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The use of autologous PRP gel for the treatment of diabetic foot ulcers

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Abstract

The purpose of this systematic literature review is to examine the efficacy of platelet rich-plasma (PRP) gel as a therapy for diabetic foot ulcers (DFUs). Infections in patients with diabetes, especially diabetic foot ulcers, are challenging to treat due to neurovascular compromise. Searches were done in PubMed utilizing the terms “diabetic foot ulcer”, “platelet rich plasma” and “autologous”. In PubMed, the following limits and terms were used: randomized control trial (RCTs), sample size greater than 30 participants, foot ulcers, and English. A meta-analysis revealed three studies meeting inclusion/exclusion criteria: Li et al, Gude et al, and Ahmed et al. The literature available demonstrates that autologous PRP gel is an effective treatment to increase DFU healing rate when compared to the current standard of care. Further studies may be necessary to determine long term outcomes and consequences of the use of autologous PRP gel.

Introduction

Over 10% of Americans are diagnosed with diabetes mellitus, a disease in which the body does not respond to or produce enough insulin.[1] Among diabetic patients, approximately 15-25% will develop a diabetic foot ulcer (DFU) due to the prevalence of neuropathy (50%) and arterial deficiency (20%), with 80% of DFUs having both.[2],[3] Neuropathy is associated with an increased risk of trauma due to impaired pain perception while arterial deficiency is associated with decreased wound healing rate due to decreased blood flow and immune response to infection. The current standard of care includes debridement, off-loading, maintaining a moist wound environment, management of infection, wound cleansing, and nutritional support for diabetic control.[4] Diabetic foot ulcers are notoriously difficult to treat, despite a wide range of options for care.

Platelet-rich plasma (PRP) is an autologous concentration of human platelets made by drawing a patient’s blood, centrifuging, and adding coagulation factors, most commonly calcium and thrombin, to form a gel.[5] PRP contains fundamental protein growth factors that initiate wound healing by acting as cell adhesion molecules to provide a matrix for bone, connective tissue, and epithelial migration.[5] Wound healing is accelerated with platelet derived growth factors that activate or induct chemotaxis, cellular proliferation, and angiogenesis, thus, increasing blood flow and immune response to wound sites.[6] Autologous PRP gel is considered a newer strategy in the treatment of diabetic foot ulcers. This review aims to determine whether autologous PRP gel, when compared to standard wound care, increases the wound healing rate of diabetic foot ulcers.

Methods

In September 2021, Articles were searched through PubMed using the following MESH terms: “diabetic foot ulcer” and “platelet rich plasma”. Non-MESH terms included “Autologous”. No

other sources were used. Results were narrowed by only using randomized control trials (RCTs) and papers printed in English which yielded 7 papers. The 4 papers not used were excluded for 1 of the following reasons: single-arm trial, ulcers located outside the foot, or a small sample size of <30 participants. (Figure 1)

Results

Study #1

Platelet-Rich Plasma for the Treatment of Clean Diabetic Foot Ulcers[7]

Objective: To compare the use of antiseptic ointment dressing with autologous platelet gel in the evaluation of healing rate and prevention of infection in clean diabetic foot ulcers.

Study Design:

This was a prospective comparative study which included 56 patients ranging from ages 18 to 80. The study was conducted at Suez Canal University Hospital in Egypt. Both males and females with clean chronic diabetic foot ulcers were included. Patients were included if they had a nonhealing foot ulcer for more than 6 weeks. Patients were excluded if their ulcer was less that $2cm^2$ or showed signs of infection. They were also excluded if they were pregnant or lactating, had an ejection fraction <30, ankle-brachial pressure index <0.8, hemoglobin less than 10 gm/dL, platelet count less than 150,000/dL, lymphedema, or refused to donate blood. Patients were randomly assigned to 2 equal groups of 28. The control group was treated according to the best practice guidelines which included antiseptic ointment dressing. Daily dressings were used which involved cleaning the wound with normal saline, treating it with iodine ointment and covering the wound with sterile dressing. These patients were seen twice weekly.

The second group was treated with platelet gel twice weekly. The PRP gel was prepared using a tabletop centrifuge and 20mL of peripheral blood from the patient. The PRP was activated with calcium chloride and thrombin to release growth factor. The thrombin was prepared using 5 mL of whole blood from the patient with centrifugation and incubation for 15-30 min. The gel was activated at the patient's bedside. The wounds were washed with normal saline and the gel was applied. Then, a sterile non absorbing dressing was applied.

All wounds were debrided, if necessary. Wounds were measured and graded. The surgeon involved in this process was blind to the type of dressing applied.

All patients had their glycemic control assessed at each visit. Random blood sugar levels were maintained in the range of 100-160 mg/dL. If a patient was outside of this range, they were referred to the Diabetes Outpatient clinic for adjustment of their diabetes treatment.

Study Results:

Results were measured over a period of 2 years. Healing, growth, and infection rate were measured. Wound characteristics were compared between the control and PRP groups. After 2 weeks, complete wound healing was achieved in 7% of the control group and 29% of the PRP group. These findings were consistent at 4 weeks. There was a growth rate decrease at 8 and 12 weeks. At 12 weeks, 68% of the control patients and 86% of the PRP group had healed ulcers. Platelet count in the PRP was measured and ranged from 1,000,000 to 1,200,000/uL for all patients.

Infection rate was also measured. 21% of the control group and 4% of the PRP group were recorded to have infected wounds. There was no recorded reaction to the materials used during the study.

Study Critique:

Strengths include equal intensity of observation for the control and study groups. Both groups were seen twice weekly. The study was a randomized control trial. Inclusion and exclusion criteria are clearly outlined in a table format. Images of diabetic foot ulcers were utilized to show healing over time. There was a clear and logical presentation of the information.

The study has a large enough sample size to demonstrate statistical significance. However, the study was only conducted at a single hospital. Furthermore, this study was conducted in Egypt. Therefore, it is important to consider whether it is possible to extrapolate these results to patients in the United States. Wound assessment was performed by a surgeon that was blinded to the type of dressing applied to each patient. This provides uniformity for patient care among the study and control group.

The decrease in wound healing rate at the 8^{th} week could suggest a ceiling effect of PRP gel. The authors of the article suggest it could be explained by a high concentration of growth factors leading to receptor down regulation.

Overall, this study had a few drawbacks but was well conducted allowing the data to be statistically significant.

Study #2

Aurix Gel Is an Effective Intervention for Chronic Diabetic Foot Ulcers: A Pragmatic Randomized Controlled Trial[8]

Objective:

To establish the efficacy of up to 12 weeks of treatment with Aurix hematogel for healing diabetic foot ulcers against usual and customary care including any wound modality.

Study Design:

This was a pragmatic randomized controlled trial that utilized 28 outpatient wound care sites in the United States and had 129 patients with various health risks, comorbidities, and any wound severity. There were two groups: Aurix with the usual and customary care and usual and customary care only. Participants were 18 or older with type 1 or 2 diabetes and a wound that was at least 1 month old. Participants were then randomized with 66 patients in the study group and 63 in the control group. Participants had a mean age of 66.9 for the control group and 64.7 years for the study group. Both groups were predominantly male and white. Patients had to be Medicare beneficiaries and have at least one nonhealing diabetic foot ulcer.

Aurix Therapy is a biodynamic hematogel that consists of a proprietary formulation of platelets and pharmaceutical-grade reagents produced at the patients' point of care. Patients receiving Aurix were treated twice weekly for two weeks and then once a week while under active treatment. However, the actual frequency of treatment was determined by the clinician. The gel was prepared by obtaining 5-20 mL of blood from the patient by venipuncture, centrifuging the blood and adding reagents to produce a gel. The gel was immediately applied to the wound, a barrier cream was added and a nonadherent dressed placed over top. Lastly, an absorbent layer was then secured over the wound for exudate.

For the patients that were treated with the usual and customary care, investigators used any treatment modality or combination of treatments available if the clinician and patients considered it to be in the best interest to health the ulcer. Additional advanced wound care was allowed in the Aurix and UCC treatment group as well as the control group.
Data from different clinics was gathered using Net Health Wound Expert electronic medical record, with a few exceptions. This study also included quality of life measurements that were wound specific.
Both the study and control groups received the standard of care for chronic cutaneous ulcers and were provided information pertaining to appropriate debridement, off-loading, maintenance of a moist wound environment, management of infection, wound cleansing, and nutrition support including blood glucose control. Wound measurements were performed at each visit. If patients were unable or unwilling to attend the two treatment visits within the first 2 weeks, then a single treatment each week was acceptable.

Study Results:

The study reports that 48.5% of patients treated with Aurix healed within the 13 weeks study period versus 30.2% of the patients treated with the usual and customary care. With a p value of 0.0476, there was a statistically significant time to heal advantage for Aurix. The study indicated that Aurix, when used along or in combination with other advanced wound care therapies, improves the healing rate of chronic diabetic foot ulcers when compared to patients treated with the usual and customary care.

Study Critique:

This study addresses a wide patient population with comorbidities and various health risks. This means the study can be better applied to the general population. However, since the study included health risks and comorbidities, it is possible that the unequal representation of smoking and PAD between the control and study groups skewed the results. The patients in the study also had varying wound severity, which can be better applied to the general population as well. Patients with varying wound severity, comorbidities, and health risks are more likely to be the type of patients that are seen in a clinic. However, certain demographics were underrepresented considering the study was mostly white males and all patients had insurance. This potentially makes the study findings challenging to apply to the general population. The inclusion and exclusion criteria were clearly outlined. The study had a large number of participants, allowing for significant statistical power.
While the patient populations were seen twice weekly for two weeks and then once a week while under active treatment, treatment frequency was determined by the clinician. Therefore, it is possible that treatment differences affected the results. Also, the study intensity had potential to be unequal. Patients were permitted to attend a single treatment per week if they were unable to or unwilling to attend two treatment visits within the first two weeks. The authors do not outline which groups that occurred in, which means it is possible there was unequal intensity in this study.
The study allowed additional advanced wound care in both the study and control group. As a result, patient care was not standardized, and comparison is difficult. However, the advanced therapies used were clearly outlined in the article, with the healing rates included.

Study #3

Autologous platelet-rich gel for treatment of diabetic chronic refractory cutaneous ulcers: A prospective, randomized clinical trial[9]

Study Objective:

To understand the efficacy and safety for the use of autologous PRP gel on refractory diabetic ulcers (DUs) when compared to suile ointment and wound dressings.

Study Design:

This study was a randomized control trial done in a single wound care center located in Suchan China between 2007 and 2009. Inclusion criteria for the 117 participants included age >18 with >1 diabetic ulcer, diabetic foot ulcers Wagner grade 2-3, ankle-brachial index >0.6, and platelet count >100,000. Participants were excluded for acute diabetic complications, such as diabetic ketoacidosis, active infections, systemic medications use within 3 weeks, chemotherapy/radiation use within 3 weeks, low compliance, and severe heart, lung, liver, or kidney disease. Participants were randomized into either the control group (n = 58) or treatment group (n = 59) and each received suile wound care dressings during the trial that were changed every 3 days, with the former receiving topical autologous PRP gel prior to wound dressing application. DFUs were a subgroup analysis done within the study and contained a majority of the participants (n = 103). Participants were divided into a treatment group (n = 48) or control group (n = 55).

Prior to enrollment, participants underwent a 12-week period of standard wound care and systemic treatment. Standard wound care consisted of cleaning, debridement, drainage, and dressing changes of DUs. Systemic therapies consisted of insulin treatment, infection control, nerve and vessel trophic therapies, hypertension and lipid control, and nutritional support. Following the 12-week pretrial treatment, ulcers were graded using the S(AD) SAD grading system which considers area, depth, sepsis, arteriopathy, and denervation classification. No significant differences between the treatment and control groups S(AD) SAD scores were found. Outcomes for this study consisted of primary wound healing and the timing in which the wound healed. Outcomes were assessed by taking photographs, using ImageJ, during each dressing change every 3 days over the 12-week trial period. Grades were then assigned to wound healing based on the percent reduction of the ulcer. Grade 1: 100% reduction (complete epithelial cover in the absence of discharge). Grade 2: 80-89% reduction. Grade 3: 40-79% reduction. Grade 4: 0-39% reduction. Grade 5: amputation or other aggressive orthopedic treatment provided.

Study Results:

Both total wound healing and time to heal for DFUs were significant in the PRP treatment group when compared to the control group with P-values of .031 and .017, respectively. 84.5% of the PRP treatment group had complete epithelial coverage of the wound area following the 12-week treatment course (Grade 1) compared to 67.3% of the control group. Average time to

heal for the was 36 days (about 1 month 5 and a half days) for the PRP treatment group and 45 days (about 1 and a half months) for the control group.

Study Critique:

The first strength of this study is that it is an RCT that has expanded upon other studies which have shown comparable results. Another strength is a large sample size (n=103) that shows no significant difference in demographics between the experimental and control group (P>.05), which was compared using the Mann-Whitney U test. Demographics included age, gender, wound location, wound grading, duration of the wound, and lab data such as platelet count, Hb creatine, hemoglobin, and albumin. Other strengths included equal treatment of experimental and control groups and the use of frequent image-guided comparisons of ulcers using S(AD) grading system which was interpreted by a double-blind researcher.

Considering this test has expanded upon previous studies and received the same results it may seem useful for practitioners, but a few considerations should be examined before being applied to practice. First, the large sample size was taken from a single wound care center which is based in Suchan China. This may limit the applicability to US populations and patients. Another consideration would be the absence of comorbidities. Severe cardiovascular, pulmonary, hepatic, and renal disease were included within the exclusion criteria of the study. Diabetes is often associated with these comorbidities and therefore this study cannot show how these other disease states may affect results and the usefulness of PRP gel in practice. Lastly would be the use of exclusion criteria for severe DFUs. Wagner grades 2-3 were considered for the study and excluded grades 4 and 5. Therefore, the usefulness of PRP gel in severe DFUs is inconclusive from this study.

Discussion

DFUs are a time-consuming and costly side effect of diabetes mellitus that can pose serious health risks to patients[8]. Many options are currently available for the treatment, but DFUs are still known to be difficult to treat and are often classified as non-healing wounds which can reduce the functionality of patients for extended periods of time even while using best practices in management[9]. This 3-study review aimed to explore the use of a cost-effective treatment that could increase the likelihood of overall healing as well as decrease the time in which DFUs would heal.

Each of the available studies assessed the usefulness of autologous PRP gel when compared to standard of care treatment and showed a significant increase in the overall healing of DFUs. Limitations to these studies could include long-term adverse events. Currently, Becaplermin, a non-autologous PRP gel approved for use on DFUs by the FDA, has had post-marketing reports of connective tissue disorders, malignancy, dermal ulcers, and local pain/erythema at the site of use and is also contraindicated in patients with a known malignancy[10]. These findings may be diminished with autologous gel use when compared to

non-autologous gels, but further studies should be performed to assess long-term complications following therapy as well as the use of autologous PRP gel in patients with a known malignancy.

Conclusion

The goal of this review is to examine the usefulness of Autologous PRP gel in decreasing the total wound healing and time to heal for DFUs. After analysis of the available literature, it has been concluded that Autologous PRP gel has been shown to be useful in the treatment of DFUs for both total healing and reduction in time to heal when compared to the current standard of care treatment which includes debridement, off-loading, maintaining a moist wound environment, management of infection, wound cleansing, and nutritional support. The recommendation to incorporate autologous PRP gel into practice is based on the minimal side effect profile that poses no increase in risk for patients, consistent results of studies that have been carried out on DFUs of varying sizes and severity and in a variety of settings and clinics, and low cost of production averaging less than 30$ for 6 sessions[11].

Citations

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Figures

Figure 1: Prisma Diagram