

Platelet-rich plasma in clinical practice

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Abstract

The concept of using a patient's own blood or components thereof (autologous), to enhance the physiological process of healing has been in place for many years. Autologous platelet-rich plasma (PRP) has been used for both soft tissue and bone healing and rejuvenation. PRP has also been used in orthopaedics for bone, tendon and muscle injuries, dentistry for dental implants, dermatology for wound healing, and in pathological conditions such as *alopecia areata*. However, more recently, it has been used in the fast-growing field of aesthetic and anti-ageing medicine for skin rejuvenation. PRP seems like a logical, safe, relatively, cheap and easy procedure, but is this the case? Although safety and improved short-term outcomes for orthopaedic indications have been demonstrated in a few reviews, long-term improvement has not been demonstrated. Randomised controlled trials in dermatology and aesthetic indications are sparse, but show promise for *alopecia areata* and skin rejuvenation.

Keywords: autologous, indications, platelet-rich plasma, PRP, skin rejuvenation

Introduction

The concept of using a patient's own blood or components thereof (autologous) to enhance the physiological process of healing has been in place for many years.¹ PRP injection is a therapeutic approach in which the tools of the biological regeneration of autologous cells and tissue are used, rather than their replacement.² Platelet-rich plasma (PRP) is cell-free plasma with a concentrated level of platelets above baseline, obtained from the patient's own blood.² As PRP is produced from the patient's own blood, it has minimal side-effects and is relatively easy to administer.² Athletes such as golfer, Tiger Woods, have undergone PRP therapy for sports injuries, while reality star, Kim Kardashian, received PRP facial injections for skin rejuvenation. The accompanying media attention has led to PRP gaining popularity and momentum.^{3,4} Although originally used for bone healing in orthopaedics, maxillofacial surgery and dental implants, PRP treatment for muscle, tendon, dermatology and skin renewal is gaining popularity.⁵⁻⁹

What is platelet-rich plasma?

A whole blood sample is drawn and processed in a centrifuge and the red blood cells removed, leaving a high concentration of platelets and growth factors. PRP also contains hormone nutrients, protein stabilisers, e.g. albumin, and other important compounds for cellular growth and homeostasis. PRP is then activated by thrombin or calcium chloride, resulting in the cascade and release of growth factors (Table 1) from the platelets over the next 7–10 days.⁴⁻⁷ The combination of calcium

chloride and PRP in a defined ratio results in the initiation of fibrin polymerisation, leaving the platelets intact.⁶ The result is a platelet-rich fibrin matrix which serves as a scaffold for the platelets to enable sustained growth factor release.⁸⁻¹⁰ However, the mechanism of action of PRP is only partly understood.^{9,10}

Harvesting kits are commercially available, but are costly, and variation exists in the platelet and growth factor content. Trade names include Regen[®], Selphyl[®], CelluVance[™], Plateltex[®] and Fibrinet[®]. Some of them are not available in South Africa.

Factors to consider are:

- The volume of blood required.
- Time of centrifugation.
- The nature of the plasmapheresis.
- The activating agent and effect on the pH.
- Final platelet, growth factor and leukocyte count.
- Purity of the product.
- Sterile procedure.

The lowest blood draw, as well as shortest time of centrifuge, is the most beneficial for treatment. The activating agent may alter the pH, and the closer the pH remains to the physiological pH of the injected area, the better the cellular integrity is maintained, and the less pain experienced by the patient. A lower red cell count leads to less haemosiderin staining from the leaking haemoglobin. A higher leukocyte count leads to a more pronounced inflammatory reaction and more pain experienced by the patient, but more tissue augmentation.²

Table 1: Growth factors released by platelets

Growth factors	Function
Platelet-derived growth factor	Proliferation and chemotaxis of fibroblasts Mitogenesis of mesenchymal stem cells and endothelial cells Synthesis of extracellular matrix and hyaluronan production
Transforming growth factors α and β	Promotes cell mytosis Collagen production Stimulates DNA synthesis Expression of antimicrobial peptides Keratinocyte stimulation Angiogenesis
Vascular endothelial growth factor	Angiogenesis Cell proliferation
Epidermal growth factor	Cell growth Proliferation and differentiation of epidermic cells Promotes granulation tissue formation Co-stimulates angiogenesis
Fibroblast growth factor	Fibroblast chemotaxis Angiogenesis Matrix (collagen fibre) deposition Wound contraction

Therapeutic indications of platelet-rich plasma

Orthopaedic indications

PRP has been used for muscle, bone and tendon pathology.

Long bone fractures

There was no significant difference in patient-reported or clinician-assessed functional outcomes between groups at one year. There was a statistically significant benefit from PRP therapy in the proportion of bones united at one year. However, this benefit was not maintained when assuming poor outcomes in participants who were lost to follow-up. Therefore, while a potential benefit of PRP therapies to augment long bone healing in adults cannot be ruled out, the currently available evidence from a single trial is insufficient to confirm it.¹¹

Tendon injuries and overuse tendinopathy

No better or quicker rate of healing or complications and no disadvantages, was shown in a Cochrane review.¹² However, the reviewed cases were tendon ruptures, and the PRP was administered during surgical intervention. It is questionable whether or not less severe cases, i.e. tendinitis, could possibly benefit.

No long-term benefit was found in rotator cuff injuries.¹²⁻¹⁵

PRP injected in *patellar tendinitis* (Jumper's knee) as a series of two injections over two weeks led to better results at six and 12 months, compared with shock wave therapy, as a series of three treatments, in one randomised controlled trial. The

two treatments were comparable in the short term, i.e. at two months. Notably, a control group was not included, and the study participants could not be blinded.¹⁵

While the efficacy of autologous blood injection compared with placebo, has not been assessed in any trials for plantar fasciitis, this treatment with a glucocorticoid injection was compared in two trials. While participants improved over time, irrespective of the treatment received, significant differences in benefit that favoured the glucocorticoid groups were reported in both trials.

Although the evidence is limited to small observational studies, autologous PRP is reportedly as effective as glucocorticoid injections in reducing pain scores. There is also evidence that it decreases plantar *fascia* thickness, and improves functional ability.¹⁵

Cartilage pathology

Animal studies have identified the potential utility of PRP, both in isolation and as an adjunct to surgical procedures, to restore normal hyaline cartilage in articular injuries. A systematic review of PRP for use in articular cartilage pathology was published by Dold *et al.* in 2014.¹⁶

In summary, the majority of evidence on the use of injected PRP relates to osteoarthritis of the knee. The data suggest definite benefits of reduced pain and improved clinical scores, even superior to hyaluronic acid, but that the benefits begin to lessen after six months. Presently, there is no available conclusive or high-quality evidence to support the use of PRP for either traumatic or degenerative chondral pathology, or to suggest any lasting clinical benefit to its use in this regard.¹⁵ The only trial to date performed on infiltration of the facet joints could not demonstrate long-term efficacy, but short-term effects were demostarted.¹⁵

Muscle injuries

It was shown in a meta-analysis that PRP had no effect, and that there was a superior outcome with rehabilitation exercises, in muscle injuries. Limited evidence revealed that agility and trunk stabilisation may reduce re-injury rates in this regard. The limitations identified in the majority of randomised controlled trials (RCTs) should lead to an improvement in the design of new RCTs on hamstrings:¹⁷ "From those studies, I'd say that 'Yes, PLP does seem to hold some promise,'" said Cohen, medical director of the blood bank at the University of Minnesota, USA, who recently reviewed the literature. "I think that to date, no serious adverse events have been reported, which is encouraging. I think, though, that it is dicey territory". Cohen said that she wanted more research in which the procedures were standardised, and to test them in clinical trials before she would be comfortable using PRP in patients with hamstring injuries.¹⁸ Improvement in pain, inflammation and function for non-surgical conditions, i.e tendonitis, were reported anecdotally by patients and doctors, and in unblinded, non-placebo controlled trials with a limited number of patients done by companies that manufacture and sell PRP kits.¹⁵

Dermatological indications

Acute wounds heal in an orderly fashion, whereas chronic wounds do not, and produce granulation tissue and reduced levels of platelet-derived growth factor, epidermal growth factor, transforming growth factor β and increased levels of enzymes which degrade protein in the wound.¹⁹ Ageing and wrinkling can be considered to be a chronic wound which cannot heal completely owing to environmental factors, such as smoking and ultraviolet radiation due to the production of collagenase. The result is wrinkles, dryness, roughness, loss of laxity and pigmentation. Growth factors have the ability to induce the synthesis of collagen and other matrix components by activating fibroblasts, therefore reversing skin damage and ageing.¹⁹

Wound healing

Statistically significant evidence was not found to support the use of PRP in treating chronic wounds in a 2012 Cochrane review. Two of the RCTs included in the Cochrane study were specific to diabetic foot ulcers, and a statistically significant difference between PRP and the control in the diabetic foot ulcer treatment was not found. Overall, the study was unable to establish evidence-based support for PRP by ulcer aetiology or by the procedure used to obtain autologous PRP.²⁰

Alopecia areata

PRP injection was found to be most effective in inducing hair regrowth in a trial in which 45 patients with chronic recurring *alopecia areata* of at least two years' duration were randomly assigned to intralesional injections of autologous PLP, triamcinolone acetonide or placebo, administered once per month for three months.²¹ PRP therapy was also associated with a reduction in symptoms of burning or itching in the affected areas. Additional studies are necessary to validate the findings of this trial.

Alopecia androgenetica

Positive results with PRP were demonstrated in a randomised, evaluator-blinded, placebo-controlled, half-head group study in which hair regrowth with PRP versus placebo was compared, with the aid of computerised trichograms. Three treatments were administered to each patient at 30-day intervals. The end-points were hair regrowth and hair dystrophy, as measured by dermoscopy, and the patients were followed up for two years.²²

Skin rejuvenation

Since 2005, PRP has been used as a modality in anti-ageing and the fast-growing field of aesthetic medicine. Hollywood celebrities have praised the treatment known as the "vampire facial".⁴

An improvement in wrinkles, acne, solar-damaged skin, hypertrophic scars, and hyper- and hypopigmentation, was demonstrated following positive anecdotal reports by doctors and patients, and the results of small trials commissioned by PRP manufacturers. The treatment is well tolerated, relatively quick,

with limited downtime and no adverse reactions, but the cost of the PRP kit is relatively high.

PRP was effective in a study on 50 patients in which the efficacy and safety of PRP combined with micro needling for the treatment of atrophic acne scars was evaluated. Both sides of the face were micro needled, and the right side of the face treated with PRP intradermally and topically.²³

Scalfani and McCormick used PRP as a single treatment filler, and noted that it was well tolerated and produced significant correction of the nasolabial folds, compared to the saline-injected group.²⁴

Zenker noted in a multi-centered trial with more than 200 patients that PRP could be used as primary or adjunctive therapy for skin rejuvenation. However, follow-up treatment was necessary, and the younger patients required fewer follow-ups, spaced further apart. Linear threading and mesotherapy were the injection techniques that were used.²

Platelet-rich plasma technique

The technique differs for skin versus orthopaedic indications. The PRP preparation remains the same for all indications, but the administration is either intra-articular, into or surrounding the area of pathology; or intradermally, in the case of dermatology. Often, the superficial dermal mesotherapy technique (multiple micropapular injections, whether by puncture, rollers or pen-puncturing devices) is the technique used in dermatology and aesthetics.²⁵ The mesotherapy technique can be combined with intradermal injections using a multilayered approach. Usually, 30-G needles are used in mesotherapy. On its own, the technique leads to percutaneous collagen induction, whether or not PRP is utilised.

The procedure starts with a blood draw, and while the blood is processed by centrifuge, the patient is prepared by applying a topical anaesthetic in the case of skin, and a local anaesthetic, as needed, for other indications. Once the PRP has been readied, the skin is cleaned and thereafter administered by aseptic technique.²⁵ Administration to the skin results in punctate bleeding and erythema, which resolves within 24 hours. The integrity of the skin is compromised during the procedure, and patients are cautioned not to apply anything to their skin or to scratch.

Treatment guidelines for skin rejuvenation are outlined in Table 2.²

Table 2: Treatment guidelines for skin rejuvenation²

Patient age (years)	Follow-up
≤ 35	Booster injections: 12–24 months
36–45	Follow-up: 9–12 months, then yearly
45–60	Follow-up: 6 months, then yearly
≥ 60	Follow-up: 3, 6 and 18 months

Pain and stiffness may be experienced in orthopaedic indications, but is short lived. A minimum of two treatments, spaced two,

four or six weeks apart, can be administered for orthopaedic indications.

Conclusion

The current use of PRP is driven by marketing and revenue, as much as treatment efficacy. Further investigation of short-term benefits in patients with osteoarthritis and *patellar tendinitis* is warranted using RCTs in which materials and methods are standardised. The same applies to skin rejuvenation. Although PRP is a safe treatment, it is costly for patients. The 31st annual meeting of the American Academy of Pain Medicine was held in March 2015, and an article highlighted the statement, according to Lamer, an associate professor of anesthesiology and pain medicine at the spine center at Mayo Clinic, Rochester, USA, that: "All major payers consider PRP for musculoskeletal conditions to be experimental".

Davis, the medical director of Orthopedic Pain Specialists in Santa Monica, USA, argued for PRP, noting that benefits specifically for osteoarthritis have been shown in some randomised, controlled trials, but added that lack of interest from the pharmaceutical industry was an important reason for the paucity of such trials: "There's no money in this for them, so they're not investing in the kind of clinical trials that are needed".¹⁶

Thus, further studies are needed, and should comprise high-quality RCTs, both on PRP injections in the treatment of osteoarthritis compared with placebo; and surgical treatment supplemented by PRP, compared with operative management alone, in musculoskeletal injuries and dermatology.

Conflict of interest

The author declares that she has no financial or personal relationships which may have inappropriately influenced her when writing this paper.

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