Appendix A of Rappl Public Comment Letter
AutoloGel-Aurix PRP Gel Body of Evidence

To provide evidence based medicine, Cytomedix (Nuo Therapeutics) has been documenting the outcome data on the use of AutoloGel™ (PRP Gel) to treat chronic wounds through a variety of study designs. These study designs complement each other as the consistent outcomes are demonstrated through multiple analyses thus building the body of evidence for the use of AutoloGel to treat chronic wounds. These studies include:

- A prospective, randomized, blinded, multi-center, controlled trial on diabetic foot ulcers
- A comparative study of the run in data outcomes on multiple types of wounds compared to the outcomes of these same wounds after being treated with AutoloGel. Each wound served as its own control.
- An observational study of 49 patients with 65 wounds of multiple etiologies treated in real world settings.
- An observational study of 20 spinal cord injured patients with 20 wounds.
- An observational study of 200 patients with 285 wounds of multiple etiologies treated in real world settings.
- A cost effectiveness study comparing the cost and quality of life of diabetic foot ulcer patients over a 5 year period when treated with AutoloGel or other advanced wound therapies.
- A systematic review and meta-analysis of the platelet rich plasma (PRP) literature over the past 10 years.

Prospective, Randomized, Blinded, Multi-Center, Controlled Trial

Driver, V. R., Hanft, J., Fylling, C. P., Beriou, J. M., & Autologel Diabetic Foot Ulcer Study Group. (2006). A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Management 52(6), 68-87.

Nonhealing diabetic foot ulcers are a common cause of amputation. Emerging cellular therapies such as platelet-rich plasma gel provide ulcer management options to avoid loss of limb. The purpose of this prospective, randomized, controlled, blinded, multicenter clinical study was to evaluate the safety and efficacy of autologous platelet-rich plasma gel for the treatment of nonhealing diabetic foot ulcers. One hundred, twenty-nine (129) patients were screened; 72 completed a 7-day screening period and met the study inclusion criteria. Patients were randomized into two groups — the standard care with platelet-rich plasma gel or control (saline gel) dressing group — and evaluated biweekly for 12 weeks or until healing. Healing was confirmed 1 week following closure and monitored for another 11 weeks. An independent audit led to the exclusion of 32 patients from the final per-protocol analysis because of protocol violations and failure to complete treatment. In this group, 13 out of 19 (68.4%) of the platelet-rich plasma gel and nine out of 21 (42.9%) of the control wounds healed. After adjusting for wound size outliers (n = 5), significantly more platelet-rich plasma gel (13 out of 16, 81.3%) than control gel (eight out of 19, 42.1%) treated wounds healed (P = 0.036, Fisher's exact test). Kaplan-Meier time-to-healing also was significantly different between groups (log-rank, P = 0.0177). No treatment-related serious adverse events were reported and bovine thrombin used in the preparation of PRP did not cause Factor V inhibition. When used with good standards of care, the majority of nonhealing diabetic foot ulcers treated with autologous platelet-rich plasma gel can be expected to heal.

Key Points

- In the most common sized diabetic foot ulcers, 81.3% healed versus 42.1% control ($p<0.036$)

- This RCT included a *clinically relevant cohort*; the most common sized diabetic foot ulcers, area ≥.5 - ≤7 cm^2. The mean area of 95.6% of wounds in 9 published prospective, randomized, controlled trials of advanced therapies used to treat diabetic ulcers were within this size range.
- The mean time to healing was 6 weeks
- The Kaplan-Meier time-to-healing was statistically significant in favor of the AutoloGel treated group (log-rank, P = 0.0177)
- The use of bovine thrombin during multiple treatment interventions did not cause any coagulopathies.
- There were no adverse events attributable to AutoloGel

<u>Comparison Studies: Run-In Treatment vs AutoloGel Treatment</u>

Carter, M., Fylling, C., Li, W., De Leon, J., Driver, V., Serena, T., et al. (2011). A statistical analysis of a wound outcomes registry using run-in data: clinical impact of platelet rich plasma gel on healing trajectory. Int Wound J. 2011; 8:638–650.

Randomised controlled trials in chronic wounds typically exclude patients with comorbidities and confounding factors. Well-designed observational studies can provide complementary clinical evidence that randomised trials cannot address. This study determined if wound care registry outcomes could be an alternative data source and if the results would be robust and valid. Changes in wound area and depth were hypothesised to be different between run-in therapies and platelet-rich plasma (AutoloGel™, Cytomedix, Inc) treatment. From a treatment registry of 285 chronic wounds, 46 had run-in and post-treatment data. Seven chronic wound categories were identified. Mean wound age at study start was 52.4 weeks. General linear model repeated measures showed a credible and robust data set. Statistically significant differences for wound area and depth were observed between run-in and post-treatment period at multiple time points. Wound area and depth ≥50% reduction were analysed using Kaplan–Meier methods. During run-in, 15% of wound area improved compared to 28% post-treatment and 11% of wound depth improved during run-in compared to 39% post-treatment. Significant clinical outcomes indicated many previously non responsive wounds began actively healing in response to platelet-rich plasma therapy, indicating that registry data can be used as a complementary source of evidence.

Key Points

- Mean wound area and depth either remained the same or increased during the run-in period
- Once the wounds were treated with AutoloGel, the wound area and depth reduced immediately and significantly thus demonstrating that the non-healing trajectory was changed to a healing trajectory.
- Therapies used during the run-in phase pre-AutoloGel treatment took >2.5 weeks longer than post-PRP treatment to achieve ≥50% reduction.

Sakata J, Sasaki S, Handa K, Uchino T, Sasaki T, Higashita R, Tsuno N, Hiyoshi T, Imakado S, Morimoto S, Rinoie C, Saito N. A retrospective, longitudinal study to evaluate healing lower extremity wounds in patients with diabetes mellitus and ischemia using standard protocols of care and platelet-rich plasma gel in a Japanese wound care program. Ostomy Wound Management 2012;58(4):36–49.

Chronic wounds, especially in patients with diabetes mellitus (DM), are a major health challenge in Japan. The goal of wound care centers (WCCs) in Japan is to facilitate healing and prevent lower extremity amputations (LEAs) using standardized protocols of patient and wound care. The standard

treatment algorithm includes a complete patient and wound assessment, history, physical exam, and a variety of diagnostic tests that determine the need for infection control intervention, revascularization, excision and debridement, growth factor/platelet rich plasma (PRP) gel therapy, skin graft/ flap, wound protection, and education. All patient and wound data are entered in a secure central database for all WCCs. To evaluate the outcomes of standard care regimens compared to the use of a topical PRP gel treatment in patients with a variety of complex wounds, a retrospective, longitudinal study was conducted. Wound outcomes from 39 patients with 40 chronic, nonhealing, lower extremity wounds were evaluated between two time periods: between first presentation at the WCC (T1) and after using standard topical treatments (T2) and between T2 and after using the PRP gel treatment (T3). Patient average age was 66.8 years (SD: 10.60) and mean wound duration was 99.7 days before treatment (SD: 107.73); and the majority of patients (85%) had DM. Wounds were classified as ischemic diabetic (n = 24), diabetic (n = 10), ischemic (n = 5), and pressure ulcer (n = 1). DFUs were Wagner lll (77%) and lV (23%). Of those, 60% were in patients with arteriosclerotic obliterans (ASO). Infection (abscess, cellulitis, osteomyelitis, and/or gangrene) was present in all wounds and treated using debridement, antibiotic therapy, and surgery as deemed appropriate. During the first treatment period (T1 to T2) of 75.3 days, which included revascularization and/or debridement along with standard of care, none of the wounds healed and the average wound area, depth, and volume increased. Following topical PRP gel treatment, 83% of wounds healed within 145.2 days (T2 to T3) (P = 0.00002). Only one patient required an LEA. The results of this study suggest that good healing outcomes and a low amputation rate can be obtained with a protocol of supportive care (including revascularization procedures) and the PRP gel treatment. Prospective controlled studies comparing the use of this PRP gel to other advanced treatments are warranted.

Observational Studies (deLeon Article Includes Comparison Analysis)

Frykberg, R. G., Driver, V. R., Carman, D., Lucero, B., Borris-Hale, C., Fylling, C. P., et al. (2010). Chronic wounds treated with a physiologically relevant concentration of platelet-rich plasma gel: a prospective case series. Ostomy Wound Management, 56(6), 36-44.

Chronic wounds are characterized by a long inflammatory phase that hinders regenerative wound healing. The purpose of this prospective case series was to evaluate how a physiologically relevant concentration of an autologous platelet-rich plasma (PRP) gel affects initial wound healing trajectories of chronic, nonhealing wounds of various etiologies and in different care settings. Using convenience sampling methods, 49 patients (average age: 60.6 years, SD 14.7) with 65 nonhealing wounds (mean duration 47.8 weeks, range 3 to 260) at eight long-term acute care (LTAC) hospitals and three outpatient foot or wound clinics who were prescribed PRP gel for their nonhealing wound were enrolled. The majority of patients had low albumin, hematocrit, and/or hemoglobin levels. After wound assessments and measurements were obtained and the gel prepared, a skin barrier was applied to the periwound skin and the gel applied and protected with cover dressings. The most common wounds were pressure ulcers (n = 21), venous ulcers (n = 16) and diabetic foot ulcers (n = 14). Mean wound area and volume were 19 cm2 (SD 29.4) and 36.2 cm3 (SD 77.7), respectively. Following a mean of 2.8 (SD 2.4) weeks with 3.2 (SD 2.2) applications, reductions in wound volume (mean 51%, SD 43.1), area (39.5%, SD 41.2), undermining (77.8%, SD 28.9), and sinus tract/tunneling (45.8%, SD 40.2) were observed. For all wound etiologies, 97% of wounds improved. The results of this study suggest the application of this PRP gel can reverse nonhealing trends in chronic wounds.

Key Points

- Number of patients = 49, Number of wounds = 65
- Mean previous duration without healing = 47.8 weeks

- All etiologies: In 2.8 weeks with 3.2 AutoloGel applications
    - 89.2% of the wounds had 62% volume reduction
    - 84.6% of the wounds had 50.9% area reduction
    - 100% of the wounds had 77.8% undermining reduction
    - 100% of the wounds had 45.8% sinus tract/tunneling reduction
- Pressure ulcers (n=17 wounds) : In 2.8 weeks with 3.2 AutoloGel applications
    - 85.7% of the wounds had 58% volume reduction
    - 76.2% of the wounds had 49% area reduction
    - 100% of the wounds had 66.7% undermining reduction
    - 100% of the wounds had 38.9% sinus tract/tunneling reduction
- Venous ulcers (n=11 wounds) : In 2.8 weeks with 3.2 AutoloGel applications
    - 93.8% of the wounds had 61.5% volume reduction
    - 93.8% of the wounds had 47.7% area reduction
    - No wounds with undermining, sinus tracts/tunneling
- Diabetic ulcers (n=10 wounds): In 2.8 weeks with 3.2 AutoloGel applications
    - 85.7% of the wounds had 75.4% volume reduction
    - 85.7% of the wounds had 67.2% area reduction
    - 100% of the wounds had 77.3% undermining reduction
    - 100% of the wounds had 69.1% sinus tract/tunneling reduction
- Overall, in wounds that had been present for 47.8 weeks, 97% of them responded positively with a fast healing trajectory which corroborates with the Carter (2011) study on run-in data analyzed on page 8 of this document.
- While the comparison studies by Driver (RCT) and Carter (run-in article) demonstrate the positive effect of either healing diabetic foot ulcers or changing the trajectory of multiple wound etiologies from non-healing to healing, the question is whether this positive healing trajectory can occur in "real world" very ill wound patients with multiple co-morbidities. This large observational study documents that this occurs.

Rappl LM. (2011) Effect of platelet rich plasma gel in a physiologically relevant platelet concentration on wounds in persons with spinal cord injury. Intl Wound Journal. 8(2), 187-195.

The objective of the study was to investigate the use of a 1.3 times normal platelet concentration platelet-rich plasma (PRP) gel to move chronic wounds towards healing in persons with spinal cord injury (SCI). The study design was a case series of 20 persons with SCI with non healing wounds. The outcome measures were, in wound area, volume, undermining and sinus tracts/tunnels (ST/Ts), calculated average, (i) percent of change from baseline, (ii) change per day from baseline, (iii) number of treatments and (iv) number of weeks. In a mean of 4.0, after treatments over 3.4 weeks, the wounds closed on an average of 47.9% in area and 56.0%in volume. Undermining closed on an average of 31.4% using 3.5 treatments over 2.6 weeks. ST/Ts closed on an average of 26.1% after 2.3 treatments over 1.5 weeks. Clinical relevance by percent of positive responders and their response: in area, 90.0% of the subjects responded positively, the average reduction was 53.8%. In volume, 90.0% responded, with an average reduction of 67.3%. Of four subjects with undermining, 75% closed 47.0% on average. Of the three with ST/Ts, 100% closed 26.1% on average. Average hemoglobin and hematocrit levels were below normal. To conclude, 1.3× PRP gel appears to progress chronic, non healing wounds in SCI patients into the granulation phase of healing quickly. Review of the literature shows these results may not be applied to all PRP preparations.

Key Points

- Number of spinal cord injured (SCI) patients = 20, Number of wounds = 20 (largest wound if patient had multiple wounds)
- 18/20 of the wounds were pressure ulcers. 2/20 were lower leg ulcers.
- Mean previous duration without healing = 79.4 weeks
- All etiologies: In 3.4 weeks with 4 AutoloGel applications
    - 90% of the wounds had 67.3% volume reduction
    - 90% of the wounds had 53.8% area reduction
    - 75% of the wounds had 47% undermining reduction
    - 100% of the wounds had 26.1% sinus tract/tunneling reduction
- These positive outcomes occurred even though the patient's hemoglobin and hematocrit were below normal.
- The Carter comparative run-in article demonstrates the change in the wound from non-healing to healing. This observational study corroborates this action of change.
- In SCI wounds with a mean duration of 79.4 weeks, 90% started healing with AutoloGel in a short period of time

de Leon J, Driver VR, Fylling CP, Carter MJ, Anderson C, Wilson J, et al. (2011) The clinical relevance of treating chronic wounds with an enhanced near-physiological concentration of platelet rich plasma (PRP) gel. Advances in Skin and Wound Care, 24(8), 357-368.

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 along-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.

Key Points

- Number of patients = 200, Number of wounds = 285

- Mean previous duration without healing = 48.1 weeks
- All etiologies: In 2.2 weeks with 2.8 AutoloGel applications
    - 90.5% of the wounds had 63.6% volume reduction
    - 86.3% of the wounds had 47.5% area reduction
    - In 1.8 weeks with 2.5 AutoloGel applications:
        - 89.4% of the wounds had 71.9% undermining reduction
        - 85.7% of the wounds had 49.3% sinus tract/tunneling reduction
- Pressure ulcers (n=142 wounds) : In 2 weeks with 2.6 AutoloGel applications
    - 90.8% of the wounds had 61.0% volume reduction
    - 88.0% of the wounds had 46.8% area reduction
    - 90.9% of the wounds had 66.5% undermining reduction
    - 94.1% of the wounds had 39.0% sinus tract/tunneling reduction
- Venous ulcers (n=32 wounds) : In 2.1 weeks with 2.4 AutoloGel applications
    - 93.8% of the wounds had 56.6% volume reduction
    - 87.5% of the wounds had 40.2% area reduction
    - 100% of the wounds had 100% undermining reduction
    - No wounds with sinus tracts/tunneling
- Diabetic ulcers (n=41 wounds): In 3.4 weeks with 4.0 AutoloGel applications
    - 87.9% of the wounds had 74.0% volume reduction
    - 90.2% of the wounds had 60.2% area reduction
    - In 1.8 weeks with 2.5 AutoloGel applications:
        - 100% of the wounds had 77.8% undermining reduction
    - In 2.5 weeks with 2.3 AutoloGel applications:
        - 100% of the wounds had 80.0% sinus tract/tunneling reduction
- Overall, in wounds that had been present for 48.1 weeks, 97% of them responded positively with a fast-healing trajectory which corroborates with the Carter run-in study.
- The mean area reduction per day varied by wound size with the largest wounds having the largest reduction (1.59 cm^2/day); medium wounds (0.189cm^2/day); and small wounds (0.068 cm^2/day). The differences between small and medium and small and large wounds were significant ($p = 1.0 \times 10^{-14}$, and $p = 1.0 \times 10^{-250}$, respectfully)
- Deeper wounds had the same positive healing trajectory as shallow wounds.
- These succeeding 210 wounds had the same positive healing trajectory as the initial 65 wounds in the registry (Frykberg, 2010) indicating consistency in outcomes.
- Patients with low lab values (n = 32) had the same positive healing trajectory as those patients with higher lab values (n = 33).
- Medicare beneficiaries (n = 111 wounds) had the same positive healing trajectory as non-Medicare beneficiaries (n = 135 wounds).

<u>Cost Effectiveness</u>

Dougherty EJ. (2008) An evidence-based model comparing the cost-effectiveness of platelet-rich plasma gel to alternative therapies for patients with nonhealing diabetic foot ulcers. Adv Skin Wound Care 21(12):568-75

OBJECTIVE: A cost-effectiveness analysis compared the potential economic benefit of an autologous, platelet-rich plasma (PRP) gel to alternative therapies in treating nonhealing diabetic foot ulcers.

DESIGN: An economic model used peer-reviewed data to simulate clinical and cost outcomes and quality-adjusted life-years (QALYs) associated with PRP gel and other treatment modalities.

PATIENTS: The model varies rates of healing, recurrence, infection, amputation, death, and associated costs for a hypothetical group of 200,000 patients with full-thickness,
nonhealing diabetic foot ulcers for 5 years or until death.

MAIN OUTCOME MEASURES: The model simulates the clinical, cost, and QALY outcomes associated with PRP gel versus other modalities in treating nonhealing diabetic foot ulcers over a 5-year period.

MAIN RESULTS: The average 5-year direct wound care cost per modality and QALYs were PRP gel, $15,159 (2.87); saline gel, $33,214 (2.70); standard of care, $40,073 (2.65); noncontact kilohertz ultrasound therapy, $32,659 (2.73); human fibroblast-derived dermal substitute, $40,569 (2.65); allogenic bilayered culture skin substitute, $24,374 (2.79); bilayered cellular matrix, $37,340 (2.71); negative pressure wound therapy, $20,964 (2.81); and recombinant human platelet-derived growth factor BB, $47,252 (2.69).

CONCLUSION**:** Use of PRP gel resulted in improved quality of life and lower cost of care over a 5-year period than other treatment modalities for non healing diabetic foot ulcers. Although actual treatment outcomes may differ from those modeled, PRP gel represents a potentially attractive treatment alternative for insurers and health care providers to address the cost burden and health effects of non healing diabetic foot ulcers.

Key Points

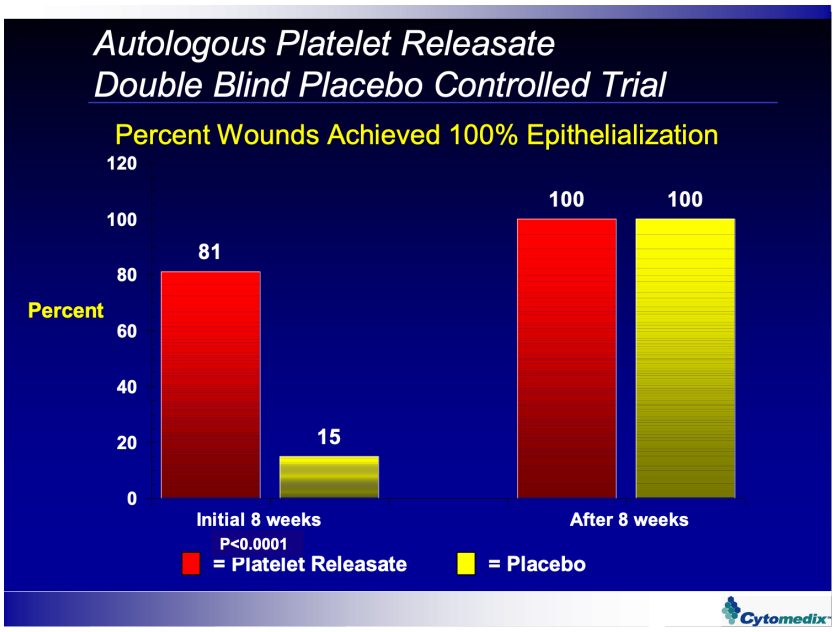
- When evaluating wound healing, wound recurrence, incidence of infection, amputation and death of diabetic foot ulcer patients over a 5 year period, AutoloGel was the most cost effective therapy for the treatment of diabetic foot ulcers with the best Quality of Life.
- Other diabetic foot ulcer treatments were more costly with lesser Quality of Life. These treatments included: NormlGel, standard of care alone, MIST Therapy® Ultrasound System, Dermagraft®, Apligraf®, Orcel™, V.A.C.® NPWT, and REGRANEX Gel.

Appendix B of Rappl Public Comment
Studies on the Precursor to PRP - Platelet Releasate

Prospective Studies

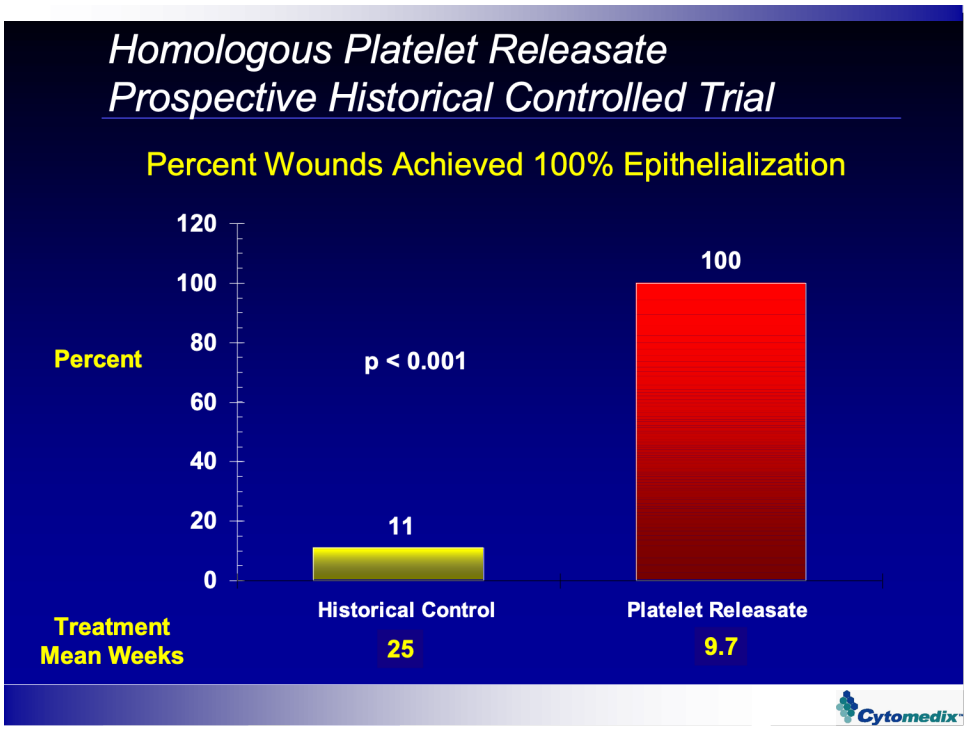
Knighton DR, Ciresi K, Fiegel VD, Schumerth SJ, Butler EL, Cerra FB. Stimulation of repair in chronic nonhealing cutaneous ulcers: a prospectively randomized blinded trial using platelet-derived wound healing formula. Surg Gynecol Obstet. 1990;170:56-60.

In a prospective, double-blind, randomized, crossover trial, 24 patients with 34 wounds were studied. Twenty-one wounds were treated topically with autologous Platelet-Derived Wound Healing Formula (PDWHF) (Platelet Releasate delivered in a collagen vehicle) in the positive group, and 13 wounds in the control group were treated with a placebo. At the 8 week crossover, 81% of the wounds in the positive group had achieved 100% epithelialization, whereas only 15% in the control group had achieved that level of healing. In the control group, 54% of the wounds actually increased in size during that time. Once the 85% unhealed wounds were treated with PDWHF, all achieved 100% epithelialization. The average time to 100% epithelialization from the start of the study was 8.6 weeks in the positive group and 15 weeks in the control group (p=.0002).



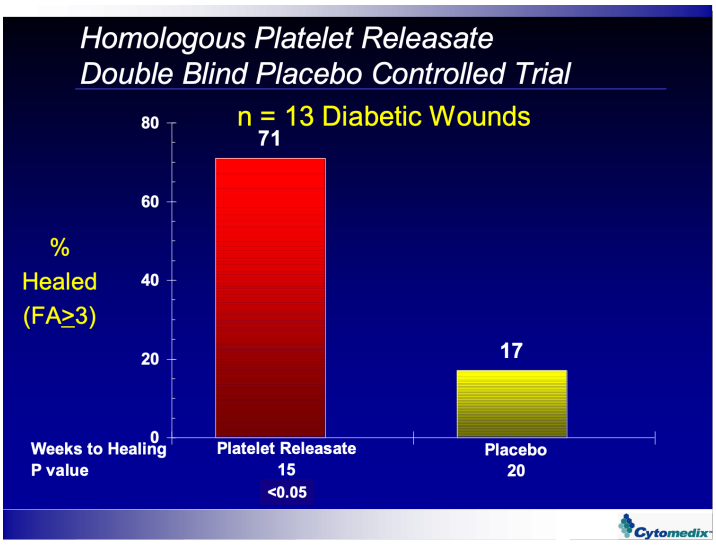
Atri SC, Misra J, Bisht D, Misra K. Use of homologous platelet factors in achieving total healing of recalcitrant skin ulcers. Surgery. 1990;108:508-12.

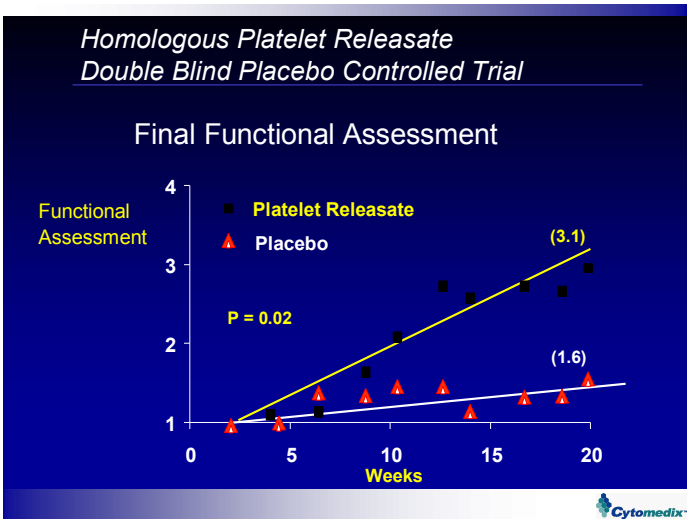
A prospective study using homologous platelet derived wound healing factors (HPDWHF) (Platelet Releasate delivered in a collagen vehicle) was conducted in India. Diabetic and venous stasis ulcers in 23 patients with 27 skin ulcers were treated initially during a historical control period with conventional wound care for an average of 25 weeks after which they were placed on the Platelet Releasate. During the historical control period, 11% of the wounds achieved 100% epithelialization. In contrast, during the Platelet Releasate treatment period, all of the wounds achieved 100% epithelialization in an average of 9.7 weeks ($p<0.0001$).



Steed DL, Goslen JB, Holloway GA, Malone JM, Bunt TJ, Webster MW. CT-102 activated platelet supernatant, topical: a randomized, prospective, double blind trial in healing of chronic diabetic foot ulcers. Diabetes Care. 1992;15:1598-1604.

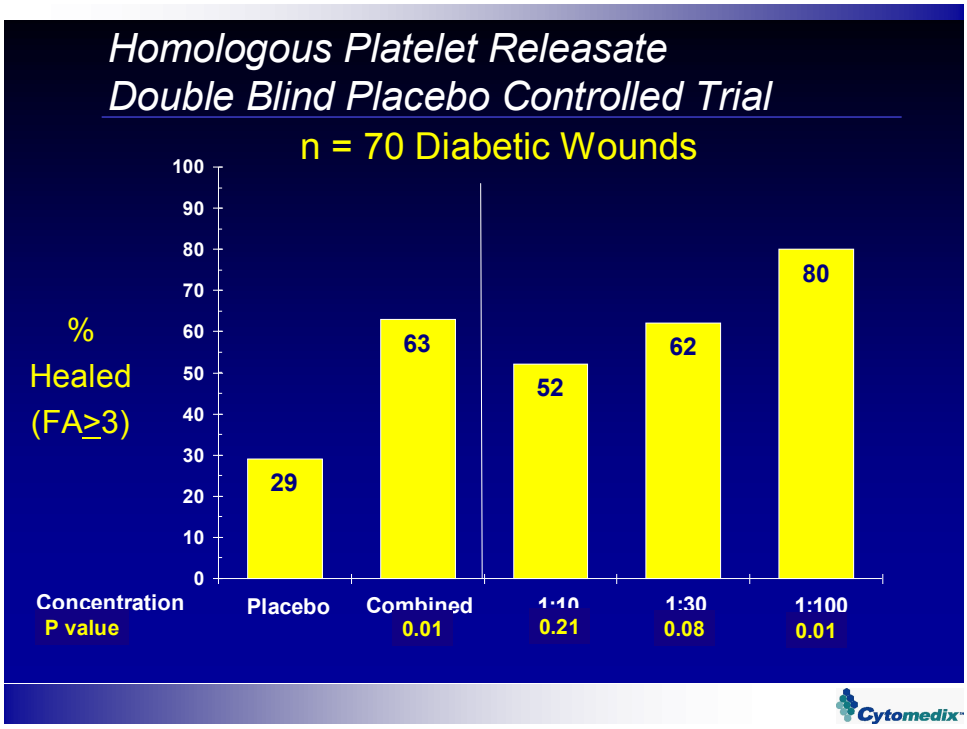
A two-center prospective double-blind placebo controlled trial was conducted. Only diabetic patients with wounds of at least 8 weeks duration were studied. Of the 13 patients with 13 wounds studied, 6 were treated with a placebo and 7 were treated with homologous Platelet Derived Wound Healing Factor (Platelet Releasate diluted 1:100 in aqueous buffer). Seventy-one percent (71%) of the patients treated with homologous Platelet Releasate were substantially healed in an average of 15 weeks, while only 17% of the placebo treated patients showed equivalent healing in 20 weeks ($p<0.05$). Placebo patients averaged a functional maturity (a measure of completeness of wound healing on a scale of 1 to 4, with ≥3 denoting healing) of 1.6 at 20 weeks versus 3.1 for the homologous Platelet Releasate treated group ($p=0.02$).





Holloway GA, Steed DL, DeMarco MJ, Matsumoto T, Moosa H, Webster MW, Bunt TJ, Polansky M, Newman D. A randomized, controlled dose response trial of activated platelet supernatant, topical CT-102 in chronic, nonhealing, diabetic wounds. Wounds. 1993;5:160-168.

A prospective, double-blind, placebo controlled, dose ranging trial was conducted at 4 centers on 70 patients with 70 wounds using the same protocol as the above-referenced study. In addition to the placebo treated group, the positive arm of the study included 3 groups of wounds treated with various dilutions (1:10,1:30,1:100) of homologous Thrombin Induced Platelet Releasate. Of the wounds treated with homologous Platelet Releasate, in all 3 groups combined, 63% of the wounds healed versus only 29% of the placebo group (p=0.01). It was found that the 1:100 dilution was the most efficacious with 80% of the wounds healing in comparison to 29% of the placebo treated wounds (p=0.01).



Retrospective Studies

Wound Healing

Knighton DR, Ciresi KF, Fiegel VD, Austin LL, Butler EL. Classification and treatment of chronic nonhealing wounds: successful treatment with autologous platelet-derived wound healing factors (PDWHF). Ann Surg. 1986;3:322-30.

A study of forty-one (41) patients with 71 nonhealing wounds of an average of 4 years previous duration were treated with this protocol. The wounds achieved 100% epithelialization in an average of 10.6 weeks with no complications or side effects.

Fylling CP, Knighton DR, Gordinier RH. The use of a comprehensive wound care protocol including topical growth factor therapy in treatment of diabetic neuropathic ulcers. In: Ward J and Goto Y. Diabetic Neuropathy. New York: John Wiley & Sons; 1990:567-578.

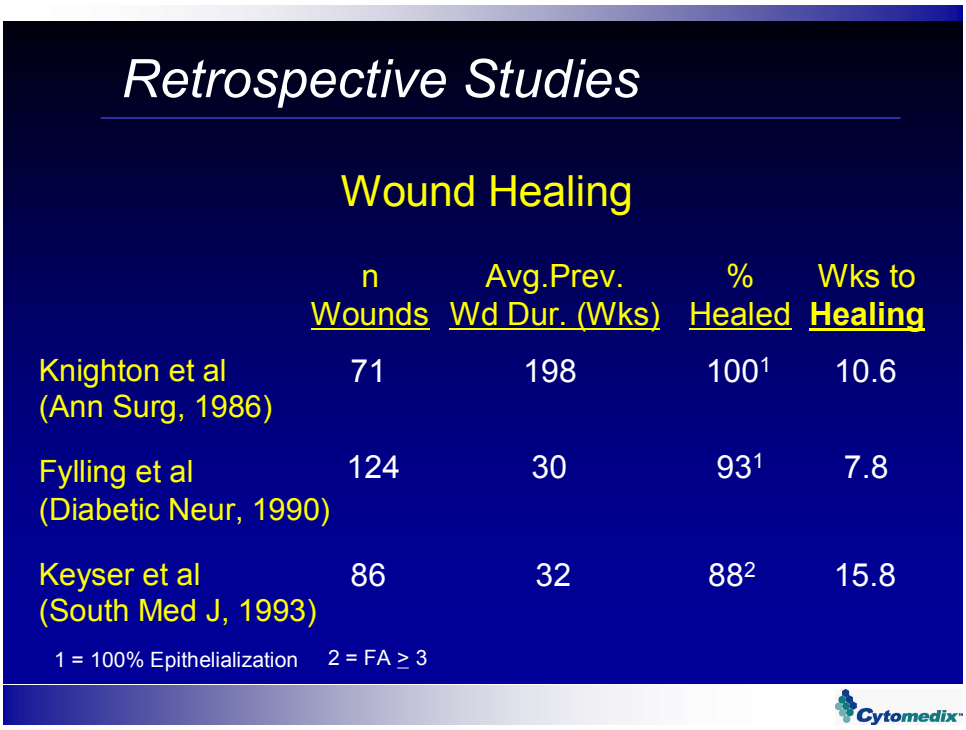
Eighty-eight (88) diabetic patients with 124 nonhealing neuropathic ulcers were studied. Previously, they had received multiple treatment interventions over an average of 30 weeks with no healing. Upon treatment with the comprehensive wound care protocol, 93% of the wounds healed in an average of 7.8 weeks with no recurrence during a 12 month follow-up period.

Fylling CP. A five center study of diabetic wound healing in comprehensive wound management programs. Diabetes. 1992. Supplement 1;41:82A.

One hundred fifty-seven patients with 373 nonhealing diabetic wounds were studied at 5 Wound Care Centers®. Average previous wound duration was 32 weeks without healing. Eighty-three percent (83%) of the wounds healed in an average of 9.2 weeks. The recidivation rate on these wounds was <5%.

Keyser JE. Diabetic wound healing and limb salvage in an outpatient wound care program. South Med Jour. 1993;86:311-317.

A study was conducted of eighty-six (86) wounds on fifty-four (54) patients treated in a comprehensive wound management program using Platelet Derived Wound Healing Formula (PDWHF-Procuren) (Thrombin Induced Platelet Releasate, Autologous). The average previous wound duration was 8 months. Fifteen (15) limbs had a previous recommendation of amputation. Healing occurred in 88.4% of the wounds in an average of 15.8 weeks. Ninety-three percent (93%) of the limbs previously recommended for amputation were salvaged.



Glover JL, Weingarten MS, Buchbinder DS, Poucher RL, Deitrick GA, Fylling CP. A four-year multicenter retrospective study of topical multiple growth factor therapy for chronic wounds. Adv Wound Care 1997;10(1):27-32.

A retrospective study was conducted to evaluate wound healing rates and limb salvage. A standardized, customized database was utilized to gather data on patients treated for chronic wounds of various etiologies during a 52-month period in 39 hospital-affiliated ambulatory wound care centers. A total of 3,830 patients were studied. Wound healing and limb salvage rates in 2,811 patients treated with a comprehensive wound care (CWC) regimen plus autologous topical multiple growth factor therapy—platelet releasate (PR)—was compared to 1,019 patients who received only a CWC regimen. There was no statistical significance between the two groups except that the CWC + PR wounds were more severe (P=0.00032) and had larger wound volume (P=0.00004).

Overall healing rates were higher in the CWC + PR group relative to the CWC group (65.7%/50.8%; P<0.00001), respectively; amputation rates were lower for CWC + PR than for CWC patients (4.1%/7.6%; P=0.00005). Healing rates per etiology were higher for the CWC + PR group vs. the CWC group:

diabetes, 66.8%/46.6% (P<0.00001);
venous insufficiency, 65.5%/58.1% (P=0.0495);
pressure ulcers, 63.6%/41.5% (P=0.00005);
arterial insufficiency, 59.5%/43.8% (P=0.034); and
other, 67.7%/54.1% (P=0.0004).

Diabetic amputation rates were lower in the CWC + PR group, 6.0%, than in the CWC group 13.3% (P=0.00012).

In diabetic wounds of increasingly greater severity (demonstrated by incremented wound grades), the rate of healing was higher and the rate of amputation lower in the CWC + PR group vs. the CWC group:

Healing:
Grade 2—66%/49% (P=0.014);
Grade 3—70%/46% (P=0.00103);

Grades 4,5—64%/46% (P=0.01918), and

Amputations:
Grade 2—5%/8% (P=0.00024);
Grade 3—5%/18% (P=0.00008);
Grades 4,5—9%/21% (P=0.015).

No clinically significant adverse events were observed. The study concluded that CWC + PR produced higher rates of wound healing and increased limb salvage for all wounds.

Margolis DJ, KantorJ, Santanna J, et al. Effectiveness of Platelet Releasate for the Treatment of Diabetic Neuropathic Foot Ulcers Diabetes Care 2001. 24:483-488.

OBJECTIVE—The goal of this study was to specifically estimate the effectiveness of platelet releasate, a widely available treatment administered by a proprietary group of wound care centers (WCCs) for the treatment of diabetic neuropathic foot ulceration.

RESEARCH DESIGN AND METHODS—Treatment effectiveness was estimated in a retrospective cohort study controlling for treatment selection bias using logistic regression–derived propensity scores.

RESULTS—Platelet releasate was more effective than standard care. The relative risk for a wound to heal after treatment with platelet releasate compared with standard care at a WCC varied from 1.14 (95% CI 1.03–1.27) to 1.59 (1.49–1.70). The effect was greatest in those with the most severe wounds, i.e., large wounds that affect deeper anatomical structures.

CONCLUSIONS—Within the limitations of the ability of propensity score analysis to control for selection bias, platelet releasate is more effective than standard therapy. This effect is more pronounced in more severe wounds. Unfortunately, severe wounds have not been evaluated in randomized clinical trials of new interventions. We encourage the inclusion of these patients in future trials.

Amputation Prevention

Doucette MM, Fylling CP, Knighton DR. Amputation prevention in a high-risk population through a comprehensive wound healing protocol. Arch Phys Med Rehabil. 1989;70:780-85.

A study of 24 patients with a previous recommendation of amputation at the TMA level or higher were treated at the Wound Care Center. Eighty-three percent (83%) were salvaged and remained salvaged during the 18-month follow-up period.

Knighton DR, Fylling CP, Doucette MM. Wound healing and amputation in a high-risk diabetic population. Wounds. 1989;2:107-14.

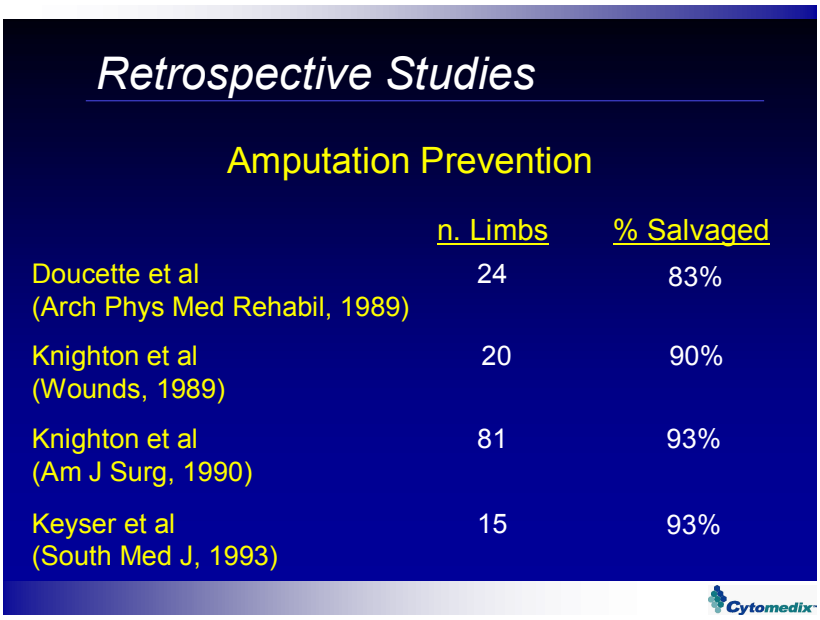
In a further study of 20 patients, 90% of limbs recommended for amputation on diabetic patients were salvaged.

Knighton DR, Fylling CP, Fiegel VD, Cerra FB. Amputation prevention in an independently reviewed at-risk diabetic population using a comprehensive wound care protocol. Amer J Surg. 1990;160:466-72.

A study was conducted in which an independent panel of experts in the field of amputation prevention conducted a case study review of 71 diabetic patients with 124 wounds on 81 limbs. They predicted that 80% of the limbs would be salvaged. Using the comprehensive wound care protocol, actual outcome was that 93% of the limbs were salvaged ($p< 0.005$).

Glover JL, Weingarten MS, Buchbinder DS, Poucher RL, Deitrick GA. A four-year multicenter retrospective study of topical multiple growth factor therapy for chronic wounds. Adv Wound Care 1997; 10(1):27-32.

(See summary under Retrospective Studies: Wound Healing.)



Cost Effectiveness

Bentkover JD, Champion AH. Economic evaluation of alternative methods of treatment for diabetic foot ulcer patients: cost effectiveness of platelet releasate and wound care clinics. Wounds. 1993;5:207-215.

A diabetic ulcer cost effectiveness study was conducted by Arthur D. Little. They initially studied the cost effectiveness of two treatment modalities at the wound care clinic; comprehensive wound management utilizing alternating platelet releasate and saline dressings, and comprehensive wound management using only saline dressings. In addition, the Wound Care Clinic with platelet releasate therapy added was compared with traditional wound care outside the program. It was found that the comprehensive wound management wound care clinic including platelet releasate therapy was approximately 40% less expensive per patient healed compared to the other two treatment approaches.