Journal of Diabetes Science and Technology
Volume 4, Issue 5, September 2010

SYMPOSIUM

Novel Use of Platelet-Rich Plasma to Augment Curative Diabetic Foot Surgery

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Abstract

Autologous platelet-rich plasma (PRP) may enhance wound healing through the formation of a platelet plug that provides both hemostasis and the secretion of biologically active proteins, including growth factors such as platelet-derived growth factor, transforming growth factor (TGF)-β, TGF-β2, and epidermal growth factor. The release of these growth factors into the wound may create an environment more conducive to tissue repair and could accelerate postoperative wound healing. To our knowledge, there are no reports of combining the use of PRP with curative diabetic foot surgery. This article provides a summary of the literature regarding PRP and wound healing and presents a case of a 49-year-old man with diabetes and a three-month history of a deep, nonhealing plantar hallux wound in which PRP was combined with a first metatarsophalangeal joint arthroplasty. Through the use of the PRP and bioengineered tissue to supplement curative diabetic foot surgery, the patient healed uneventfully at seven weeks.

J Diabetes Sci Technol 2010;4(5):1121-1126

Introduction

People with diabetes often develop many factors such as neuropathy, tissue hypoxia, and hyperglycemia-related immunopathy that contribute to their increased susceptibility to infection and decreased ability to heal. This is evidenced by research studies that report defects in matrix-related cells and imbalances in key protesases, cytokines, and growth factors.[1–3]

An increased understanding of the physiological roles of platelets in wound healing has furthered the role of platelets as a novel therapeutic tool in wounds.[4] Studies have demonstrated a significant increase in the limb salvage rate/amputation prevention among high-risk diabetes patients,[5–8] as well as reduced total treatment expenses[9,10] when combined with a comprehensive local wound care protocol.

Regarding lower extremity wounds, the plantar hallux is one of the most common locations of foot wounds in people with diabetes.[11,12] Armstrong and colleagues[13] reported that first metatarsophalangeal joint arthroplasty is a safe and effective curative procedure in the treatment

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Abbreviations: (EGF) epidermal growth factor, (IGF) insulin-like growth factor, (MTPJ) metatarsophalangeal joint, (PDGF) platelet-derived growth factor, (PIPJ) proximal interphalangeal joint, (PRP) platelet-rich plasma, (TGF) transforming growth factor, (VEGF) vascular endothelial growth factor

Keywords: diabetic, foot surgery, platelet rich plasma, wound

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of noninfected, nonischemic wounds of the plantar hallux, leading to faster and more durable healing when compared with a matched cohort. We are unaware of reports in the literature combining autologous platelet-rich plasma (PRP) with curative diabetic foot surgery.

Significance of Platelet-Rich Plasma

In the natural healing process of the body, surgical intervention and trauma initiate the healing cascade through platelet activation (α-degranulation) and the formation of a platelet plug and blood clot, providing both hemostasis and the secretion of biologically active proteins. The naturally occurring hematoma is composed of 95% red blood cells, 4% platelets, and 1% white blood cells. Through the use of PRP, hematomas with a composition of 95% platelets, 4% red blood cells, and 1% white blood cells can be created.[14,15] Platelet-rich plasma also contains the full complement of clotting factors and secretory proteins. Among the 30 biologically active proteins [e.g., platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β1, TGF-β2, platelet factor IV, interleukin-1, platelet-derived angiogenesis factor, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), osteocalcin, osteonectin, fibrinogen, vitronectin, fibronectin, and thrombospondin-1], the bulk of research focus has centered around PDGF, TGF-β, VEGF, EGF, and IGF.[14–21]

Autologous PRP is a limited volume of plasma enriched in platelets that is derived from the patient's whole blood. The whole blood is then separated by centrifuge into layers of platelet-poor plasma, red blood cells, and platelets with white blood cells. The platelet concentrate is then activated through thrombin generation by an anticoagulant, either ascorbic acid or 10% calcium citrate, resulting in the formation of a fibrin scaffold. This activation of the platelets causes the release of concentrated growth factors and proteins locally to create an environment conducive to tissue repair and accelerated postoperative wound healing.[21–26] Platelet-derived growth factor, TGF-β, VEGF, and EGF have all been shown to be increased three to seven times in autologous PRP.[27] The low concentration of IGF in PRP is to be expected, as it is secreted by the liver into the blood plasma, which is removed in the separation process, and platelets themselves only generate negligible amounts of IGF.[28]

Platelet-derived growth factor is the only growth factor approved by the Food and Drug Administration for clinical use, and it has been shown through phase III of a multicenter clinical human trial to generate a 10% increase in the rate of complete healing in diabetic wounds.[29–31] Topical application of platelet-derived wound-healing factors has been shown to stimulate repair of chronically nonhealing human wounds, thereby resulting in accelerated granulation tissue formation and epithelialization.[32] Platelet-derived growth factor is a key growth factor in wound healing that is secreted by macrophages, endothelial cells, fibroblasts, and megakaryocytes. Its actions include activation of immune cells and fibroblasts, extracellular matrix deposition, collagen synthesis, matrix metalloproteinase and tissue inhibitor of metalloproteinase synthesis, and angiogenesis.[33–35] Platelet-derived growth factor, a powerful mitogen for fibroblasts and smooth muscle cells, is involved in all three phases of healing, including angiogenesis, formation of fibrous tissue, and reepithelialization. Release of PDGF into the wound bed also has a chemotactic effect on monocytes, neutrophils, fibtoblasts, mesenchymal stem cells, and osteoblasts.[36] Platelet-derived growth factor is a stable protein and has been shown to have resistance to changes in heat and pH. This property enables PDGF to be resistant to destructive proteases present in the hostile, metalloproteinase-rich environment.[37]

TGF-β is a potent inhibitor of immune reactivity that attracts macrophages that then stimulate the secretion of additional cytokines.[38] TGF-β also enhances fibroblast and smooth muscle cell chemotaxis, induces the deposition of bone matrix, and stimulates the synthesis of type I collagen.[27] TGF-β also promotes angiogenesis and extracellular matrix production.[39,40]

TGF-β2 has shown improvement in healing rates in diabetic foot ulcers in phase II of a clinical human trial, but TGF-β1 is the predominant isoform in wound healing and has never been tested in human clinical trials. Studies conducted on young rabbits have shown it to increase wound healing by new granulation tissue formation and reepithelialization in ischemic and non-ischemic wounds.[41]

Many different cells produce VEGF or release factors that regulate the expression of VEGF. Fibroblast growth factor-4, PDGF, tumor necrosis factor-α, IGF, and some interleukins potentiate the effects of VEGF while nitric oxide enhances VEGF's effects on blood vessels and hydrogen peroxide activates it.[42,43] VEGF indirectly stimulates endothelial growth and promotes angiogenesis while enhancing capillary permeability and leakage of tissue plasma extracellularly.[38,44] Unlike PDGF, VEGF almost exclusively binds to endothelial cells[45,46] and does

not act on macrophages, fibroblasts, or smooth muscle. Human clinical trials studying the effects of VEGF on wound healing have not yet been conducted, but animal studies on rabbits have shown a doubling of granulation tissue formation in ischemic wounds.[47]

Epidermal growth factor is a cytokine that has been linked with angiogenesis and collagen deposition at wound sites, and it has been shown to stimulate wound repair in fibroblasts and epithelial cells.[38,44] It is a mitogen for fibroblasts, endothelial cells, and keratinocytes, and it also stimulates reepithelialization, augments angiogenesis, and influences the synthesis and turnover of extracellular matrix.[40]

Case Presentation

The following is a presentation of a 49-year-old man with type 2 diabetes that presented with a three-month history of a nonhealing nonischemic neuropathic plantar hallux wound of his right foot. Prior to surgery, the patient's physical exam revealed a full-thickness noninfected ulceration with a punched-out appearance at the plantar hallux of the right foot measuring 1.5 cm around with depth of 2–3 mm that did not probe to bone (**Figure 1**). There was a granular base with a small central area of fibrotic tissue. There was no undermining of the wound edges, no purulence, and no serosanguinous drainage noted. Dorsiflexion motion at the first metatarsophalangeal joint (MTPJ) was <10°, both loaded and unloaded. A dorsal contracture of the second digit at the MTPJ and corresponding flexion contracture at the proximal interphalangeal joint (PIPJ) was also observed in the right foot.

The patient was treated surgically with a combination of arthroplasties, a first MTPJ arthroplasty (Keller) and second PIPJ arthroplasty, and autologous PRP as a curative procedure for a plantar hallux wound. The patient's past medical history included diabetes, hypertension, and hypercholesterolemia. Previous wound care included local wound care with serial sharp debridements, topical aquacell, and traditional offloading.

The patient was treated surgically with sharp debridement of the wound and an arthroplasty of the hallux and an arthroplasty of the second proximal interphalangeal joint (**Figure 2**). Additionally, the wound was filled with an injection of 3 cc of Angel (Sorin Inc., Mirandola, Italy) autologous PRP to fill the wound defect (**Figures 3–5**).

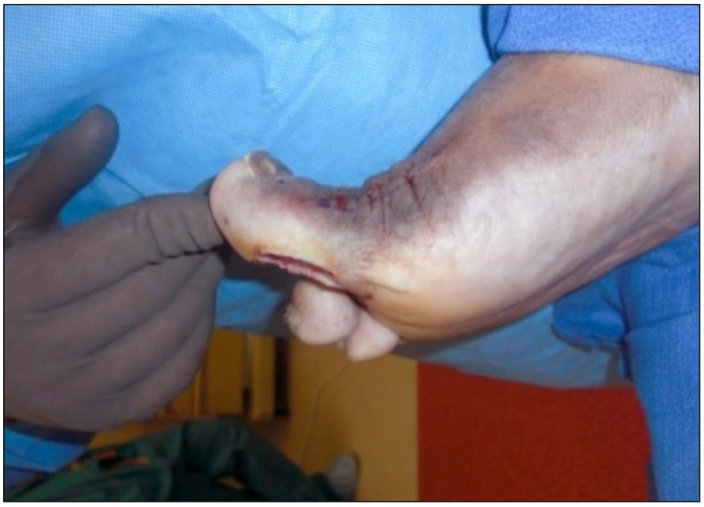

Figure 2. Increased dorsiflexion achieved through the arthroplasty of the hallux.

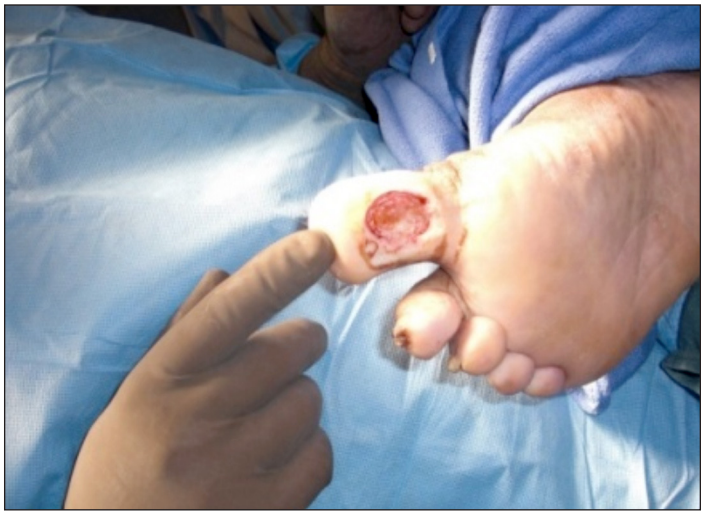

Figure 1. Noninfected ulceration at the plantar hallux of the right foot.

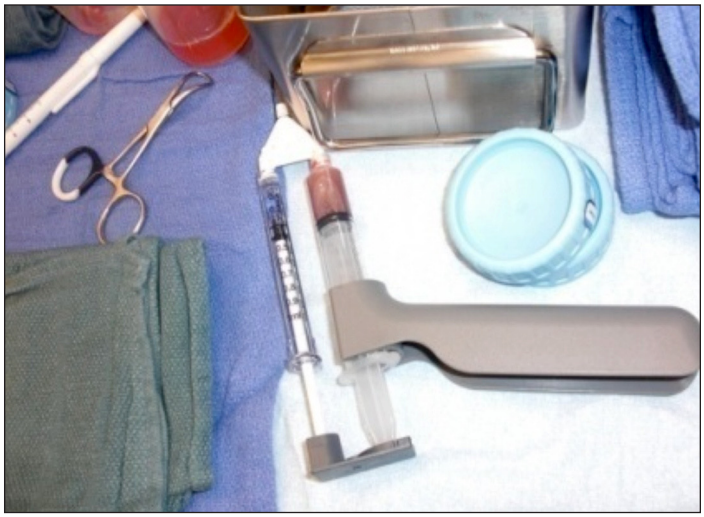

Figure 3. Dual syringe used for PRP.

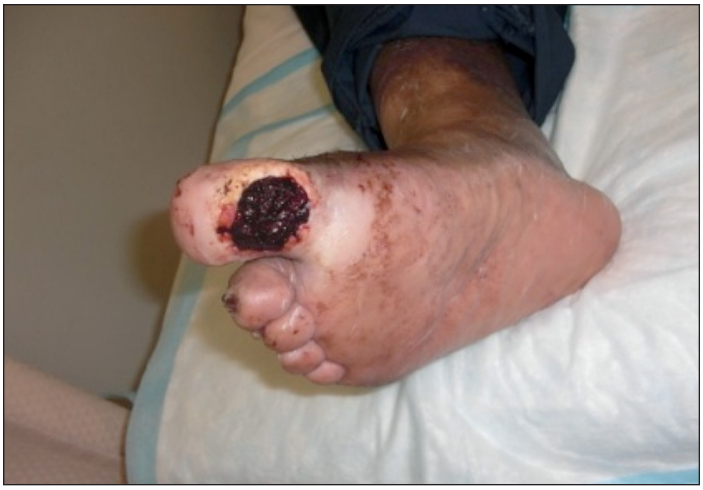

Figure 4. Wound defect filled with 3 cc of PRP.

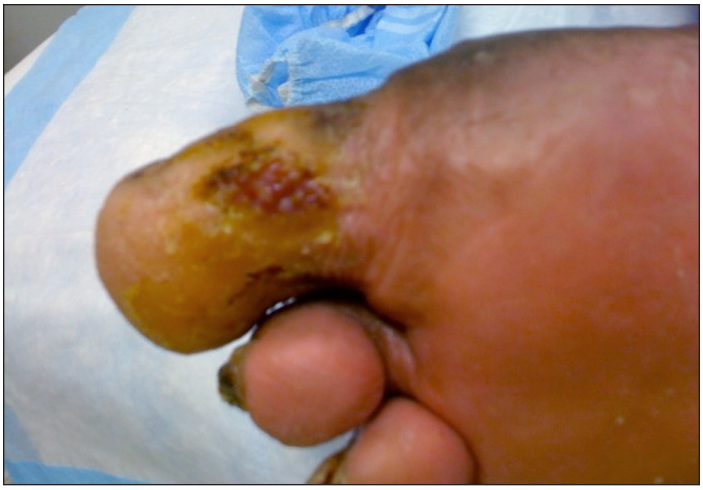

Figure 5. Superficial wound at four weeks postoperation. At this time, a Dermagraft bioengineered graft was applied to the remaining superficial wound, and by seven weeks postoperation, the wound had completely epithelized.

Conclusion

Platelet concentrates may be potentially useful in wound-healing applications because they function as both a tissue sealant and a delivery system that contains a variety of mitogenic and chemotactic growth factors. Studies have shown that platelets can be sequestered and concentrated eight-fold from whole blood without premature activation.[48] There is an increasing cause for optimism in the use of PRP in treatment of diabetic and other chronic wounds as numerous clinical trials have reported favorable results in wounds treated with PRP and platelet-rich concentrate.[49–56]

This article described the novel use of autologous PRP to augment healing of a stalled plantar foot ulceration when combined with curative diabetic foot surgery. Proper offloading of the wound afforded by the first MTPJ resectional arthroplasty was paramount to healing in our patient. The authors look forward to further works to better determine whether augmentation with PRP during curative diabetic foot surgery provides a more consistent, cost-effective treatment approach in a difficult population.

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