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SCIENTIFIC ARTICLE

Needle tenotomy with PRP versus lidocaine in epicondylopathy: clinical and ultrasonographic outcomes over twenty months

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Abstract

Objective To investigate whether pathological changes in elbow epicondylopathy, as assessed by conventional ultrasonography and clinical outcomes, could be modified following tenotomy with platelet-rich plasma (PRP) versus tenotomy with lidocaine.

Methods This prospective sub-study was part of a patient- and assessor-blinded, superiority-type, randomized, lidocaine-controlled trial that was performed in a tertiary hospital to assess the effectiveness of PRP versus lidocaine as tenotomy adjuvants in patients with epicondylopathy. Patients were followed after two sessions of tenotomy with either PRP or lidocaine adjuvants (4 ml) within a 2-week interval. Tendon thickness, echotexture, and neovascularization were assessed as secondary outcome measurements at baseline and at 3, 6, 12, and 20 months after treatment, and correlations with clinical outcomes were examined.

Results Twenty months after treatment, tenotomy induced changes in tendon structure, thickness ($\pm = 0.0006$), vascularity ($p < 0.0001$), and echotexture ($p < 0.0001$). In Disabilities of the Arm, Shoulder and Hand (DASH-E) and pain (VAS-P) scores, 80.85% and 90.91% of patients showed a meaningful clinical improvement, respectively, without differences between PRP and lidocaine. There were significant differences in between-group changes in vascularity over time, $p = 0.037$ and $p = 0.049$ in the unadjusted and adjusted models, respectively. There was no relationship between pain or function and sonographic entities at the various time points.

Conclusions Two successive needle tenotomies induced structural changes in recalcitrant epicondylopathy, with PRP displaying more vascularization and increased thickness over time compared to lidocaine. PRP compared with lidocaine did not result in improved function or decreased pain over 20 months.

Keywords Elbow · Tendinopathy · Ultrasound · Needle tenotomy · PRP · RCT · Vascularization

Introduction

Tendinopathies are degenerative conditions that involve fibroblastic and vascular changes, disruption of collagen fibres and modifications in extracellular matrix composition, and they are often associated with pain and functional impairment [1]. These biological features are increasingly recognized as a failed healing response to microtrauma; tendon attempts to heal, but the process is not accomplished [2].

A wide variety of injection therapies have been studied for tendinopathies. They include needle tenotomy [3], saline high volume [4], hypertonic dextrose and morrhuate sodium [5], autologous blood, platelet-rich plasma (PRP), PRP rich in leukocytes, L-PRP, [6–8] and corticosteroids [9]. However, the ideal treatment remains poorly defined. Injections of platelet-rich plasma (i.e., PRP and L-PRP) aim to regenerate tendons by releasing a complex pool of active cytokines that

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enhance cell proliferation, migration, and the synthesis of extracellular matrix, as shown in laboratory studies [10]. In doing so, PRPs can modulate inflammation, angiogenesis, and tissue anabolism in tendinopathies [11–13]. However, despite positive experimental data, the clinical benefits of PRP injections for tendinopathies are controversial [6–8]. There is only rudimentary knowledge of the PRP mechanism of action in the clinical context because of scarce data demonstrating the biological changes induced by intratendinous PRP injections [14, 15]. Randomized clinical trials and subsequent meta-analyses based on pain and functional outcomes have been inconclusive, and changes in the tendons are seldom reported.

Severe tendinopathies, in all anatomical locations, show a similar spectrum of structural changes that can be assessed by ultrasonography (US). Commonly, changes in tendon thickness and Doppler activity, as well as focal regions of hypoechogenicity accompanied by fading of the normal fibrillary pattern, are described in severe tendinopathies. Therefore, decreased tendon thickness, recovery of echotexture, and remission of neovascularization are considered findings that represent improvement [16].

Elbow tendons are superficial, and research concerning the diagnostic value of US in lateral epicondylalgia has indicated that the hypoechogenicity of the common extensor origin has the best combination of diagnostic sensitivity and specificity [17], while neovascularity inside the enthesis and cortical irregularities have strong specificity. In addition, thickness measurements could help to evaluate structural adaptations [18]. Thus, conventional US provides the opportunity to investigate whether pathological changes (neovascularization, echotexture, and tendon thickness) could be modified with tenotomy and PRP.

This study is based on the hypothesis that recovery of tendon structure is part of the intended effect of the proposed management (tenotomy associated with PRP). Thus, we performed repeated ultrasonographic measurements at different time points in order to determine if conventional sonography could identify structural changes after two sessions of needle tenotomy within a 2-week interval. We also investigated if there is a relationship between ultrasound assessments and clinical outcomes.

Methods

This prospective sub-study was part of a patient- and assessor-blinded, superiority-type, randomized, lidocaine-controlled trial that was performed in a tertiary hospital to assess the effectiveness of PRP as a tenotomy adjuvant. The hospital ethics medical committee approved the study protocol that was registered at clinicaltrials.gov (number NCT01945528). The full details of the randomized control study have been reported elsewhere [19]. Initially, the randomized controlled trial (RCT) was scheduled with a 1-year follow-up, but those patients who were blinded to treatment allocation were contacted for a longer-term follow-up (20 months).

Inclusion criteria were the presence of elbow tendinopathy (clinically diagnosed), the failure of conservative treatments, including analgesic and anti-inflammatory medications (NSAIDs), physiotherapy associated with the orthosis and symptoms lasting 3 months or longer. Patients with BMI > 35 and full tendon tears were excluded. Baseline characteristics obtained included demographic and metabolic status variables, DASH-E, VAS-P, color Doppler activity, and tendon thickness.

Procedures

Patients were randomized to the PRP group (needle tenotomy + PRP) or lidocaine group (needle tenotomy + lidocaine) and followed through two sessions of needle tenotomy within a 2-week interval. PRP was prepared by single centrifugation at 570 $\times g$ for 6 min. The plasma fraction was collected with a syringe and activated just before the intervention with $CaCl_2$, final concentration 22.6 μM, All patients received 2 ml of lidocaine in the subcutaneous tissue to mitigate tenotomy pain; then, the syringe containing the injection was connected to the needle, which was inserted intratendinously parallel to the tendon fibers. We performed percutaneous interventions with a 22-gauge needle. Punctures were performed from distal to proximal parallel to the tendon long axis. The tendon was repeatedly fenestrated (15–25 times) by redirecting the needle in different directions until tissue softening is achieved. The periosteum was abraded with the tip of the needle. Simultaneously, the injectable was delivered to the hypoechogenic and surrounding areas. The second intervention was milder and involved approximately ten perforations and no abrasions of the periosteum [20]. Injected volumes were 4.23 ± 1.09 ml (range, 1–5 ml) of lidocaine and 4.47 ± 1.11 ml (range, 1–5 ml) of PRP in the first session and 4.18 ± 1.14 ml (range, 1–5 ml) of lidocaine and 4.53 ± 0.88 ml (range, 2–5 ml) of PRP in the second session. There were no differences between the injected volumes. No exercise therapy was added to the treatment. The clinical assessors, the patients, and the statisticians that collected the data and performed the analyses were all blinded to group allocation. A radiologist with more than 20 years of experience in musculoskeletal interventional US performed the needle tenotomies, guided with a 4–13-MHz high-frequency linear probe (Esaote MyLab 70 XVG, Esaote S.p.A. Genoa, Italy).

Ultrasound assessments

Serial echographic images were obtained with the patient in supine position, the elbow flexed 110° and forearm in pronation, and the transductor parallel to the tendon fibres.

Thereafter, the findings were corroborated in the axial short-axis plane, which is especially relevant for echotexture assessments (Fig. 1a, b). The echotexture was graded 0–4 as follows: normal (0); 3° of structural damage (1–3) according to the hypoechogenic area, including mild (hypoechogenicity involves less than 1/3 of the area), moderate (hypoechogenicity involves between 1/3 and 2/3) or severe (hypoechogenicity involves more than 2/3); and lastly, tendons with partial small tears (4). When present, the partial tear size was measured in both axes. Vascularization was assessed by means of power Doppler with pulse repetition frequency (PRF) set at 500 Hz and graded from 0 to 4 as follows: no vessels (0); one or two vessels on the tendon surface (1); few (1–4) intratendinous vessels (2); more than four but less than eight intratendinous vessels (3); and hypervascularity with flame appearance (4). The tendon thickness ratio was obtained by built-in on-screen electronic calipers using a split screen. Tendon thickness (mm) was measured by placing one caliper on the cortical interface (approximately 5 mm from the joint margin) and another caliper on the tendon surface at the point where maximum thickness was observed. Representative images were obtained at baseline (prior to tenotomies), and repetitive measurements were then performed at 3, 6, 12, and 20.57 months (2.68) after treatment. Images were stored using the picture archiving and communication system (PACS) for evaluations.

The ultrasound outcomes were evaluated by two trained radiologists (blinded to treatment allocation) using the same ultrasound machine and algorithm. Another senior radiologist independently scored the stored ultrasonographic images. Inter-evaluator discordances between scores were reviewed and settled. Figure 1 shows representative images of the ultrasonographic measurements.

Clinical outcome measurements

Clinical outcomes were obtained from serial DASH-E and VAS-P self-reported questionnaires at 3, 6, 12, and 20 months.

Statistical analysis

Data are shown as the mean with standard deviation and frequencies. The Levine test was used to assess homogeneity of variance. The initial differences between groups were based on a two-sample *t* test. Comparisons of categorical data were made with Pearson χ^2 test. Generalized linear mixed models were used to estimate the changes in ultrasonographic and clinical outcomes and to evaluate the differences between [tenotomy+PRP] and [tenotomy+lidocaine] treatment groups over the 20-month follow-up duration. The treatment, time of measurement, and treatment-by-time interaction were included as fixed effects in the models. Patients were included as random effects in the intercept of different repeated measurements. This process was performed assuming that each measurement was a category and without autocorrelation within

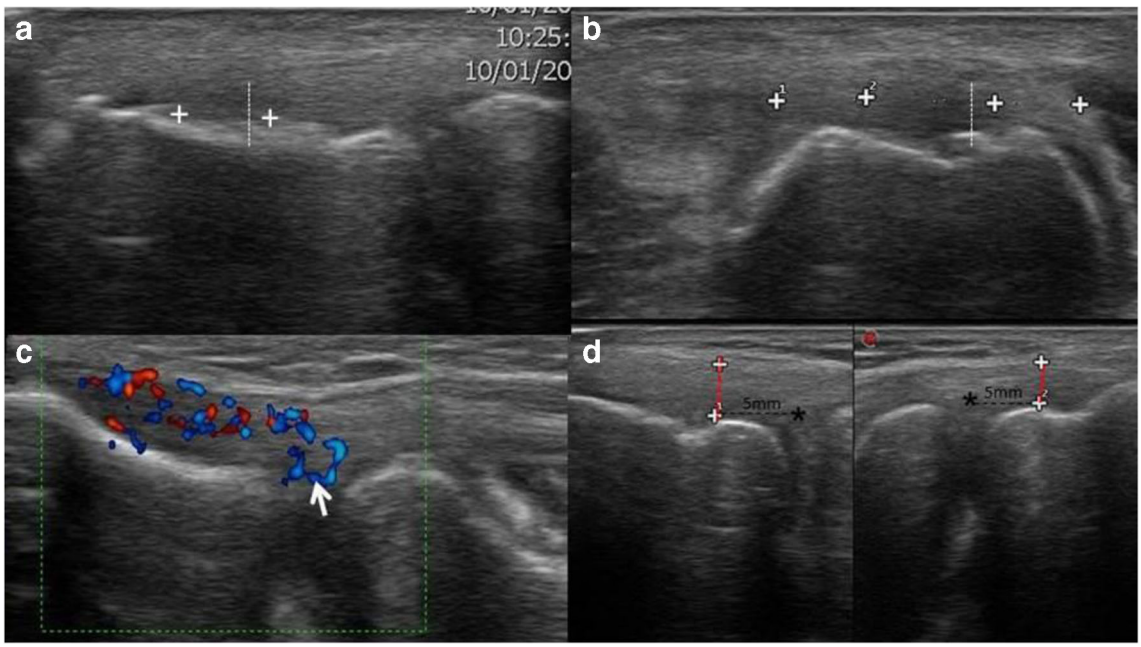

Fig. 1 Representative ultrasonograms of the common lateral extensor tendons illustrating the three ultrasound criteria used to assess potential changes over a 20-month period after tenotomy. Echotexture evaluated in the longitudinal (**a**) and axial (**b**) planes is defined as moderate (affected area between 1/3 and 2/3 of the tendon) as the probe is moved 90° along the *dotted line*; (**c**) Doppler activity is graded as 4 in the longitudinal sonogram, with the *white arrow* showing vascularization in the radial collateral ligament; and (**d**) thickness is expressed as the ratio between the longitudinal measurements of the affected (*right*) and contralateral (*left*) tendons

an individual. The overall effect of the treatment was assessed by testing the interaction between treatment and time of measurement. Additionally, these models were also adjusted for baseline values of outcome variables, socio-demographics, and risk factors. Likewise, to simplify the fixed effects' structure, maximum likelihood ratio tests were used following backward, forward, and stepwise strategies. Spearman's tests were used to assess the association between ultrasonographic and clinical variables. No imputation method was used to handle the missing data. All analyses were performed using the PROC MIXED and GLIMMIX procedures of the SAS 9.4 statistical package.

Results

Participants and clinical outcomes at 20 months after treatment

Patients treated from April 2014 to May 2017 were included. A flow diagram of the progress of study participants up to 12 months after treatment has been published previously [21] (submitted Martin JOSR). A total of 71 patients were treated. Informed consent was obtained from all individuals. One patient in the PRP group and four patients in the lidocaine group were lost to follow-up. Fifty-one patients (blinded to treatment allocation), including 27 patients in the PRP group and 24 patients in the lidocaine group, were examined in the 20th month.

Twenty months after treatment, 80.85% and 90.91% of patients showed a meaningful clinical improvement, i.e., a change of more than 25% was observed in the responses to the DASH-E and VAS-P, respectively, relative to the baseline. There were no significant clinical differences between the PRP and lidocaine groups. The DASH-E changed from 42.76 (15.93) and 44.60 (17.20) in the lidocaine and PRP groups, respectively, before treatment to 14.47 (10.01) and 12.62 (14.54) in the lidocaine and PRP groups, 20 months after treatment. The VAS-P changed from 5.87 (1.52) before treatment to 1.73 (2.08) after 20 months in the lidocaine group and from 5.97 (1.77) to 1.39 (1.40) after 20 months in the PRP group. There were no differences in complications between groups. A similar number of patients in both groups reported pain and tingling sensation, which resolved spontaneously in the short term.

Structural changes over time (0–20 months) in the entire patient cohort and differences between treatment groups concerning thickness, vascularity, and echotexture

Patients had similar US characteristics at baseline (Table 1). Structural changes in the tendons, as assessed by US over 20 months, are shown in Table 2**.** Overall, there was a significant decrease in tendon thickness ($p = 0.0006$), vascularity ($p < 0.0001$), and echotexture ($p < 0.0001$) comparing the baseline and 20-month post-intervention assessments.

The tendon thickness ratio decreased over time in both groups (3 vs. 20 months ($T = 2.47$, $p = 0.014$); 3 vs. 20 months ($T = 4.07$, $p < 0.001$); 6 vs. 20 months ($T = 2.66$, $p = 0.008$)). However, there was no statistical significance for the global between-group comparison of 20-month modifications in thickness ratio ($p = 0.089$ in the adjusted model). Interestingly, 6 months after treatment, the thickness ratio remained significantly higher in the PRP group than in the lidocaine group ($p < 0.001$).

Figure 2 shows the distribution of patients in the five Doppler categories at the time-points evaluated. Twenty months after treatment, 19.55% of patients in the lidocaine group versus 40.15% of patients in the PRP group showed no vascularization, and 15.66% of patients in the lidocaine group versus 6.3% of patients in the PRP group showed more than five intratendinous vessels. There were significant differences in between-group changes in vascularity over time, $p = 0.037$ and $p = 0.049$ in the unadjusted and adjusted models. Vascularity was adjusted for baseline degree, diabetes, affected tendon, and statin treatment*time.

Table 3 describes the baseline prognostic factors of the vascularization category that were included in the adjusted model. Anatomical location (medial or lateral) and diabetes showed a constant effect that did not change at the follow-up time-points. Instead, taking statins showed a main effect on vascularization and interaction over time.

Association between sonographic parameters and clinical outcomes (correlations)

There was no relationship between pain or function and sonographic categories for Doppler or echotexture, either at baseline or at any other time point. However, VAS-P and DASH-E correlated positively at baseline ($r_s = .390$, $p = 0.001$, $n = 68$) and during the follow-up ($r_s = .761$, $p < 0.001$, $n = 53$ at 3 months; $r_s = .865$, $p < 0.001$, $n = 48$ at 6 months; $r_s = .894$, $p < 0.001$, $n = 38$ at 12 months; and $r_s = .766$, $p < 0.001$, $n = 45$ at 20 months).

On the other hand, sonographic characteristics were associated between them. In particular, there was a positive association between echotexture and tendon thickness before and up to 12 months after treatment with values as follows: baseline ($r_s = .241$, $p = 0.045$, $n = 69$), 3 months ($r_s = .428$, $p < 0.001$, $n = 67$), 6 months ($r_s = .414$, $p = 0.001$, $n = 62$) and 12 months ($r_s = .276$, $p = 0.031$, $n = 61$). The positive correlation disappeared at 20 months ($r_s = .117$, $p = 0.471$, $n = 40$). Doppler and echotexture showed no association at baseline but a significant association at all time points after treatment

Table 1 Ultrasonographic characterization before treatment

	Lidocaine ($n = 35$)	PRP ($n = 34$)	Total ($n = 69$)
Mean tendon thickness ratio (SE)	1.16 (0.21)	1.18 (0.22)	1.17 (0.21)
% Vascularization, no. (%)			
No vessels	7 (20.00)	5 (14.71)	12 (17.39)
1 or 2 vessels on tendon surface	1 (2.86)	3 (8.82)	4 (5.80)
1 to 4 intratendinous vessels	10 (28.57)	17 (50.00)	27 (39.13)
5 to 8 intratendinous vessels	11 (31.43)	6 (17.65)	17 (24.64)
Vascular ball	6 (17.14)	3 (8.82)	9 (13.04)
% Echotexture, no. (%)			
Normal	3 (8.57)	1 (2.94)	4 (5.80)
Hypoechogenicity < 1/3 of the tendon	2 (5.71)	4 (11.76)	6 (8.70)
Hypoechogenicity > 1/3 and < 2/3	10 (28.57)	10 (29.41)	20 (28.99)
Hypoechogenicity > 2/3	15 (42.86)	16 (47.06)	31 (44.93)
Partial-thickness tear	5(14.29)	3 (8.82)	8 (11.59)

($r_s = .340$, $p = 0.005$, $n = 67$ at 3 months; $r_s = .420$, $p = 0.001$, $n = 63$ at 6 months; $r_s = .423$, $p = 0.001$, $n = 61$ at 12 months, and $r_s = .478$, $p = 0.001$, $n = 43$ at 20 months post-treatment) (Figs. 3, 4, and 5).

Discussion

In this study, PRP influenced tendon thickness and vascularity outcomes differently than lidocaine, but PRP was not superior to lidocaine with regard to reducing pain and disability after 20 months in patients with recalcitrant elbow epicondylopathy. Initially, this study had an RCT design with a 12-month follow-up, and changes in pain and function were the primary outcomes [19]. Because of the loss of clinical data, we were not able to detect clinical differences [21], and we planned another follow-up visit after 20 months. Importantly, the length of follow-up in most RCTs ranges from 3 to 6 months [6–8], and only one in every three RCTs has a 12-month follow-up. Long-term follow-up is important because PRP actions rely on paracrine mechanisms, i.e., the molecular pool activates local cells, which respond to PRP by synthesizing further signaling proteins that are mainly involved in angiogenesis and inflammation [10]. These can have repercussions on pain and function in the mid and long term. Actually, in contrast to corticosteroids, PRP effects are not observed immediately after injection, but are evident after a few months [7].

However, in our study, despite the long-term follow-up, we found no measurable clinical benefit (DASH-E and VAS-P) to the addition of PRP over lidocaine. This could be expected as, according to a recent systematic review and meta-analysis [7], the impact of PRP on clinical outcomes is not detectable with a sample size below 70 patients per group; thus, we were unable to detect significant clinical differences.

However, the likelihood of detecting significant treatment effects may be improved, not only by performing larger trials with longer follow-up periods but also by measuring parameters that are relevant to the biological properties of the product. Essentially, with laboratory studies claiming to regenerate the injured tendon with PRP, measuring US parameters that are relevant to the biological properties of the product could help to elucidate which mechanism of action is important for efficacy and how these biological interventions could be improved. In this study, PRP was prepared in a cleanroom following our standard operating procedures, and PRP cost per treatment was 46 €. Tenotomy took the same time when performed with either PRP or lidocaine adjuvants; radiology room occupancy was 15–20 min in both cases.

Using five serial ultrasonographic assessments over 20 months, we found that the degree of neovascularization was downregulated over time differently by PRP than lidocaine. Additionally, tendon thickness over time was different in tendons treated with PRP. These findings are in accordance with experimental data reporting the influence of PRP on inflammation, angiogenesis, and tissue anabolism [11–13] and with ultrasonographic data in epicondylopathies [22] that showed an increase in tendon thickness 3 months after PRP injection compared to that of saline. PRP releases a myriad of signaling proteins, for instance, vascular endothelial growth factor (VEGF), platelet factor (PF4), thrombospondin (TSP-1), platelet derived growth factor (PDGF), basic fibroblastic growth factor (bFGF), and endostatin that modulate angiogenesis. In addition, insulin-like growth factor (IGF-I) and transforming growth factor (TGF-b1) stimulate the synthesis of collagen 1 by tendon cells.

There are varied procedures for PRP delivery that can influence clinical and structural outcomes. Our technique

Table 2 Serial ultrasonographic measurements and clinical assessments over time

Outcome	Unadjusted change			Treatment-time measurement interaction (*p* value)	Multivariate-adjusted attributable difference (*p* value) a,b,c
	Lidocaine	PRP	Total		
Echography outcomes					
Mean tendon thickness ratio (SE)[a]				0.102	0.089
3 months	1.14 (0.03)	1.17 (0.03)	1.15 (0.02)		
6 months	1.06 (0.03)	1.17 (0.03)*	1.12 (0.02)		
12 months	1.08 (0.03)	1.11 (0.03)	1.09 (0.02)		
20 months	1.04 (0.03)	1.03 (0.03)	1.04 (0.03)		
% Vascularization[b], no. /total no. (%)				0.037	0.049
3 months					
No vessels	6/35 (17.14)	1/33 (3.03)	7/68 (10.29)		
1 or 2 vessels on tendon surface	3/35 (8.57)	5/33 (15.15)	8/68 (11.76)		
1 to 4 intratendinous vessels	13/35 (37.14)	12/33 (36.36)	25/68 (36.76)		
5 to 8 intratendinous vessels	8/35 (22.86)	8/33 (24.24)	16/68 (23.53)		
Vascular ball	5/35 (14.29)	7/33 (21.21)	12/68 (17.65)		
6 months					
No vessels	11/33 (33.33)	6/33 (18.18)	17/66 (25.76)		
1 or 2 vessels on tendon surface	3/33 (9.09)	5/33 (15.15)	8/66 (12.12)		
1 to 4 intratendinous vessels	10/33 (30.30)	13/33 (39.39)	23/66 (34.85)		
5 to 8 intratendinous vessels	8/33 (24.24)	7/33 (21.21)	15/66 (22.73)		
Vascular ball	1/33 (3.03)	2/33 (6.06)	3/66 (4.55)		
12 months					
No vessels	13/29 (44.83)	12/33 (36.36)	25/62 (40.32)		
1 or 2 vessels on tendon surface	5/29 (17.24)	7/33 (21.21)	12/62 (19.35)		
1 to 4 intratendinous vessels	7/29 (24.14)	8/33 (24.24)	15/62 (24.19)		
5 to 8 intratendinous vessels	3/29(10.39)	3/33 (9.09)	6/62 (9.68)		
Vascular ball	1/29 (3.45)	3/33 (9.09)	4/62 (6.45)		
20 months					
No vessels	9/26 (34.62)	18/24 (75.00)	27/50 (54.00)		
1 or 2 vessels on tendon surface	7/26 (26.92)	2/24 (8.33)	9/50 (18.00)		
1 to 4 intratendinous vessels	7/26 (26.92)	3/24 (12.50)	10/50 (20.00)		
5 to 8 intratendinous vessels	1/26 (3.85)	0/24 (0.00)	1/50 (2.00)		
Vascular ball	2/26 (7.69)	1/24 (4.17)	37/50 (6.00)		
% Echotexture[a], no. /total no. (%)				0.210	0.259
3 months					
Normal	6/34 (17.65)	4/33 (12.12)	10/67 (14.93)		
Hypoechogenicity < 1/3 of the tendon	9/34 (26.47)	7/33 (21.21)	16/67 (23.88)		
Hypoechogenicity > 1/3 and < 2/3	10/34 (29.41)	11/33 (33.33)	21/67 (31.34)		
Hypoechogenicity > 2/3	8/34 (23.53)	11/33 (33.33)	19/67 (28.36)		
Partial-thickness tear	1/34 (2.94)	0/33 (0.00)	1/67 (1.49)		
6 months					
Normal	7/31 (22.58)	9/32 (28.13)	16/63 (25.40)		
Hypoechogenicity < 1/3 of the tendon	13/31 (41.94)	4/32 (12.50)	17/63 (26.98)		
Hypoechogenicity > 1/3 and < 2/3	9/31 (29.03)	13/32 (40.63)	22/63 (34.92)		
Hypoechogenicity > 2/3	1/31 (3.23)	6/32 (18.75)	7/63 (11.11)		
Partial-thickness tear	1/31 (3.23)	0/32 (0.00)	1/63 (1.59)		
12 months					
Normal	7/29 (24.14)	12/32 (37.50)	19/ 61 (31.15)		

Table 2 (continued)

Outcome	Unadjusted change			Treatment-time measurement interaction (*p* value)	Multivariate-adjusted attributable difference (*p* value) a,b,c
	Lidocaine	PRP	Total		
Hypoechogenicity < 1/3 of the tendon	13/29 (44.83)	7/32 (21.88)	20/61 (32.79)		
Hypoechogenicity > 1/3 and < 2/3	7/29 (24.14)	10/32 (31.25)	17/61 (27.87)		
Hypoechogenicity > 2/3	1/29 (3.45)	3/32 (9.38)	4/61 (5.56)		
Partial-thickness tear	1/29 (3.45)	0/32 (0.0)	1/61 (1.64)		
20 months					
Normal	11/27 (40.74)	9/19 (47.37)	20/46 (43.48)		
Hypoechogenicity < 1/3 of the tendon	7/27 (25.93)	6/19 (31.58)	13/46 (28.26)		
Hypoechogenicity > 1/3 and < 2/3	4/27 (14.81)	4/19 (21.05)	8/46 (17.39)		
Hypoechogenicity > 2/3	1/27 (3.70)	0/19 (0.00)	1/46 (2.17)		
Partial-thickness tear	4/27 (14.81)	0/19 (0.00)	4/46 (8.70)		
Clinical Outcomes					
Mean DASH-E scores (SE)				0.438	0.390
3 months	20.78 (3.50)	27.31 (3.42)	24.04 (2.44)		
6 months	18.12(3.55)	20.26 (3.53)	19.19 (2.51)		
12 months	20.52 (3.59)	21.11 (3.63)	20.82 (2.56)		
20 months	14.70 (3.47)	15.43 (3.67)	15.07 (2.52)		
Mean VAS-P scores (SE)				0.412	0.479
3 months	2.92 (0.40)	3.67 (0.40)	3.30 (0.28)		
6 months	2.58 (0.40)	2.39 (0.41)	2.48 (0.29)		
12 months	2.18 (0.45)	2.26 (0.44)	2.22 (0.31)		
20 months	1.78 (0.41)	1.87 (0.46)	1.83 (0.31)		

P values represent the statistical significance for the global between-group comparison of the evolution of US outcomes over 20 months

[a] Tendon thickness and echotexture were adjusted for baseline degree

[b] Vascularization was adjusted for baseline degree, diabetes, affected tendon, and statin treatment*time

[c] DASH-E and VAS-P scores were adjusted for baseline scores, affected tendon, and statin treatment*time

*$p = 0.000$

can be described as two sequential needle tenotomies (within a 2-week interval) under US guidance with intratendinous delivery of the product (and probably extratendinous), along with a local anesthetic (lidocaine) injected peritendinously and no associated exercise program. We and other authors surmised that repetition of the PRP injection might prolong the exposure of growth factors and other cytokines released from the PRP to the tendons, thereby improving the results [23–26]. PRP in combination with tenotomy can modulate neovascularization, a typical feature of the failed healing response to the underlying tendinopathy. However, although tendon structure improved in terms of vascularity and thickness, complete fiber continuity was not restored. Moreover, corroborating other studies, we failed to show any association between clinical and sonographic parameters at different time points.

Although we found correlations between vascularization and DASH, VAS-P, and echotexture in the entire set of data (data not shown), we failed to show correlations at the specific time points. The reason for this temporal mismatch is poorly understood and can be related not only to limitations on clinical scores but also to the way in which degenerative changes in the tendon interact with peripheral nerves, with subsequent activation of nociceptive pathways controlled by higher CNS mechanisms [27]. Moreover, in a previous study, we showed that, depending on patients' clinical characteristics and baseline ultrasonographic entities (not on tenotomy adjuvant), clinical improvements manifested at different time points [20].

This study has several limitations that need to be considered when deciding how to generalize our findings (both positive and negative). First, we performed a combined intervention, i.e., tenotomy + PRP, and whether tenotomy is synergistic with PRP is underresearched. Few studies have compared dry tenotomy

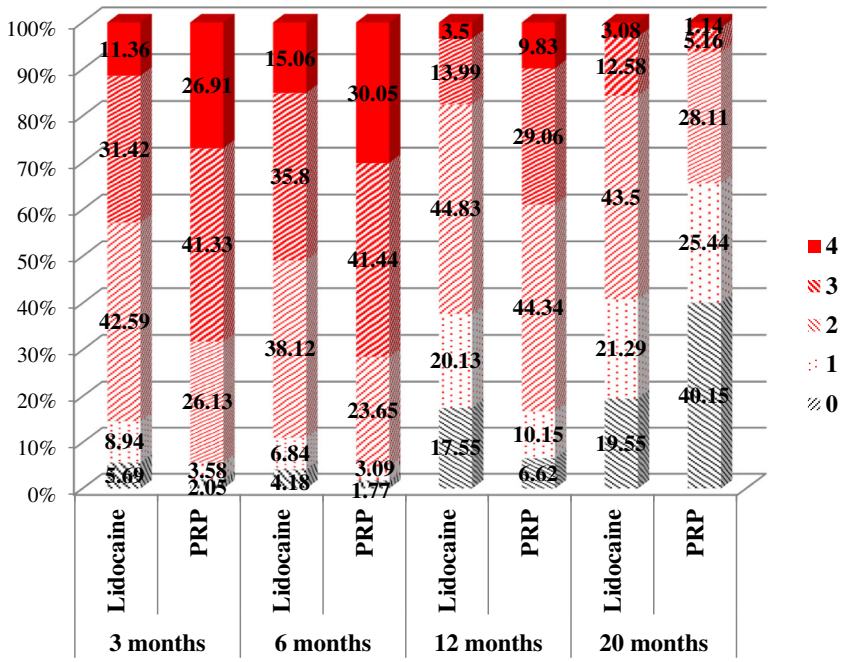

Fig. 2 Bar chart illustrating the estimated distribution of the Doppler categories in both groups at the various time points. Data were adjusted by baseline degree, diabetes, affected tendon, and statin treatment by time-point

with PRP injections as alternative treatments [28, 28]. Second, according to most recent meta-analyses condensing PRP information [6–8], our study was underpowered to detect differences in clinical outcomes and sonographic changes. We calculated the sample size for primary functional outcomes based on a previous RCT [28] comparing PRP with corticosteroids in lateral epicondylopathies, but we did not estimate the sample size for sonographic variables. Second, an ultrasound investigation was performed using conventional Doppler US. Although we carefully developed our sonographic assessment protocols, operator-dependent variability is unavoidable; we are aware that the determination of echotypes by means of computerized ultrasound tissue characterization (UTC) could help to eliminate this variability. Moreover, contrast-enhanced ultrasound may be more efficient in assessing vascularity after PRP injection [14]. However, limited time in the ultrasound room is an intrinsic limitation of our health service organization, and our pragmatic research was performed in a general tertiary hospital. Third, we have included patients with both lateral and medial epicondylopathies, adding heterogeneity to our results. Further limitations include lack of a control group, small sample size, and loss of clinical data.

In summary, two-needle "wet" tenotomies reduced pain, enhanced function, and induced structural changes in elbow tendons over 20 months. Changes in tendon thickness and vascularity over time differed depending on the adjuvant; PRP had a stronger influence over temporal changes of vascularity and tendon thickness. There were relationships between thickness, echotexture, and vascularity, but these ultrasonographic characteristics showed no correlations with clinical outcomes.

Table 3 Distribution of patients according to affected tendon (i.e., medial or lateral), statin intake, and diabetes diagnosis

	No vessels	1 or 2 vessels on tendon surface	1 to 4 intratendinous vessels	5 to 8 intratendinous vessels	Vascular ball
Tendon affect, %					
Lateral	4.11	6.76	37.88	35.99	15.26
Medial	14.80	17.69	46.64	17.09	4.50
Statins, %					
No	4.09	6.72	37.79	36.06	15.34
Yes	14.15	17.74	46.62	17.01	4.48
Diabetes, %					
No	43.52	25.12	25.76	4.54	0.99
Yes	0.90	1.62	14.30	37.32	45.86

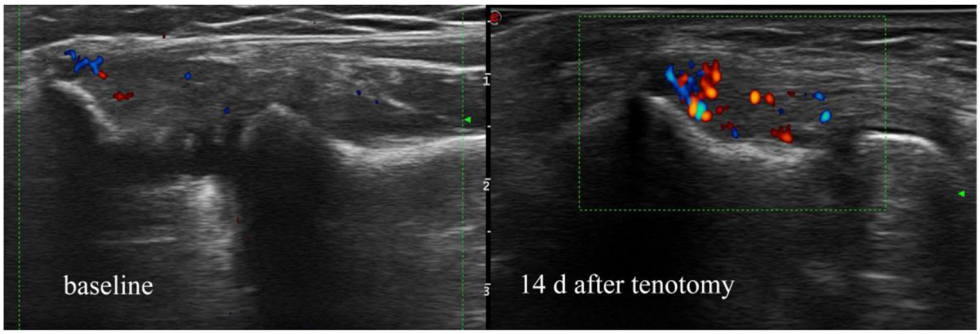

Fig. 3 Representative ultrasonograms of the common lateral extensor tendons at baseline and 14 days after tenotomy

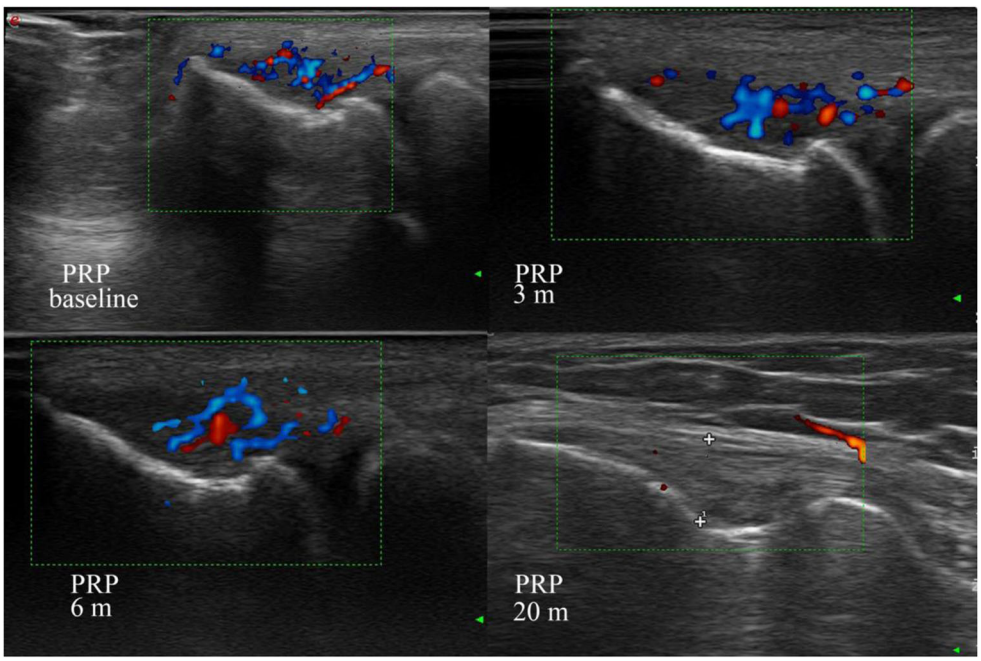

Fig. 4 Representative ultrasonograms at baseline and 3, 6, and 20 months after two tenotomies within 2 weeks interval with PRP as adjuvant

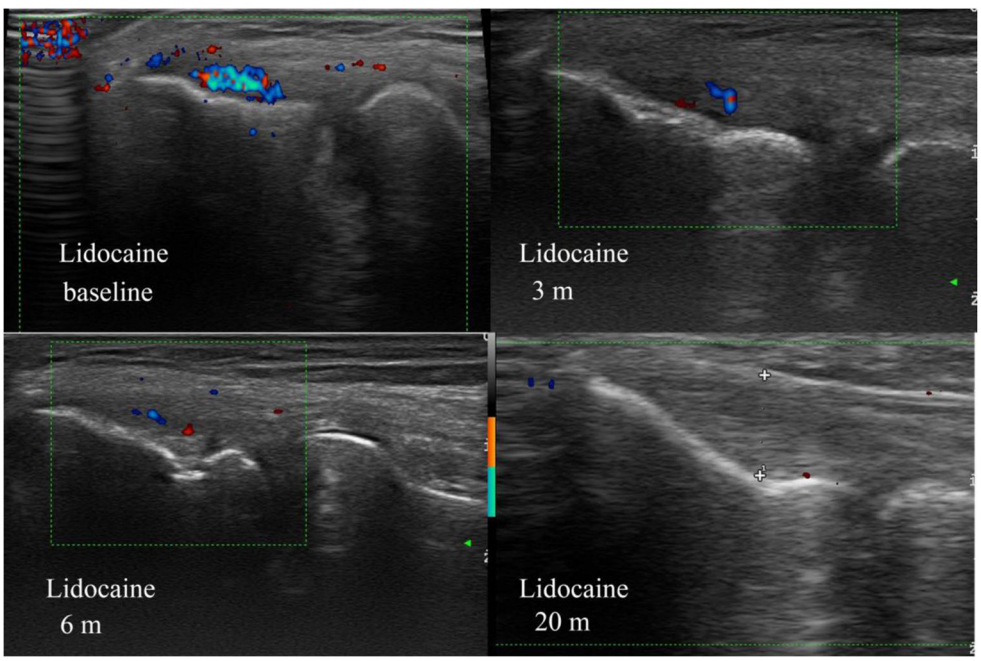

Fig. 5 Representative ultrasonograms at baseline and 3, 6, and 20 months after two tenotomies within 2 weeks interval with lidocaine as adjuvant

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Compliance with ethical standards

Clinical trial registration: Ethics approval and consent to participate This study was approved by the Ethics Committee of Hospital Universitario Cruces (No. CEIC 13/04). All enrolled patients provided written informed consent. The study protocol was registered at ClinicalTrials.gov (identifier NCT01945528) EUDRACT No.2013–000478-32.

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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