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Platelet-rich plasma for chronic lateral epicondylitis: Is one injection sufficient?

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Abstract
Introduction Chronic lateral epicondylitis is generally treated using nonsurgical methods including physiotherapy and infiltrations of cortisone or platelet-rich plasma (PRP). The latter is known for its simple application as well as associated low risk of adverse events, which lend to its widespread use in treating various musculoskeletal conditions. There is limited evidence on the effectiveness of PRP injections to optimally treat chronic lateral epicondylitis. This study explored the effectiveness of single or repeated injections for patients with symptoms that spanned 6 months or more and were unresponsive to alternate conservative measures.
Methods and materials Patients with chronic lateral epicondylitis received PRP injections in 4-week intervals that were complemented with standardized physical therapy. Patient-reported outcomes based on the patient-rated elbow evaluation (PREE), quick disabilities of the arm, shoulder and hand (qDASH), and EuroQol (five dimensions) 3-level version (EQ5D3L) questionnaires were documented at each visit including 6 months after the first injection. These outcomes were compared between patients receiving 1 vs. 2 or 3 PRP injections.
Results Sixty-two patients received one ($n = 36$) or more ($n = 26$) PRP injections. The mean baseline to 6-month follow-up scores of the PREE and qDASH questionnaires improved significantly from 54.0 to 23.0 and 50.3 to 20.7, respectively. The mean baseline EQ5D3L-visual analogue scale score improved from 62.5 to 82.9 by 6 months post-injection. These outcomes did not significantly differ between the patients who received varying numbers of injections.
Conclusions Patients with chronic lateral epicondylitis reported significant pain relief and gain in function as well as quality of life 6 months after localized PRP treatment. A single PRP injection may be sufficient.

Keywords Epicondylitis · Platelet-rich plasma · Injection · Healing · Elbow · Patient-rated outcomes

Introduction

Lateral epicondylitis is the most common elbow condition for an individual to seek medical treatment, and affects 1–3 % of the population [1]. The natural course of the disease is favorable with a high spontaneous healing rate within 3 years after the onset of symptoms. Once the symptoms become chronic, treatment is generally nonsurgical and may include physical therapy, bracing and local cortisone infiltration, shock wave therapy or platelet-rich plasma (PRP) injections [2]. In the case of failed conservative treatment, surgical options involving open or arthroscopic extensor tendon debridement may be evaluated. Underlying posterolateral instability mimicking lateral epicondylitis should be excluded or treated appropriately [3]. PRP is an autologous blood product obtained by centrifugating a patient's blood sample and was first used in heart surgery in 1987 [4]. The simplicity of its use and low risk of associated adverse events such as local pain for several days after the injection, contributed to

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a widespread application of PRP in the treatment of various musculoskeletal conditions [5–11]. Depending on their leucocyte and fibrin content, platelet concentrates may be classified into four categories: pure PRP; leucocyte and PRP; pure platelet-rich fibrin; and leucocyte- and platelet-rich fibrin [12]. Platelets function as a carrier for several growth factors promoting cell proliferation, matrix regeneration and angiogenesis [9]. Anti-inflammatory effects have also been identified in cell model studies [13, 14]. The wide range of PRP products available complicate comparison of clinical studies on the effects of PRP application in musculoskeletal disorders [15]. Various clinical studies investigated the effects of PRP in chronic epicondylitis [16–20]. Two randomized controlled trials showed a significant benefit of PRP compared to corticosteroid injections 1 and 2 years following the intervention [17, 20]. On the other hand, a systematic review on the efficacy of PRP included four high-quality studies and found evidence against the use of PRP in chronic lateral elbow tendinopathy [21]. Radial and ulnar tendinopathies seem to react differently to PRP treatment, which still cannot be fully explained. A study focusing on the treatment of medial epicondylitis with PRP infiltrations found inferior results compared to the reported outcomes for extensor tendinopathy of the elbow [22]. In a case–control study of 20 patients, Mishra and Pavelko showed a significantly higher success rate based on the modified Mayo Clinic Elbow score after PRP injections compared to a single bupivacaine injection [19]. Thanasas et al. compared the effects of PRP and whole blood injections and found PRP to have a significant effect in reducing pain at 6 weeks post-treatment [23]. The preparation of plasma and frequency of injections greatly vary among studies [15], and the optimal number and timing of injections remains unclear [16].

This study investigated the effectiveness of single and repeated PRP injections in a cohort of patients with chronic lateral epicondylitis that spanned 6 months or more and was unresponsive to alternate conservative measures. The main question of whether repeated injections offer a benefit for the patient was explored. Any adverse effects of previous cortisone injections and the use of tobacco on the outcome of PRP injections were also investigated.

Materials and methods

Between November 2010 and July 2012, patients who received PRP for the treatment of chronic lateral epicondylitis were identified from our clinical register. The chronic symptoms at the time of the first injection had been defined as ongoing for a period of 6 months or more and unresponsive to nonsurgical treatment. An initial trauma of the affected elbow was reported in eight patients. Both corticosteroid and PRP infiltrations were offered to all patients; since many had already undergone corticosteroid treatment, none were willing to receive further corticosteroid injections. Patients with bilateral epicondylitis were excluded as well as those receiving previous cortisone injections within 3 months of the initial PRP injection. Patients receiving additional PRP treatment of the ipsilateral ulnar side after developing medial epicondylitis during the follow-up period were not excluded from the analysis. All patients and their data were handled according to routine practice. Ethical approval and patient informed consent were obtained to use the clinical data for research purposes.

For PRP preparation, the Autologous Conditioned Plasma® (Arthrex, Naples, FL) system was used. This double syringe system involves a one-step procedure, which facilitates the isolation of PRP to achieve a platelet concentration of approximately 2.5 times greater than native blood that is free of leucocytes. A 10 mL blood sample was collected from each patient and centrifuged at 1500 rpm ($350\times g$) for 5 min. From each sample, between 2 and 3 mL of PRP was gained from the centrifugation procedure and directly injected under sterile conditions using a peppering technique. Five penetrations through the fascia of the extensors were performed without the use of local anesthetics. Injections were administered at the point where maximal pain was present, without ultrasound guidance. After the infiltration, patients were advised to rest the treated arm for the next 24 h before returning to their daily activities. All patients were instructed to follow a standardized stretching program under the supervision of a physical therapist once per week, which started after the rest period following the first injection. Paracetamol was prescribed as required, and the use of nonsteroidal anti-inflammatory drugs was discouraged based on evidence of their growth factor inhibiting effects [24]. At both 4 and 8 weeks after the primary injection, second and third infiltrations, respectively, were offered by the treating doctor based on the local treatment scheme applicable for each patient; repeated PRP injections were then performed only upon each patient's preference to receive further treatment.

At the 4- and 8-week follow-up visits, a clinical examination was performed to record range of motion, strength and presence of tenderness at the lateral epicondyle. Furthermore, patients completed the patient-rated elbow evaluation (PREE) [25, 26] and quick disabilities of the arm, shoulder and hand (qDASH) questionnaires [27, 28] before treatment (i.e., baseline) and at 4 and 8 weeks as well as 6 months after the initial injection. Radiographic imaging was performed as a standard part of all clinical examinations. Magnetic resonance images were available

for 13 patients with only six obtained in an extended arm position; no patient presented with a tear of the extensor tendon insertion >20 % of the footprint in the coronal plane. To measure quality of life, patients were also asked to complete the EuroQol (five dimensions) 3-level version questionnaire (EQ5D3L) [29] at the nominated time points. The EQ5D3L consists of a descriptive system and visual analogue scale (VAS). The descriptive system considers five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ5D health states were defined by combining the levels from each of the five dimensions; each state was associated with a utility value index ranging from 0 (death) to 1 (perfect health) and derived from the German population. The EQ5D-VAS records patient self-rated health on a vertical VAS where the endpoints are labeled "best imaginable health state" and "worst imaginable health state"; this score provides a quantitative measure of health outcome based solely on the individual response. Patient satisfaction with their elbow condition was recorded at each examination using a 5-point Likert scale ranging from very dissatisfied to very satisfied. Local complications were also documented.

Standard descriptive statistics including means and standard deviations for continuous variables, and absolute and relative frequencies for categorical variables were used. Baseline demographics and 4-week outcome scores were compared between patients receiving 1 vs. 2 or 3 PRP injections using nonparametric statistical testing as well as clinical judgment. Multiple imputation was used to estimate the 6-month PREE scores of non-responding patients, which were compared with available scores from responding patients to assess for potential attrition bias. Estimations were performed on the basis of available data for the following parameters: age; gender; smoking status; pre-PRP cortisone infiltration(s); PRP injections (1 vs. 2–3); and other PREE scores documented at baseline and 4 and 8 weeks. The overall effect of PRP injections on the PREE, qDASH, EQ5D value index, and EQ5D-VAS scores documented at the 8-week and 6-month follow-ups was explored using a mixed linear regression model considering the repeated measures for each patient. The 4-week scores were included in respective models to account for potential confounding (i.e., if the decision for multiple PRP injections was at least partly related to outcome). Considering the available sample size at the 6-month follow-up, the analysis had 72 % power to identify a difference of 10 points (effect size of 0.8 with a standard deviation of 12 points) in the PREE pain subscale between PRP injection groups (1 vs. 2–3). The effects of previous cortisone infiltration as well as smoking status on the outcome scores were explored by including these variables separately in the models. In addition, outcome changes from baseline and outcome differences between PRP injection groups were assessed at each time point using the Wilcoxon matched pairs signed-rank test and Wilcoxon rank-sum (Mann–Whitney) test, respectively. The level of significance was set at 0.05.

Results

Sixty-two patients comprising 35 females and 27 males with a mean age of 48.2 years (range 32–65) were included in the analysis (Table 1) and 61 % ($n = 38$) were available for final follow-up 6 months after the first PRP injection. The right arm was affected in 49 (79 %) patients, and 21 (34 %) were smokers. Forty-three (72 %) patients were working without restrictions, while seven (12 %) were on sick leave due to their elbow disease; the remainder (15 %; $n = 9$) were either partly working or retired (2 %; $n = 1$). Thirty-six patients (58 %) received a single injection, while 26 received either two ($n = 23$) or three ($n = 3$) injections 4 and 8 weeks after the primary intervention. Three patients developed ipsilateral medial epicondylitis during the 6-month follow-up period and requested additional PRP treatment of the ulnar side at 35, 36 and 84 days after the index intervention, respectively; the final total PREE score for these patients was below average and a potential influence of medial epicondylitis on the treatment results for the lateral elbow pain can be appreciated. Eighteen patients (29 %) had previously received up to a maximum of four corticoid injections outside the defined 3-month exclusion time period.

Patients receiving only one PRP injection were similar to those receiving two or three injections with regard to baseline characteristics ($P \geq 0.289$) (Table 1). In addition, there were no differences between the patient groups according to the outcome parameters reported at the first follow-up visit 4 weeks after the index intervention ($P \geq 0.082$) (Tables 2, 3).

The mean pre-injection PREE total score improved significantly from 54 (range 18–94) to 23 (range 0–70) at the 6-month follow-up (Wilcoxon signed-rank test; $P < 0.001$) (Fig. 1). Before the first PRP injection, the patient cohort had a mean qDASH score of 50.3 (range 11.4–79.5), which decreased by 29.2 points (range 1.1–65.9) to 20.7 (range 0–54.5) at the final 6-month examination ($P < 0.001$). The mean baseline EQ5D-VAS score improved significantly from 62.5 (range 0–99) to 82.9 (range 50–100) at 6 months ($P < 0.001$). Over the same period, the average EQ5D value index improved significantly from 0.74 (range 0.18–0.89) to 0.92 (range 0.79–1.00) ($P = 0.0001$).

Additional injections at 4 and 8 weeks after the primary injection did not result in significantly different patient-reported outcomes to those documented for patients who

Table 1 Baseline parameters of the patients according to the number of injections received

Baseline parameters	Number of PRP injections		*P* value*	All patients
	One	Two or three		
Age at first infiltration (years), *n*	36	26		62
Mean (sd)	48.3 (7.3)	48.0 (8.6)	0.870	48.2 (7.8)
Gender, *n* (%)			0.798	
Female	21 (58)	14 (54)		35 (56)
Male	15 (42)	12 (46)		27 (44)
Smoker, *n* (%)			0.289	
No	25 (71)	15 (58)		40 (66)
Yes	10 (29)	11 (42)		21 (34)
Other upper extremity joint problem, *n* (%)			0.788	
No	23 (64)	18 (69)		41 (66)
Yes	13 (36)	8 (31)		21 (34)
Affected body side, *n* (%)			1.000	
Right	28 (78)	21 (81)		49 (79)
Left	8 (22)	5 (19)		13 (21)
Number of pre-PRP cortisone infiltrations, *n* (%)†			0.972	
0	26 (72)	18 (69)		44 (71)
1	5 (14)	5 (19)		10 (16)
2	3 (8)	2 (8)		5 (8)
3	1 (3)	1 (4)		2 (3)
4	1 (3)	0 (0)		1 (2)

sd standard deviation

* Indicates the Wilcoxon rank-sum and Fisher's exact test *P* values for "age" and categorical parameters, respectively

† Pre-PRP cortisone infiltrations were administered ≥3 months after the initial PRP injection

received only a single PRP injection (overall mixed linear regression model; $P \geq 0.281$) (Table 3). In particular, the mean differences in PREE pain subscale scores between the single and multiple PRP injected patient groups were −0.8 (95 % CI −8.9 to 7.2) and −2.0 points (95 % CI −9.5 to 5.5) at the 8-week and 6-month follow-ups, respectively (Fig. 2). The estimated PREE total score of non-responding patients at 6 months was similar to the score for responding patients receiving a single PRP injection (mean difference = 5.5; 95 % CI −5.1 to 16.2; $P = 0.317$), but was on average 16.0 points (95 % CI −31.0 to −1.0; $P = 0.047$) higher compared to the score for responding patients receiving two or three PRP injections.

Full strength in extension was observed in 61 % (38/62), 71 % (36/51) and 82 % (27/33) of the patients prior to the first injection and at the 4- and 8-week follow-up examinations, respectively ($P = 0.123$ for the change between baseline and 8 weeks). Range of motion parameters did not significantly change over the observation period (data not shown). Range of motion and strength parameters documented at 8 weeks did not significantly differ between the two PRP injection groups (data not shown) (Wilcoxon signed-rank test; $P \geq 0.286$).

Prior to the first injection, 85 % of the patients were unsatisfied with their elbow pain. Despite pain reduction and improved function, 47 % (18/38) of the examined patients were still unsatisfied at 6 months post-treatment, which was unrelated to the number of PRP injections applied (i.e., nine patients received one PRP injection and the other nine received two or three injections). No adverse events other than increased pain for up to 5 days after the PRP injections were noted.

Neither cortisone injections administered outside the 3-month exclusion period prior to PRP treatment ($P = 0.967$) nor smoking ($P = 0.980$) significantly influenced the reduction in pain over the 6-month follow-up period (Fig. 3a, b, respectively).

Five patients decided to undergo surgical treatment after completion of their final follow-up examination due to ongoing symptoms; surgical treatment included diagnostic arthroscopy, resection of the synovial plica and open debridement with transosseous refixation of the common extensor tendons. Of these five patients, two received one injection, and the remaining three patients received two infiltrations ($P = 0.641$). None of the patients chose to be injected with cortisone after unsuccessful PRP treatment.

Table 2 Clinical and patient-reported outcomes of the patients at the 4-week follow-up according to the number of injections received

Clinical and patient-reported outcomes*	Number of PRP injections				*P* value†
	One		Two or three		
	n	Mean (sd)	*n*	Mean (sd)	
Strength in extension, *n* (%)					0.859
Movement against gravity possible	1 (3)		0 (0)		
Movement against resistance possible	7 (24)		7 (32)		
Full power	21 (72)		15 (68)		
PREE total score	33	43.5 (20.1)	22	40.5 (18.9)	0.606
PREE pain subscale‡	34	27.0 (10.4)	23	25.9 (10.1)	0.708
PREE function subscale‡	33	16.5 (11.0)	22	15.0 (10.0)	0.606
qDASH score EQ5D questionnaire items	32	42.9 (20.4)	23	40.7 (14.7)	0.891
Mobility, *n* (%)					1.000
No problem	28 (85)		19 (83)		
Some problem	5 (15)		4 (17)		
Confined to bed	0 (0)		0 (0)		
Self-care, *n* (%)					0.638
No problem	30 (88)		22 (96)		
Some problem	4 (12)		1 (4)		
Unable	0 (0)		0 (0)		
Usual activities, *n* (%)					1.000
No problem	12 (35)		8 (35)		
Some problem	22 (65)		15 (65)		
Unable	0 (0)		0 (0)		
Pain/discomfort, *n* (%)					0.272
No pain	1 (3)		3 (13)		
Moderate	26 (76)		18 (78)		
Extreme	7 (21)		2 (9)		
Anxiety/depression (*n*, %)					0.366
None	22 (65)		18 (78)		
Moderate	9 (26)		5 (22)		
Extreme	3 (9)		0 (0)		
EQ5D index DE	33	0.74 (0.25)	23	0.83 (0.19)	0.082
EQ5D-VAS	34	70.4 (20.0)	23	68.7 (20.4)	0.794

sd standard deviation, *PREE* patient-related elbow evaluation (PREE total score; *0* best, *100* worst), *qDASH* quick disabilities of the arm, shoulder, hand (qDASH score; *0* best, *100* worst), *EQ5D index DE* value index gained from the German population, *VAS* visual analogue scale

* Other clinical parameters such as range of motion and strength in other directions (i.e., flexion, pronation, supination) were also similar between PRP injection groups

† The Wilcoxon rank-sum and Fisher's exact test *P* values for the continuous parameter "age" and categorical parameters, respectively

‡ PREE subscales are calculated on a scale ranging from 0 best to 50 worst outcomes

Discussion

This study aimed to evaluate the benefits of single and repeated PRP injections in treating chronic lateral epicondylitis. Patients showed significant improvement in function and level of pain 6 months after the primary injection. Adverse events were negligible; increased pain in the first days after injection is an inherent transient observation associated with the intervention [30], and thus was not considered a complication. With comparable patient-rated outcomes 4 weeks after the initial treatment, repeated injections did not provide a benefit compared to a single injection.

Lateral epicondylitis is the most common elbow disease and conservative treatment is successful in the majority of cases [1]. While range of motion is rarely a problem,

Table 3 Change in patient-reported outcomes over the 6-month follow-up period for patients according to the number of injections received

Patient-reported outcomes	Number of PRP injections				*P* value	
	One		Two or three			
Follow-up time point	*n*	Mean (sd)	*n*	Mean (sd)	Wilcoxon*	Mixed†
PREE total score						
4 weeks	33	43.5 (20.1)	22	40.5 (18.9)	0.606	0.324
8 weeks	21	31.1 (20.3)	17	32.7 (21.6)	0.860	
6 months	22	22.2 (17.7)	16	24.1 (18.9)	0.779	
Change 4 weeks to 6 months	19	−16.5 (22.0)	15	−10.0 (18.7)	0.425	
PREE pain subscale						
4 weeks	34	27.0 (10.4)	23	25.9 (10.1)	0.708	0.557
8 weeks	21	20.1 (12.4)	17	20.9 (11.7)	0.791	
6 months	22	14.8 (10.5)	16	16.8 (12.2)	0.689	
Change from 4 weeks to 6 months	20	−10.0 (12.4)	16	−7.2 (13.5)	0.426	
PREE function subscale						
4 weeks	33	16.5 (11.0)	22	15.0 (10.0)	0.606	0.281
8 weeks	21	11.0 (8.6)	17	11.8 (10.7)	0.895	
6 months	22	7.4 (7.7)	16	7.3 (7.2)	0.894	
Change from 4 weeks to 6 months	19	−7.1 (11.2)	15	−4.3 (7.4)	0.435	
qDASH score						
4 weeks	32	42.9 (20.4)	23	40.7 (14.7)	0.891	0.819
8 weeks	21	32.9 (17.2)	17	31.0 (18.3)	0.659	
6 months	22	19.6 (15.3)	16	22.1 (16.6)	0.790	
Change from 4 weeks to 6 months	18	−18.3 (17.5)	16	−12.8 (17.6)	0.427	
EQ5D index DE						
4 weeks	33	0.74 (0.25)	23	0.83 (0.19)	0.082	0.865
8 weeks	21	0.84 (0.17)	17	0.85 (0.18)	0.797	
6 months	22	0.90 (0.08)	16	0.94 (0.06)	0.161	
Change from 4 weeks to 6 months	19	0.09 (0.18)	16	0.04 (0.07)	0.745	
EQ5D-VAS						
4 weeks	34	70.4 (20.0)	23	68.7 (20.4)	0.794	0.861
8 weeks	21	75.2 (20.9)	17	77.4 (14.2)	0.735	
6 months	22	83.2 (14.3)	16	82.5 (11.2)	0.561	
Change from 4 weeks to 6 months	20	10.3 (20.1)	16	10.3 (23.3)	0.725	

sd standard deviation, *PREE* patient-related elbow evaluation (PREE total score; *0* best, *100* worst), *qDASH* quick disabilities of the arm, shoulder and hand (qDASH score; *0* best, *100* worst), *EQ5D index DE* value index gained from the German population, *VAS* visual analogue scale

* Indicates the Wilcoxon rank-sum test *P* values comparing outcome scores between patient subgroups at each time point

† *P* values showing overall significance of the treatment variable (i.e., 1 vs. 2 or 3 PRP injections) on 8-week and 6-month follow-up outcomes, adjusted for 4-week values (baseline values prior to the first PRP injection were not considered) using a mixed linear regression model

patient complaints focus mainly on pain and loss of strength [2]. Surgery for chronic epicondylitis is the last line of defence that does not result in satisfactory outcomes for all patients. Studies show that up to 24 % of operated patients still suffer moderate to intense pain 1 year after surgery [31]. Since glucocorticoid injections may have a time limited effect and show destructive side effects on soft tissues and cosmesis, new strategies including orthobiologic treatments are evolving [32]. PRP is an autologous blood product isolated from a patient's blood sample using simple centrifugation techniques. Platelet concentration is increased but highly dependent on the type of commercially available system in use [8]; the system used in this study has a proven concentration of 2.5 times greater than baseline [15].

Various studies showed inconclusive evidence concerning the efficacy of PRP in chronic lateral epicondylitis [16, 18, 23, 30, 33]. In one of the first reports, Mishra and

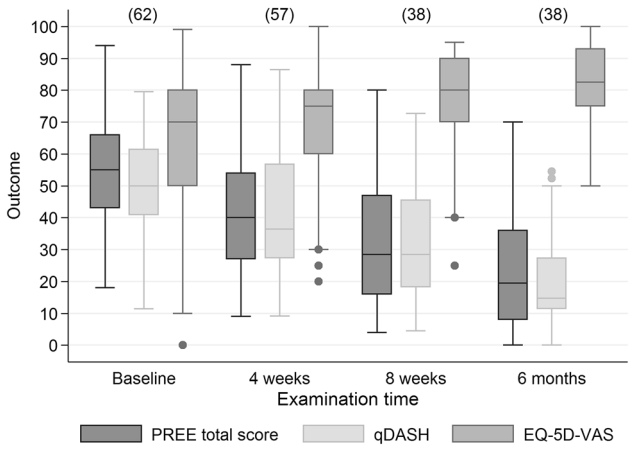

Fig. 1 *Box* plots* of the patient-rated elbow evaluation (PREE) total score, quick disabilities of the arm, shoulder and hand (qDASH), and EuroQol-visual analogue scale (EQ5D-VAS) at baseline and throughout the 6-month follow-up period for PRP-treated patients. Numbers in parentheses indicate *n.* *The *rectangle ends* correspond to upper and lower quartiles of the data values. The *line* drawn through the *rectangle* corresponds to the median value. The *whiskers*, starting at the *rectangle ends* (or points representing extreme values), indicate minimum and maximum values

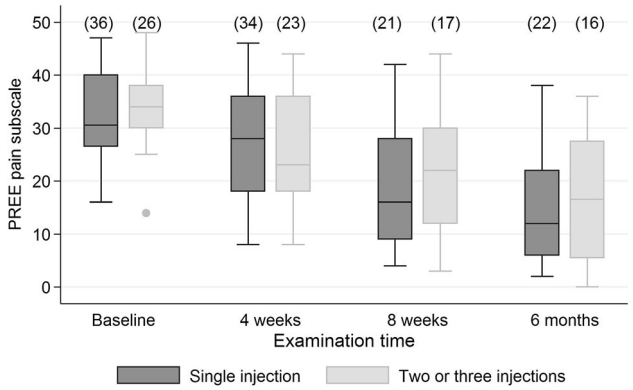

Fig. 2 *Box* plots* comparing PREE pain subscale scores between patients receiving one and two or three PRP infiltrations throughout the 6-month follow-up period. Numbers in parentheses indicate *n.* *The *rectangle ends* correspond to upper and lower quartiles of the data values. The *line* drawn through the *rectangle* corresponds to the median value. The *whiskers*, starting at the *rectangle ends* (or points representing extreme values), indicate minimum and maximum values

Pavelko compared 15 patients treated with PRP to five individuals injected with bupivacaine and reported a 93 % reduction in pain for the group receiving PRP [19]. The study design did not allow conclusions to be drawn about the comparability of the test to the control cohort. The working group of Gosens and Peerbooms most recently presented two randomized controlled trials showing significant improvement in patients treated with PRP compared to a control group treated with corticoid injections at 1 and 2 years after treatment [17, 20]. Krogh et al.

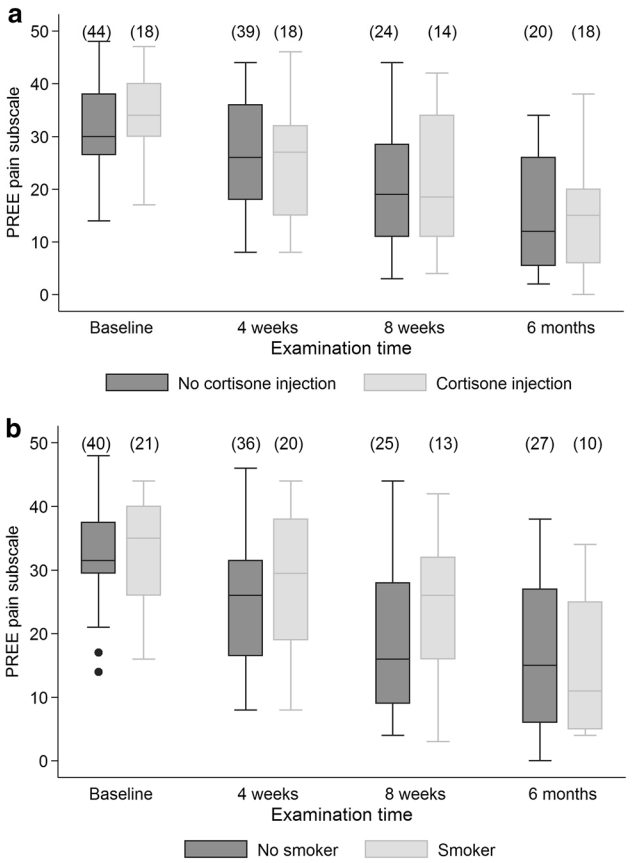

Fig. 3 *Box* plots* comparing PREE pain subscale scores between patients who received prior cortisone treatment or not (**a**) and nonsmokers vs. smokers (**b**) throughout the 6-month follow-up period. Numbers in parentheses indicate *n.* *The *rectangle ends* correspond to upper and lower quartiles of the data values. The *line* drawn through the *rectangle* corresponds to the median value. The *whiskers*, starting at the *rectangle ends* (or points representing extreme values), indicate minimum and maximum values

randomized 60 patients to either single PRP, corticosteroid or saline injection treatment groups; the final follow-up was performed 3 months after the injection and a reduction in pain was observed in all groups without any significant group difference [18]. This suggests that a placebo effect cannot be fully excluded in our study because of the lack of a control group. Nevertheless, the rapid improvement observed following months of a painful and nonfunctional elbow supports the beneficial effect of PRP injection treatment. A recent meta-analysis, however, did not find conclusive evidence to support PRP injections for lateral elbow pain [21]. Our study was pragmatic and reflects routine clinical practice. Hence, we did not analyze the injected PRP for growth factor concentration, which is dependent on the time of sample collection, female hormone cycle and preparation technique [15].

We are not aware of any previous study investigating the effect of the number of applied PRP injections. Current

literature provides no conclusive answer to the question of the ideal frequency of injections and if "more is really better" [6, 7, 11, 17–19, 23, 33, 34]. Patients who received a second or third injection did not present a better overall outcome at final follow-up, which supports the hypothesis that a second injection is not needed. In practice, PRP treatment is more time-consuming and expensive than an injection of glucocorticoid. In addition, the direct cost of one PRP injection in our clinic is approximately 100 Swiss francs higher than that for corticosteroid therapy.

In our study, 34 % of the included patients were smokers whose final outcome was not significantly different compared to nonsmokers at 6 months, despite a tendency for slightly higher PREE pain subscale scores at 4 and 8 weeks after the primary injection. This observation should be further investigated with a larger patient cohort, since tobacco use might adversely affect the potential benefits of orthobiologic treatment [35].

In an experimental study, Carofino et al. showed that corticosteroids in combination with PRP treatment significantly reduced the proliferation of tenocytes, thus limiting the potential benefits of PRP [36]. To elucidate the clinical relevance of these findings, we compared our patients who had previous corticosteroid injections with those who did not. A corticosteroid injection administered outside the minimum time window of 3 months until PRP injection did not alter the final outcome of pain and function in this study. Although the rate of unsatisfied patients in our cohort was high, we still believe that the risk–benefit assessment of a PRP injection is more advantageous compared to a surgical procedure, in particular, for patients with no or only mild morphological changes at the level of the common extensor tendons.

Our analysis has several limitations in design and methodology. The most important limitation is the lack of a control group, however, most patients in our cohort had already undergone unsuccessful corticosteroid treatment. In our opinion, it would be difficult and unethical to compare the effect of PRP injection for lateral epicondylitis with placebo injections or no further treatment, and continuing corticoid injections was not a medical option. However, a potential placebo effect of the PRP injection may be assumed. The vast majority of patients had a high level of frustration due to chronic pain. By comparing treatment with 1 vs. 2 or 3 PRP injections, patients were not randomized but single and repeat-injection groups were comparable 4 weeks after the initial injection. Another important limitation is that we were able to follow only 61 % of the included patients. Follow-up at 6 months post-initial injection was implemented with a patient postal questionnaire as part of a quality control step, which was difficult to collect once patients had completed their treatment; we cannot fully exclude that a lack of response could be associated with their treatment outcome. By including only those patients with complete data, information regarding loss to follow-up would be concealed. Therefore, we assessed the risk of attrition bias by implementing the multiple imputation process and estimated that non-responding patients receiving two or three PRP injections may have had a poorer outcome (i.e., a higher PREE score) at 6 months compared to responding patients; this was not observed for patients receiving just one PRP injection, which supports the hypothesis that repeated injections may not be justified. The individual variations for the PREE, EQ5D and qDASH results were relatively large; therefore, it is difficult to predict the outcome for an individual patient. The challenge would be to identify those patients most likely to benefit from our study cohort, yet our numbers are quite small. Last, a 6-month follow-up time period only allows the monitoring of short-term effects.

Conclusion

From the available 6-month patient-rated outcome data, we observed local pain reduction and improved function and quality of life following local PRP injection in patients with lateral epicondylitis. Multiple injections had no beneficial effect 6 months after the initial injection. In our clinic, PRP is the second line of treatment for chronic lateral epicondylitis behind well-known conservative measures such as physical therapy, stretching and bracing.

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Compliance with ethical standards

Conflict of interest None.

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