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Treatment of Lateral Epicondylitis With Platelet-Rich Plasma, Glucocorticoid, or Saline

A Randomized, Double-Blind, Placebo-Controlled Trial

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Investigation performed at the Diagnostic Centre, Region Hospital Silkeborg, Silkeborg, Denmark

Background: Lateral epicondylitis (LE) is a common musculoskeletal disorder for which an effective treatment strategy remains unknown.

Purpose: To examine whether a single injection of platelet-rich plasma (PRP) is more effective than placebo (saline) or glucocorticoid in reducing pain in adults with LE after 3 months.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: A total of 60 patients with chronic LE were randomized (1:1:1) to receive either a blinded injection of PRP, saline, or glucocorticoid. The primary end point was a change in pain using the Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire at 3 months. Secondary outcomes were ultrasonographic changes in tendon thickness and color Doppler activity.

Results: Pain reduction at 3 months (primary end point) was observed in all 3 groups, with no statistically significant difference between the groups; mean differences were the following: glucocorticoid versus saline: -3.8 (95% CI, -9.9 to 2.4); PRP versus saline: -2.7 (95% CI, -8.8 to 3.5); and glucocorticoid versus PRP: -1.1 (95% CI, -7.2 to 5.0). At 1 month, however, glucocorticoid reduced pain more effectively than did both saline and PRP; mean differences were the following: glucocorticoid versus saline: -8.1 (95% CI, -14.3 to -1.9); and glucocorticoid versus PRP: -9.3 (95% CI, -15.4 to -3.2). Among the secondary outcomes, at 3 months, glucocorticoid was more effective than PRP and saline in reducing color Doppler activity and tendon thickness. For color Doppler activity, mean differences were the following: glucocorticoid versus PRP: -2.6 (95% CI, -3.1 to -2.2); and glucocorticoid versus saline: -2.0 (95% CI, -2.5 to -1.6). For tendon thickness, mean differences were the following: glucocorticoid versus PRP: -0.5 (95% CI, -0.8 to -0.2); and glucocorticoid versus saline: -0.8 (95% CI, -1.2 to -0.5).

Conclusion: Neither injection of PRP nor glucocorticoid was superior to saline with regard to pain reduction in LE at the primary end point at 3 months. However, injection of glucocorticoid had a short-term pain-reducing effect at 1 month in contrast to the other therapies. Injection of glucocorticoid in LE reduces both color Doppler activity and tendon thickness compared with PRP and saline.

Keywords: lateral humeral epicondylitis; tendinopathy; growth factors; platelet-rich plasma; glucocorticoid; ultrasonography; injection therapy; pain; randomized controlled trial

Tennis elbow, also known as lateral epicondylitis (LE), has an estimated prevalence of 1% to 3%, peaks at age 45 to 54 years, and is as common in men as in women.^{34,42,53} The incidence rate of LE is estimated to be 4 to 7 per 1000 patients per year.^{22,59} A common work-related disorder, LE has a prevalence of up to 14.5% in strenuous jobs such as those in the meat and fish industries.^{6,29,42,52} The average duration of a typical episode of LE is reported to

be between 6 months and 2 years.^{24,39} In a general practice trial of an expectant waiting policy, 83% of the patients with LE of more than 6 weeks' duration recovered after 1 year.⁵⁵ The costs associated with LE are substantial in terms of both lost productivity and health care use.⁵⁴ The majority of cases are believed to be caused by a musculotendinous lesion of the common tendon origin at or near the attachment to the lateral epicondyle, often as a result of overload injury, typically after minor and often unrecognized trauma (microtrauma).^{39,62}

The treatment of LE varies widely, from "watchful waiting," nonsteroidal anti-inflammatory drugs, physical therapies including exercise and bracing, injection therapies,

and uncommonly as a last option, surgery. Injection with glucocorticoid has been used since the 1950s and has for many years been the treatment of choice.⁹ However, because several studies have shown no long-term effect,^{28,31,40,55} the search for alternative treatments has intensified. During the past 10 years, therapies have become available focusing on the use of growth factors as a stimulant of tendon repair. Platelet-rich plasma (PRP) is blood plasma with an increased concentration of autologous platelets, which is now being used as a part of wound treatment, bone healing, alloplastic surgery, and muscle/tendon damage.^{2,38,51} It can potentially enhance tendon healing and tissue regeneration by delivering various growth factors and cytokines, thereby effecting cell proliferation, chemotaxis, cell differentiation, and angiogenesis. Among these growth factors are platelet derived, transforming, vascular endothelial, epidermal, and fibroblast. The theory is that application of PRP intratendinously will stimulate the repair mechanisms and promote tendon healing.^{4,10,14}

Ultrasonography (US) is an important diagnostic tool in sports medicine and rheumatology and a common outcome measure in clinical trials.^{16,20,25} It is a reliable, noninvasive, widely available, and inexpensive imaging technique for assessing tendon lesions.^{21,25} The high acoustic contrast with the surrounding tissue makes tendons particularly suitable for US examination.²¹ The US findings in tendinopathy in general are characterized by increased tendon size, Doppler activity, irregularity of the fibrillar appearance, focal hypoechoic areas, and calcifications.^{1,27,33,61} Several studies have described these US features in patients with LE.^{7,30,32,36,48} Our objective was to determine whether 1 injection of PRP or glucocorticoid reduces pain more effectively than isotonic saline in adults with LE.

MATERIALS AND METHODS

Study Design and Participants

The study was a double-blind, randomized controlled trial (RCT) including 60 patients with LE. The local injection treatments were PRP, glucocorticoid, or isotonic saline, with 20 patients in each treatment arm.

Inclusion criteria were LE symptoms for more than 3 months in which LE was defined as pain on the lateral side of the elbow and pain at the lateral epicondyle on direct palpation and during resisted dorsiflexion of the wrist.^{46,49} Ultrasonography of the common tendon origin required

a definite sign of tendinopathy with a color Doppler flow of at least grade 2 (range, 0-4) assessed at baseline.¹²

Exclusion criteria were age younger than 18 years, glucocorticoid injection within the past 3 months, previous tennis elbow surgery, inflammatory diseases (eg, rheumatoid arthritis, psoriatic arthritis, or inflammatory bowel disease), neck pain, shoulder pain on the ipsilateral side, and other chronic widespread pain syndromes.⁴⁵

The diagnosis was verified in all patients by the same physician, who also performed the inclusion, randomization, and treatment procedures. Another masked study physician, the same in all patients during the entire follow-up, was responsible for outcome assessments at 4 weeks (by mail) and at 3, 6, and 12 months (at clinical visit). Patients who did not achieve a satisfactory treatment response (assessment made by patient and doctor) at 3 or 6 months had the option to discontinue the study and receive the standard treatments available at the department. In such cases, there would be no further trial follow-up.

The patients were referred to the Rheumatology Unit at the Diagnostic Centre at the Region Hospital Silkeborg by general practitioners or other rheumatology/orthopaedic departments. The study was approved by the institutional review board and independent ethics committee of Central Denmark Region (No. 20080067) and was carried out in accordance with the principles of the Convention on Human Rights and Biomedicine of Oviedo in 1997. All enrolled patients provided written informed consent. The study protocol was registered at ClinicalTrials.gov (identifier: NCT 01109446).

Randomization

Sequence Generation. Eligible participants were randomly assigned in permuted blocks of 6, using a simple "shuffling envelopes" procedure to undergo PRP, glucocorticoid, or saline injection.

Allocation Concealment and Implementation. To ensure concealment of the assigned intervention, the treating rheumatologist obtained the sequentially numbered, opaque, sealed envelope containing the participant's assigned intervention from the study nurse.

Blinding

As part of the blinding technique, a blood sample was obtained from all the patients. The time from blood sampling to intervention was the same, approximately 20 minutes, at all visits, and preparation of the 3 injectants took place out of sight of the patient. All patients were

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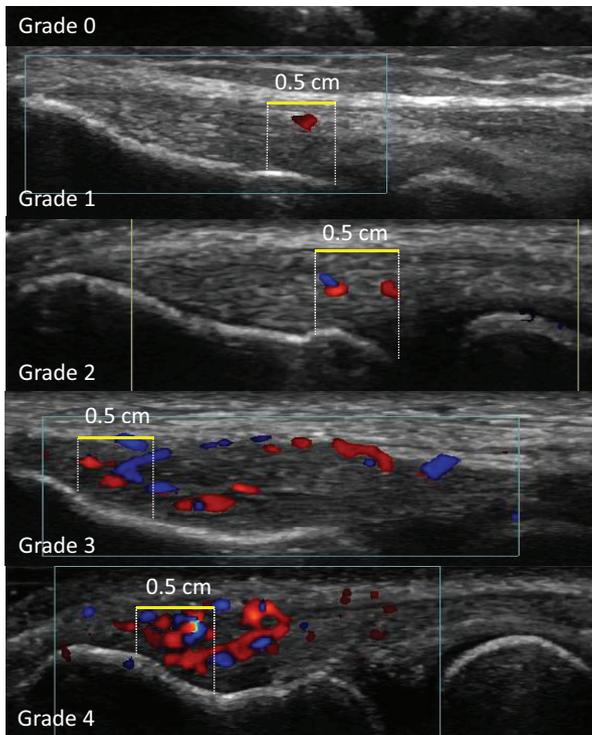


Figure 1. Longitudinal ultrasonogram of the common tendon origin, illustrating grading of color Doppler activity from grade 0 to 4. The grading is performed in the region of interest (ROI) defined as a 0.5-cm longitudinal part of the tendon with maximum color Doppler activity. A horizontal yellow line measuring 0.5 cm marks the superficial border of the ROI, white dotted lines mark the proximal and distal borders, and the bone marks the deep border. Grade 0 = no activity; grade 1 = single vessel in the ROI; grade 2 = Doppler activity in <25% of the ROI; grade 3 = Doppler activity in 25%-50% of the ROI; grade 4 = Doppler activity in >50% of the ROI.

blindfolded during blood sampling and while receiving the intervention. Before the intervention, all patients received 10 to 15 mL of lidocaine 10 mg/mL in the peritendon of the common tendon origin guided by US. The patient and outcome assessor were blinded to the treatment, but the treating physician was not.

US Evaluation

The US evaluation was performed at all clinical visits, at baseline, and at 3, 6, and 12 months. Patients were examined in a sitting position with the elbow flexed to 90°, the wrist pronated, and the arm resting on a table. We used a high-quality ultrasound scanner (EUB 900, Hitachi Medical Europe, Zug, Switzerland) with a 14-MHz linear transducer. The transducer was aligned with the long axis of the radius over the common tendon origin. The common tendon origin was examined with color Doppler US in the longitudinal plane by moving the transducer from side to side, locating the part with the most Doppler activity. The color Doppler activity is usually seen in an area limited

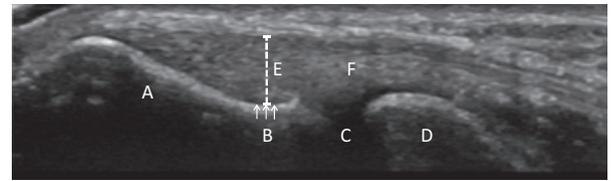


Figure 2. Longitudinal ultrasonogram illustrating the tendon thickness measure of the common tendon origin. A, Lateral epicondyle; B, arrows indicate the “plateau”; C, radiohumeral joint; D, radial head; E, dotted line indicates tendon thickness; and F, common tendon origin.

proximally by the tip of the lateral epicondyle and distally by the humeroradial joint space. The superficial border was the most superficial fibers, and the deep border was the bone. Doppler settings were the same for all patients, with a gain setting just below the noise level and the V-Scale set to 350.⁵⁷ We ranked the color Doppler activity in a new ranking scale from grade 0 to 4. The grading was estimated in a 0.5-cm longitudinal part of the tendon with the maximal Doppler activity (region of interest) (Figure 1): grade 0 = no activity; grade 1 = single vessel; grade 2 = Doppler activity in <25% of the region of interest; grade 3 = Doppler activity in 25% to 50% of the region of interest; and grade 4 = Doppler activity in >50% of the region of interest. This ranking method is similar to that used by Poltawski et al.⁴⁷ Tendon thickness²⁶ was measured at an anatomic landmark at the bony surface of the lateral epicondyle, which we labeled the “plateau.” This plateau is located at the capitellum between the insertion of the tendon and the humeroradial joint. Tendon thickness is measured from the plateau to the tendon surface perpendicular to the length of the tendon (Figure 2). At baseline, a US print, a “template,” was made from each patient, indicating where the tendon thickness was measured. This template was used to ensure that the outcome assessor measured the tendon thickness at exactly the same anatomic spot at each follow-up.

Intervention Procedure

The ultrasound-guided injection technique was performed with the elbow bent to 90°. The ultrasound probe positioned perpendicular to the common tendon origin, making a longitudinal image, was used to guide all the injections longitudinally. A 0.8 × 50-mm syringe was used. The PRP and saline were injected using an antiseptic pepping technique by making 1 skin portal and about 7 tendon perforations evenly distributed in the common tendon origin from the most proximal part of the lateral epicondyle toward the humeroradial joint. The glucocorticoid injection was made with 1 skin portal, and the content was injected at the deepest aspects of the common tendon origin to limit the risk of skin atrophy.

The treatment solutions were as follows. Glucocorticoid injection consisted of 1 mL triamcinolon 40 mg/mL + 2 mL lidocaine 10 mg/mL. Saline injection consisted of 3 mL saline 0.9%. For the PRP, 27 mL of whole blood

(autologous) was collected into a 30-mL syringe containing 3 mL sodium citrate (anticoagulant) and then placed in a disposable cylinder in a centrifuge for 15 minutes at a speed of 3.2 ($\times 1000$ rpm). Platelets were collected using the Recover GPS II system (Biomet Biologics Inc, Warsaw, Indiana). The outcome of this process is approximately 3 to 3.5 mL of PRP, with a platelet concentration increased on average by 8-fold compared with whole blood.¹³ To achieve a physiological pH, the PRP was buffered with 8.4% sodium bicarbonate. The PRP was injected right after preparation. One injection was given at baseline. The post-treatment protocol was the same in all participants. Patients were asked not to use or minimally use the arm for 3 to 4 days and thereafter gradually return to normal activities if the pain level was acceptable. If analgesic drugs were needed, acetaminophen was recommended. A standard tennis elbow stretching and training program from www.sportnetdoc.com was prescribed.¹⁵

Outcomes

Baseline characteristics included demographic variables, age, sex, body mass index, tender points, dominant hand, smoking history, duration of LE, location of symptoms, pain intensity,⁵⁰ functional score,⁵⁰ color Doppler activity, tendon thickness assessed by US, working full time, analgesics use, LE related to work, and previous glucocorticoid treatment.

The primary efficacy outcome was changes in pain intensity after 3 months using the pain section of the Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire.^{41,50}

The secondary end points included changes in functional disability using the functional section of the PRTEE, US changes in color Doppler signal and tendon thickness, adverse events, and any additional pain caused by the injection therapy itself. For both pain and functional disability, the PRTEE validated for LE was applied.^{41,50} The PRTEE assesses the average pain and function of the affected arm during the preceding week. It consists of 2 parts, 1 assessing pain and 1 assessing function using a numeric rating scale from 0 to 10, with 5 and 10 questions, respectively. We used a validated Swedish version of the PRTEE⁴¹ translated into Danish because the culture and language are very similar.

All patients were evaluated for safety, including all reported adverse events. To monitor the pain caused by the treatment and how long it lasted, we asked on a 0-to-10 numeric rating scale (0 = no pain, 10 = worst pain imaginable) how much pain/discomfort was caused by the treatment during the first months. The pain duration was measured on a 0-to-5 verbal rating scale (0 = treatment did not actually cause any additional pain, 1 = additional pain lasted <1 week, 2 = 1-2 weeks, 3 = 2-3 weeks, 4 = 3-4 weeks, 5 = additional pain after 4 weeks).

Statistical Analysis

The power and sample size estimations were calculated to detect a treatment difference in the primary analysis of the patients' self-reported changes in pain intensity according

to the PRTEE for the PRP, steroid, or saline groups. A priori calculations were originally made on an anticipated 12-month result. Because of a huge dropout rate with very few participants left after 3 months, the 3-month data were chosen post hoc as the primary outcome (all participants still in the study). Secondary analyses at 6 and 12 months were based on both last observation carried forward and per protocol. Prospectively, this study was not powered with a superiority design to compare the 2 active arms (PRP vs glucocorticoid). For a 2-sample pooled *t* test of a normal mean difference with a 2-sided significance level of .05, assuming a common standard deviation of 10 PRTEE score points, a sample size of 17 per group is required to obtain a power of at least 80% to detect a mean difference of 10 PRTEE pain score points (ie, the actual power is .807). Thus, enrolling 20 patients in each group as the intention-to-treat (ITT) population would correspond to a statistical power of 86.9% to detect a mean difference in the PRTEE pain score of 10 in any given 2-group comparison. The part of the PRTEE that evaluates pain is a score ranging from 0 to 50 points.

All patients who were randomized according to the opened envelopes, whether they had a dose of study medication or not, were assessed for efficacy and safety after 3 months in the trial; that is, they were considered the ITT population. The primary analyses were based on the ITT population. Secondary analyses at 6 and 12 months were based on both last observation carried forward and per protocol. Per protocol was applied because of the huge attrition and the exploratory nature of these analyses. When considering the longitudinal part of the randomized trial, a linear approach was used for repeated measurements using the model proposed by Diggle,¹¹ fitted in SAS (SAS Institute Inc, Cary, North Carolina) using the procedure "PROC MIXED" based on maximum likelihood estimates of the parameters. The factor [Subject] was considered as a random-effects factor. The assessment of the treatment and time effects was of interest in testing for a possible interaction, and both treatment and time were considered as systematic factors using the baseline value as a covariate to reduce the random variation⁶⁰ and increase power.¹⁹

Data were collected by the authors, with no communication with the sponsors. The data were interpreted and the report written by the authors. The corresponding author (T.E.) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study Flow and Patient Characteristics

Between January 2009 and July 2010, a total of 165 patients were assessed for eligibility, and 60 were included in the trial. The groups had similar clinical characteristics at baseline (Table 1). Figure 3 presents the flow of participants through the trial. Twenty patients were allocated to receive PRP, 20 to receive saline, and 20 to receive

TABLE 1
Baseline Characteristics^a

Characteristic	PRP (n = 20)	Saline (n = 20)	GC (n = 20)	Total (N = 60)
Age, mean ± SD, y	47.6 ± 7.1	44.7 ± 7.9	43.9 ± 8.7	45.4 ± 8.0
Female sex, n (%)	11 (55)	11 (55)	9 (45)	31 (52)
Body mass index, mean ± SD	24.4 ± 3.0	27.8 ± 5.3	26.5 ± 4.6	26.2 ± 4.5
Tender points (n = 0-18), mean ± SD	2.8 ± 2.9	3.3 ± 2.8	2.7 ± 2.7	2.9 ± 2.8
Right-hand dominant, n (%)	19 (95)	14 (70)	18 (90)	51 (85)
Location of symptoms, n (%)				
Right elbow	16 (80)	13 (65)	15 (75)	44 (73)
Dominant elbow	17 (85)	13 (65)	15 (75)	45 (75)
Both elbows	4 (20)	9 (45)	9 (45)	22 (37)
Smoking history, n (%)				
Current	6 (30)	2 (10)	7 (35)	15 (25)
Previous	4 (20)	8 (40)	8 (40)	20 (33)
Never	10 (50)	10 (50)	5 (25)	25 (42)
Previous GC treatment for LE, ^b n (%)				
Never	8 (40)	9 (45)	8 (40)	25 (42)
1 injection	6 (30)	4 (20)	4 (20)	14 (23)
>1 injection	6 (30)	7 (35)	8 (40)	21 (35)
Analgesics use, ^c n (%)	10 (50)	12 (60)	13 (65)	35 (58)
LE symptoms related to work, n (%)	15 (75)	15 (75)	12 (60)	42 (70)
Not working full time because of LE, ^d n (%)	5 (25)	7 (35)	4 (20)	16 (27)
Duration of symptoms, mo				
Mean ± SD	18.1 ± 36.0	15.5 ± 12.8	35.6 ± 54.1	23.1 ± 38.7
Median	9.6	12.3	15.4	11.4
Range	3.8-169.8	4.1-57.1	5.1-232.7	3.8-232.7
Pain intensity ^e (scale = 0-50), mean ± SD	27.5 ± 7.5	25.0 ± 7.3	28.0 ± 8.0	26.8 ± 7.6
Functional score ^f (scale = 0-100), mean ± SD	51.5 ± 19.1	47.1 ± 22.3	51.1 ± 22.3	49.9 ± 21.0
Color Doppler activity (grade = 0-4), mean ± SD	3.8 ± 0.4	3.7 ± 0.7	3.2 ± 0.9	3.5 ± 0.7
Tendon thickness, ^g mean ± SD, mm	5.4 ± 0.6	5.3 ± 0.8	5.1 ± 0.8	5.3 ± 0.7

^aPRP, platelet-rich plasma; GC, glucocorticoid; LE, lateral epicondylitis.

^bAll patients with GC injection within the past 3 months were excluded.

^cUse of paracetamol and/or nonsteroidal anti-inflammatory drug.

^dNot working full time (37 h/wk).

^ePatient-Rated Tennis Elbow Evaluation (PRTEE) pain score during the last week.

^fPRTEE functional score during the last week.

^gTendon thickness measured at the "plateau."

glucocorticoid. During the study, there were no patients lost to follow-up. All patients were assessed at 1 month and at primary outcome at 3 months.

Of the 20 patients in each treatment arm, only 8 patients in the PRP group (40%), 5 in the saline group (25%), and 3 in the glucocorticoid group (15%) completed the entire 12-month trial period (Figure 3). The patients not completing the 12-month follow-up (n = 44) left the study because of an unsatisfactory effect of the initial treatment and were treated as follows after leaving the study: 26 patients chose PRP, 12 glucocorticoid, 2 surgery, 2 sclerosing injections, and 2 declined further treatment.

Clinical Outcomes

Table 2 shows the mean scores for PRTEE pain and disability at baseline and at 1 and 3 months and the US changes in color Doppler and tendon thickness at baseline and at 1 and 3 months. Results are given as mean (95% confidence interval [CI]).

PRTEE Pain Score. Figure 4 shows a difference in pain reduction at 1 month in favor of glucocorticoid versus both saline and PRP. The mean difference between glucocorticoid and saline was -8.1 (95% CI, -14.3 to -1.9) and between glucocorticoid and PRP was -9.3 (95% CI, -15.4 to -3.2). At 3 months (primary end point), there was no statistically significant difference between the groups (glucocorticoid vs saline: -3.8 [95% CI, -9.9 to 2.4], PRP vs saline: -2.7 [95% CI, -8.8 to 3.5], and glucocorticoid vs PRP: -1.1 [95% CI, -7.2 to 5.0]).

Our a priori sample size calculation did not take into account the huge dropout after 3 months. Because of this, data are presented as 3-month data (no attrition). The 6- and 12-month PRTEE pain scores are presented in the Appendix (available in the online version of this article at <http://ajs.sagepub.com/supplemental/>). This table includes both per protocol and last observation carried forward statistics, but we emphasize that these data are not strong regarding statistical power. At 12 months, only 16 of 60 patients were left in the study: 8 in PRP, 5 in saline, and 3 in glucocorticoid.

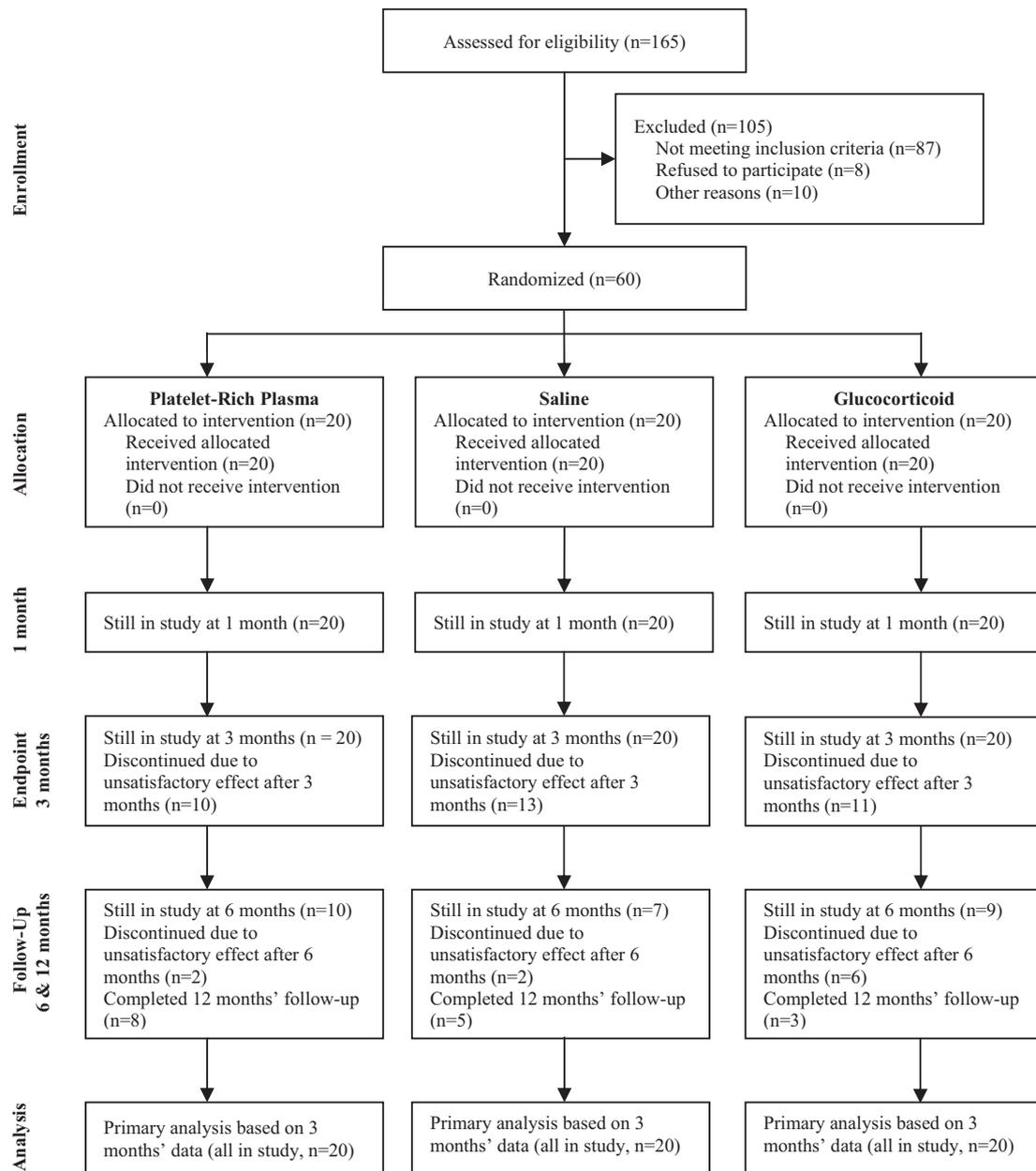


Figure 3. Flow diagram of patients through the study.

In a subgroup analysis, we looked at glucocorticoid-naïve patients and smoking status, and in both cases, we found no significant effect on pain reduction at 3 months. However, regarding patients with a disease duration of more than 1 year, a significant difference in pain reduction was observed comparing glucocorticoid versus saline; the mean difference was -9.9 (95% CI, -18.3 to -1.6) at 3 months' follow-up.

PRTEE Disability Score. The disability score results closely follow the pattern observed in the pain score. At 1 month, glucocorticoid was superior to both PRP and saline (glucocorticoid vs saline: -18.5 [95% CI, -30.6 to -6.3], and glucocorticoid vs PRP: -16.7 [95% CI, -28.8 to -4.5]).

At 3 months, there was no statistically significant difference between the groups (glucocorticoid vs saline: -6.2 [95% CI, -18.4 to 5.9], PRP vs saline: -9.0 [95% CI, -21.2 to 3.1], and glucocorticoid vs PRP: 2.8 [95% CI, -9.4 to 14.9]).

US Evaluation. Similar US characteristics were observed at baseline (Table 1). Detachment from the bone of the common tendon origin was not observed in any of the patients on inclusion. Table 2 shows the results of the US evaluation of tendon thickness and color Doppler activity at baseline and at 3 months. A decrease in tendon thickness was seen in glucocorticoid versus PRP (mean difference, -0.5 mm [95% CI, -0.8 to -0.2 mm]) and glucocorticoid versus saline (mean difference, -0.8 mm [95%

TABLE 2
Outcome Measurements and Group Differences^a

Outcome	PRP		Saline		GC		GC vs Saline		PRP vs Saline		GC vs PRP	
	Mean	SE	Mean	SE	Mean	SE	MD (95% CI)	P Value	MD (95% CI)	P Value	MD (95% CI)	P Value
Pain at baseline ^b	27.5	1.7	25.0	1.6	28.0	1.8						
ΔPain at 1 mo	-0.5	2.2	-1.7	2.2	-9.8	2.2	-8.1 (-14.3 to -1.9)	.011	1.2 (-5.0 to 7.3)	.703	-9.3 (-15.4 to -3.2)	.003
ΔPain at 3 mo ^c	-6.0	2.2	-3.3	2.2	-7.1	2.2	-3.8 (-9.9 to 2.4)	.229	-2.7 (-8.8 to 3.5)	.395	-1.1 (-7.2 to 5.0)	.717
Disability at baseline ^d	51.5	4.3	47.1	5.0	51.1	5.0						
ΔDisability at 1 mo	-5.2	4.3	-3.4	4.3	-21.9	4.3	-18.5 (-30.6 to -6.3)	.003	-1.8 (-14.0 to 10.4)	.770	-16.7 (-28.8 to -4.5)	.008
ΔDisability at 3 mo	-16.6	4.3	-7.6	4.3	-13.8	4.3	-6.2 (-18.4 to 5.9)	.310	-9.0 (-21.2 to 3.1)	.144	2.8 (-9.4 to 14.9)	.649
Doppler at baseline ^e	3.8	0.1	3.7	0.2	3.2	0.2						
ΔDoppler at 3 mo	-0.4	0.2	-1.0	0.2	-3.0	0.2	-2.0 (-2.5 to -1.6)	<.0001	0.6 (0.2 to 1.0)	.007	-2.6 (-3.1 to -2.2)	<.0001
Tendon thickness at baseline ^f	5.4	0.1	5.3	0.2	5.1	0.2						
ΔTendon thickness at 3 mo	0.3	0.1	0.6	0.1	-0.2	0.1	-0.8 (-1.2 to -0.5)	<.0001	-0.3 (-0.7 to -0.01)	.044	-0.5 (-0.8 to -0.2)	.002

^aΔPain, ΔDisability, ΔDoppler, and ΔTendon thickness are the difference from baseline. PRP, platelet-rich plasma; GC, glucocorticoid; SE, standard error; MD, mean difference between groups; CI, confidence interval.

^bPatient-Rated Tennis Elbow Evaluation (PRTEE) pain score during the last week (scale = 0-50).

^cPrimary outcome.

^dPRTEE functional score during the last week (scale = 0-100).

^eColor Doppler activity (grade = 0-4).

^fTendon thickness (mm) measured at the "plateau."

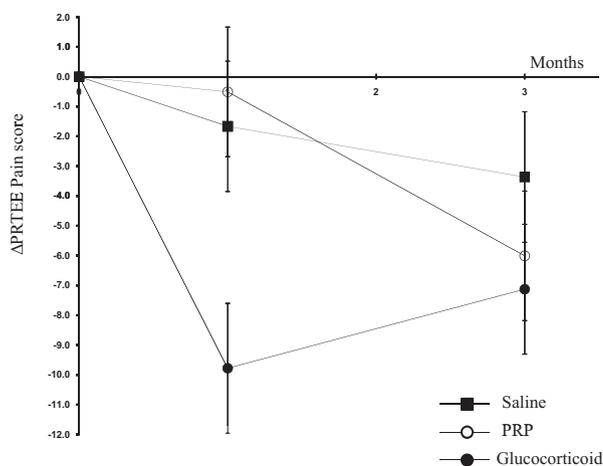


Figure 4. Changes in pain from baseline at 1 and 3 months using the Patient-Rated Tennis Elbow Evaluation (PRTEE) in patients treated with 1 injection of platelet-rich plasma (PRP), glucocorticoid, or saline. Values are least squares mean \pm standard error.

CI, -1.2 to -0.5 mm]). Both PRP and saline caused an increase in tendon thickness, and the between-group comparison showed a marginally statistical mean difference in PRP versus saline of -0.3 mm (95% CI, -0.7 to -0.01 mm). Glucocorticoid had a marked effect on color Doppler signal at 3 months, with a mean difference from baseline of -3.0 (95% CI, -3.4 to -2.7); 18 of 20 patients (90%) had no Doppler activity at all. The between-group comparison demonstrated that glucocorticoid was superior to both PRP and saline in reducing color Doppler activity (glucocorticoid vs saline: -2.0 [95% CI, -2.5 to -1.6], and glucocorticoid vs PRP: -2.6 [95% CI, -3.1 to -2.2]).

Pain Associated With Injection Therapy. At the 1-month follow-up, participants were asked by mail whether the injection therapy had caused any additional pain on a numeric rating scale from 0 to 10. Results indicated that PRP caused the most additional pain, with median score = 9.0 (standard error [SE], 0.2) compared with saline = 7.0 (SE, 0.7) and glucocorticoid = 6.0 (SE, 0.7). A between-group comparison found PRP to be significantly more painful than both glucocorticoid and saline (median difference: PRP vs glucocorticoid: 3.0 [95% CI, 1.5 to 4.5], and PRP vs saline: 2.0 [95% CI, 1.0 to 3.0]), while there was no statistically significant median difference between glucocorticoid versus saline (-1.0 [95% CI, -12.5 to 10.5]). The median duration of postinjection pain (ranked on a 0-5 verbal rating scale) was as follows: PRP = 3.0 (corresponding to 2-3 weeks; SE, 0.4), saline = 2.5 (corresponding to 1-3 weeks; SE, 0.4), and glucocorticoid = 1.0 (corresponding to <1 week; SE, 0.3). Between-group comparison showed that postinjection pain after glucocorticoid injection lasted significantly shorter than pain after both PRP and saline injection (median difference: glucocorticoid vs PRP: -2.0 [95% CI, -3.1 to -0.9], and glucocorticoid vs saline: -1.5 [95% CI, -2.8 to -0.2]). No statistically significant difference was found between PRP and saline (median difference, 0.5 [95% CI, -1.1 to 2.1]).

Safety. There were no serious adverse events (events leading to hospitalization) in any of the groups and no reports of infections after the injection therapies. One person in the PRP group underwent tonsillectomy, and 1 person in the glucocorticoid group was seen by his general practitioner because of suspicion of asthma; in neither case was the illness considered related to their LE treatment. One person in the glucocorticoid group had a minor rash around the injection site that resolved spontaneously. Four patients from the PRP group contacted the

department within days after the initial treatment, being concerned about the level of persisting pain (3 of the 4 also reported reduced movement of the elbow). In the saline group, 3 patients contacted the department concerned about persisting pain, whereas this was the case for only 1 person in the glucocorticoid group (who also reported reduced movement of the elbow). In the glucocorticoid group, skin atrophy was observed in 3 of 20 patients, 1 of whom had received 1 previous glucocorticoid injection. Loss of pigmentation was observed in 1 patient, who had received 2 previous glucocorticoid injections.

DISCUSSION

We found that a single injection with either PRP or glucocorticoid was not significantly superior to a saline injection for reducing pain and disability over a 3-month period in patients with LE. Glucocorticoid showed a significant short-term reduction in pain and disability at 1 month, but at 3 months, the difference between glucocorticoid and saline was no longer statistically significant. Initially, this study had an RCT design with a 12-month follow-up. Our intention was to present the 12-month data as the primary outcome, but because of the massive dropout in all 3 treatment arms, we present the 3-month data as the primary outcome. This issue reflects the consequence of not being able to deliver the expected pain relief to the participants. It is an indication of treatment failure of the active treatments in our study during the first 3 months. The participants would have no reason to leave the study if they were satisfied with the treatment. On joining this study, the participants were told that at any time after 3 months they would have the option to leave the study and receive other treatments if the initial treatment had an unsatisfactory pain-reducing effect. The number of patients who chose to leave the study after 3 months appears to have been greater than what has been seen in similar studies.^{8,43} An explanation could be that many patients chose to enroll in this study, hoping to receive the PRP treatment. When not experiencing any pain-reducing effect, they assumed that they had not received the PRP treatment and left the study to apply for the PRP treatment. Our results do not match the promising results observed in previous studies with PRP. The first trial was presented in 2006 by Mishra and Pavelko,³⁷ which was a small cohort study (n = 20), PRP versus bupivacaine, showing promising results. In a recent well-designed, double-blind RCT (n = 100), PRP versus glucocorticoid, Peerbooms et al⁴³ demonstrated that PRP was superior to glucocorticoid at 12 months' follow-up. Recently, 2 RCTs, by Creaney et al⁸ (n = 150) and by Thanasas et al⁵⁶ (n = 28), compared injection with PRP versus autologous blood over a 6-month period. These trials found a pain-reducing effect of both PRP and autologous blood but without any statistically significant difference between the 2 treatment arms. A recent network meta-analysis by Krogh et al²⁸ on injection therapies for LE found a limited but statistically significant effect of PRP compared with placebo. The trial by Peerbooms et al⁴³ with a 12-month follow-up was one of the

few trials in the study that was acknowledged as having an overall low risk of bias. When comparing the results of Peerbooms et al⁴³ indirectly to a general LE placebo group, no statistically significant difference between PRP and placebo was found in the network meta-analysis. Our trial is the first RCT for LE treatment including a placebo group for the evaluation of PRP. A placebo group instead of a glucocorticoid group could have changed the results in the trial by Peerbooms et al⁴³ because of the lack of long-term glucocorticoid efficacy on pain reduction.^{18,55} In the 2 RCTs assessing PRP versus autologous blood,^{8,56} a placebo group could have helped in determining whether the positive effect was caused by the injected substances, the needling procedure, or the natural course of the disease.

The fact that so many participants left the trial after 3 months allows us to draw conclusions based on this time period only. The regeneration of tendon tissue is a process that probably lasts more than 3 months. This implies that if the treatment effect has a late onset, it would not have been recognized in this trial, which could have been the case for PRP.

The observed short-term effect at 4 weeks but no long-term effect of glucocorticoid in our trial matches the results from previous studies and systematic reviews. A recent systematic review by Gaujoux-Viala et al¹⁸ included 16 RCTs on pain intensity after local glucocorticoid injections for both shoulder and elbow tendinitis. Here, they found evidence supporting a short-term (1-3 weeks and 4-8 weeks) beneficial effect of glucocorticoid injection on pain. Furthermore, other trials comparing glucocorticoid injection to naproxen or placebo,²³ or physical therapy or a wait-and-see approach,^{3,55} have found that glucocorticoid injection was significantly better than the comparators concerning short-term pain reduction (4-6 weeks), but at long-term follow-up, no difference for pain could be detected. A recent network meta-analysis identified 10 trials on LE assessing the pain-reducing effect of glucocorticoid.²⁸ We found no effect of glucocorticoid compared with placebo when looking at pain reduction at the study end point. Possible explanations for the absence of a long-term effect of glucocorticoid could be related to the known short half-life of glucocorticoid injections⁴⁴ and a favorable natural history of LE. Furthermore, when patients become pain free, they resume the injurious activity that caused the tendinopathy without sufficient rehabilitation and before the tendon has regained its full strength.

The subgroup analysis looking at glucocorticoid-naïve patients and looking at smoking status found no difference in pain reduction at 3 months, which is in agreement with our main conclusion. In patients with a disease duration of more than 1 year, it appears that glucocorticoid is more effective than saline in reducing pain at 3 months. These results, however, should be interpreted with caution because of the limited number of patients in each group (saline: n = 11, glucocorticoid: n = 11).

Glucocorticoid injection had an impressive effect on color Doppler activity at 3 months' follow-up, reducing color Doppler activity to 0 in 18 of 20 (90%) patients. In another study, Torp-Pedersen et al⁵⁸ showed that 78% were reduced to 0 at 2 weeks' follow-up. Because a majority

in the glucocorticoid group left the study after 3 months, we were not able to reach a conclusion regarding the duration of the reduced color Doppler activity. Interestingly, the observed glucocorticoid effect on Doppler activity did not correlate well with the modest effect on pain reduction at 3 months. Saline seems to have only a modest but still a greater reduction in Doppler activity than PRP. Speculations about the reason why PRP did not follow the same pattern as saline could be because of the role of the platelet-releasing growth factors, thereby maintaining an increased intratendinous blood flow. It appears that glucocorticoid reduces tendon thickness more effectively than both PRP and saline at 3 months' follow-up. The reduction in tendon thickness observed after glucocorticoid injection goes well in hand with the study by Fredberg et al¹⁷ showing a reduction in tendon thickness in both patellar and Achilles tendons.

Side Effects and Postinjection Pain

The PRP injection caused more postinjection pain than both saline and glucocorticoid. However, the duration of postinjection pain after PRP treatment did not last longer than what was observed in the saline control group. Our injection procedures regarding PRP and saline were exactly alike: 5 to 7 tendon perforations (glucocorticoid injections were made with as few perforations as possible). This implies that the increased postinjection pain observed in the PRP group is related to the presence and physiological effect of the platelets and not caused by the perforations of the tendon. Contrary to previous PRP trials, we used US to guide injections. Therefore, we were probably able to deliver a higher volume of PRP into the tendon compared with blind injection techniques. Theoretically, this could partly explain why patients treated with PRP in this trial reported more postinjection pain compared with other studies.

There were no serious adverse events, no infections, and no dropouts due to adverse events. It is fair to conclude that both PRP and glucocorticoid are safe to use.

Limitations

In the glucocorticoid group, 60% were not naïve to this treatment, and it is not surprising that they also failed the second time they were treated with glucocorticoid. Therefore, we cannot rule out the possibility that most of our patients treated with glucocorticoid had been treated previously with a poor result because patients treated with glucocorticoid with a good effect will of course not be referred for further treatment. This could contribute to the dropout rate in the glucocorticoid group and influence the conclusions of the study. Therefore, it is not possible to conclude that the result of the glucocorticoid treatment in this study is the same in glucocorticoid-naïve patients with LE. It would have been desirable only to include glucocorticoid-naïve patients, but treatment of LE with glucocorticoid is so widespread in general practice that nearly all patients are treated with glucocorticoid before referral to specialists. Almost half of the

participants (42%) stated that their daily work was the reason for LE. In an ideal setting, the time from treatment to return to work could have been much longer, allowing time for proper tendon healing and gradual building up of strength. The severity of LE in the included patients was above average, with a mean duration of 23 months. In patients with a shorter duration of LE, the treatment response could be different. An issue that could affect the between-group comparison is that the saline injection could be more than an inactive comparator.^{35,63} In both the PRP and saline treatment groups, the injection technique included making 5 to 7 perforations into the common tendon origin. Thus, it is not certain that the saline injection serves as an innate placebo control for the PRP injection.

In the process of clarifying the properties of PRP, it is important to know the actual platelet content of PRP. We did not test that ourselves but relied on the manufacturer's description.

In a recent in vitro study, Carofino et al⁵ demonstrated an inhibitory effect of lidocaine, bupivacaine, as well as glucocorticoid on tenocyte proliferation and viability in the presence of PRP. However, this in vitro effect has not yet been demonstrated in vivo. Our study cannot answer this question, but it is important to address this issue in future in vitro as well as in vivo studies. In our study, we did not mix lidocaine with either PRP or saline. All injections were guided by US. Lidocaine was injected outside the tendon, around the peritendon, whereas saline and PRP were injected intratendinously. However, it is still possible that the presence of lidocaine in the area would have a negative effect on tendon healing.

In conclusion, we were not able to reproduce the promising results of PRP treatment presented in recent studies.^{8,43,56} The effect of PRP or glucocorticoid injection on pain and disability at a primary end point of 3 months (no attrition) was not statistically different from saline injection. Injection with glucocorticoid demonstrated a short-term effect on both pain and disability but no long-term effect. Glucocorticoid reduces significantly both color Doppler activity and tendon thickness compared with PRP and saline. Regarding safety, both PRP and glucocorticoid are safe to use. Postinjection pain is the most dominant complaint, with PRP being more painful than glucocorticoid and saline.

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