lateral epicondylosis, Krogh et al (4) did not find enough evidence from unbiased trials on which to base treatment recommendations regarding injection therapies for lateral epicondylosis. Regarding the treatment of patellar tendinopathy, Vetrano et al (19) found a better improvement at 6-month and 12-month follow-up of PRP intratendinous injection compared with microwave therapy in 46 patients.

Filardo et al (20) showed that multiple injections of PRP provided a good clinical outcome for the treatment of chronic recalcitrant patellar tendinopathy in 43 patients with a mean follow-up of 48.6 months. This study did not include a control group, and PRP platelet concentration was not performed. A level I randomized controlled trial comprising 54 patients suggested that PRP treatment for chronic Achilles tendinopathy did not alleviate pain or improve patient activity compared with a saline control. This study failed to report platelet or leukocyte counts in the PRP treatment, patient age, lesion size, or chronicity of the condition (21). Finally, in a systematic review assessing the efficacy of injectable treatments for noninsertional Achilles tendinosis, Gross et al (22) found variable results regarding the efficacy of PRP intratendinous or peritendinous injection owing to conflicting methodologies.

By assessing PRP in a large population (n = 408) with a systematic US and clinical long-term follow-up, our study provides strong evidence that intratendinous PRP injection under US guidance might be a useful strategy to treat tendinopathy. We strictly used a fixed platelet concentration in PRP (×3) and no adjuvant to avoid adding to the variety of PRP preparations reported in the literature (23–25). We also used a leukocyte-reduced PRP with systematic counting to minimize the acute inflammatory response as reported in the literature (26). In our study, all processing steps were completely standardized and documented from the exact knowledge of platelet and leukocyte concentrations up to the injection control US scan. In addition to these results, this controlled methodology may serve as a pilot to design future prospective studies assessing the efficacy of intratendinous injection of PRP.

Our study has several limitations. First, our injection protocol was based on a single intratendinous injection of PRP (27,28) with a low platelet concentration. Tendon healing might have been even faster had we used higher platelet concentrations or performed multiple injections. However, we chose the lowest concentration of platelets and injected once only to minimize potential secondary effects. Second, we used US to assess the pathologic status of tendons at D0 and W6 but not on long-term follow-up, which was based on a telephone survey. Third, we excluded 15 patients from our long-term clinical follow-up analysis because of additional medical or surgical treatment and potentially artificially improved long-term QuickDASH, WOMAC, and VAS scores. To assess this bias, we recalculated long-term analysis scores allocating worse QuickDASH, WOMAC, and VAS long-term scores for each of our 15 patients and found a QuickDASH score of 11.9 ± 4.8 (n = 408) instead of 11.7 ± 3.8 (n = 393), a WOMAC score of 5.6 ± 5.9 instead of 5.5 ± 3.8, a VAS score of 1.25 ± 1.6 instead 1 ± 1.5, and a long-term satisfaction score of 85.5% instead of 88.8% (results based on real satisfaction data), confirming significant clinical improvement when comparing functional tests at D0, W6, and long-term follow-up (P < .001 for upper and lower limb).

Finally, our study is limited by a lack of histologic assessment and the absence of a control group and requires future confirmation. No placebo group was formed in our series, but in the literature and in our personal experience, tendinopathy does not evolve naturally toward healing in these patients (2). However, this study represents an important descriptive pilot study with imaging guidance performed in a musculoskeletal interventional department, exact knowledge of PRP and leukocyte concentration, and reproducible clinical scores to assess PRP efficacy and tolerance.

In conclusion, despite the absence of a placebo group, this study suggests that intratendinous injection of PRP under US guidance allows rapid tendon healing and decrease in clinical complaints in patients presenting with tendinosis and tendon tear, with excellent tolerance. Additional preclinical and randomized clinical studies comparing PRP with other currently used methods would be of great interest to consolidate clinical practice.

REFERENCES


