The Clinical Relevance of Treating Chronic Wounds with an Enhanced Near-Physiological Concentration of Platelet-Rich Plasma Gel

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ABSTRACT

OBJECTIVE: This study investigated clinical outcomes in chronic nonhealing wounds following the short-term use of an enhanced, near-physiological concentration of platelet-rich plasma (PRP) gel (AutoloGel System, Cytomedix, Inc, Gaithersburg, Maryland).

DESIGN: Study design was a large, observational case series using a multicenter registry database (all wounds included), which compared different populations within the database.

SETTING: Thirty-nine centers contributed to the registry, including long-term acute-care centers, outpatient clinics, a durable medical equipment company, a home health agency, and a long-term-care center.

PATIENTS: The target population included 285 chronic wounds (patient $n = 200$). Wound etiologies included diabetic, pressure, or venous ulcer; dehisced, surgical, or traumatic wound; and wounds of other etiologies.

INTERVENTION: Therapeutic, PRP gel is produced from patient blood utilizing autologous platelets and plasma that contribute growth factors, cytokines, and chemokines, in a fibrin matrix.

MAIN MEASURES: Area and volume of the wound and the linear total of undermining and sinus tracts/tunneling were calculated. Clinical relevance was determined by analyzing outcomes in wounds that responded to treatment.

MAIN RESULTS: A positive response occurred in 96.5% of wounds within 2.2 weeks with 2.8 treatments. In 86.3% of wounds, 47.5% area reduction occurred, and 90.5% of wounds had a 63.6% volume reduction. In 89.4% undermined and 85.7% of sinus tracts/tunneling wounds, 71.9% and 49.3% reductions in linear total were observed, respectively.

CONCLUSION: In chronic wounds recalcitrant to other treatments, utilization of PRP gel can restart the healing process. Rapid treatment response was observed in 275 of 285 wounds, and the magnitude of response was consistently high, with statistically significant outcomes reported for various subgroups.

KEYWORDS: platelet-rich plasma gel, PRP gel, chronic wounds and PRP, AutoloGel System, efficacy of PRP gel

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INTRODUCTION

Chronic wounds are "wounds that fail to progress through the normal, orderly, and timely sequence of repair; or wounds that pass through the repair process without restoring anatomic and functional results."[1] Others suggest that a wound that does not completely heal after 30 days of standard medical treatment is chronic.[2] When these wounds do not respond to standard wound care, the longevity of care alone becomes very expensive. Additional events such as infection, hospitalization, and amputation add significantly to the cost. Unfortunately, management of vulnerable patients with wounds recalcitrant to standard care is a common clinical dilemma.

When chronic wounds do not respond, a more aggressive, and sometimes more expensive, treatment is required to stimulate natural healing.[3,4] Despite the difference in cost between advanced therapies and basic dressings, advanced therapies will be more cost-effective if healing restarts.[4,5] Optimally, a short period of advanced therapy to stimulate healing can result in the transition of an intractable wound to a treatable one, which can then be treated with less expensive, standard care.

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Chronic wounds have been shown to stall in the inflammatory phase of wound healing and either do not heal or continue to deteriorate.[6,7] These stalled wounds have consistently high levels of matrix metalloproteinases and proinflammatory cytokines (ie, tumor necrosis factor α) and consistently low levels of tissue inhibitors of matrix metalloproteinases and growth factors (ie, platelet-derived growth factor).[6–10] Multiple growth factors, such as platelet-derived growth factor, insulinlike growth factor, vascular endothelial cell growth factor, platelet-derived angiogenic factor, and transforming growth factor β, can influence the inflammatory phase when released by platelets.[11] Platelets contain these growth factors, cytokines, and chemokines, which are all crucial in the early stages of wound healing. Harnessing factors from platelets and applying them to a nonhealing wound, as well as providing the anti-inflammatory properties of the plasma, could restart the healing process, moving the wound out of the inflammatory cycle into the proliferative phase of healing.

A platelet-rich plasma (PRP) gel formulation (AutoloGel System, Cytomedix, Inc, Gaithersburg, Maryland) utilizes autologous platelets and plasma extracted from a small amount of a patient's blood and processed via centrifugation. At the point of care, the platelet and plasma fraction is enhanced with ascorbic acid and then mixed with calcified thrombin in a standardized ratio to activate the platelets and form a gel containing a fibrin matrix. Unlike other highly concentrated PRP products, this enhanced autologous PRP gel is applied topically at near-physiological levels (1.3× baseline platelet concentration).[12] This standardized PRP gel technique was cleared by the Food and Drug Administration in 2007 and can be used on exuding wounds, such as leg ulcers, pressure ulcers (PrUs), and diabetic ulcers, as well as for the management of mechanically or surgically debrided wounds.[13] A prospective, randomized, controlled, double-blind, multicenter study of 72 diabetic foot ulcer patients demonstrated that common-size ulcers treated with PRP gel healed significantly more (81.3% vs 42.1%) than their control gel counterparts (P = .036).[14]

Previously, in a multicenter case series, 49 patients with 65 nonhealing chronic wounds from long-term acute-care (LTAC) hospitals or outpatient wound clinics were treated with the PRP gel.[15] Most patients had poor albumin, hematocrit, and/or hemoglobin levels. Despite this, in 2.8 weeks with just 3.2 PRP gel treatments, in 58 wounds (89.2%), the volume decreased 62%. In 55 wounds (84.6%), the area decreased 50.9%. In addition, in 23 wounds with undermining and/or sinus tracts/tunneling, 100% of wounds reduced in linear total by 77.8% and 45.8%, respectively.

The purpose of the current study was to perform a larger, more detailed analysis to investigate the clinical outcomes following the short-term therapeutic application of PRP gel in chronic nonhealing wounds. This study is a continuation and expansion of the aforementioned initial 65 wound multicenter case series.[15] Because of the objectivity of complete healing, randomized controlled trials (RCTs) in wounds commonly evaluate efficacy of products to achieve complete healing. However, in clinical practice, improvements in wound healing are a more realistic short-term goal, especially in the chronic wound population.

This large case series assesses the clinical relevance of the PRP gel treatment in chronic wounds. The hypothesis was that the application of an enhanced near-physiological concentration of PRP gel would provide rapid, consistent, and therefore, predictable outcomes in chronic wounds in all populations. In this study, clinical relevance is defined as the potential of a therapy to provide positive results in a group of patients by examining the group that responded positively, the magnitude of the response, time to respond, and the number of treatments to achieve the response.[16] Clinical relevance is determined by analyzing the group that responded positively to the PRP gel with a decrease in wound area, volume, or length of undermining, sinus tracts, or tunneling. In the initial multicenter 65-wound case series, clinical relevance showed improvements in 97% of PRP gel–treated wounds with a mean reduction of 45.8% to 77.8% (parameters of sinus tracts/tunneling, wound area, volume, and/or undermining) within 2.8 weeks following 3.2 PRP gel applications. For this study, data analysis was performed to determine the clinical relevance of the outcomes by analyzing the group that responded positively to the treatment, the consistency of results by comparison of subgroups, and to compare the established outcome benchmarks with other studies in the literature.

MATERIALS AND METHODS

Treatment Registry Database

A treatment registry database of use and outcomes for patients receiving a standardized PRP gel (AutoloGel System) is maintained by Cytomedix, Inc. Clinicians using PRP gel voluntarily submit patient wound and treatment information to the registry. No other PRP gels are included in the registry. No other restrictions are applied on the data submitted, nor is submission required as part of the product usage. Missing parameters are permitted because some data points, such as laboratory values, are not always gathered in certain healthcare settings. Wounds that improved, showed no change, or worsened are included. If a patient had more than 1 wound treated with PRP gel, the wounds were numbered consecutively for identification, and all wounds were included. Patient privacy was protected by deidentification of personal health information patient data in compliance with the Health Insurance Portability and Accountability Act regulations for studying aggregate data for research purposes, per the National Institutes of Health Authorization for Research Uses and Disclosures. The Health Insurance Portability and Accountability Act Privacy Rule does not require internal review board approval and informed consents as the data were gathered by the clinicians during normal clinical care, and all protected health information about the patients was deidentified prior to analysis.[17]

The multicenter registry database consisted of a general chronic wound population of 285 wounds (n = 200 patients). Thirty-nine centers contributed to the registry: 22 LTAC centers had 161 wounds, 14 outpatient clinics had 80 wounds, 1 durable medical equipment (DME) company had 38 wounds, 1 home health agency had 4 wounds, and 1 long-term-care center had 2 wounds. Previously, 65 registry nonhealing wounds (n = 49 patients) treated with PRP gel between December 15, 2008, and June 18, 2009, were analyzed.[15] This study analyzed the subsequent 220 consecutive wounds (n = 151 patients) that were treated with PRP gel between June 19, 2009, and September 19, 2010, both in conjunction with the initial 65 wounds and as a separate group, and compared outcomes between subgroups defined by wound type, Medicare and non-Medicare beneficiaries, and patients who had 2.5 g/dL of albumin or less and 10.5 g/dL hemoglobin or less versus patients who had higher values of these clinical indicators.

Indications for use of PRP gel include (1) an open, cutaneous wound that has failed to respond to standard wound care per each facility protocol (eg, appropriate offloading, adequate compression, cleaning, debridement, appropriate dressings) during the pretreatment phase; (2) the wound has a mostly clean wound bed just before product application; and (3) wound(s) did not show any clinical signs and symptoms of active infection. Contraindications are (1) malignancy in the wound bed, (2) current use of chemotherapy, or (3) allergy to bovine products. All 285 wounds were verified to be appropriate for PRP gel use.

Treatment Procedure

Clinicians verbally described the procedures to each patient. Patients were positioned comfortably, and dressings were removed. Prior to PRP gel treatments, the wound bed was cleaned thoroughly using sharp debridement (aggressive or conservative), mechanical debridement, cleansing with a wound cleanser and gauze, cleansing with normal saline, or ultrasound. Wound measurements were taken by the treating clinician and recorded, and a moisture barrier preparation was applied to intact periwound skin.

Clinicians were trained previously by the manufacturer on how to prepare and handle the PRP gel in accordance with the instructions for use, which were included within the product kit and described in part in the Introduction. Approximately 20 mL of each patient's blood was spun for 60 seconds in a specially designed centrifuge calibrated to maximize the PRP. Only the PRP fraction is transferred into a mixing chamber and reagents added as described earlier. Immediately after the PRP liquid converted to a clear gelatinous consistency (usually within 15–30 seconds), the gel was applied topically to the wound and covered with a nonabsorbent contact layer followed by a moisture vapor–permeable film dressing and a secondary absorbent dressing to manage any strikethrough. Offloading and compression devices/wraps were used as appropriate. Platelet-rich plasma gel was typically applied 1 or 2 times per week, depending on the wound characteristics and the physician's or treating clinician's judgment.

Wound Type

Wound etiology was documented in the database for each entry. Seven wound types were identified: diabetic, pressure, or venous ulcer; dehisced, surgical, or traumatic wounds; and wounds of other etiology. Because of the small numbers of arterial ulcers and wounds of other etiology, these were combined to form a group of other wounds.

Wound Measurements

Treating clinicians trained on the measurement technique described obtained all measurements. Cotton-tipped applicators were used to probe, and disposable paper rulers with centimeter markings were used to measure the length, width, and depth of the visible wound, as well as undermining and sinus tracts and/or tunneling (ST/T). Measurements were taken and recorded prior to each gel application, before each dressing change, and at the time that PRP gel treatments were discontinued.

The length and width of the wound opening were measured using the standard "clock face" method described.[18] Length was 12:00 to 6:00 with 12:00 toward the head, and width was 9:00 to 3:00. Depth measurement was taken from the deepest point of the wound bed to the level of usual skin surface and at a 90-degree angle to skin surface. In wounds with undermining or ST/T, a clock face was superimposed over the wound bed, and measurements of undermining at each of 4 points (12:00, 3:00, 6:00, and 9:00) were recorded. These measurements were totaled to achieve the linear total for undermining, which was used in data analysis. Locations of ST/T were also measured using the same 4 points. The measurements of the ST/T were also totaled to obtain the linear total for ST/T for data analysis.

Using the common calculation of area (length × width) overestimates wound sizes that are more commonly seen in a clinical population. Therefore, the area was calculated as an ellipse using the formula: length × width × 0.7854, to ensure a more accurate area measurement for all wound types. When volume was calculated, the elliptical formula was multiplied by depth. Calculating the wound size using ellipse formulas has been used in a database of more than 120,000 wounds and in RCTs.[19,20]

Assessment Times

Assessment times were classified by treatment periods. Data for length, width, and depth were available at baseline when a prior treatment was discontinued and PRP gel was initiated (T0), first post–PRP gel treatment point (T1), second post–PRP gel treatment point (T2), and third post–PRP gel treatment point (T3). The number of days between time assessment points varied by wound. Because a considerable amount of the data for the second post–PRP gel treatment point (T2) was not provided, this assessment period was not used in the analysis. Also, for some wounds, T1 equaled T3 when only 1 measurement after baseline was available.

Data Transformation

Baseline variables for wound depth, volume, and area were set at 100%, and all measurements at other assessment times were calculated as percentages changed in relation to the initial depth or area to this time point.

Statistical Analysis

Wound measurements (area, depth, volume, undermining, and ST/T) were the primary variables used in the analysis of all wounds and all clinically responding wounds. Secondary variables (wound etiology and duration, laboratory values, patient age, and Medicare/non-Medicare payer) were also analyzed to compare outcomes between registry subgroups as a secondary analysis to determine the consistency of outcomes. The percentage of area, depth, or volume change from baseline to the end of the treatment period was analyzed for significance. The analyses required the use of various statistical methods and models as appropriate. These included paired *t* test, 1-way analysis of variance (ANOVA), χ^2, Fisher exact test, Kaplan-Meier (KM) analysis, and general linear modeling (GLM). Statistical analysis was performed using PASW 19 (SPSS, Inc, Chicago, Illinois).

RESULTS

Demographics

Two hundred patients with 285 wounds were in the registry database. Age was available for 143 patients (71.9%); the mean age was 59.6 (SD, 16.65) years with a range of 19 to 96 years. Data for insurance were available for 51.3% of patients, of whom 86% had Medicare coverage. In regard to healthcare setting (n = 285 wounds), 56.5% (n = 161) were treated in LTAC facilities, 28.1% (n = 80) were in outpatient clinics, and 15.4% (n = 44) were being seen by the DME company nurse or had home healthcare. Of the 285 wounds in the study, nearly half of all wounds (142 of 285) were PrUs (Table 1). Mean age of the wounds prior to PRP gel treatment was 337 (SD, 545.9) days (n = 179) with a median age of 154 days or 22 weeks.

Mean baseline area was 26.0 (SD, 50.40) cm^2 with a range of 0.03 to 530.2 cm^2. Mean baseline depth was 1.40 (SD, 1.54) cm with a range of 0.09 to 9.0 cm. Diabetic ulcers, traumatic wounds, and other wound types were relatively small in baseline area compared with other categories. The baseline depths of venous ulcers and other wound types were shallower than other study wounds.

Clinical Relevance

Of the 285 wounds, in a mean of 2.2 weeks (range: 0.4–11) with 2.8 PRP gel treatments (range: 1–7), 86.3% of the wounds responded with a reduction of 47.5% in area, and 90.5% of the wounds responded with a reduction of 63.6% in volume (Table 2A). Sixty-three wounds (22.9%) had undermining. In a mean of 1.8 weeks (range: 0.4–9) with 2.5 PRP gel treatments (range: 1–8), 89.4% of the wounds responded with a 71.9% reduction in undermining (Table 2B). Twenty-eight wounds (10.2%) had ST/T. In a mean of 1.8 weeks (range: 0.4–3.1) with 2.5 PRP gel treatments (range: 1–4), 85.7% of these wounds responded with a 49.3% reduction in ST/T (Table 2B). The response per wound etiology per measured dimension is depicted in Table 2.

Of the 285 wounds, only 10 wounds failed to respond as measured by reduction in area, volume, undermining, or ST/T reduction. The high rate of response (96.5%) corresponds with the 97% response rate in the initial 65-wound data set. Thus, the following analysis on these 275 clinically relevant responders further supports the magnitude of the response.

Table 1.

FREQUENCIES OF WOUND TYPES

Wound Type	285-Wound Population	65-Wound Population	220-Wound Population
Pressure ulcer	49.8 (142)	32.2 (21)	55 (121)
Diabetic ulcer	14.4 (41)	21.5 (14)	12.3 (27)
Venous ulcer	11.2 (32)	24.6 (16)	7.3 (16)
Dehisced wound	8.4 (24)	7.7 (5)	8.6 (19)
Surgical wound	9.5 (27)	9.2 (6)[a]	9.5 (21)
Traumatic wound	3.9 (11)	See above	5 (11)
Other wound type	2.8 (8)	4.6 (3)	2.3 (5)

Values are presented as % (n).

[a]In the study of Frykberg et al,[15] the surgical and trauma wounds were combined.

Table 2.

CLINICAL RELEVANCE, PROPORTION OF WOUNDS RESPONDING TO TREATMENT, AMOUNT OF THE RESPONSE, TREATMENT DURATION, AND NUMBER OF PRP TREATMENTS

A	No. of Patients	No. of Wounds	Previous Wound Duration, wks	Area Reduction: Baseline Area, cm^2	Area Reduction: Proportion of Wounds, %	Area Reduction: Mean Reduction, % (SD)	Volume Reduction: Baseline Volume, cm^3	Volume Reduction: Proportion of Wounds, %	Volume Reduction: Mean Reduction % (SD)	No. of Weeks to Outcome	No. of Treatments to Outcome
All wound etiologies	200	285	48.2	26.0	86.3	47.5 (31.5)	57.70	90.5	63.6 (27.9)	2.2	2.8
Arterial	2	2	20.0	17.2	50.0	12.5	6.30	100.0	44.9	2.9	1.5
Dehiscence	21	24	9.0	27.5	66.7	53 (35.2)	77.40	87.5	68.5 (24.8)	1.7	2.2
Diabetes	32	41	37.9	9.7	90.2	60.2 (33.4)	12.60	87.9	74 (24.5)	3.4	4.0
Pressure ulcers	89	142	58.7	22.0	88.0	46.8 (31.9)	49.50	90.8	61 (28.7)	2.0	2.6
Sickle cell	1	1	20.0	8.7	100.0	65.2	1.70	100.0	82.6	3.3	3.0
Spinal cord injury	20	37	72.8	18.3	83.8	55.9 (26.9)	37.70	91.9	68.6 (24.9)	2.8	3.2
Surgical/trauma	30	38	18.5	60.9	86.8	36.6 (25.1)	169.90	89.5	63.3 (27.6)	1.8	2.8
Venous	22	32	70.0	26.3	87.5	40.2 (26.6)	17.60	93.8	56.6 (29.5)	2.1	2.4
Other	3	5	37.6	8.5	100.0	69.2	1.40	100.0	85.8	3.4	3.6

B	Undermining Reduction: No. of Wounds	Undermining Reduction: Proportion of Wounds, %	Undermining Reduction: Mean Reduction, % (SD)	Undermining Reduction: No. of Weeks to Outcome	Undermining Reduction: No. of Treatments to Outcome	Sinus Tract/Tunneling Reduction: No. of Wounds	Sinus Tract/Tunneling Reduction: Proportion of Wounds, %	Sinus Tract/Tunneling Reduction: Mean Reduction, % (SD)	Sinus Tract/Tunneling Reduction: No. of Weeks to Outcome	Sinus Tract/Tunneling Reduction: No. of Treatments to Outcome
All wound etiologies	66	89.4	71.9 (33.2)	2.2	2.8	28	85.7	49.3 (35.9)	1.8	2.5
Arterial	1	100.0	100.0	1.0	1.0	0				
Dehiscence	3	100.0	48.4 (23.9)	1.6	2.3	2	50.0	6.7	1.0	1.5
Diabetes	5	100.0	77.8 (31)	4.1	3.8	3	100.0	80 (34.6)	2.5	2.3
Pressure ulcers	44	90.9	66.5 (30.3)	2.3	2.9	17	94.1	39 (32.3)	1.6	2.4
Sickle cell	0					0				
Spinal cord injury	7	85.7	59.6 (37)	2.0	2.7	3	100.0	26.1 (6.7)	1.5	2.3
Surgical/trauma	12	75.0	94.5 (41.4)	1.5	2.5	6	66.7	78 (25.9)	2.2	3.2
Venous	1	100.0	100.0	1.0	1.0	0				
Other	0					0				

Area, Depth, and Volume

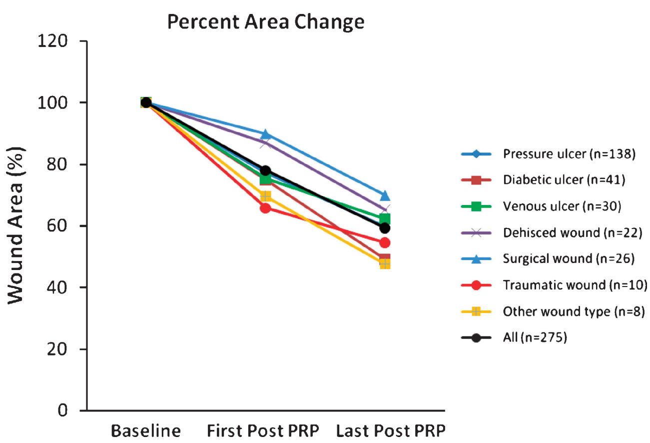
When percent change of area and depth between baseline and final PRP gel posttreatment assessment were compared, the mean wound area was reduced by 40.8% (SD, 36.16), and mean wound depth by 38.5% (SD, 47.17) (Figures 1 and 2). Mean reduction in area, volume, and depth for each wound type is shown. For all wounds, the difference in terms of changes of area and depth on a percentage basis between baseline and the third treatment assessment point was statistically significant ($P = 7.4 \times 10^{-51}$ and 2.4×10^{-32}, respectively; paired-sample *t* test).

Undermining and Sinus Tracts/Tunneling

In wounds with undermining, the mean difference of linear undermining values between baseline and last treatment period was 2.4 cm (baseline mean, 4.6 [SD, 3.56]; T3 mean, 2.1 [SD, 3.01]; $P = 1.4 \times 10^{-10}$, paired *t* test on log-transformed values). Pressure ulcers had the highest amount of undermining (29%), whereas venous ulcers had the lowest amount (3%) ($P = .003$; Fisher exact test). The decrease in undermining from baseline to the last treatment assessment was similar between all wound types (1-way ANOVA).

In wounds with ST/T, the mean difference of linear ST/T values between baseline and last treatment period was 2.3 cm (baseline mean, 6.1 [SD, 4.26]; T3 mean, 3.8 [SD, 3.50]; $P = 0.003$, paired *t* test on log-transformed values). Venous ulcers had the lowest frequency or percentage of ST/T (0%), whereas PrUs had the highest (14%). The amount of ST/T in diabetic ulcers and that of other wounds were 7% and 9%, respectively ($P = .10$, Fisher exact test). Only 7 wounds (2.5%) had both undermining and ST/T.

Figure 1.
CHANGE IN PERCENT AREA BY WOUND TYPE



Posttreatment Healing Trajectory

An area reduction of 50% in 4 weeks has been documented as being clinically significant.[21,22] In a mean of 2.2 weeks, 96 wounds (34.9%) achieved a reduction in area of 50% or greater, whereas 113 wounds (41.1%) achieved a depth reduction of 50% or greater. Some wound types achieved a higher percentage of wound area reduction than others, and this was statistically significant (P = .016 [χ^2]: 33% PrUs, 56% diabetic ulcers, 30% venous ulcers, and 27% other wound types). Likewise, for a depth reduction of 50% or greater, some wound types achieved a higher rate of reduction: 38% PrUs, 39% diabetic ulcers, 40% venous ulcers, and 48% other wound types; however, this was not significant between wound types. Although healing was not anticipated in the short 2.2 weeks of follow-up of these wounds, of interest, 26 wounds (9.5%) healed completely.

Logistic Regression Model

An attempt to predict partial healing was made by developing a logistic regression model for wounds that reached a reduction of 50% or greater in area by the last assessment time. The final model utilized the enter method (1 block: log initial area + log initial depth + provider simplified). Four outliers were identified and removed from the analysis using standardized residuals less than 2.58. The final model R^2 (Nagelkerke) was 0.422 with an omnibus model P value of 1.9×10^{-20}.

The odds ratios for log initial area and depth were 0.245 and 0.291, respectively, indicating that for every increase of initial area or depth by a factor of 10, there is a decrease by approximately a factor of 4.1 and 3.4, respectively, in terms of the probability of a wound decreasing in area by 50% or greater. In terms of providers using home health and DME nurse as the reference category, being in an LTAC facility slightly increases the odds of a reduction in area by 50% or greater (1.50; not significant), but being an outpatient significantly increased the odds of a reduction in area by 50% or greater (3.9).

Model sensitivity (true positive rate) was 59.1%; specificity (true negative rate), 84.8%; false-positive rate, 32.9%; and false-negative rate, 20.1%, using a cutoff of 0.5. It was not possible to create a logistic regression model for reduction in depth by 50% or greater with available data.

KM Analysis

The study population had an average wound duration of 337 days at baseline prior to initiating PRP gel treatment. A KM analysis was utilized to analyze the number of wounds reduced in area or depth by 50% or greater during the PRP gel treatment time. The steeper the curve, the better the healing trajectory, meaning that healing is progressing more quickly in a shorter period. The baseline wound area was categorized into 3 levels: small (0–5 cm^2), medium (5.01–20 cm^2), and large (≥20.01 cm^2). The baseline wound depth was categorized into 3 levels: shallow (0.1–0.4 cm), medium (0.41–1.5 cm), and deep (≥1.5 cm). Kaplan-Meier plots were then constructed with all levels of the baseline area factor and baseline depth factor and tested between each level.

Overall, for small wounds, a reduction of 50% or greater in wound area showed 62 improvements (59%), whereas for medium and large wounds, 27 (31%) and 7 wounds (8%) improved, respectively. These differences were significant when tested by χ^2 ($P = 2.4 \times 10^{-12}$). The mean time for a reduction of

Figure 2.
CHANGE IN PERCENT DEPTH BY WOUND TYPE

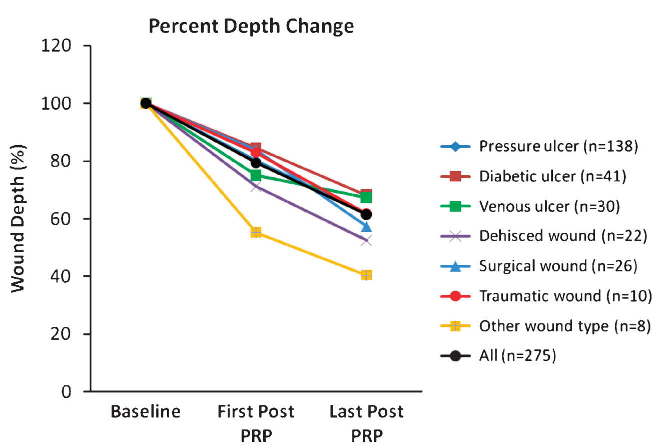
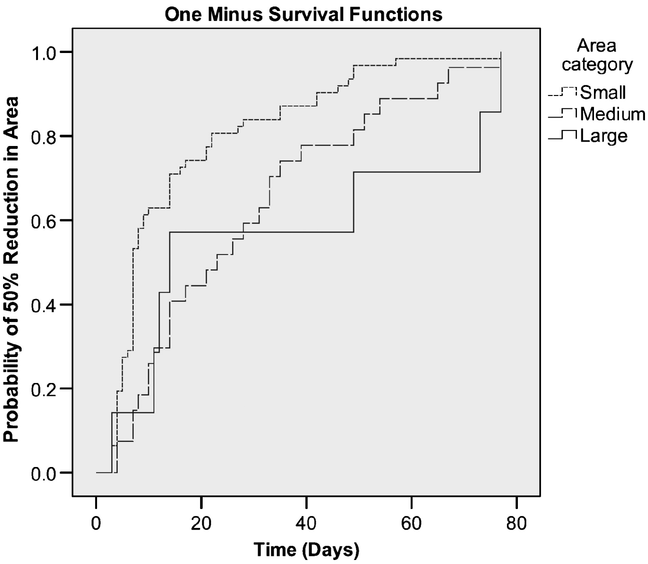


Figure 3.

KAPLAN-MEIER ANALYSIS OF REDUCTION IN AREA BY 50% OR GREATER



50% or greater by baseline wound area size was 15.4 days for small wounds (95% confidence interval [CI], 11.38–19.46), with a median of 7 days; 27.9 days for medium (95% CI, 19.98–35.72), with a median of 23 days; and 34.1 days for large (95% CI, 10.78–57.51), with a median of 14 days (Figure 3). Differences were significant between small and medium wounds ($P = .006$, log rank, Mantel-Cox; $P = .001$, Breslow); significant between small and large wounds depending on the test used ($P = .043$, log rank, Mantel-Cox; $P = .103$, Breslow); and not significant between medium and large wounds.

A 50% reduction in wound depth or greater for shallow wounds showed that 43 improved (44%), whereas for medium and large wounds, 46 (53%) and 24 wounds (27%) improved, respectively. These differences were significant when tested by χ^2 ($P = .001$). The mean time for a reduction of 50% or greater by baseline wound depth was 12.4 days for shallow wounds (95% CI, 8.32–16.52), with a median of 7 days; 15.5 days for medium (95% CI, 11.01–20.04), with a median of 10 days; and 16.1 days for deep (95% CI, 9.34–22.83), with a median of 11 days (Figure 4). Differences between the 3 depth classifications were not statistically significant.

General Linear Model

To further evaluate the data, 2 types of GLM models were constructed based on the dependent variable: percent reduction in area and area reduction per day (rate of healing).

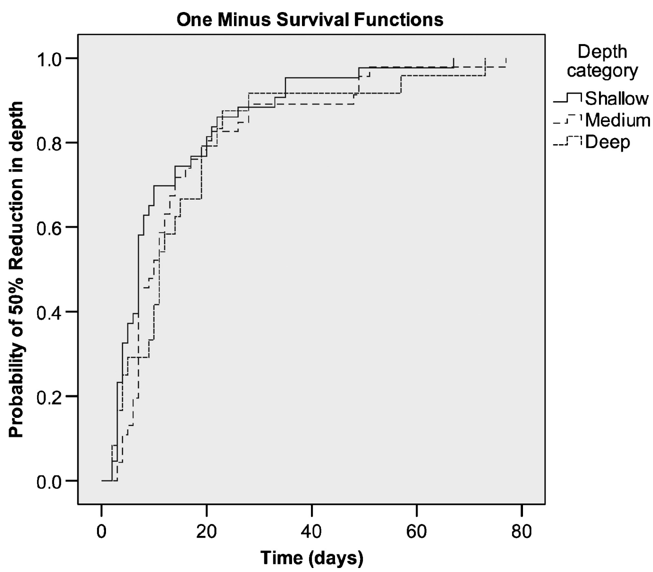
The percent reduction in area model included log depth at baseline (covariate), area (3 levels: small, medium, and large), and healthcare provider (simplified: LTAC, outpatient, and home health/DME nurse) ($R^2 = 0.278$, adjusted $R^2 = 0.264$). Lack of fit was not significant. The percent reduction in area for all wounds compared with baseline area was statistically significant: $P = 6.7 \times 10^{-10}$. The mean percentage reduction in area varied considerably by wound size, with the largest reduction for small wounds (61.3%; SE = 3.183) and similar size reduction for medium (35.0%; SE = 3.359) and large wounds (33.3%; SE = 3.901) after adjusting for baseline depth and healthcare provider. The differences between small and medium wounds and small and large wounds were significant ($P = 4.9 \times 10^{-8}$ and $P = 7.9 \times 10^{-8}$, respectively).

There are some limitations to the model, although they are not expected to impact the conclusions greatly. First, the homogeneity of variance was violated slightly between the covariate and area category ($P = .044$). Second, Levene's test of equality of the error variances (across factor levels) was significant: $P = .002$.

The percent reduction in depth using GLM to compare all wounds to the log baseline depth was significant, $P = .004$. To compare percent reduction in depth between groups, a 1-way ANOVA was used and showed that the groups did not differ significantly. The means were as follows: shallow, 37.0%; medium, 45.4%; deep, 33.6%.

Figure 4.

KAPLAN-MEIER ANALYSIS OF REDUCTION IN DEPTH BY 50% OR GREATER



The percent area reduction per day (rate of healing) model included area (3 levels: small, medium, and large), wound type (simplified: PrU, diabetic ulcer, venous ulcer, and other wound type), and the interaction between the 2 factors (R^2 = 0.385, adjusted R^2 = 0.359). Three cases were removed as standardized residuals were greater than ±2.58. The rate of healing (percent area reduction per day) for all wounds compared with baseline area was statistically significant: $P = 9.8 \times 10^{-20}$. The mean area reduction per day varied considerably by wound size, with the largest reduction for large wounds (1.59 cm^2/d; SE = 0.123), followed by medium (0.189 cm^2/d; SE = 0.113) and small (0.068 cm^2/d; SE = 0.101) after adjustment for wound type. The differences between small and medium wounds and small and large wounds were significant ($P = 1.0 \times 10^{-14}$ and $P = 1.0 \times 10^{-250}$, respectively). There is a limitation to the model in that Levene's test of equality of the error variances (across factor levels) was extremely significant ($P = 1.7 \times 10^{-27}$). However, although this is unlikely to change the qualitative conclusions, it is likely to heavily impact the quantitative results.

Subgroup Outcomes

Wound data were subdivided into subgroups and compared by using either a χ^2 or Fisher exact test where appropriate. Full Bonferroni corrections (α level) were calculated for each group.

The 285-wound study population is made up of the 65 wounds originally reported by Frykberg et al[15] and the subsequent 220 wounds in this registry. As shown in Table 1, each study population is not identical in wound etiology proportion, and thus, the outcomes may differ. When comparing the initial 65 wounds to the 220 wounds, there was no statistically significant difference between percentage of responders, area, volume, undermining, ST/T reduction, weeks to outcome, or number of treatments, indicating the consistent outcomes even in the larger data set (Table 3A and B). Given that no significant differences were detected for any variable between the 2 clinical populations, the chronic wound outcomes following PRP gel treatments appear to be consistent in the response. Because the study populations are not identical in etiology proportion, the consistency in outcomes is promising.

Clinically, patients with albumin levels of 2.5 g/dL or less and hemoglobin levels of 10.5 g/dL or less are considered to be very ill. Two subgroups, those with albumin levels of 2.5 g/dL or less and hemoglobin levels 10.5 g/dL or less versus those with albumin levels of greater than 2.5 g/dL and hemoglobin levels of greater than 10.5 g/dL, were compared for differences in clinical outcomes. When comparing these groups, there was no significant difference between percentage of responders, area or volume reduction, weeks to outcome, or number of treatments (Table 3A and B). There were not enough data values to determine differences in undermining or ST/T wound outcomes between the 2 groups (Table 3B). Given that no significant differences were detected for area or volume reduction between the 2 clinical populations, the chronic wound outcomes in the wounds with low laboratory values following PRP gel treatments appear to be consistent in the response similar to their healthy counterparts.

Medicare and non-Medicare patient subgroups were also analyzed because Medicare patients tend to be older adults, and age is a risk factor for slow wound healing. When comparing these groups, there were no significant differences between percentage of responders, area, volume, undermining, ST/T reduction, weeks to outcome, or number of treatments (Table 3A and B). Given that no significant differences were detected in any variable between the 2 insurance populations, the chronic wound outcomes following PRP gel treatments appear to be consistent in the response despite possible environmental and age-related factors.

DISCUSSION

In wound care, it has been well documented that not all wounds will respond to standard wound care.[23,24] The chronic wound, which is recalcitrant to basic wound care, will languish or deteriorate unless a clinical intervention or alternative care is provided.[23,24] Similar to other studies in the literature, the wound population in this study had a previous wound duration average of 337 days.[25] If these wounds were going to heal spontaneously, they would have done so prior to the application of PRP gel. The fact that 96.5% (n = 275) of wounds responded to PRP gel with a mean size reduction of 47.5% or greater in 2.2 weeks is highly encouraging. This response rate to PRP gel treatment is similar to those previously reported as 97%, 97.8% (as reported by some of this article's authors in work submitted for publication), and 100%, even though the study populations were different in each study.[14,15]

There were highly statistically significant differences in percent area and depth reduction between the baseline and the last assessment point during treatment. Moreover, the characteristics of the wounds and the patients and minimal exclusions mean that these wounds are representative of real-world wound care populations. In addition, for those wounds that had undermining or ST/T, PRP gel treatment was statistically significant and clinically beneficial in reducing the linear dimensions rapidly (<2.2 weeks). In this short period, clinically significant area and depth reductions (≥50%) were reached in 35% and 41% of chronic wounds. Of particular clinical interest was the KM analysis demonstrating that healing trajectory occurred fairly rapidly with a median of 7 to 23 days, depending on original wound size. This suggests that for wounds in which area or depth is reduced by 50%, the majority were quick to begin

Table 3.

COMPARISON BETWEEN REGISTRY SUBGROUPS

A	No. of Wounds	Proportion of Wounds with Area Reduction, %	Mean Area Reduction, %	No. of Wounds with Volume Reduction	Proportion of Wounds with Volume Reduction, %	Mean Volume Reduction, %	No. of Weeks to Outcome	No. of Treatments to Outcome
65-Wound Data	55	84.6	50.9	58	89.2	62.0	2.8	3.2
220-Wound Data	191	86.6	46.5	201	91.4	63.9	2.1	2.7
α with Bonferroni = .0125		*P* = .65			*P* = .60			
Albumin ≤2.5 and hemoglobin ≤10.5	32	78.0	42.8	36	87.8	58.5	1.3	2.1
Albumin >2.5 and hemoglobin >10.5	33	86.8	44.6	36	94.7	65.4	1.8	2.8
α with Bonferroni = .025		*P* = .23			*P* = .20			
Medicare patients	111	86.0	46.9	116	89.9	64.6	2.2	2.8
Non-Medicare patients	135	86.5	48.0	142	91.0	62.9	2.3	2.8
α with Bonferroni = .0125		*P* = 1.0			*P* = .75			

B	No. of Wounds with Undermining	Proportion of Wounds with Undermining Reduction, %	Mean Undermining Reduction, %	No. of Weeks to Undermining Reduction	No. of Treatments to Undermining Reduction	No. of Wounds with ST/T Reduction	Proportion of Wounds With ST/T Reduction, %	Mean ST/T Reduction, %	No. of Weeks to ST/T Reduction	No. of Treatments to ST/T Reduction
65-Wound data	23	100.0	77.8	2.8	3.2	10	100.0	45.8	2.8	3.2
2010 Wound data	36	83.7	68.1	2.3	2.8	15	78.9	48.8	1.7	2.6
α with Bonferroni = .0125		*P* = .086					*P* = .27			
Albumin ≤2.5 and hemoglobin ≤10.5	8	80.0	70.4	1.1	2.1	3	75.0	27.4	1.3	2.8
Albumin >2.5 and hemoglobin >10.5	0	n\a	n\a	n\a	n\a	n\a	n\a	n\a	n\a	n\a
Medicare patients	19	82.6	65.6	2.4	3.2	8	88.9	61.6	1.6	2.4
Non-Medicare patients	40	93.0	74.9	2.1	2.7	16	84.2	43.1	1.9	2.5
α with Bonferroni = .0125		*P* = .23					*P* = 1.0			

healing again. The deeper wounds healed at the same rate as the more shallow wounds over time, whereas the wounds with larger areas healed quickly, but took more time in healing than the smaller wounds. It should be noted that published literature often uses a surrogate end point of 50% healing at 4 weeks. In this study, however, the wounds that achieved 50% healing occurred in a mean of 2.2 weeks.

Although percentage healing rate decreased with increased wound size, absolute healing rates increased enormously with initial wound size as shown in the GLM results. Analysis showed that the rate of healing occurred equally in all wound etiologies. In other words, the PRP gel therapy appeared to stimulate healing regardless of wound type. Every wound uses activated platelets and numerous growth factors upon injury. Platelet-rich plasma gel contains many of the same factors imperative to the healing process of all wounds and may be the key to transforming a chronic wound into a healing one. This may also explain, in part, why the clinical response is almost identical despite different study populations.

When treating complex wounds, both the patient and the healthcare professional want to use a therapy that will provide positive, consistent, and rapid results. Clinical variables of wound area, volume, depth, undermining, and ST/T were further scrutinized to determine if differences could be detected between key subgroups. Wound healing outcomes were consistent between healthy and clinically ill patients as well as in the Medicare versus non-Medicare subgroups. The consistent healing response in these subgroups of real-world patients would seem to indicate that similar results could be expected outside this study. Furthermore, the consistency in healing between the initial wounds (n = 65) and the subsequent registry wounds (n = 220) was similar, even though the etiologies of the wounds were different and the groups were treated during different times. In this study, the fact that statistical significance occurred for all wound types from baseline to the final assessment indicates that the PRP gel provides consistent reduction in area, volume, undermining, and ST/T in the majority of wounds. Being able to expect consistent outcomes with patients is important in daily clinical practice.

The reduction in percent of area based on a clinically significant reduction of 50% in a logistic regression model showed that the larger area and depth initial values decreased the probability of the wound decreasing by 50% or greater during the short time observed. This observation has been reported previously in the literature and is a reasonable expectation.[26,27] The model also showed that outpatient care setting significantly increased the likelihood that the wound would decrease in area by 50% or greater. This may be because the patients have fewer comorbid conditions than their LTAC counterparts.

In RCTs and some observational studies, complete wound healing is the criterion standard to measure the effectiveness of a treatment. However, it is impractical to use a single therapy to achieve complete healing in real-world chronic wounds. Chronic wound care often requires multiple overlapping treatments in order to close a wound. For example, negative-pressure wound therapy is often used before surgical closure with a flap or application of a skin graft.[28,29] It would be useful to know if a therapy could reliably reduce a wound by a specified amount, especially if the wound was chronic. In diabetic foot ulcers, several studies have investigated percent reduction in wound size and confirmed that reduction is an early predictor of treatment outcome. One study concluded that protocols of care should be reevaluated if a 50% reduction in wound size has not occurred within 4 weeks.[30] A similar conclusion was reached in an analysis of a cohort of 704 diabetic patients.[31] In addition, earlier work from an RCT in which subjects had relatively few comorbidities showed a 53% reduction in wound area at 4 weeks led to 82% of wounds completely healed.[32] In our study, a 60% reduction in wound area within 3.4 weeks was attained by 90% of the diabetic wounds following PRP gel therapy. This wound trajectory suggests that PRP-treated wounds would likely go on to complete healing. Of further interest, the wounds in our study were more than 6 times larger in size (17.2 vs 2.8 cm^2) compared with those in the cited study,[32] and they had not responded to standard wound care for an average of 38 weeks prior to therapy. Similarly, a study observed that PrUs in patients who were 60 to 70 years old, who had a good nutritional status at baseline and whose ulcers reduced at least 39% in size after 2 weeks, were found to heal much more expediently.[33] Our results showed a 47% reduction in size within 2 weeks by 88% of PrUs (clinical responders). Finally, several studies have laid the groundwork for predicting wound healing in venous ulcers at early healing stages, with a healing trajectory at 4 weeks having the best reliability.[34–36] In this study, at 2 weeks, 87.5% of venous ulcers (clinical responders) were reduced an average of 40% in area, which is higher than that reported for compression alone in much smaller ulcers.[37]

This study's strengths include a relatively large sample size and accurate measurement of wound parameters. This study's limitations include missing data for certain variables and lack of specific comorbid patient factors that could be used to explain some of the results, but did not negatively affect the study analyses. The study outcomes in these complicated recalcitrant wounds repeatedly demonstrated the wounds began healing following this enhanced, near-physiological PRP gel application. Using a clinical relevance analysis helps the clinician identify the likelihood of a positive response and the magnitude of the response from a treatment modality.

CONCLUSION

This study demonstrates that the application of an enhanced formulation of a near-physiological (1.3x baseline) concentration of PRP gel provides rapid and consistent improvement in healing of chronic wounds. The study highlighted the utility of PRP gel in various healthcare settings to restart the healing process in complex nonhealing wounds, even wounds recalcitrant to other treatments, and those of patients with advanced age, compromised laboratory values, and comorbidities. The PRP gel intervention demonstrated a clinical relevance response rate of 96.5% of all wounds within 2.2 weeks and 2.8 treatments. These results have important clinical implications and suggest that this treatment can reverse the nonhealing trend in chronic wounds. ●

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