

## Review on use of platelet- rich plasma for wound care in medicare population



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Wound care management has continued to evolve and considering the Medicare population (ages 65 and above), the implications of management are significant. In the Medicare population, chronic wounds rank among the topmost reasons for seeking care. One sixth of Medicare patients are affected by chronic wounds which takes a major toll economically and medically (Nussbaum et al, 2018). Platelet rich plasma (PRP) is an important aspect of management due to its regenerative properties and its ability to accelerate healing. Some researchers have opined that PRP has the unique ability to completely heal wounds, however, research findings are conflicting with regards to the outcomes based on the types of wounds such as pressure ulcers and venous ulcers. PRP is a combination of thrombocytes, cytokines and multiple growth factors which include, but are not limited to, Platelet-Derived Growth Factor, Fibroblast Growth Factor, Insulin Growth Factor, Vascular Endothelial Growth Factor, Transforming Growth Factor- $\beta$ , and Hepatocyte Growth Factor. Owing to the growing need and concern for PRP, especially in the area of regulation and consistency of outcomes of treatment, the authors have presented an overview of this modality of wound care in the older population.

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**P**latelets are circulating blood components, known for their ability to release various growth factors, which are essential in the key stages of wound healing and tissue regeneration. Platelets promote haemostasis, cell migration, differentiation, proliferation, neovascularisation and epithelialisation, thereby promoting wound healing (Coppinger and Maguire, 2007; Pagel et al, 2017).

The concept of platelet-rich plasma (PRP) was born in the 1970s, when haematologists described supra physiologically high-platelet concentrates derived from centrifuging plasma, this was initially used as a transfusion product for patients with thrombocytopenia (Alves and Grimalt, 2018). However, the therapeutic use of PRP in regenerative medicine constitutes a

relatively new approach with emerging evidence of clinical benefits in a wide range of medical fields, including wound care, it is considered an advanced wound therapy (Bielecki and Dohan Ehrenfest, 2012; Jain et al, 2015).

### Classification of platelet-rich plasma products

There is high variability in the compositions and types of PRP products in use, the lack of consensus in the preparation method and product characteristics has been acknowledged by the International Society on Thrombosis and Hemostasis (ISTH), hence, in the Scientific Standardization Committee (SSC) meeting in 2018, they proposed a comprehensive classification model that puts into consideration multiple key variables to better characterise PRP products based on the following:

- Sample collection conditions (anticoagulated blood or not)
- Sample purity (red blood cells (RBC) or white blood cells (WBC) content)
- Number of platelets in the product
- Whether or not platelets have been activated, or whether the PRP product has been frozen/thawed prior to use or applied fresh (Harrison, 2018).

This standardised nomenclature would facilitate comparison of beneficial results and adverse reactions among different PRP product groups (Acebes-Huerta et al, 2020).

### Evidence behind the use of PRP for wound healing

#### Use of PRP for diabetes foot ulcers

Foot ulcer is a major complication of diabetes mellitus and frequently results in leg amputation. The use of platelet-rich plasma, which is rich in multiple growth factors and cytokines is gaining popularity. A systematic review with meta-analyses was performed to evaluate the safety and clinical effectiveness of PRP for the treatment of diabetic foot ulcers compared to standard treatment or any other alternative therapy.

The electronic databases Medline, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials were consulted in March 2017 with no restrictions placed on the publication date. Predefined criteria were used to determine inclusion of studies and to assess their methodologic quality.

Eight randomised clinical trials (RCTs) and two prospective longitudinal-observational studies with control group were included. Platelet-rich plasma treatment increased the likelihood of chronic wound healing (RR=1.32; 95% CI: 1.11, 1.57,  $I^2=15%$ ) while the volume of the ulcer (MD = 0.12cm<sup>2</sup>; 95% CI: 0.08, 0.16;  $P<0.01$ ;  $I^2=0%$ ) and time to complete wound healing (MD=-11.18 days; 95% CI: -20.69, -1.68;  $I^2=53%$ ) decreased.

With regards to safety profile, platelet-rich plasma did not differ from standard treatment in terms of probability of occurrence of wound complications (RR = 0.57; 95% CI: 0.25, 1.28;  $I^2=0%$ ) or recurrences (RR=2.76; 95% CI: 0.23, 33.36;  $P=0.43$ ;  $I^2=82%$ ) but it decreased the rate of adverse events (RR=0.80; 95% CI: 0.66, 0.96;  $P=0.02$ ;  $I^2=0%$ ; Pino-Sedeño et al, 2019).

The study demonstrated that platelet-rich plasma treatment increased the likelihood of chronic wound healing and the safety profile of platelet-rich plasma did not differ from standard treatment in terms of probability of occurrence

of wound complications, though some of the studies included presented methodologic flaws, the cumulative meta-analysis suggested that there is enough evidence to demonstrate a statistically significant benefit (Pino-Sedeño et al, 2019).

Another systematic review of literature involving 18 selected studies, seven (39%) of which were RCTs. Five of the seven RCTs studied ulcers of diabetic aetiology. The results of meta-analysis showed that PRP favours the healing process (95% CI: 2.94-20.31), and concluded that there is scientific evidence regarding favourable outcomes of the use of PRP for the treatment of diabetic ulcer (Villela and Santos, 2010).

#### Use of PRP for Venous ulcers

Venous ulcers are wounds that are thought to occur due to improper functioning of venous valves, defective calf muscle function resulting in venous hypertension. They frequently affect the lower extremities and may constitute up to 70% to 90% of chronic wound cases, which is associated with high costs and patient suffering (Escamilla Cardeñosa et al, 2017).

In a clinical trial that investigated the efficacy and safety of using platelet rich plasma in growth factor (PRGF) as a local treatment for venous ulcers, 102 venous ulcers (58 patients) were randomly assigned to the study group (application of PRP) or the control group (standard cure with saline). For both groups the healed area was calculated before and after the follow-up period (24 weeks). Pain was measured at the start and end of treatment as a secondary variable for each group by record obtained by means of self-evaluation visual analogue scale.

The results showed, the average percentage healed area in the platelet rich plasma group was 67.7 ± 41.54 compared to 11.17 ± 24.4 in the control group ( $P=0.001$ ). Similarly, in the experimental group a significant reduction in pain occurred on the scale ( $P=0.001$ ). No adverse effects were observed in either of the two treatment groups. Thus, this study results demonstrated that application of plasma rich in platelets is an effective and safe method to speed up healing and reduce pain in venous ulcers (Escamilla Cardeñosa et al, 2017).

#### Pressure ulcers

A systematic review and a search was conducted in the PubMed database, which evaluated the literature up to October 31, 2018. In total, 14 articles met the inclusion criteria for this review. In studies representing Levels of Evidence 1b-4 according to the Centre for Evidence-

Based Medicine, Oxford ; PRP was found to significantly improve wound healing in chronic pressure ulcers. And this was also true for ulcers of multifactorial aetiologies, including diabetic ulcers, leprosy ulcers and even acute traumatic wounds (Hesseler and Shyam, 2019).

### Use of PRP for chronic wounds

Chronic wounds are generally considered to be deficient in growth factors, hence, use of PRP (known to contain growth factors) has been studied in the management of chronic wounds.

A meta-analysis, that searched for RCTs and comparative group studies that used platelet rich plasma therapy in cutaneous wounds and published over the past 10 years was conducted. Eligible studies compared the treatment to standard care or other interventions. All citations were screened and eligible studies were assessed for validity, quality and bias using accepted scoring methods. The primary outcomes were effect of PRP and control wound care on wound healing and related healing measurements. Secondary outcomes related to healing, such as infection, pain, exudate, adverse events and quality of life were also considered. The meta-analysis utilised appropriate statistical methods to determine the overall treatment effect on chronic and acute wound healing and infection.

The search terms resulted in 8,577 citations and after removing duplicates and screening for protocol eligibility, a total of 24 papers were used. The meta-analysis of chronic wound studies revealed PRP therapy is significantly favored for complete healing.

The meta-analysis of acute wounds with primary closure studies demonstrated that presence of infection was reduced in PRP treated wounds (Carter et al, 2011), thus, on the basis of the past 10 years of research, the results of this systematic review and meta-analysis suggested that PRP therapy can positively impact wound healing and associated factors, such as pain and infection in both chronic and acute cutaneous wounds (Carter et al, 2011).

### Limitations

Variability of products, poor description and lack of adequate categorisation of PRP products used in many publications makes it challenging to compile adverse effects associated with specific types of PRP, generally the products have very few side effects reported. The products that have generated inflammatory reactions are either products with leukocytes or products used fresh, or both, because the

living cells (including platelets) considering their immunomodulatory functions might exacerbate local inflammatory responses (Acebes-Huerta et al, 2020).

There were also a limited number of older patients in the study population: most of the clinical trials did not include a robust number of older adults (Medicare beneficiaries). Results from younger population may not accurately reflect the response of older adults to PRP.

In terms of cost, unfortunately, PRP is not routinely covered by most health insurance programmes, including Medicare. It may cost between US\$1,000–US\$2,000 or more, insurance coverage may be limited for approved clinical trials in select cases.

Becaplermin was approved by the FDA in 1997 for diabetic foot ulcers, and may be less expensive than PRP. Becaplermin 1 mg costs US\$4,250, and an 8-week course (800 ug total) at 100 ug/week (US\$425 per dose) showed a 43% increased incidence in complete wound closure and decreased time to complete wound closure by 32% compared to placebo (Steed, 1995).

Thus, becaplermin is more cost effective than PRP with an out-of-pocket cost of \$1,000–2,000 per dose.

### Coding

The following code is allowed for BlueCHIP for Medicare as part of a CMS approved clinical study and not medically necessary for Commercial products:

G0460 — autologous PRP for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment. Claims for services rendered as part of a CMS approved clinical study must be billed with an appropriate modifier:

Modifier Q0 — investigational clinical service provided in a clinical research study that is in an approved research study (BlueCHIP for Medicare claims filed without the Q0 modifier will deny as not covered)

Modifier Q1 — routine clinical service provided in a clinical research study that is in an approved clinical research study. The following code is not covered for BlueCHIP for Medicare and not medically necessary for commercial products: 0232T injection(s), PRP, any site, including image guidance, harvesting and preparation (Medicare Coverage Database, 2008).

### Conclusion

Though, the use of PRP in wound healing was

controversial in the past, recent emerging evidence seems in favour of PRP as a promising treatment modality for wound healing.

Efforts to standardise and homogenise the production method variables are necessary to better evaluate the efficiency and adverse effects of the products (Ojea-Perez et al, 2019).

More high-powered RCTs that will predominantly include older adult as participants, will be essential for this mode of treatment to be endorsed as standard of care among Medicare patients who are seeking advanced and safe wound care therapy.

PRP warrants further investigation because it clearly represents a potential therapeutic option with favourable side effect profile for Medicare beneficiaries with wound care challenges (Hesseler and Shyam, 2019).

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