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Autologous Blood and Platelet-Rich Plasma Injections in the Treatment of Achilles Tendinopathy: A Critically Appraised Topic

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Clinical Scenario: Achilles tendinopathy is a painful condition commonly affecting the general and athletic population. It presents with localized pain, stiffness, and swelling in the midportion of the Achilles tendon. The physical stress placed on the tendon results in microtrauma, which leads to subsequent inflammation and degeneration. While it is not surprising that this condition affects the physically active, nearly one-third of Achilles tendinopathy cases occur in sedentary individuals. Etiology for this condition stems from a change in loading patterns and/or overuse of the tendon, resulting in microscopic tearing and degenerative changes. There are numerous causes contributing to the maladaptive response in these patients, such as mechanical, age-related, genetic, and vascular factors. The treatment for these patients is typically load management and eccentric strengthening of the gastrocnemius–soleus complex. Unfortunately, conservative treatment can lead to surgical intervention in up to 45% of cases. A relatively new phenomenon in the treatment of this condition is the use of autologous blood injections (ABI) and platelet-rich plasma injections (PRPI). This need for a less invasive treatment fostered more investigation into ABI and PRPI to treat these nonresponsive patients. However, the evidence concerning the effectiveness of these treatments in patients with Achilles tendinopathy has not been synthesized. **Focused Clinical Question:** In patients with Achilles tendinopathy, how do variations of ABI and PRPI compared with a placebo and/or eccentric training affect pain and function?

Keywords: Achilles tendon, therapy, degeneration, placebo

Clinical Scenario

Achilles tendinopathy is a painful condition commonly affecting the general and athletic population.^{1,2} It presents with localized pain, stiffness, and swelling in the midportion of the Achilles tendon.³ The physical stress placed on the tendon results in microtrauma, which leads to subsequent inflammation and degeneration.⁴ While it is not surprising that this condition affects the physically active, nearly one-third of Achilles tendinopathy cases occur in sedentary individuals.² Etiology for this condition stems from a change in loading patterns and/or overuse of the tendon, resulting in microscopic tearing and degenerative changes.⁵ There are numerous causes contributing to the maladaptive response in these patients, such as mechanical, age-related, genetic, and vascular factors.⁶ The treatment for these patients is typically load management and eccentric strengthening of the gastrocnemius–soleus complex. Unfortunately, conservative treatment can lead to surgical intervention in up to 45% of cases.⁷ A relatively new phenomenon in the treatment of this condition is the use of autologous blood injections (ABI)

and platelet-rich plasma injections (PRPI). This need for a less invasive treatment fostered more investigation into ABI and PRPI to treat these nonresponsive patients. However, the evidence concerning the effectiveness of these treatments in patients with Achilles tendinopathy has not been synthesized.

Focused Clinical Question

In patients with Achilles tendinopathy, how do variations of ABI and PRPI compared with a placebo and/or eccentric training affect pain and function?

Summary of Search, “Best Evidence” Appraised, and Key Findings:

- The literature was searched for studies of level 2 evidence (based on Levels of Evidence, Centre for Evidence-Based Medicine [CEBM], 2011) or higher that investigated the effect of ABI and PRPI on pain and function in patients with Achilles tendinopathy.
- The literature search produced 16 possible studies related to the clinical question; 4 randomized control trials met the inclusion and exclusion criteria (Figure 1).

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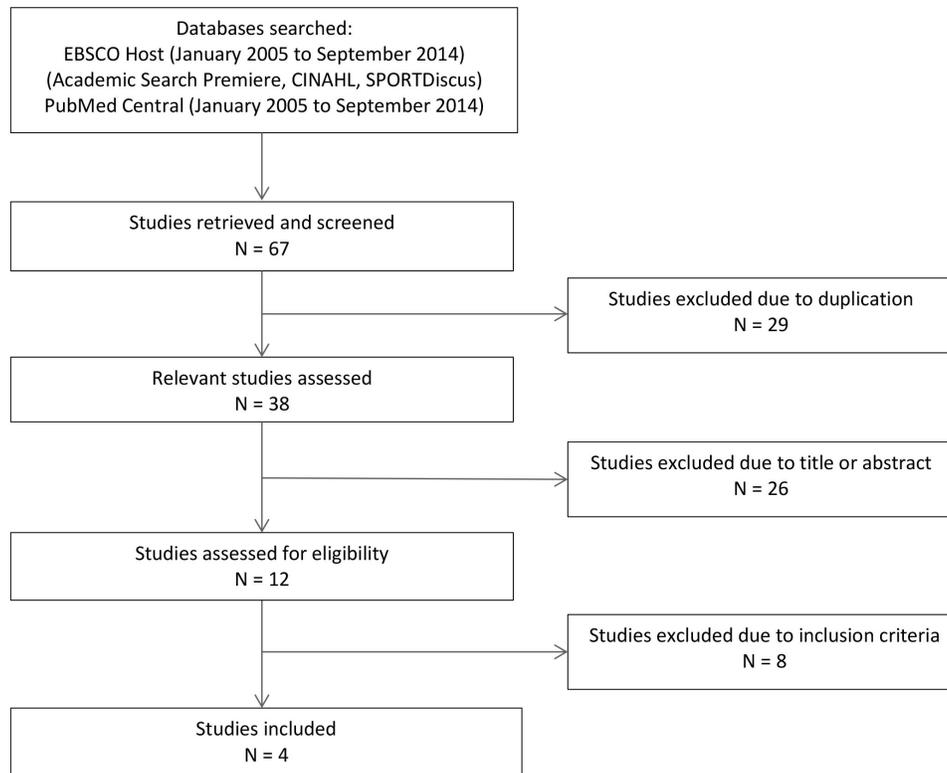


Figure 1 — Summary of search history and included studies.

- Two of the included studies^{1,8} compared PRPI with saline injections, 1 of the studies² compared ABI with tendon needling with no saline, and 1 of the studies⁴ compared ABI with eccentric exercises.
- All groups in the included studies^{1,2,4,8} had improvements in VISA-A scores; however, there were no significant differences found between groups.

- **Intervention (or assessment):** *platelet-rich plasma injections OR autologous blood injections with eccentric training*
- **Comparison:** *saline injection OR needling AND/OR eccentric training*
- **Outcomes:** *pain AND function* [as measured by Victorian Institute of Sports Assessment (VISA-A)]

Clinical Bottom Line

The evidence does not support the use of ABI and PRPI in conjunction with eccentric training to improve outcomes for Achilles tendinopathy. Therefore, eccentric training alone is sufficient to treat chronic Achilles tendinopathy.

Strength of Recommendation: In accordance with the 2009 CEBM levels of evidence, there is grade B evidence that does not support the addition of ABI or PRPI for the short-term treatment for chronic Achilles tendinopathy. Consistent level 2 evidence was found in the 4 included studies.

Search Strategy

Terms Used to Guide Search Strategy

- Patient/Client group: *Achilles tendinopathy*

Sources of Evidence Searched

- Academic Search Complete
- CINAHL
- MEDLINE
- SPORTDiscus
- Additional resources obtained via review of reference lists and hand search

Inclusion and Exclusion Criteria

Inclusion Criteria

- Studies identified as level 2 evidence or higher.
- Patients diagnosed with Achilles tendinopathy
- Patients with a symptom duration >2 months
- Patients treated using PRPI or ABI

- Use of eccentric exercises for standardized care
- Patients age 18 years or older
- Use of VISA-A as an outcome measure
- Limited to English
- Limited to humans
- Limited to publications within the last 10 years (2006–2015)

Exclusion Criteria

- Patients with history of Achilles rupture
- Confounding pathologies or diseases affecting the Achilles

Results of Search

Four relevant studies^{1,2,4,8} were located and categorized as shown in Table 1 (based on Levels of Evidence, CEBM, 2011).

Best Evidence

The studies in Table 2 were identified as the best evidence and selected for inclusion in this clinically appraised topic (CAT). These studies were selected because they were graded with a level of evidence of 2, they examined the use of PRPI or ABI in the treatment of Achilles tendinopathy for pain and function, and the outcome of interest (VISA-A scores) was described.

Implications for Practice, Education, and Future Research

The studies included in this CAT addressed the use of ABI and PRPI to treat patients with Achilles tendinopathy. Based on this appraisal, three^{1,2,8} of the four^{1,2,4,8} studies found no significant difference in the primary outcome, VISA-A scores, in any of the experimental groups. The main components of the VISA-A are pain and function, which are the biggest complaints in patients with this type of pathology. However, Pearson et al⁴ found small short-term symptom improvements when ABI was added to the standard of care. The findings of these articles indicate that there is no significant evidence to support using any

level of ABI at this time. The designs of the appraised studies varied slightly, from eccentric strength training in conjunction with ultrasound-guided intratendinous PRPI^{1,8} to peritendinous ABI and the standard of care.^{2,4} All 4 studies found improvement in VISA-A scores regardless of treatment allocation.

In the ABI performed in the included studies,^{2,4} 3 mL of venous blood was drawn from the patient's ante-cubital fossa and injected at the Achilles tendon using an unguided peritendinous technique. One study² described using a 3-pass injection technique that involved a single puncture site and 1-mL injections in 3 different directions. The injections were done perpendicular to the tendon, 20° superiorly and 20° inferiorly. The numerous platelet-derived growth factors are thought to be the "active ingredient" of whole blood.¹ The growth factors, as well as other cytokines present in the blood, are proposed to be catalysts of tissue healing, as they aid in the production of type I collagen in tissue of the degenerating tendon.²

In the PRPI performed in the included studies,^{1,8} 54 mL of blood was collected from the subject's cubital vein. Six milliliters of citrate was added to the blood sample to prevent early clotting. The blood underwent centrifugation for 15 minutes, and the platelet rich plasma (PRP) was obtained from the sample. Three-tenths of a milliliter of 8.4% sodium bicarbonate buffer was added to the PRP in an effort to match the pH of the PRP with the pH of the tendon tissue. Four milliliters of the pH-corrected PRP was collected for injection. Through ultrasound-guided injection, the PRP was injected through 3 different puncture locations. Five small depositions were made, totaling 4 mL.^{1,8} The platelets in the PRPI obtained from the whole blood release various growth factors that may play a role in regenerating damaged tendon tissue through the proliferation of new tendon cells, collagen synthesis, and vascularization of new tissue.⁸

There are many uncertainties surrounding PRPI, as it is a relatively new procedure. In intratendinous PRPI, the volume of the substance that remains within the damaged tendon is unknown; some believe that the PRP may leak into the peritendinous space.⁸ This may be due, in part, to the increased pressure within the tendon from the injection. The exact composition of PRP is also unknown, and there is little consistency in preparation across providers.^{1,8} The exact amount of growth factors present in each PRPI is not quantified as a part of standard procedure, making it difficult to make concrete conclusions about its effectiveness.^{1,8} When comparing ABI with PRPI, ABIs are simpler and more cost-effective, as special processing or equipment is not needed.² ABIs can be done without ultrasound guidance and require a much smaller volume of blood to be taken from the patient.^{2,4}

Practitioners should use caution when suggesting or prescribing ABI or PRPI to patients with Achilles tendinopathy. All the included studies^{1,2,4,8} were level 2 evidence and resulted in injection outcomes that were no better than those in the control groups. This suggests that the control was just as effective, and much more cost-efficient, than the injections. All 4 studies^{1,2,4,8} used

Table 1 Summary of Study Designs of Articles Retrieved

Level of evidence	Study design	Number located	Reference
2	Randomized controlled trial	4	de Vos et al ¹ de Jonge et al ⁸ Pearson et al ⁴ Bell et al ²

Table 2 Characteristics of Included Studies

	de Vos et al¹	de Jonge et al⁸	Pearson et al⁴	Bell et al²
Design	RCT	RCT	Prospective RCT	Prospective RCT
Participants	54 randomized patients: 27 PRP, 27 saline placebo; age 18–70 y (mean age PRP = 49, mean age saline = 50) with chronic Achilles tendinopathy 2–7 cm above the tendon insertion.	54 randomized patients, age 18–70 y, with chronic Achilles tendinopathy 2–7 cm proximal to insertion.	33 patients (18 women, 15 men) of mean age 50 y (SD 9) with 40 Achilles tendinopathies for a mean duration of 11 mo. Some patients were affected by bilateral Achilles tendinopathy.	53 patients with mean age of 49, affected by unilateral midportion Achilles tendinopathy with symptoms lasting for at least 3 mo.
Intervention investigated	PRP injection or saline injection along with eccentric exercises.	Participants received a blinded ultrasonographic injection containing PRP (treatment group) or saline (placebo group), at 3 different needle locations, in addition to an eccentric-training program. After the injection, patients had to avoid sports activities for 4 wk; in the second week, they performed a stretching program. After this, all patients started an eccentric-exercise program for 12 wk.	Randomized blinded peritendinous ABIs were administered to participants in addition to standard treatment (eccentric-loading exercises) or standard treatment alone for 12 wk.	All participants underwent 2 unguided peritendinous injections 1 mo apart with a standardized protocol with follow-up at 1, 2, 3, and 6 mo. The standardized program consisted of a 12-wk eccentric calf-training program that was executed by both groups. The treatment group received a 3-mL injection of their own whole blood, while the control group had needling only with no substance injected.
Outcome measures	<i>Primary:</i> VISA-A was collected at baseline, 6, 12, and 24 wk. <i>Secondary:</i> subjective patient satisfaction, return to sport, and adherence to eccentric exercises.	<i>Primary:</i> VISA-A. <i>Secondary:</i> Subjective patient satisfaction, return to sport activity.	VISA-A score and ratings of discomfort during and after the injection measured at baseline and 6 and 12 wk.	<i>Primary:</i> change in symptoms and function from baseline to 6 mo with the VISA-A score. <i>Secondary:</i> participant perceived rehabilitation and ability to return to sport.
Main findings	Mean VISA-A score improved significantly after 24 wk in the PRP and placebo groups. There was no significant difference in improvement on VISA-A score between treatment groups or in secondary outcome measures between PRP and placebo groups.	Both the PRP group and the placebo group had improved mean VISA-A scores after 1 y. There was no significant difference in increase between the groups. In both groups, 59% of the patients were satisfied with the received treatment. Ultrasonographic tendon structure was not significantly different between groups but was significantly improved.	Improvements in VISA-A were observed in the treatment and control groups at 6 wk relative to baseline, with no clear effect of blood injection. At 12 wk VISA-A score improved in the treatment group, revealing a blood-injection effect, relative to a comparatively unchanged condition in control. A 21% rate of postinjection flare was a noted side effect, with all other predictors of response to treatment being unremarkable.	At 6 mo there were clear and clinically worthwhile improvements in the VISA-A score in both the treatment and control groups. The overall effect of treatment was not significant, and there was no significant difference between groups in secondary outcomes. There was also no significant difference between groups in levels of compliance with the eccentric calf-strengthening program.

(continued)

Table 2 (continued)

	de Vos et al¹	de Jonge et al⁸	Pearson et al⁴	Bell et al²
Level of evidence	2	2	2	2
Validity score	PEDro 9/10	PEDro 10/10	PEDro 6/10	PEDro 8/10
Conclusion	Results showed no greater improvements in pain or activity function in patients being treated with an eccentric exercise program and either PRP injection compared with a saline injection among patients with chronic midportion Achilles tendinopathy.	There was no clinical or ultrasonographic superiority of PRP injection over a placebo injection in chronic Achilles tendinopathy at 1 y combined with an eccentric-training program.	Small short-term symptomatic improvements with the addition of ABI to standard treatment for Achilles tendinopathy were revealed. Studies with larger sample size are required that include double-blinding and longer follow-up.	There were no additional benefits in the treatment of midportion Achilles tendinopathy by the administration of 2 unguided peritendinous ABIs along with an additional standardized eccentric-training program.

Abbreviations: RCT, randomized controlled trial; PRP, platelet-rich plasma; ABI, autologous blood injection.

Alfredson eccentric calf-muscle training.³ This training protocol consisted of 180 eccentric heel-drop exercises a day for 12 weeks. Clinicians can have confidence in using eccentric training as the standard of care for patients suffering from Achilles tendinopathy until better evidence is found to support the use of ABI.

Tendinopathy is a response to overuse, degeneration of the tendon, and disorganization of collagen fibers, with little to no inflammation.⁹ The included studies used various ways to grade or categorize the level of tendinopathy in the sample population. de Vos et al¹ did not investigate the level of tendinopathy present in their patients, while de Jonge et al⁸ examined the severity of the present tendinopathy based on the level of neovascularization. This was scored using the modified Ohberg scoring system.¹⁰ This scoring system classified 0 as no vessels, 1 as 1 vessel (mostly anterior to the tendon), 2 as 1 or 2 vessels throughout the tendon, 3 as 3 vessels throughout the tendon, or 4, which consisted of more than 3 vessels throughout the tendon. Bell et al² used ultrasound scans to determine the level of tendinopathy based on a grading scale that ranged from mild to severe. A mild classification was awarded if the tendon displayed only fusiform thickening, a moderate classification if there were additional hypochoic areas present, and a severe classification if neovessels were also present on Doppler scanning. Pearson et al⁴ classified patients with ultrasound scans to confirm the presence of tendinopathy. They also assessed the presence and degree (nil = 0, mild = 1, moderate = 2, or severe = 3) of neovascularization. Not having a consistent and universal scoring system is a large limiting factor in the treatment of these patients.

One major limitation of 3 of the included studies was the use of needling or saline injections as the control/placebo.^{2,4,8} The trauma to the tendon tissue induced by needling likely created bleeding sufficient to induce a healing response in the tissue, making the needling a treatment in itself and not a true control. Another limitation of the included studies was the use of NSAIDs by subjects despite being told to refrain from doing so.^{1,4} Each study had its own confounding issues. de Vos et al¹ and de Jonge et al⁸ had compliance issues in both groups after 12 weeks. Several patients also had additional treatments consisting of a tendon-binding band and foot orthotics. Four of the PRPI patients needed an additional procedure due to their lack of improvement.^{1,8} Those authors also wrote that increasing the peritendinous volume could destroy the neural and vascular growth that is causing the pain.^{1,8} Bell et al² used a second injection, which could have interrupted the steady-state effect of the first injection, and both injections lacked ultrasound guidance. They also exhibited a 6% dropout rate. Pearson et al⁴ allowed participants to continue low-impact exercise and had a 30% dropout rate. All of these limitations should be considered in future studies.

Suggestions for future research in all 4 studies^{1,2,4,8} included a need to investigate the etiology and pathophysiology of Achilles tendinopathy. Knowing the cause and level of tendinopathy is crucial in effectively treating the

condition. The 4 randomized controlled trials included in this CAT all used different ways to classify tendinopathy severity, since there is currently no validated classification for the condition on a histological level. For clinicians it is critical to know the source of the problem, not just the solution. Differentiating between tendinopathy, tendinitis, and tendinosis is often difficult from a clinician's standpoint. These conditions are very different histologically, but based on the limited information we can get from an evaluation, we often treat them the same. More research, and subsequent training, into diagnostic ultrasound techniques (with and without Doppler sonography) could help us identify individualized disease severity and lead to better treatment outcomes. If there were more knowledge surrounding a diagnosis based on histology and severity, we could provide a treatment more specific to whatever histological malady the patient is dealing with. Research also needs to be done to identify what happens at a histological level after injection therapy takes place. There is a discrepancy in what happens to the blood once it is injected, specifically, what happens at varying injection sites. Until future research and imaging illuminate what the dispersion and absorption rate of the injected substance actually is, it will remain unclear which injection site is the most appropriate. Researchers may try investigating an ABI- or PRPI-only intervention group to elucidate findings related to pain and function without the inclusion of confounding variables. At this point in time we believe that the treatment is not working because we are injecting patients based on a theory of what will happen on the microlevel without the appropriate data to support it. This CAT should be reviewed in 2 years or when additional evidence is available that may change the clinical bottom line for the research question posed.

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