The Journal of Orthopaedics

Case Report

Treatment of noninsertional tendinitis of the Achilles with platelet-rich plasma in two case compilation: No discernible difference in efficacy between PRP with high and low leukocyte counts.

Vlaus Kedderkopp

Orthopedic Department, Hospital of Southwestern Jutland, Esbjerg, Denmark.

***Corresponding Author :**
Vlaus Kedderkopp, Orthopedic Department, Hospital of Southwestern Jutland, Esbjerg, Denmark.

Received : July 22, 2023
Accepted: July 23, 2023
Published : August 23, 2023

Abstract

Background : Although there is a lack of clinical evidence to support the use of platelet-rich plasma (PRP) in treating chronic tendinopathies, treatment algorithms are lacking, and it is unclear which type of PRP is most effective, it can be considered a potential treatment option for chronic Achilles tendinopathies (CATs) due to its theoretical basis. This research aimed to determine the following two things by comparing two case series: 1) how PRP affects CAT; and 2) whether leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP) have different effects when treating CAT.

Patients and procedures : Using a natural experiment/quasi-experimental study approach, two distinct series of achilles tenodinopathies treated with either LR-PRP or LP-PRP were examined. The effect and stability of the treatment were investigated by short-term (2 months) and long-term (8–42 months) follow-ups. A total of 84 patients who had not responded to basic CAT treatment for at least six months were treated with either Arthrex ACP LP-PRP (48 patients) or Biomet's GPS III recovery kit with LR-PRP (36 patients).

Findings : In terms of the visual analogue scale (VAS), the likelihood of achieving a minimal clinically important change (MCIC) of at least 30% was highest during activity (63%) and rest (81%), and it was lowest for the Victorian Institute of Sport Assessment Scale (VISA-A) (61%). Between patients treated with LP-PRP and LR-PRP, there was no statistically significant difference in the change in either the VAS or the VISA-A score.

Conclusion : PRP appears to be a viable therapy option with a respectable chance of success in obtaining MCIC when all other treatment plans have failed. There were no appreciable differences between patients treated with LR-PRP and LP-PRP, suggesting that the decision to choose either treatment modality is a matter of personal preference.

Keywords : *platelet-rich plasma, leukocyte-rich PRP, leukocyte-poor PRP, Achilles tendinopathy*

INTRODUCTION

Treatment for chronic Achilles tendinopathy, or CAT, can be challenging. Positive results from a number of treatments have been reported1,2, yet certain instances appear to be resistant to all of them. PRP, or platelet-rich plasma, may be used as a treatment in several cases.3,4 Injections of glucocorticoids are commonly used, although there is a risk of major side effects, including tendon rupture, and there is no conclusive proof that this is an effective treatment.5 PRP is typically taken from the patient's own blood, as opposed to glucocorticoids, and its potential for side effects is likely far smaller than that of glucocorticoid injections. As a result, since Goosen et al. reported positive outcomes in treating tendinopathy of the tendon-insertion of the wrist extensors on twenty years ago, the lateral humerus epicondyle (tennis elbow). There is evidence that tendon stem cells can be differentiated into active tenocytes and that this process induces healing by raising the immunoreactivity for types I and III collagen.6–8 Leukocyte-poor PRP (LP-PRP) and leukocyte-rich PRP (LR-PRP) have both

been used and seem to be "safe" in converting tendon stem/progenitor cells into active tenocytes; however, because LR-PRP induces an inflammatory and catabolic response in tendon cells, it may slow down the healing process and worsen the condition of injured tendons. Because LR-PRP appears to have an excessive cellular anabolic impact, using it to treat severely wounded tendons may cause an excessive amount of scar tissue to grow.9, 10 Furthermore, it is widely acknowledged that the LR-PRP induces inflammation, which results in discomfort following treatment. As a result, patients frequently require painkillers in the initial days following therapy. Therefore, even though there isn't enough clinical evidence to support its usage, PRP has a theoretical foundation and can be taken into consideration as a potential treatment for CAT.11 Additionally, there aren't many treatment algorithms available, and it's unknown which kind of PRP works best.

This study set out to determine 1. the apparent "effect" of PRP on CAT and 2. whether LR-PRP and LP-PRP differed in their treatment outcomes for CAT.

Research Methodology

The research employs a quasi-experimental study design and is a natural experiment. It includes two follow-up periods, two months and eight to forty-two months, to evaluate the treatment's effectiveness and stability.

Patients and techniques

Between mid-2012 and July 2015, Biomet's GPS III recovery kit (LR-group: 36 patients) or Arthrex ACP (LP-group: 48 patients) were used to treat 84 patients who had not improved after at least six months of the "normal" CAT treatment. 54 mL of the patients' own blood from the LR-group was centrifuged for 15 minutes at 3,200 U/min after being buffered with 6 mL bicarbonate. Five distinct regions of the lesion were injected with approximately 5-7 mL of L-PRP under ultrasound guidance. Biomet states that using this procedure yields concentrations of leukocytes five times and thrombocytes 9.4 times higher than the basal level. 15 mL of blood were taken in a double syringe for the LP group, and the sample was centrifuged at 1,500 U/min for 5 minutes. About 5 mL of plasma are produced as a result, with thrombocyte concentrations twice as high as the baseline. It used the same injection technique. From one week prior to treatment until two months afterwards, all patients were urged to cease using any nonsteroidal anti-inflammatory drug treatments. Both morphine and paracetamol were accepted. For two weeks, nonweight bearing was advised, however free ankle mobility was encouraged.

A visual analogue scale (VAS) score (0–10) was used to measure pain severity both at rest and during activity. The Victorian Institute of Sport Assessment Scale (VISA-A) was used to gauge the severity of the CAT. These self-reported results were finished two months after the commencement of treatment and at baseline. The aforementioned surveys were delivered to patients in order to evaluate the long-term follow-up. In order to get the missing information through a structured interview, a phone call was placed to patients who had not responded to the questions within two weeks.

Declaration of ethics

According to national guidelines and Danish law, ethical approval is not required for patient-reported outcome and questionnaire studies. The law states that questionnaire surveys and medical database research projects must be notified to the research ethics committee system if they involve human biological material.12

Evaluations

Constant values are presented as means with standard deviations. In categorical data, counts and percentages are presented. 95% confidence intervals (CIs) were used to examine the differences in VAS pain and VISA-A score across treatment groups (LR and LP). A change was deemed significant if there was no overlap between the CIs. We examined the overall and individual results for both therapies, taking into account a 30% reduction in pain based on the VAS score and a minimally clinically important change (MCIC) is indicated by a 30% increase in the VISA-A score. Using robust standard errors (SEs) in logistic regression, the difference between treatments was examined to see if any treatment had more patients meet the MCIC. Additionally, as a sensitivity study, we investigated the effects of applying a 10-point increase in VISA-A on the percentage of patients who saw changes in CAT severity that were clinically significant.

Robust SE was used in numerous linear and logistic regression multivariate analyses. The continuous variable, the difference in VAS pain and VISA-A values between treatments, was evaluated using multiple linear regression. To determine the variation in

the likelihood of reaching an MCIC, multiple logistic regression was conducted utilising the dichotomized variable of whether

Results

The 18 females in the LR-group had a median age of 51.9 (SD 11.6), and the 18 men had a median age of 50.9 (SD 7.6). Bilateral treatment was given to five patients. Within the LP-group, the median age was 53.6 (SD 9.5) for 27 females and 49.7 (SD 11.7) for 21 men. Bilateral treatment was given to fifteen individuals. PRP was used to treat 104 Achilles tendon patients in total. Five patients and five out of 41 tendons in the LR-group failed to reach MCIC eight weeks following treatment. The VAS for pain decreased from 4.0 (95% CI 3.0, 5.5) to 1.1 (95% CI 0.5, 1.8) when the patient was at rest, and from 7.3 when the patient was active.(median time 36.9) to 3.4 (95% CI 2.5, 4.4) and then to 1.8 (95% CI 1.0, 2.6) at the endpoint.

months, interquartile range 26–46). From 45.4 (95% CI 28.6, 62.4) to 56.5 (95% CI 30.2, 82.8), VISA-A rose. Eight experienced recurrences, while nineteen reported no pain. Twenty-seven were satisfied, one had a problem (thrombosis), and 26 said they would get PRP treatment again if they developed new tendinopathy. After PRP, nine underwent additional therapies, and one underwent surgery. Following the PRP treatment, eleven took morphine.

Eight weeks following therapy, 15 patients and 15 out of 63 tendons in the LP-group did not reach MCID. The VAS measure of pain at rest decreased from 4.2 (95% CI 4.0, 5.5) to 9.5% CI (-0.5, 1.8) = 1.1. At the endpoint (median time 36.9 months, IQR 26–46), pain under exercise decreased from 7.8 (95% CI 7.3, 8.2) to 4.8 (95% CI 4.0, 5.6) and then to 3.6 (95% CI 2.3, 4.8). From 29.7 (95% CI 24.0, 35.4) to 44.7 (95% CI 38.1, 51.2) on the VISA-A scale, two individuals attained a score higher than 90.

Three experienced a recurrence, while twelve reported no pain. Eleven said they would select PRP therapy once more in the event of fresh tendinopathy, whereas nineteen reported satisfaction and none reporting any complications. After PRP, five underwent additional therapies, and eight took morphine.

Between the patients receiving LP- and LR-PRP treatment, there was no statistically significant difference in the change in VAS or VISA-A scores. Although LR-PRP tended to produce better results, this difference was not statistically significant (Table 1).

Very little change that is clinically significant For VAS while activity (95% CI 54%, 73%) and VAS during rest (95% CI 73%, 88%), the overall chance of reaching an MCIC was 63%. It was 61% (95% CI 47%, 75%) for VISA-A. Based on the sensitivity analysis, there was a 59% (95% CI 46%, 73%) chance of meeting the MCIC. The likelihood of reaching MCIC did not significantly differ between the LR- and LP-groups. For the LR-group, the likelihood of reaching the MCIC was 68% for VAS when engaged in activity (95% CI 54%, 83%) and 88% for VAS while at rest (95% CI 78%, 98%).

Discussion

When all other options for treating CAT have been exhausted, we discovered that PRP may be a viable option. PRP recipients had a 61% chance of attaining an MCIC during an activity and an 81% chance of achieving an MCIC in pain intensity at rest. Additionally, 63% of patients had MCIC in terms of CAT severity. Regarding CAT severity and pain intensity, there were no appreciable variations between patients treated with LR-PRP and LP-PRP. Furthermore, the sensitivity analysis revealed no discernible variation in the percentage of patients who attained the MCIC; nonetheless, merely a pair of patients achieved a VISA-A score of 90 is a value that may be regarded as clinical resolution. Future studies assessing PRP for CAT will benefit from these findings, which also help with effect size and sample size calculation. For instance, the sample size calculation for the likelihood ratio test for the number required to show a statistical difference yielded 330 patients for resting pain intensity, 1,146 patients for pain during activity, and 74,336 patients for the VISA-A score when using the proportions of patients reaching the MCIC. Consequently, it may appear impractical to carry out a randomised controlled trial (RCT) when multiple thousand patients are needed in each group to demonstrate a meaningful difference in one of the primary findings.

Because we believe that PRP treatment is still experimental, we utilised a rather cautious estimate for the MCIC. Thus, we only included patients who had not responded to previous therapy, such high-load strength training, and whose symptoms had persisted for more than six months.Thirteen While PRP is frequently used to treat chronic tendinopathies, the best PRP procedure is yet unknown. Specifically, it is unknown how beneficial single injections are compared to several injections and how long is the optimal break between treatment sessions. PRP treated epicondylitis with good results in one pilot research (14). This is consistent with two randomised clinical trials that

have shown PRP to be beneficial.15, 16 A recent multicenter RCT on 230 patients with humerus epicondylitis was conducted by Mishra et al16, with a follow-up of three and six months. They suggested that PRP be administered before to surgery after finding that 83.9% of patients benefited from it. They discovered that PRP was less costly and safer than surgery, although the results were frequently noticeable three months later. Results for Achilles tendinopathy patients getting LP-PRP at 4.5 years in terms of long-term pain intensity and symptom severity are encouraging. Exercise treatment added to PRP may provide further benefits. When PRP was paired with eccentric workouts, as opposed to eccentric exercise alone, Boesen et al. reported better results.4 Given that every patient received a trial of eccentric exercise therapy before receiving PRP, this is pertinent to the findings of the current study. It is advised that patients return to eccentric activity 14 days after beginning PRP treatment.

PRP did not, however, appear to enhance function, discomfort, or healing, according to other research. There were no changes in the clinical outcome between LR-PRP and placebo18 or between LR-PRP and steroid injections and saline injections for Achilles tendinopathy, according to two prior double-blind randomised clinical trials. Using healthy rabbit patella tendons as an animal model, Dragoo et al. studied LR- vs. LP-PRP. Five days following the injection, they saw a larger acute inflammatory response, which led them to theorise that leucocytes may raise the risk of discomfort and inflammation.20 It's unclear, though, if this reaction is detrimental or helpful for tendon recovery. When Salini et al. (29) examined the VISA-A results of 15 older and 29 younger patients with Achilles tendinopathy, they discovered that PRP was less successful in the latter group. In the current investigation, the average age of the patients was 49 (range 31–68) in the LP-group and 52 (range 34–71) in the LR-group. It is unclear how age affects treatment result in the current investigation because of the high degree of heterogeneity. It's probable that there are significant variations in tendinopathy between age groups. From a clinical standpoint, for instance, it might not be acceptable to presume that tendinopathy in a thirty-year-old patient who runs regularly is comparable to tendinopathy in a seventy-year-old patient who is sedentary. Future study on tendinopathy outcomes will need to take the effect of age into account.

Restrictions

The potential for systematic error resulting from the nonrandom patient sampling is one of the study's limitations. We enrolled individuals who had been referred to the orthopaedic department with intractable Achilles tendinopathy; one of the two clinicians handled the patients. As a result, it is unclear whether these findings hold true outside of the study group. Regarding the outcome measurements, recollection bias is also a possibility. Ultimately, before PRP can confidently used in clinical settings, these results need to be replicated and the efficacy of the treatment further examined through reliable clinical trials.

Conclusion

Depending on the outcome, we discovered that 61%–81% of individuals with recalcitrant CAT saw a clinically meaningful improvement from PRP treatment. Furthermore, we examined the efficacy of two distinct PRP products—LR-PRP and LP-PRP—in the management of patients suffering from persistent, noncompliant Achilles tendinopathy. Between LR-PRP and LP-PRP, we did not find any statistically or clinically significant differences in pain intensity or CAT severity.

REFERENCES

1. Mani-Babu S, Morrissey D, Waugh C, Screen H, Barton C. The effec- tiveness of extracorporeal shock wave therapy in lower limb tendinopa- thy: a systematic review. Am J Sports Med. 2015;43(3):752–761.

2. Wasielewski NJ, Kotsko KM. Does eccentric exercise reduce pain and improve strength in physically active adults with symptom- atic lower extremity tendinosis? A systematic review. J Athl Train. 2007;42(3):409–421.

3. Andia I, Latorre PM, Gomez MC, Burgos-Alonso N, Abate M, Maffulli N. Platelet-rich plasma in the conservative treatment of painful tendi- nopathy: a systematic review and meta-analysis of controlled studies. Br Med Bull. 2014;110(1):99–115.

4. Boesen AP, Hansen R, Boesen MI, Malliaras P, Langberg H. Effect of high-volume injection, platelet-rich plasma, and

sham treatment in chronic midportion Achilles tendinopathy: a randomized double-blinded prospective study. Am J Sports Med. 2017;45(9):2034–2043.

5. Shrier I, Matheson GO, Kohl HW. Achilles tendonitis: are corticosteroid injections useful or harmful? Clin J Sport Med. 1996;6(4):245–250.

6. Kajikawa Y, Morihara T, Sakamoto H, et al. Platelet-rich plasma enhances the initial mobilization of circulation-derived cells for tendon healing. J Cell Physiol. 2008;215(3):837–845.

7. Aspenberg P, Virchenko O. Platelet concentrate injection improves Achilles tendon repair in rats. Acta Orthop Scand. 2004;75(1):93–99.

8. Zhang J, Wang JH. Platelet-rich plasma releasate promotes differen- tiation of tendon stem cells into active tenocytes. Am J Sports Med. 2010;38(12):2477–2486.

9. Zhou Y, Zhang J, Wu H, Hogan MV, Wang JH. The differential effects of leukocyte-containing and pure platelet-rich plasma (PRP) on tendon stem/progenitor cells – implications of PRP application for the clinical treatment of tendon injuries. Stem Cell Res Ther. 2015;6(1):173.

10. Mccarrel TM, Minas T, Fortier LA. Optimization of leukocyte concen- tration in platelet-rich plasma for the treatment of tendinopathy. J Bone Joint Surg Am. 2012;94(19):e143–148.

11. Engebretsen L, Steffen K, Alsousou J, et al. IOC consensus paper on the use of platelet-rich plasma in sports medicine. Br J Sports Med. 2010;44(15):1072–1081.

12. ETHICS TDNCOHR. Act on Research Ethics Review of Health Research Projects. Copenhagen: The Danish National Committee on Health Research Ethics; 2011.

13. Rathleff MS, Mølgaard CM, Fredberg U, et al. High-load strength training improves outcome in patients with plantar fasciitis: a random- ized controlled trial with 12-month follow-up. Scand J Med Sci Sports. 2015;25(3):e292–e300.

14. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buff- ered platelet-rich plasma. Am J Sports Med. 2006;34(11):1774–1778.

15. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. Am J Sports Med. 2010;38(2):255–262.

16. Mishra AK, Skrepnik NV, Edwards SG, et al. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multi- center, randomized controlled trial of 230 patients. Am J Sports Med. 2014;42(2):463–471.

17. Filardo G, Kon E, Della Villa S, Vincentelli F, Fornasari PM, Marcacci M. Use of platelet-rich plasma for the treatment of refractory jumper's knee. Int Orthop. 2010;34(6):909–915.

18. de Jonge S, de Vos RJ, Weir A, et al. One-year follow-up of platelet- rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. Am J Sports Med. 2011;39(8): 1623–1629.

19. Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, Ellingsen T. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. Am J Sports Med. 2013;41(3):625–635.

20. Dragoo JL, Braun HJ, Durham JL, et al. Comparison of the acute inflammatory response of two commercial platelet-rich plasma systems in healthy rabbit tendons. Am J Sports Med. 2012;40(6):1274–1281.

21. Salini V, Vanni D, Pantalone A, Abate M. Platelet rich plasma therapy in non-insertional Achilles tendinopathy: the efficacy is reduced in 60-years old people compared to young and middle-age individuals. Front Aging Neurosci. 2015;7(e37839):228.