Original Article

Role Of Corticosteroids And Platelet-Rich Plasma Injections In Management Of Chronic Plantar Fasciitis General View

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Abstract

Background: The most frequent cause of persistent heel pain in adults, plantar fasciitis can afflict both younger, active and older, inactive people. It occurs when the plantar fascia is repeatedly abused at its beginning, on the medial tubercle of the calcaneus. A clinical diagnosis can be determined using a physical exam, a medical history, and, to a lesser extent, imaging. Aching plantar heel pain is the most typical presenting symptom, and it is worst with the first step in the morning or after periods of rest. Tenderness at the plantar fascia's origin on the medial tubercle of the calcaneus serves as confirmation of the diagnosis. Altering one's activities, using anti-inflammatory drugs, stretching the gastrocnemius and plantar fascia, and wearing an orthosis to raise and cushion the heel are the first steps in therapy. Ninty percent of people who get these nonoperative procedures experience total pain relief, however it may take 3-6 months. Patients who experience symptoms after a six-month non-operative therapy may be candidates for surgery or minimally-invasive therapy. Therapeutic ultrasonography and platelet-rich plasma injections are two minimally invasive procedures that promote the body's healing process. Injections of corticosteroids may provide transient pain relief, but they also raise the possibility of plantar fascia rupture and fat pad atrophy. Injections of botulinum toxin reduce tension in the plantar fascia by relaxing the calf muscles. Operative treatments include partial plantar fasciotomy, which promotes healing, and gastrocnemius recession, which lessens tension on the plantar fascia

Keywords: plantar fasciitis- platelet-rich plasma- corticosteroids

INTRODUCTION

Heel pain is a common presenting complaint in the foot and ankle practice, The most frequent cause of heel pain was plantar fasciitis **(1)** and also was the most common injury of the plantar fascia. It often occurs more frequently in women, middle-aged people, athletes, and obese people **(2).** Ten percent of people will get plantar fasciitis at some point in their lives **(3).** The peak incidence occurring at 40-60 years of age **(4)**.

The patient's medical history, risk factors, and physical examination findings all play a role in the diagnosis of plantar fasciitis. The majority of patients experience heel pain and tightness after getting out of bed in the morning or after remaining still for a prolonged period of time. Usually, walking makes the heel pain worse. However, if the patient continues to walk or stands in one place for a long time, the pain may worsen towards the end of the day **(5).**

Usually, nonoperative therapy, such as rest, ice application, stretching, exercise, appropriate footwear, arch supports, orthotics, night splints, extracorporeal shockwave therapy (ESWT), and anti-inflammatory drugs, is the first line of treatment for plantar fasciitis. Up to 90% of people with the illness respond well to this nonoperative therapy. Injection treatments such as corticosteroid (CS), platelet-rich plasma (PRP), prolotherapy, autologous whole blood, botulinum toxin, or ozone may be used on individuals who do not respond to nonoperative treatment **(6).**

The injection of PRP into the plantar fascia begins the healing phases required to reverse the degenerative process at the base of the plantar fascia, whereas steroid injection is a frequent therapy for plantar fasciitis but seems to be only marginally effective (**7)**.

The 1970s saw the development of platelet rich plasma (PRP), which is autologous, meaning it comes from your own body. It is blood plasma that has had its platelet concentration increased to 5–10 times that of a typical person's blood **(8).**

PRP injections are believed to be safe and won't affect biomechanical function of the foot. It is a part of whole blood that is condensed by centrifugation, treated with an activator, and then injected into the injured region **(9).** PRP's basic biologic mode of action is straightforward; after being injected into a damaged region, it causes a localised inflammation. At various stages of wound healing, the pro-inflammatory mediators and growth factors released from the platelet granules cause localised inflammation and the wound healing cascade, which leads to cellular migration and proliferation, glycosaminoglycan and collagen deposition, collagen maturation, and remodelling of the healing tissue **(10).**

- **PLATELET-RICH PLASMA (PRP):**
  - **Platelet origin & structure:**

Platelets, otherwise known as thrombocyte, were derived from fragments of their precursor megakaryocytes found in bone marrow. They were small anucleated cells, rounded or oval in shape **(11).** The mean diameter of platelets ranges from approximately 2 to 5μm **(12),** and its thickness was about 0.5 μm **(13).** The average platelet count in whole blood ranges from 150,000–350,000 per μL **(11).**

Platelets, released from the bone marrow, circulate in the blood stream for 7 - 10 days before being replaced. The interior can be divided into three zones, the peripheral zone, the solgel zone and the organelle zone, each with distinct functions **(12).**The peripheral zone includes the cell membrane, glycolcalyx and the open canalicular system. The glycolcalyx was a sticky coat on the outside of the membrane and participates in adhesion and aggregation. The open canalicular system was a path for delivery of secretory products of platelet granules. The solgel zone, also known as the structural zone, was made up of microtubules and microfilaments. It was responsible for maintaining the platelet structure and participates in shape changes during activation .The organelle zone was centrally located in the platelet and includes granules, lysosomes, mitochondria and glycogen **figure (1) (13).**

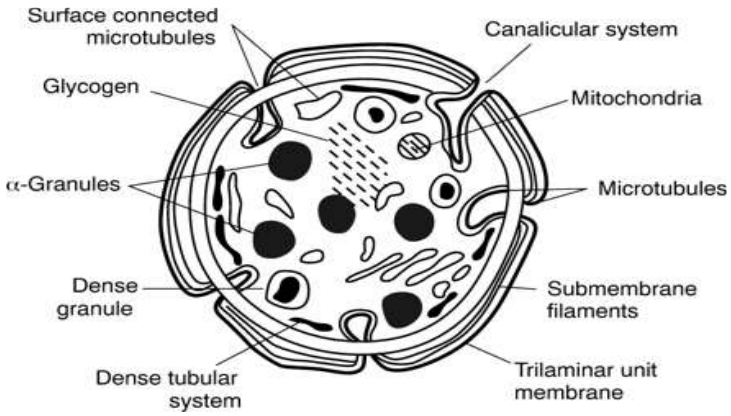

Figure (1) : Platelet structure (Platelets contain various cellular organelles and their structure can be divided into three zones; the peripheral zone consisting of the outer surface of the platelet membrane, sol-gel zone consisting of microtubules and the organelle zone, which contains the α-granules) **(14).**

Electron microscopy shows that platelets contain various organelles: mitochondria, peroxisomes, and ribosomes as well as glycogen and granules, the latter were divided into three types: alpha, delta (or dense granules) and lambda granules **(15).**

Alpha granules were the most abundant granule type of platelets, numbering approximately 50 to 80 per platelet **(16).** Alpha granules were 200 to 500 nm in diameter, they were considered the storage unit of the platelets and contains more than 1500 bioactive proteins such as fibrinogen, von willebrand factor, platelet-derived growth factor and other growth factors. These active proteins were responsible for enhancing tissue regeneration and healing **(17).** The platelet-dense granules (delta granules) contain histamine, serotonin, calcium, adenosine diphosphate (ADP), adenosine triphosphate(ATP) ,and dopamine ,which may also contribute to healing after platelet rich plasma (PRP) injection (**18).** Finally, lambda (lysosomes) help dissolve the clot once it has served its function **(15)**.

  - **Platelet functions:**

Functionally, platelets were involved with both hemostasis and the initiation of wound healing **(11).** In addition it has recently been reported that despite the absence of a nucleus and DNA ,platelets have a system for protein synthesis, have copies of mRNA for almost one third of the known proteins in the human genome, process mRNA and effectively translate the different proteins **(19).** These discoveries have changed the way that platelets were seen, recognizing that they have the ability to synthesize proteins in response to changes in its environment **(11).**

The presence of transcription factors has been demonstrated and, because platelets do not have a nucleus, some nongenomic functions of these factors were also being investigated such as its effect on signaling pathways involving platelet activation and its role in the de novo synthesis of pro as well as anti-inflammatory factors **(19).**

A. Role of platelets in hemostasis When it comes to hemostasis, platelets are essential since they take part in both the main and secondary stages of the process. When the vascular endothelium is damaged, platelets cling to it and produce platelet-derived growth factor (PDGF), which helps the endothelium heal. The vascular wall adhesion also activates platelets, changing their form from smooth discs to structures with pseudopods that promote platelet aggregation. In order to stop blood loss from the broken artery, fibrinogen binds to platelets that are already attached to the damaged vascular wall. This forms a platelet plug. Adenosine diphosphate, serotonin, calcium, and platelet-specific molecules such thrombospondin, platelet factor 4, and -thromboglobulin stimulate aggregation and constrict blood vessels when secreted. The platelet plug reinforced during secondary hemostasis after forming during the original stage through activation of coagulation factors present in the plasma, to further reduce bleeding **(12).**

B. Role of platelets in wound healing The three vital stages of healing were inflammation, proliferation, and remodeling **(10).** All three stages were important for the injured tissue to be repaired. The first step of the healing process was clot formation and platelet activation **(11).**

❖ **Definition of platelet Rich Plasma (PRP):**

Platelet- rich plasma was defined as a volume of plasma that has a platelet count above the baseline of whole blood **(20).** There were different types of platelet rich plasma: allogenic, and the safest and most frequently used autologous. Autologous means that the platelet rich plasma was derived from the same person that it will ultimately be applied to, thus helping to prevent the spread of transmission of diseases such as HIV and hepatitis **(21).**

❖ **Mechanism of PRP in wound healing:**

PRP's basic mode of action in the healing of wounds was straightforward: following injection into a damaged region, PRP causes local inflammation. Growth factors and proinflammatory mediators were both released from the platelet granules. Platelet derived growth factors (PDGF), Vascular endothelial growth factor (VEGF), Fibroblast growth factor (FGF), Platelet derived epidermal growth factor (PD-EGF), Insulin like growth factor1-2 (IGF-1 IGF-2), and Transforming growth factor alpha (TGF-) are some of the growth factors mentioned. At various stages of wound healing, released growth factors such as transforming growth factor beta (TGF-), which trigger localised inflammation and the wound healing cascade, cause cellular migration and proliferation, glycosaminoglycan and collagen deposition, collagen maturation, and remodelling of the healing tissue **(10).**

❖ **Bioactive factors in PRP:**

Platelets have been shown to release many growth factors from intracellular alpha granules, these factors play a variety of roles in tissue regeneration and healing, and the following table shows the role of each **(22).**

(Table 1): Platelet growth factors and their functions **(22):**

Growth factors	**Function**
Platelet derived growth factors (PDGF).	Messenchymal stem cell proliferation, ostoid production, endothelial cell replication, collagen synthesis, protein synthesis. Synthesis of other factors e.g. (IGF-1)resulting in fibroblast proliferation and differentiation, collagen deposition, and angiogenesis.
Vascular endothelial growth factor (VEGF).	Tendon cell proliferation, collagen-I synthesis and anti-apoptosis.
Insulin like growth factor (IGF-1,2).	Growth factor for normal fibroblasts, enhance synthesis of collagen.
Fibroblast growth factor (FGF).	Influencing angiogenesis and satellite cell number.
Transforming growth factor alpha (TGF-α).	Stimulate the growth of mesenchymal cells, endothelial and epithelial cells, also affect bone formation and regeneration.
Transforming growth factor beta (TGF-β). B-I B-2 B-3	 -Cellular migration, proliferation ,collagen synthesis, production of the extracellular matrix reconstruction of basement membrane of damaged myofibres and satellite cells, scar tissue formation of wounds. -Increase collagen production. -Reduction of scar tissue formation after healing, more favorable ratio of collagen-1 to collagen-3 ratio.
Platelet derived epidermal growth factor (PD-EGF).	Proliferation and chemo attractant of epithelial cells and fibroblasts, influence extra cellular matrix synthesis and metabolism, stimulate increased differentiation of epithelial cells.

❖ **Beneficial effects of PRP:**

PRP's platelet-derived growth factors were the most widely used method of delivering a biological stimulation to a variety of injured tissues, including cartilage, tendons, and muscle, which may benefit from this specific method (**23).**

Injection of PRP initiates healing process that can be summarized in the following phases:

Phase1 (hemostasis and inflammation) is brought on by tissue damage and lasts for two to five days. When platelets come into contact with wounded tissue in phase 1, they get activated and stick to the exposed collagen, aggregating to form a clot **(24).** Inflammation is caused by the degranulation of platelets and the release of growth, bioactive, and hemostatic factors.

Within the first 10 minutes following tissue damage, platelets release 70–95 percent of the growth factors they had accumulated, and more growth factors continue to be produced for 7-9 days **(18).**

Phase 2 (proliferation) starts two days after the injury and lasts for three weeks. During this phase, blood vessels are formed,

fibroblasts deposit collagen, the wound contracts, and modest amounts of growth factors are still released **(18).**
Phase 3 (remodeling) This process, which can take over a year to complete, involves the maturation of collagen and the development of scar tissue.

A- Effect of PRP in tendon and ligament injuries A tendon will likely go through the standard three stages of healing after suffering an acute injury: cellular proliferation, inflammation, and remodelling **(25).**
B- Effect of PRP on muscle injuries Similar to how tendons mend, muscles repair in three stages: early degradation and inflammation, followed by regeneration, and ultimately fibrosis **(26).**
C-Effect of PRP on cartilage degeneration By supplying a high concentration of growth factors that facilitate healing and remodelling, biological treatments for localised knee osteoarthritis, such as platelet-rich plasma, have been proposed to enhance clinical and structural results **(27).**
D- Effect of PRP on bone fracture Numerous growth factors and cytokines that support bone mineralization, tissue healing, and blood coagulation have been shown to naturally accumulate in platelets.

❖ **Uses of PRP in various clinical conditions:**

A new method for treating persistent tendinopathies is PRP injection. Given its safety and accessibility for outpatient preparation and delivery, its usage for musculoskeletal injuries has expanded recently**: Plantar Fasciitis, Achilles Tendinopathy, Patellar tendinopathy, Rotator cuff tendinopathies, Tennis elbow & Osteoarthritis (28).**

➢ **CORTICOSTEROIDS (CS):**

The adrenal cortex of vertebrates produces a group of steroid hormones known as corticosteroids, as well as their synthetic counterparts. Glucocorticoids and mineralocorticoids are the two primary families of corticosteroids **(29).**
The actions of cortis
ol are mimicked by synthetic glucocorticoids. Under physiologically normal circumstances, cortisol was produced in a circadian, diurnal rhythm, peaking in the early morning (about 8 AM) and troughing between midnight and 4 AM. The hypothalamus's release of ACTH controlled the amount of cortisol produced. Increased blood levels of ACTH in turn encourage the adrenal gland to produce more cortisol **(30).**
Stress also significantly boosted the release of cortisol, popularly known as the "stress hormone," in the body. In intense "fight-or-flight" circumstances, cortisol's metabolic effects were helpful. It is engaged in a variety of physiological processes, such as stress response, immunological response, and control of inflammation, glucose metabolism, protein catabolism, and blood electrolyte levels **(30).**

❖ **Classification of corticosteroids:**

A) By route of administration (31):
***Topical steroids:** for use topically on the skin, eye, and mucous membranes.
***Oral forms:** Such as Prednisone, Prednisolone or Dexamethasone.
***Inhaled steroids:** for use to treat the nasal mucosa, sinuses, bronchi, and lungs. This group includes: Flunisolide, Fluticasone furoate, Fluticasone propionate, Triamcinolone acetonide, Beclomethasone dipropionate & Budesonide.
*** Injectable forms:** Available for systemic and local use such as: Methylprednisolone, Triamcinolone, Hydrocortisone, Dexamethasone & Betamethasone.
B) By duration of action (32):
The preparation of steroids can be divided into 2 groups: **particulate** such as methylprednisolone, betamethasone, and triamcinolone; and **non-particulate** like dexamethasone phosphate. Particulate steroids have a longer duration of action due to a local depot effect resulting in continuous release of the active drug from the injection site over a long time period **(33)**. On the other hand non-particulate steroids are water soluble steroid with small particle size and limited aggregation. This results in rapid clearance from the blood and a short duration of action **(Table 2).**

Table (2): Classification of corticosteroids according to duration of action:

Short-acting (Half-Life 12 hours)	**Intermediate-acting (Half-Life 12 to 36 hours)**	**Long-acting (Half-Life 48 hours)**
Hydrocortisone	Prednisone	Paramethasone
Cortisone	Prednisolone	Betamethasone
	Methylprednis-olone	Dexamethasone
	Triamcinolone	

➢ **Mechanism of action:**

The majority of glucocorticoids' effects come from the steroid's initial binding to intracellular glucocorticoid receptors (GRs),

which is followed by translocation to the nucleus and alterations in gene transcription.
By limiting the translocation of additional transcription factors from the cytosol into the nucleus, the activated GR complex, in turn, regulates the production of anti-inflammatory proteins in the nucleus (transactivation) and suppresses the expression of proinflammatory proteins in the cytoplasm (transrepression) **(34).**
Transactivation (Figure 2) The cytosolic glucocorticoid receptor (GR) is where glucocorticoids bind (a type of nuclear receptor). Gene expression is regulated as a result of the newly formed complex's (GR) translocation into the cell nucleus, where it binds to glucocorticoid response elements (GRE). Transactivation or transcriptional activation were terms used to describe this process **(34).**
Transrepression (Figure 2) Transrepression, also known as transcriptional repression, is the opposing process. According to the traditional theory of this process, activated GR binds to DNA at the same location where another transcription factor would bind, preventing that factor's activity from causing the transcription of genes that would otherwise be transcribed. For all cell types and circumstances, the results were inconsistent**(34).**

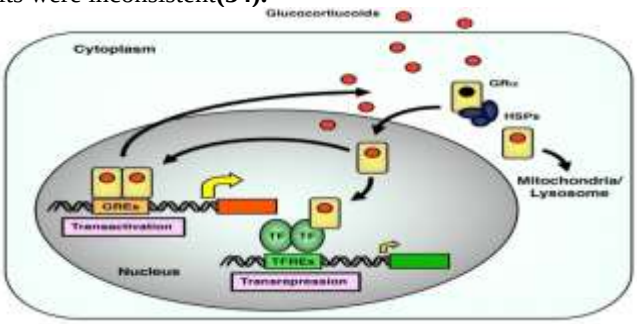

Figure (2): Intracellular circulation of GR and its transcription regulation.

Non-genomic effects Experimental evidence demonstrates that activated GR has effects that are unrelated to any effects on transcription and that these effects can only result from direct binding of activated GR with other proteins or with mRNA. Glucocorticoids' non-genomic actions seem to be mediated through a mix of hormone-sensitive membrane-bound and cytoplasmic receptors **(35).**

- **Effects of Corticosteroids:**

Anti-inflammatory effects: Glucocorticoids reduce inflammation through a combination of both inhibition & upregulation of gene transcription, including:
Inhibition of genes regulating expression of: COX-2, inducible Nitric oxide synthases (NOS), most inflammatory cytokines (IL-1, IL-6, IL-8, IL-10, IL-13, GM-CSF, TNF-α, Interferon-γ**) (37).**
Up regulation of the expression of Annexin A1 "a glucocorticoid signaling peptide", which: increases neutrophil detachment from the endothelium; inhibits COX-2 (post-transcriptional action); lowers neutrophil penetration through blood vessel endothelium; and directly inhibits PLA2 (reduces prostaglandin & leukotriene synthesis)**(38).**
Neutrophil migration through the vasculature to sites of inflammation was markedly reduced. This effect, combined with an enhanced release of cells from the bone marrow, and reduced neutrophil apoptosis, causes the WBC count to increase **(39).**
Corticosteroid injections (CSI) were used for refractory cases of plantar fasciitis and may be an effective modality for pain relief **(40).**
Different fields choose different corticosteroids for local injection **(41).** Systematic analyses of data from randomised trials have revealed no differences in the therapeutic effectiveness of various corticosteroid types in terms of treatment outcomes **(42).**
Since corticosteroids have a potent anti-inflammatory impact, they help hasten the pain-relieving process. Injectable corticosteroids work by inhibiting fibroblast growth and the production of ground substance proteins, both of which were seen in the clinical signs of plantar fasciitis **(43).**

Immunosuppression effect: The therapeutic aspect of glucocorticoids' immunosuppressive effects was primarily the reductions in the activity and population of lymphocytes, including both B cells and T cells **(44).**
Metabolic Effects: Under stress, cortisol is secreted to provide glucose to the body's organs as an energy source. In order to maintain energy balance during the stress response and to guarantee that vital organs (such as the brain) continue to get nutrients at a time when they are most needed for life, cortisol's effects to increase blood glucose were crucial **(45).**
Body fluid homeostasis: Glucocorticoids could act centrally, as well as peripherally, to assist in the normalization of extracellular fluid volume by regulating body's action to atrial natriuretic peptide (ANP) **(46).**
Arousal and cognition: The hippocampus, amygdala, and frontal lobes are all affected by glucocorticoids. These, together with adrenaline, help people remember situations that caused them to feel strongly **(47).**
Developmental effect: There are several ways that glucocorticoids affect embryonic development. An notable illustration of this was their support of lung maturation and the synthesis of the surfactant required for extrauterine lung function.

- **Contraindication of Local Corticosteroid Injection:**

Periarticular sepsis, bacteremia, unstable joints, intra-articular fractures, septic joints & bleeding disorders (relative contraindication) **(48)**.

- **Side Effects of Corticosteroids:**

Use of corticosteroids has many adverse effects:

Neuropsychiatric Administration of glucocorticoids has been associated with a number of neuropsychiatric adverse effects, including mood swings, memory problems, and even psychosis. Additionally, it can make pre-existing mental conditions worse **(49).**

Cardiovascular Corticosteroids can cause sodium retention through a direct action on the kidney. This can result in fluid retention and hypertension, increase the risk of ischemic heart disease, heart failure **(50**).

Metabolic The "moon face" and "buffalo hump" are the results of the redistribution of body fat brought on by corticosteroids. together with the limbs. They were viewed as anti-anabolic because amino acids were diverted to glucose**(51).**

Endocrine Corticosteroids can result in hyperglycemia, insulin resistance, and diabetes mellitus by causing an increase in the synthesis of glucose from amino acid breakdown and anti-insulin activity (**52).**

Musculoskeletal Long-term use of high-dose glucocorticoids causes osteoporosis, which impairs bone production and resorption while also reducing intestinal calcium absorption and raising renal calcium excretion **(53).**

Gastro-intestinal Gastritis, peptic ulcers, gastrointestinal haemorrhages, and severe pancreatitis were among the gastrointestinal adverse effects of systemic glucocorticoids usage**(54).**

Eyes chronic use may predispose to cataract, glucoma and retinopathy. **(55).**

Exposure to infection Steroids may cause infections to worsen by reducing immune responses **(56).**

- **Adverse effects of local corticosteroid injection:**

- Tendon rupture if corticosteroid was accidentally injected straight into the tendon, local/intra-articular infection if insufficient aseptic measures were used.
- Superficial injection can lead to local skin atrophy and hypopigmentation,
- Localized, brief post-injection arthritic flare (thought to be due to microcrystalline formation)**(57).**

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