



COMPARATIVE ANALYSIS OF PLATELET-RICH PLASMA AND TRIAMCINOLONE ACETONIDE INJECTIONS IN THE MANAGEMENT OF PLANTAR FASCIITIS: A PROSPECTIVE STUDY

Orthopedics

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ABSTRACT

Context: Plantar fasciitis, a prevalent cause of heel pain, poses challenges in treatment due to diverse therapeutic options and variable outcomes. Platelet-rich plasma (PRP) and triamcinolone acetonide injections have emerged as potential interventions, yet their comparative effectiveness remains debated. **Aims:** To compare the effectiveness of PRP and triamcinolone acetonide injections in relieving pain, improving function, and promoting healing in individuals with plantar fasciitis. **Settings And Design:** Prospective Hospital-based experimental study. **Methods And Material:** A two-year prospective hospital-based experimental study was conducted, enrolling patients aged 30-60 with plantar fasciitis. Patients received either PRP or triamcinolone acetonide injections. Pre-operative assessments and three months of monitoring were performed. Foot and Ankle Outcome Score (FAOS) survey was utilized for outcome evaluation. **Statistical Analysis Used:** t-test was applied. **Results:** Ninety patients were included, with both treatment groups demonstrating significant improvement in foot symptoms. PRP administration showed superiority in descending and ascending stairs, rising from sitting, and walking on flat surfaces compared to triamcinolone acetonide. FAOS scores indicated significant improvement post-treatment in both groups, with PRP yielding better outcomes than triamcinolone acetonide. **Conclusions:** Both PRP and triamcinolone acetonide injections effectively alleviate foot symptoms in plantar fasciitis patients. However, PRP demonstrates superior outcomes in specific functional activities and quality of life components compared to triamcinolone acetonide. These findings suggest PRP as a preferred intervention in the management of plantar fasciitis.

KEYWORDS

Plantar fasciitis, Platelet-rich plasma, Triamcinolone acetonide, Injection therapy, Foot and ankle outcome, Prospective study.

INTRODUCTION:

Plantar fasciitis is one of the most common causes of heel pain, affecting millions of individuals worldwide, particularly those involved in activities that place repetitive stress on the foot.^[1] It is characterized by inflammation and degeneration of the plantar fascia, a thick band of tissue that supports the arch of the foot. The condition often leads to significant discomfort, limitation of daily activities, and decreased quality of life for affected individuals.^[2] Among the therapeutic modalities used for plantar fasciitis, both platelet-rich plasma (PRP) injections and triamcinolone acetonide (TA) injections have gained attention for their potential to alleviate symptoms and promote healing.^[3] Platelet-rich plasma, derived from the patient's own blood, contains a concentrated amount of platelets and growth factors that are thought to stimulate tissue regeneration and repair.^[4] Triamcinolone acetonide, a corticosteroid, exerts anti-inflammatory effects and has been widely used to reduce pain and inflammation in various musculoskeletal conditions, including plantar fasciitis.

While both PRP and TA injections have shown promise in the management of plantar fasciitis, there is ongoing debate regarding their comparative effectiveness, safety, and long-term outcomes. Furthermore, existing literature presents conflicting findings regarding the superiority of one treatment modality over the other, with some studies suggesting that PRP injections offer superior pain relief and functional improvement compared to corticosteroid injections, while others report similar outcomes between the two interventions.^[5-9]

Given the need for more clarity and evidence-based guidance in the management of plantar fasciitis, this study aims to compare the effectiveness of PRP and triamcinolone acetonide injections in relieving pain, improving function, and promoting healing in individuals with plantar fasciitis. By elucidating the relative benefits and drawbacks of these two treatment modalities, this research seeks to inform clinical decision-making and optimize patient outcomes in the management of this common and debilitating condition.

Subjects and Methods: The study was conducted as a Prospective Hospital-based experimental study at D.Y.Patil Vidyapeeth, Pune. Non probable Convenience sampling technique use for data collection over a period of two-year from May 2022 to May 2024. Patients meeting the inclusion criteria, including those diagnosed with plantar fasciitis aged between 30 and 60 years, willing to participate, and without other heel

pathologies or unresponsive to conservative treatments, were randomly assigned to PRP and TA groups. Exclusion criteria comprised unwillingness to sign the consent form, presence of secondary inflammatory lesions due to conditions like Diabetes or Rheumatoid arthritis, or contraindications to injection. Ethical clearance was obtained following the Helsinki Declaration, with approval from the Institutional Review Board. Pre-operative assessments were conducted for all patients, and monitoring spanned three months with follow-ups every 3-4 weeks. The surgical technique involved palpation-guided steroid injection. Statistical analysis utilized Independent t-tests to compare pre- and post-intervention groups and between PRP and TA groups. Data analysis employed SPSS software (IBM V.25) for one sample t-test, with a significance set at $p < 0.05$.

Foot and Ankle Outcome Score (FAOS) Survey was done to compare treatment outcomes. The Foot and Ankle Outcome Score (FAOS) Survey is a validated questionnaire designed to assess the functional status and quality of life-related to foot and ankle conditions. It provides a standardized method for evaluating patient-reported outcomes, specifically focusing on the lower extremities. The FAOS consists of several subscales, each targeting different aspects of foot and ankle function and symptoms. These subscales include Pain, Symptoms, Activities of Daily Living (ADL), Sport and Recreation Function (Sport), and Foot and Ankle Related Quality of Life (QOL).

The Pain subscale evaluates the severity and frequency of pain experienced in the foot and ankle region. The Symptoms subscale assesses other symptoms such as stiffness, swelling, and limitations in joint movement. The ADL subscale measures the patient's ability to perform daily activities like walking, standing, and climbing stairs without difficulty. The Sport subscale focuses on activities requiring higher levels of physical exertion and evaluates the individual's ability to participate in sports or recreational activities. Lastly, the QOL subscale explores the impact of foot and ankle problems on overall quality of life, including emotional well-being and social interactions.

Each subscale comprises a series of questions scored on a Likert scale, where respondents rate the severity or frequency of their symptoms or functional limitations. Scores are then aggregated to obtain subscale scores, which are further combined to calculate a total FAOS score. This comprehensive assessment provides valuable insights into the patient's perceived function, symptoms, and overall well-being related

to foot and ankle conditions. The outcome of FAOS is calculated based on a standardized scoring algorithm given a score between 0 and 100 for each of the 5 subscales. A score of 100 indicates the best possible results and 0 the worst outcome. The FAOS is freely available for academic users at <https://eprovide.mapi-trust.org>.^[10]

RESULTS:

A Total 93 patients were included in the study. Out of this, 45 patients were included in each group; rest 3 patients were lost to follow up. One lost to follow up in PRP group and 2 in Triamcinolone group. Hence the result was analysed on 90 patients only.

Predominant side involved was right side in both the groups. In our

study Foot symptoms (Mean±S.D) significantly improved after 3 months of treatment in both the groups PRP as well as Triamcinolone Acetonide (TA) except descending staircase and lying in the bed was not found statically significant improvement.

In our study, patient's age range varies between 34 years to 56 years in PRP group and 32 years to 56 years in TA group. Out of total 90 patients 55.5% were in the age group 40-50, 32.2% were in the age group 30-40 years rest 12.3% were in the age group 50-60 years. Mean age in PRP Group was 42.5 with S.D. 5.42 and in TA Group it was 40.84 with S.D. 5.28. Male: female ration was 1:1 and left Vs right foot involvement was also 1:1. In PRP group, Male, female ratio was 22:23 and in TA group, it was 23:22.

Table 1: Comparison Of Pre And Post-treatment Functions And Daily Activities Score Among Intervention Groups.

Functions and daily activities related questionnaires	PRP		P- value	TA		P - value	Diff. between baseline & post-TA t/t scores	Diff. between baseline & post-PRP t/t scores	P - value
	Pre	Post		Pre	Post				
Descending stairs"	2.42±0.49	1.71±0.69	<0.001*	1.95±0.84	1.64±0.7	0.07	0.97±0.65	1.90±0.87	<0.001*
Ascending stairs"	2.6±0.78	2.24±0.8	0.03*	2.2±0.99	1.86±0.62	0.07	0.88±0.68	2.13±1.03	<0.001*
Rising from sitting"	2.44. ±0.54	1.64±0.6	<0.001*	1.6±0.88	1.42±0.58	0.25	0.84±0.82	1.5±0.9	<0.001*
Standing"	2.06±0.91	1.48±0.5	<0.001*	1.8±1.15	1.5±1.4	0.27	0.93±.68	1.77±1.18	<0.001*
Bending to the floor	2.22±1.04	1.71±0.45	<0.001*	1.91±0.73	1.51±0.69	0.01*	0.91±0.7	1.84±0.76	<0.001*
Walking on a flat surface"	1.77±0.87	1.42±0.64	<0.001*	2.1±2.9	1.28±0.76	0.06	0.88±0.74	2.06±3	0.012*
Getting in/out of a car"	1.84±0.73	1.42±0.65	<0.001*	1.8±0.9	1.13±0.75	<0.001*	1±0.8	1.9±0.8	<0.001*
Going shopping"	1.95±0.79	1.2±0.84	<0.001*	1.55±0.72	0.97±0.78	<0.001*	1.15±0.95	1.53±0.75	0.04*
Putting on socks	1.68±0.66	1.2±0.84	<0.001*	1.6±0.87	1.17±0.64	<0.001*	0.62±0.61	1.64±0.9	<0.001*
Rising from bed	1.71±0.72	0.95±0.82	<0.001*	1.53±0.78	1.11±0.77	0.05	0.97±0.94	1.48±0.8	0.007*
Taking off socks	1.64±0.6	0.88±0.71	<0.001*	1.62±0.68	1.13±0.76	<0.001*	0.97±0.78	1.3±0.9	<0.001*
Lying in bed (turning over, maintaining foot/ankle position)"	1.42±0.62	0.53±0.62	<0.001*	1.35±0.88	1.06±0.83	0.07	1.02±0.65	1.3±0.9	0.06
Getting in/out of bath"	1.75±0.82	1.11±0.48	<0.001*	1.62±0.96	1.22±0.59	0.02*	0.77±0.84	1.6±0.9	<0.001*
Sitting"	1.26±0.98	0.82±0.77	<0.001*	1.13±0.69	0.93±0.75	0.2	1.2±0.8	1.1±0.7	0.572
Getting on/off toilet"	1.84±0.85	1.08±0.07	<0.001*	1.75±1	1.11±0.61	<0.001*	0.97±0.94	1.7±1.03	0.006*
Heavy domestic duties (Ex. moving heavy boxes)"	2.8±0.91	2.13±0.45	<0.001*	2.15±1	1.97±86	0.4	0.88±0.88	2.1±1.1	<0.001*
Light domestic duties (cooking, dusting)"	2.33±0.7	1.13±0.72	<0.001*	1.55±1	1.51±0.81	.8	1.2±0.96	1.5±1.03	0.13

*: <0.05 (Difference is Significant)

As depicted in table-1, it was found that all the above functional and daily activities was significantly improved in case of Pre Vs Post PRP administration, and the P-value was found to be < 0.05. In Triamcinolone Acetonide group similar observation was found but ascending and descending staircase, lying in the bed, rising from sitting, standing, walking on a flat surface, heavy domestic duties

(moving heavy boxes, scrubbing floors, etc) and light domestic duties (cooking, dusting, etc) was not found significantly better though found to be improved. If we compare PRP vs Triamcinolone Acetonide, PRP was found better than Triamcinolone Acetonide except sitting and light domestic work.

Table 2: Comparison of pre and post-treatment Foot symptom scores among intervention groups.

Functions and daily activities related questionnaires	PRP		P value	TA		P value	Diff. in scores between baseline & post-TA t/t	Diff in score between baseline & post-PRP t/t	P value
	Pre t/t	Post t/t		Pre t/t	Post t/t				
Swelling in foot/ankle	2.64±0.608	1.6±0.53	<0.001*	1.93± 1.03	0.71±0.69	<0.001*	1.13±0.72	1.8±1.07	<0.001*
Clicking, feel grinding, or any other type of noise on movement of foot/ankle	2.6±0.57	1.5±0.59	<0.001*	2.15± 0.76	0.77±0.76	<0.001*	1.04±0.85	2.1±0.83	<0.001*
Foot/ankle catch or hang up on moving	2.7±0.62	1.7±0.66	<0.001*	2.2±1.04	0.75±0.65	<0.001*	1.08±0.79	2.15±1.08	<0.001*
Straightening of foot/ankle fully	2.3±0.56	1.8±0.66	<0.001*	2.8±0.87	1.13±0.8	<0.001*	0.68±0.59	2.04±0.92	<0.001*
Ability to bend foot/ankle fully	2.3±0.55	1.84±0.7	<0.001*	2.06±0.9	1.15±0.7	<0.001*	0.77±0.70	2.03±1.02	<0.001*
Severity of stiffness of foot/ankle in the morning	2.1±0.48	1.6±0.67	<0.001*	1.97±0.72	1.26±0.67	<0.001*	0.66±0.73	1.91±0.76	<0.001*
Severity of ankle stiffness after sitting, lying, resting later in the day	2.28±0.5	1.53±0.78	<0.001*	1.77±0.79	0.82±0.64	<0.001*	0.88±0.77	1.71±0.81	<0.001*
Symptom + Stiffness subtotal (%)	38.7±7.48	57.04±12.61	<0.001*	75.5±13.0	49.2±18.15	<0.001*	19±13.2	48.3±19.5	<0.001*

*: <0.05 (Difference is Significant)

As per table-2 it is clear that all the scores of foot symptom related questionnaire shows significant improvement after PRP treatment, P value <0.0001 After adding symptom and Stiffness subtotal (%), P

value was found highly significant, i.e., <0.0001.

From the above table it is apparent that all the knee symptoms like

swelling, grinding, audible clicking sound, and any other sensation after moving the foot, catch or hang up, while moving, ability to straighten or bend foot fully, foot stiffness after waking up in the morning, after sitting, lying, or resting later in the day as well as overall

symptoms and stiffness was significantly improved by the administration of Triamcinolone Acetonide also. Hence both the drugs were quite effective in alleviating foot symptoms but PRP is better than TA which is statistically significant.

Table 3: Comparison Of Pre And Post-treatment Pain Scores Among Intervention Groups.

Pain related questionnaires	PRP		P - value	TA		P - value	Diff. between baseline & post-TA t/t scores	Diff. between baseline & post-PRP t/t scores	P -value
	Pre t/t	Post t/t		Pre t/t	Post t/t				
Foot/ankle pain	2.4±0.65	1.6±0.59	<0.001*	1.93±0.83	1.2±0.69	<0.001*	0.84±0.73	1.88±0.88	<0.001*
Twisting/ pivoting on your foot/ankle	2.4±0.69	1.73±0.68	<0.001*	2.06±0.8	1.31±0.84	<0.001*	0.83±0.82	2.02±0.86	<0.001*
Straightening foot/ankle fully	2.3±0.57	1.4±0.5	<0.001*	2.3±0.79	1.15±0.85	<0.001*	0.91±0.66	2.26±0.86	<0.001*
Bending foot and ankle fully	2.64±0.64	1.88±0.61	<0.001*	2.04±1.02	1.57±0.89	<0.001*	0.86±0.72	1.99±1.06	<0.001*
Walking on flat surface	1.88±0.61	1.77±0.63	<0.001*	1.77±0.67	1.04±0.74	<0.001*	0.8	1.73	<0.001*
Going up or down stairs	2.33±0.53	1.8±0.78	<0.001*	2.13±0.91	1.62±0.72	<0.001*	0.8±0.78	2.06±0.96	<0.001*
At night while in bed	1.49±0.55	1.31±0.82	0.18	1.2±0.79	0.71±0.69	<0.001*	0.62±0.64	1.17±0.8	0.05
Sitting or lying	2±0.3	1.4±0.71	<0.001*	1.44±0.65	0.77±0.59	<0.001*	0.64±0.7	1.4±0.6	<0.001*
Standing upright	2.3±0.6	1.55±0.5	0.002*	1.48±0.84	1.73±1.11	<0.001*	0.89±0.75	1.64±1.14	<0.001*
Pain subtotal (%)	60.04±12.07	45.06±9.3	<0.001*	69.6±13.4	53.3±17.1	<0.001*	17.4±12.4	52.3±18.8	<0.001*

*: <0.05 (Difference is Significant)

As seen in table-3 the experience of Pain subtotal in all the headings was found to be significantly reduced after treatment with PRP

administration, except at night while in bed, there was no significant improvement pre and post-PRP treatment.

Table 4: Comparison Of Pre And Post-treatment Function, Recreation And Sports Activities Scores Among Intervention Groups.

Function, recreation and sports activities related questionnaires	PRP		P - value	TA		P - value	Diff. between baseline & post-TA t/t	Diff. between baseline & post- PRP t/t	P-value
	Pre t/t	Post t/t		Pre t/t	Post t/t				
Squatting	2.6±0.61	1.66±0.85	<0.001*	2.01±0.8	1.6±0.6	<0.001*	1.2±0.88	2.06±0.91	<0.001*
Running	2.66±0.69	1.8±0.45	<0.001*	2.13±1.15	1.82±0.87	<0.001*	0.8±0.7	2.08±1.18	<0.001*
Jumping	2.66±0.73	1.86±0.85	<0.001*	2.26±0.88	1.53±0.75	0.05	1.06±0.8	2.1±0.9	<0.001*
Twisting/ pivoting on your injured foot/ankle	2.53±0.66	1.62±0.53	<0.001*	2.08±1.1	1.53±0.75	<0.001*	0.91±0.90	2.04±1.14	<0.001*
Kneeling	2.28±1.07	1.93±0.5	<0.001*	2.02±1.02	1.4±0.88	<0.001*	1.06±0.75	1.97±1.05	<0.001*
Function, sports and recreational activities subtotal (%)	55.7±12.6	36.7±17.3	<0.001*	60.4±14.55	46.88±21.11	<0.001*	23.6±16.4	45.9±22.2	<0.001*

*: <0.05 (Difference Is Significant)

From the above table-4, it is apparent the experience of Pain subtotal in all headings was found to be significantly reduced after treatment with Triamcinolone Acetonide administration.

recreational activities was found to be improved significantly after administration of PRP except kneeling. Also, all the components of functions, sports and recreations were significantly improved after Triamcinolone Acetonide administration. But PRP was found significantly better than Triamcinolone Acetonide.

From the above table-4 it's found that the above Function, sports and

Table 5: Comparison Of Pre And Post-treatment Quality Of Life Scores Among Intervention Groups.

Quality of life related questionnaire	PRP		P - value	TA		P - value	Diff. between baseline & post-Triamcinolone Acetonide t/t scores	Diff. between baseline & post- PRP t/t scores	P - value
	Pre t/t	Post t/t		Pre t/t	Post t/t				
Frequency of your foot/ankle problem"	2.33±0.76	1.15±0.79	<0.001*	2.2±1.09	1.53±0.97	<0.05*	1.4±1.02	2.15±1.14	0.001
Any modification in life style to avoid damage in foot/ankle?	2.42±0.93	1.53±0.72	<0.001*	2.04±1.1	1.31±0.7	<0.05*	1.15±0.99	1.99±1.14	0.0003
Troubled with lack of confidence in your foot/ankle?	2.13±0.91	1.37±1.02	<0.001*	1.97±0.98	1.04±0.6	<0.001*	1.3±1.1	1.91±1.01	0.006*
Difficulty in foot/ankle in general?"	2.42±0.62	1.37±0.53	<0.001*	1.95±0.87	1.04±0.67	<0.001*	1.08±0.78	1.91±0.92	<0.001*
Quality of life subtotal (%)	66.2±15.5	41.7±18.1	<0.001*	68.5±13.6	49.6±22.4	<0.001*	28.8±21.9	48.6±24	<0.001*

*: <0.05 (Difference is Significant)

Table 6: Comparison Of Pre And Post-treatment FAOS SCORE Among Intervention Groups.

FAOS SCORE	Pre t/t	post t/t	p value
PRP	62.5±10.1	44.9±11.8	<0.001*
TA	68.6±9.7	53.2±17.7	<0.001*
Diff between Pre and Post PRP Vs Pre and Post TA	20.13±2.34	12.13±8.95	<0.001*

*: <0.05 (Difference is Significant)

significantly more advantageous with PRP than Triamcinolone Acetonide when the component of modification life style to avoid activities potentially damaging to the foot/ankle is highly significant, p value < 0.0003.

As per Table 6, FAOS score improvement was also found statistically significant after PRP administration as well as after TA administration however the improvement with PRP was found to be significantly better than TA.

DISCUSSION

If we compare the outcome of function, corticosteroid injection with other studies, is more effective than physical therapy in the short

Table-5 explains that all four components of quality-of-life were significantly improved after PRP administration as well as Triamcinolone Acetonide administration. But the quality of life are

term.^[11] Although some meta-analyses showing no significant improvement in foot scores were found in the American Orthopedic Foot and Ankle Society scale, Foot and Ankle Disability Index, or the Roles and Maudsley score after treatment with PRP, 6 weeks and 12 weeks later, PRP exhibited better efficacy than the steroid treatment after 24 weeks.^[3]

In our study, in few functions and daily activities scores, Triamcinolone Acetonide group did not show significant improvement after 12 weeks. Few studies found significantly better outcome with steroid,^[12] while O'Malley et al. showed PRP significantly improved the scores which is in agreement with our study.^[13]

Pain symptoms score significantly improved in both the groups PRP as well as Triamcinolone Acetonide group. Three investigations demonstrated notable alleviation of pain within the corticosteroid injection cohort in contrast to alternative interventions, specifically the utilization of insoles^[14], autologous blood injection^[15], and local anesthetic injection either with or without tibial nerve block.^[16] In Soraganvi et al. study PRP appears to be more effective than steroid injection in terms of pain and functional results in the treatment of chronic plantar fasciitis.^[17] But few other studies also showed the good results with platelet rich plasma in comparison to steroid injections as we have found in our study.^[18,19]

In our study function, daily activities, sport and recreation are found significantly improved by both PRP and Triamcinolone group except running, which was not improved in Triamcinolone group. McMillan et al reported an improvement of foot pain scores in the corticosteroid injection group in comparison to the placebo group at the 4, 8 and 12-week follow-up.^[20]

Quality of life was found to be significantly improved with PRP as well as TA, which is found in alignment with other study.^[21,22]

CONCLUSION:

Based on the study results, both Platelet-Rich Plasma (PRP) and Triamcinolone Acetonide (TA) were effective in improving foot symptoms, functional activities, and quality of life in patients. However, PRP was found to be superior to TA in most parameters, including symptom relief, pain reduction, and improvement in function, sports, and recreational activities. PRP also showed a more significant impact on the quality of life, particularly in lifestyle modifications to avoid activities that might harm the foot or ankle.

Strength Of Study:

Limited data is available in Indian literature on this topic to assess the efficacy of these two drugs by using FAOS survey form and the related scale. Sample size was good. Loss to follow up or attrition problem was very little. In age and gender proportions, matching was done to avoid selection bias. Use of FAOS (Foot and Ankle outcome score) scale gave an added advantages of addition of quality-of-life index. Randomization has improved the strength of our study by removing bias.

Weakness Of Our Study

The important weakness of our study was lack of blinding. This was not possible for us due to man power constraints. So, the effect of observer bias may be present in our study. Though we always tried to uniformly probe both the groups. In our study, the PRP we used was prepared and applied under the same conditions as was used Anituaetl study. But there are few limitations, like, there is no standardization in the PRP preparation as well as delivery method. This may attribute to the inconsistent results. So reproducibility standardization of preparation protocols is extremely needed for comparison Placebo effect was also not analysed in our study, though similar weaknesses like regression to mean, the placebo effect, or expectancy effects was also observed in other studies. In this study we could not do short term assessment of both drugs. So, this is an important limitation which needs emphasis. Few studies assessed plantar fascia thickness, but our study could not assess that.

TA as well as PRP is very effective in the treatment of plantar fasciitis in relieving the symptoms, pain, functions such as daily activities as well as sports and recreations QOL and FAOS score and was found statistically significant, except functions and daily activities, ascending and descending stairs, rising from sitting, walking on the flat surface, lying in bed, light as well as heavy domestic duties, and

running, were not found statistically significant in the triamcinolone group. This can be explained by the fact that we did not assess the short-term effect of TA. In the PRP group except lying in the bed which was not found to be significantly improved. We have to explore the reason for this. After comparison between plasma-rich protein and TA, platelet-rich protein was found to be better, as the difference PRP score (pre and post) versus TA score (pre and post) was found statistically highly significant, that means the effect of plasma-rich protein over TA in the improvement of relieving symptoms, pain, functions and daily activities, functions recreation and sports, QOL, and overall FAOS score was better.

Key Messages:

Platelet-rich plasma (PRP) injections exhibit superior efficacy over triamcinolone acetonide (TA) in alleviating pain and enhancing function in plantar fasciitis patients, underscoring PRP's potential as a preferred therapeutic intervention.

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