Review Article

Role of Platelet Rich Plasma in the treatment of foot ulcers- A review

Abstract: An ulcer is a breach in the continuity of epithelium of mucous membrane and skin when an inflamed necrotic tissue sloughs out. Ulcers are caused by various medical conditions. The key to treatment is daily conventional dressing till formation of healthy granulation tissue, infection control by antibiotics and surgical intervention such as debridement, and if need arises amputations. Platelet Rich Plasma (PRP) uses autologous plasma containing growth factors which helps in wound healing. PRP is being used extensively and is under research for wound treatment.

Keywords: Foot ulcers, PRP, dressing

Background:

An ulcer is a breach in the continuity of epithelium of mucous membrane and skin when an inflamed necrotic tissue sloughs out.[1] Ulcers are caused by problems related to circulation and clotting, inflammatory conditions associated with lymphedema, hypercholesterolemia, hypertension, heart disease, sickle cell anaemia, history of smoking, pressure caused by maintaining a static position (lying) for too long, malignancy, certain

medications, genetics and infections, arteriosclerosis, venous insufficiency, diabetes, leprosy, alcoholism, vitamin deficiencies, tabes dorsalis, spinal cord injury etc.[1,2,3,4]

Knowing the risk factors governing it becomes imperative for the proper treatment of ulcers. Risk factors for ulceration include reduced sensation, high foot pressures, callus formation, foot deformities, peripheral vascular disease, and a history of ulceration.[5]

Treatment includes the efficient and rapid induction of tissue repair and complete epithelialisation.[6] A daily sterile dressing, surgical debridement or amputation may be needed.[7] In managing neuropathic ulcers, pressure relief is of the utmost importance, and total contact casting, alleviation of the mechanical load on ulcers (off-loading), orthotic devices such as cushioned insoles should always be a part of treatment.[8,9]

Several researches have shown that chronic ulcers lack the growth factors (GF) required for initiating and maintaining the healing cascade due to decreased production, less release, trapping, increased degradation, or a combination of the mechanisms.[10,11] GFs provide a pathway for the cells to proliferate, migrate, and extracellular matrix (ECM) synthesis and healing.[12] This has led to the introduction and increasing use of autologous platelet-rich plasma (PRP), which contains platelet-derived growth factor (PDGF) that assist in treating chronic non-healing ulcers.[6]

Advancements in the medical field have focused on new treatments, preferably less invasive, which may efficiently heal the epithelium. Therefore, the effectiveness of PRP in the treatment of sole ulcers need to be assessed.

Methods

A comprehensive set of keywords were built like "platelet-rich plasma", "sole ulcer," "PRP", "arterial ulcer", "venous ulcer", "neurotrophic ulcer", or "risk-factors". An extensive literature review search was performed in PubMed, Medline, Scopus, Global Health, Web of Science, Cochrane, POPLINE, Adolec, Open Grey Database, Path, Gavi, WHO websites

were searched up to December 2021. The list of reference articles was also retrieved, and they were searched via automation & manually.

Data Extraction:

Data extraction was done by 2 authors into separate sheets using Excel 2016. Data extraction discrepancies were resolved through discussion. No specific date was predefined regarding publication. Automated & manual deduplication was performed.

Table 1 : Comparison of Various Studies about effectiveness of PRP in sole ulcer:

Reference	Name of Study	Comments
Anandan V et al. 2016	Platelet Rich Plasma: Efficacy in Treating Trophic Ulcers in Leprosy	PRP therapy leads to a faster induction rate of granulation tissue with rapid healing.
Prabhu R et al. 2018	Efficacy of Homologous, Platelet-rich Plasma Dressing in Chronic Non-healing Ulcers: An Observational Study	PRP is safe and enhances the healing rates of chronic wounds, thereby reducing overall hospital stay and morbidity
Suryanarayan S et al. 2014	Efficacy of autologous PRP in the treatment of chronic non-healing leg ulcers	PRP is an affordable, safe, biocompatible, and simple office-based procedure for treating non-healing ulcers.
Goda AA et al. 2018	PRP for the treatment of diabetic foot: a randomised, double-blind study	Autologous PRP is safe and effective for the treatment of diabetic foot ulcers.
Elbarbary AH et al. 2020	Autologous platelet-rich plasma injection enhances chronic venous leg ulcer healing: A prospective randomised study.	PRP injection improves the healing of chronic venous ulcers.
Tran T et al. 2014	Diabetic foot ulcer treatment by activated PRP: a clinical study	A PRP injection is an efficient method to treat non-healing foot ulcers.

Elsaid A et al. 2020	Randomised Controlled Trial on Autologous Platelet-Rich Plasma Versus Saline Dressing in Treatment of Non-healing Diabetic Foot Ulcers	The use of PRP gel resulted in a more significant reduction in the size of the ulcer when compared to regular saline dressing.

Understanding the types of leg and foot ulcers

The most frequently found Leg and foot ulcers are categorised mainly into arterial ulcers, venous stasis ulcers, and neurotrophic ulcers.[1]

Arterial ulcers

Arterial ulcers are caused due to insufficient blood supply because of advanced age, trauma, diabetes, and peripheral vascular disease. The most distinctive feature is pain during exercise, night, or resting. The common sites of arterial ulcers are heels, between the toes, tips of the toes, and feet. Characteristics of arterial leg ulcers include the "punched-out" appearance having a well-demarcated edge, usually pale, non-granulating, and a necrotic base. Gangrene can develop in extremities. On examination, the posterior tibial and dorsalis pedis arteries may have a reduced or absent pulse. Individuals with arterial ulcers need sufficient blood flow to heal and gain from revascularisation techniques.[13]

Venous ulcers

Venous ulcers are caused by perforating vein valve incompetence, history of deep vein thrombophlebitis and thrombosis, a failed calf pump, obesity, ageing, or pregnancy among women. Primary sites of venous stasis ulcer are below the knee and above the medial malleolus.[14] Lipodermatosclerosis develops as a result of chronic venous insufficiency.

Increased venous return, decreased oedema, optimal compression, and appropriate skin and wound treatment help speed up healing.**Error! Bookmark not defined.**

Neuropathic ulcers

A neuropathic ulcer is a form of chronic ulceration which develops in anaesthetic skin. These are painless, persistent and uninflamed, appearing on areas subject to trauma or pressure.[15] Aetiology includes diabetes, leprosy, peripheral neuropathy, alcoholism, syringomyelia, tabes dorsalis, spinal cord injury, etc.[16,17] Neuropathic ulcers result from distal polyneuropathy encompassing motor, sensory and sensory autonomic components. Motor involvement leads to the "rocker-bottom foot", prone to tissue breakdown and ulceration.[17] The plantar aspect of the foot is protected by fat pads, where increased pressure under the metatarsal heads and heel results in initial callosity leading to ulceration.[17]

Non-healing ulcers

Chronic ulcers, also known as non-healing ulcers, are defined as spontaneous or traumatic lesions, typically in the lower extremities, which are not responsive to initial therapy or persist despite appropriate care and do not heal within a specified time.[18]

Treatment modalities of ulcers

The primary cause of the ulcer determines the treatment of various forms of ulcers.

Venous leg ulcer

Compression is the basis of the management of venous ulcers. There are several types of compression bandage systems, such as the single and multi-layer elastic bandage systems, short stretch bandages, and elastic tubular bandages. Compression with pneumatic devices is useful in patients having edematous legs.[19] The sharp debridement of nonviable tissue increases venous ulcers healing. Among patients where other treatments failed, shave therapy

(excision of the whole ulcer) followed by skin grafting, or skin grafting alone, may be beneficial[19].[19]

Arterial leg ulcer

Enhancing peripheral blood flow is the basis of the management of arterial ulcers, which can be accomplished through reconstructive surgery or angioplasty. Smoking should be stopped, and diabetes, hypertension and hyperlipidemia should be corrected. Patients may benefit from sleeping in a bed elevated at the head end, and walking is advantageous.[19] Nonselective blockers and other vasoconstrictive medications should be avoided.[19]

Neuropathic ulcer

In treating a neuropathic foot ulcer, a multidisciplinary approach is most effective. Typically, the ulcer is debrided surgically or treated using a hydrogel followed by applying a hydrocolloid dressing. Researches have shown benefit from using the PDGF, cultured dermis and hyaluronic acid dressings in promoting wound healing in clean wounds.[20,21] An essential part of treatment is the "off-loading" of areas of abnormal pressure on the foot. A modified non-weight-bearing boot made of layers of adhesive foam padding or boots made of plaster of Paris (with a rocker base) may remove pressure points altogether.[22]

Use of Platelet Rich Plasma (PRP) in the healing of ulcers

PRP: What is it, how is it made?

PRP is an easy-to-use regenerative medical intervention. It's gaining popularity in different medical fields because of its simplicity and biosafety. In cases of cell therapy, many regulatory requirements need to be followed, like numerous pre-clinical trials to establish its safety and non-teratogenic effects, the establishment of expensive equipment in the preparation. In comparison, PRP treatment has no strict regulatory requirements, and the easy availability of PRP kits and devices make it easy to use in clinical settings.[23]

Platelet-rich plasma (PRP) is "a portion of the plasma fraction of autologous blood with a platelet concentration above the baseline (before centrifugation)". PRP mainly consists of a high concentration of platelets and a complete profile of clotting factors (at normal levels).[23] Each condition requires a specific type of PRP. Variation in the concentration of platelets and whether leucocytes are there or not and if they are active or inactive decide the kind of PRP.**Error! Bookmark not defined.**

Mainly three types of certified medical equipment are available for PRP processing. First, a tube with an anticoagulant is used to obtain blood, followed by any centrifuge. Second is medical equipment to take blood in a tube already having anticoagulant; later, any type of centrifuge can be used. And the third one is the use of medical equipment to take blood in a syringe already having anticoagulant; the secondary device is used in which the blood is transferred.**Error! Bookmark not defined.**

Three layers are obtained in the tube after the process of centrifugation. The top layer consists of platelet-poor plasma, the middle layer consists of platelet-rich plasma, and the bottom layer consists of blood cells.**Error! Bookmark not defined.** Activation of platelets can

be done before the administration of PRP. Till now, no agreement has been achieved on whether the activation is required of platelets before the administration.[24]

Roles of PRP

In maxillofacial surgery, PRP was used as PRF in the 1980s. Homeostatic and adherence properties are present in fibrin, whereas PRP is anti-inflammatory, a combination of cells stimulated proliferation.[25] PRP is extensively used in cases of sports injuries, musculoskeletal problems in other medical fields like pediatric surgery, cardiac surgery, urology, gynaecology, ophthalmology, and plastic surgery.[26] In dermatology, recently PRP is being used extensively for wound healing, tissue regeneration, scar revision, alopecia, and rejuvenating skin effects.**Error! Bookmark not defined.**

How PRP works in wound healing

Due to the significant inflammation in wounds, healing gets delayed in chronic ulcers. Also, growth factor concentration is reduced due to increased protease activity. PRP is given as it has a high concentration of growth factors, due to which it has angiogenic, mitogenic, and chemotactic properties.**Error! Bookmark not defined.** Tissue sealing and drug delivery are the two primary purposes of PRP.[27] Its mechanism involves the release of growth factors by platelets that assist the wound repair by acting locally via degranulation of alpha granules [28,29]

The secretory proteins in the α-granules of platelets are platelet-derived growth factor, epidermal growth factor, transforming growth factor, interleukins, vascular endothelial growth factor, insulin-like growth factor, etc.[29] Cell division is triggered by these growth factors. PRP suppresses cytokine release and works in conjunction with macrophage to limit inflammation.[6] In several studies, the effectiveness of PRP has been substantiated.

DISCUSSION

Evidence of effectiveness of PRP in wound healing

Margolis et al., in a cohort study on 26,599 patients with diabetic neuropathic foot ulcers, showed that complete healing occurred in 41 per cent of patients.[30] Crovetti et al. also showed PRP effectiveness by conducting a prospective non-blinded study on 24 patients presented with non-healing ulcers. Complete healing was present in more than two-thirds of patients.[31] O'Connell SM et al. conducted a prospective pilot trial among 12 patients with non-healing ulcers. Ulcers showed re-epithelisation in 66.7 per cent in venous ulcer group.[32] Suryanarayan S et al. confirmed these findings in a non-randomised, uncontrolled study on 24 patients with non-healing ulcers. Ulcers showed nearly complete resolution in 76 per cent of the patients.[33] Goda AA et al. conducted a prospective, randomised, controlled, multicenter, double-blind study on 50 patients with diabetic foot ulcers. The ulcer healing rate and complete healing in the PRP group were significantly faster than the platelet-poor-plasma group. Various other studies showed that PRP is a novel therapy and safe for treating non-healing ulcers that persist chronically in the patients[34,35,36,37]

Mean duration of treatment with PRP for effective results

Driver et al. conducted a prospective, randomised, controlled multi-centre trial on 72 patients. PRP therapy was tried biweekly for 12 weeks. Ulcers showed healing over a mean duration of 42.9 days, with 68.4 per cent of ulcers showing complete re-epithelisation.[38] Suryanarayan S et al. confirmed these findings in a non-randomised, uncontrolled study on 24 patients with non-healing ulcers. PRP therapy was tried weekly for six weeks. Ulcers showed healing over a mean duration of 5.6 weeks.[33] Bharathi MS et al. conducted a prospective study on 10 cases of non-healing ulcers. Ulcers showed healing over six weeks, with 40 per cent of ulcers showing complete re-epithelisation.[39] These studies showed that PRP is a novel therapy and safe for treating non-healing ulcers that persist chronically.

Ulcer characteristics and treatment with PRP

Ulcer length and width

Elsaid et al. found that compared to the conventional group, the PRP group had comparable maximum longitudinal diameter before treatment (4.2 vs 4.5), maximum longitudinal diameter after treatment (4.04 vs 3.23), maximum horizontal diameter before treatment (4 vs 5.4) and maximum horizontal diameter after treatment (3.7 vs 3.3). This showed that PRP helped in earlier healing of the ulcer by reducing its length and width at a faster rate.[37]

Surface area

Velayutham S et al. found a significantly better mean per cent wound contraction rate of PRP dressing group compared to the conventional dressing group (34.4% vs 13.5%).[40] Goda et al. also showed that the PRP group had a significantly faster ulcer healing rate after treatment than the control group.[34] Sarvajnamurthy et al. and Prabhu et al. also reported a significant reduction in the mean ulcer area.[41,42] This may be because after applying it to the wound, growth factors and cytokines are directly introduced, and thus led to normalisation of the metabolic process, promotion of neo-angiogenesis, improvement in cellular metabolism, and activation of the local immunity.[43] On the contrary, Driver et al. reported that in the PRP gel group, the wound area closure rate per day was 0.042 cm^2 and for the control group was 0.043 cm^2, which failed to cross the boundaries of statistical significance.[38]

Treatment with PRP reduces the hospital stay

Anandan et al. reported that the PRP treatment resulted in a significant reduction in the treatment duration, thereby decreasing the duration of hospital stay.[43] On the contrary, in a study by Li L et al., the autologous platelet-rich gel was used to treat diabetic refractory cutaneous ulcers, but there was no significant difference in the length of hospital stay between APG-treated and standard-treated patients (57 days vs 58 days). The insignificant association in the study may be due to varied population statistics, duration of ulcer and different aetiologies of the ulcer, which needs further research.[44]

Adverse effects associated with PRP treatment

No adverse effects were seen in the study by Sarvajnamurthy et al.**Error! Bookmark not defined.** Following this, Prabhu et al. also found no side effects after PRP dressing.[41]**Error! Bookmark not defined.** Even Hu Z et al., in a meta-analysis including 8 RCTs, reported that PRP resulted in improved ulcer healing without significant adverse effects in the patients who had diabetic ulcers.[45] However, Driver et al. reported adverse effects in patients in their study. Two adverse effects were associated with the treatment: one case of contact dermatitis was present in PRP gel treated wound and one case of maceration among control-treated wounds. However, these were minor side effects and were managed.[38] Overall, PRP seems to have better safety and allows for a lesser hospital stay than the conventional follow-up treatment regime with no additional side effects.

Limitations in the evidence

The parameters such as the quality of life, the number of debridement required in each week, and the total treatment cost were not studied. These studies did not adequately evaluate the complete effect of diabetes on wound healing. There was no blinding of the PRP procedure for the patients. Most of the studies were single-centric; hence, the efficacy of PRP and conventional treatment may need further validation.

Conclusion

It can be concluded from the previous studies that the use of PRP treatment in foot ulcers provides a faster resolution of the ulcers and their surface area, leading to a significantly lesser hospital stay. Overall, PRP seems to have a better efficacy and safety profile allowing for a lesser hospital stay than the conventional follow-up treatment regime with no additional side effects. PRP was also effective in reducing inflammation and pain; however, it showed no superiority against the control group, which had conventional dressing treatment. To further validate the practicality of the PRP treatment, future multicentric studies are recommended with a larger sample size to compare the use of PRP treatment in ulcers with varying aetiology. It is recommended that a more extended follow-up period with frequent in-between evaluation is required to assess whether the wound healing progresses at a similar rate. The quality of life after PRP treatment should be evaluated. Also, the total treatment cost should be assessed as it is an essential factor for choosing treatment options in developing countries such as India.

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