Synergism in Using Negative Pressure Wound Therapy With Alternated Applications of Autologous Platelet-derived Growth Factors in Treating Post-acute Surgical Wounds

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Abstract: Chronic and acute wounds with long tunneling or undermining are always a challenge to wound care providers. One of the most frequently employed treatments for closing tunneled or undermined wounds is negative pressure wound therapy (NPWT). The benefits of this treatment system are widely discussed in the professional literature, and will not be covered here. Even though NPWT allows for faster wound healing initially, in some cases, progress to wound closure is limited and healing stops after reaching a maximum potential, which may occur after just a few weeks. This adverse phenomenon is more common when the wound exhibits deep tunneling or has been extensively undermined. Trying variations of NPWT strategies geared toward closing these wounds is usually unsuccessful. This article describes cases where combined therapy, using the V.A.C.® Therapy System (KCI, San Antonio, Tex) and the autologous platelet-derived gel, AutoloGel™, (CytoMedix, Rockville, Md) was employed.

The efficacy of negative pressure wound therapy (NPWT) to promote healing of open wounds has considerable support in the literature. NPWT promotes wound healing through multiple actions: removal of exudate from the wound to help establish fluid balance, provision of a moist wound environment, removal of slough to decrease wound bacterial burden, reduction in edema and third-space fluids, increase of blood flow to the wound, increase in growth factors, and promotion of white cells and fibroblasts within the wound. Negative pressure brings tissue together, promoting coaptation, which allows the tissues to stick together through natural tissue adherence and increases healing.

It is postulated that this combination treatment affects the wound healing rate by creating a well-oxygenated, angiogenic tissue bed using NPWT and then activating fibroblasts with platelet-rich plasma gel (PRP). The idea behind applying this particular combination was to increase, according to Chen et al1, angiogenesis in the hypoxic tissue with NPWT and then to “sow”
the growth factors from the PRP into the new hypervascular tissue like seeds into "enriched soil." The NPWT prepares the “ground” by creating numerous new microcapillaries for the platelet-derived growth factors, which then function as natural fertilizer causing proliferation of the fibroblast “crop.”

Niezgoda et al provided further evidence for this approach. They found that using NPWT therapy stimulates the development of angiogenesis in the adjacent tissues underlying and surrounding the wound base to a greater degree than can be achieved with standard wound healing efforts, such as enzymatic treatments, surgical debridements, and local wound care. Chen et al reported that using NPWT promotes capillary blood flow velocity, increases capillary caliber and blood volume, stimulates endothelial proliferation and angiogenesis, narrows endothelial spaces, and restores the integrity of the capillary basement membrane.

Studies in basic science have demonstrated a dose-response relationship between platelet concentration and levels of secretory proteins, and between platelet concentration and certain proliferative events of significance to the healing wound. The platelet is a natural source of myriad growth factors and cytokines that promote wound healing. Platelet-derived angiogenesis factor is a polypeptide capable of stimulating new capillary growth by inducing migration of endothelial cells. The platelet-derived epithelial cell growth factor is partially responsible for the initial influx of neutrophils into the wound space; it is also a mitogen for many cells, including epithelial cells and fibroblasts.

Four wound treatment cases are presented. These patients were treated with a combination of two wound healing products: NPWT (V.A.C. Therapy System, KCI, San Antonio, Tex) and an autologous PRP (AutoloGel Cytomedix, Rockville, Md). The application of PRP was a key component in the treatment plan. The bedside treatment was achieved by first drawing a small amount of blood (5 cc–15 cc based on the size of treated wound), extracting the platelets and plasma. This extract was then mixed with calcified thrombin, which caused the extract to “gel” and the platelets to release a number of factors that initiated the process of fibroblast migration to the wound. The plasma-rich gel, with its fibrin scaffold, was applied topically to the wound under a protective cover dressing.

The cases described here illustrate healing rates of post-surgical wounds after treatment with NPWT and PRP.

Case Reports

Case 1. A 62-year-old man presented to the wound center with extensive necrosis of the lateral-anterior portion of a skin graft that had been applied to his right leg 6 weeks earlier. The patient had a history of extensive peripheral vascular occlusive disease, having had an aortobifemoral bypass graft and bilateral lower extremity infrainguinal revascularization several years previous. He had multiple treatments to his left leg, which ultimately led to an above knee amputation. The patient rehabilitated well with prosthesis. Six months before he arrived at the wound center, he underwent surgery on a femoral-popliteal graft above his right knee, which had thrombosed. After successful revascularization of the graft, the patient developed multicompartm ent fasciomy of his right leg, which was ultimately skin-grafted. His medical history included hypercholesterolemia—the patient carries prescriptions for Coumadin (Bristol-Myers Squibb Company, Princeton, NJ) and Lipitor (Pfizer, New York, NY).

Treatment course. The right lateral leg wound exhibited an exposed anterior tibialis tendon.

Week 0
- 62-year-old man with necrosis of a skin graft
- Necrotic tissue was debrided

Weeks 2–4
- Maggot therapy in week 2, which improved the wound
- NPWT weekly for 3 weeks

Week 5
- Healing stagnated
- PRP applied

Week 6
- NPWT

Week 7
- NPWT
- 50% reduction in wound volume

Week 8
- PRP

Week 9
- NPWT
- 75% healed

Week 10
- PRP

Week 11
- NPWT

Weeks 12–20
- Collagen to maintain
- Completely healed at week 20

Figure 1. Treatment progression in case 1.
Dimensions of the wound were 11 cm x 3.4 cm x 1.5 cm. At the wound center, necrotic tissue was debrided at initial exploration of the muscle tissue. Due to the extensive amount of necrotic tissue remaining after debridement and the severe pain experienced, maggot therapy was introduced in the second week of therapy, after which significant improvement was noted. NPWT therapy was also started during week 2 and continued on a weekly basis for 3 weeks. Healing stagnated at this point. In week 5, autologous PRP was added to the regimen. This application of PRP combined with 2 subsequent weekly NWPT applications restarted the healing process; a 50% reduction in wound volume was noted.

The next treatment (week 8 after admission) applied was PRP gel alone. At the end of week 8, 75% healing was described. Subsequently, in weeks 9 to 11, NPWT therapy was alternated on a weekly basis with PRP. At week 12, because of the significant reduction in wound size and depth, only collagen maintenance therapy was applied. The patient’s wound healed completely in 20 weeks. Figure 1 shows the treatment progression timeline.

**Case 2.** A 75-year-old woman presented to the treatment center with an open wound on her left hip, which had lasted for 1 year. The wound resulted from a fall after which she developed a hematoma. The hip area then became infected and was surgically drained. The wound had not closed from the time of injury to her admission at the wound center. The wound dimensions were 0.8 cm x 0.7 cm x 4.0 cm and had a sinus tract extending in...
2 directions: at a position corresponding to 9 o’clock (9.5 cm), and at 12 o’clock (7.5 cm). A small amount of granulated tissue was present external to the wound but there was no slough or other evidence of necrotic tissue. The patient’s medical history included rheumatoid arthritis and depression.

**Treatment course.** In her first week in the clinic, the patient’s wound was treated with Iodosorb (Smith & Nephew, Fort Lauderdale, Fla). Special packing sponges were placed inside both sinus tracts. In week 2, NPWT was started. After 5 weeks of NPWT, visible healing effects on the wound were negligible. Since NPWT did not result in any significant improvement, PRP was added to the treatment regimen. The PRP was applied weekly for the first 2 weeks. At this point, intermittent weekly dosing of NPWT and PRP was used (Figure 2). After 5 weeks of this alternating treatment, the wound volume was reduced by 50%. The treatment was finished with one more NPWT and one more PRP application. Both sinuses closed completely following this treatment. Although there is a photograph of the wound at week 18, the wound was actually healed at week 15 with minimal dimensions. It was purposefully not closed at that time since the patient’s comorbidities—rheumatoid arthritis and depression—were thought to contribute to closure issues. When the patient returned at week 18, the wound had officially closed.

**Case 3.** An 88-year-old woman presented to the wound center with a left buttock ulcer that had developed 2 months previously. Initially, the patient experienced painful erythema and swelling over the ulcerated area. Three weeks before admission to the wound center, the patient had the infected abscess surgically drained and a moderate amount of purulent discharge was removed.
The patient’s medical history included ulcerative colitis, seizure disorder, heart disease, Parkinson’s disease, and osteoarthritis. Upon presentation, the wound dimensions were 1.5 cm x 1.5 cm x 3 cm, with 4 cm of tunneling at the 10 o’clock position.

**Treatment course.** Wound debridements were performed weekly for 1 month over which time, most of the necrotic tissue was removed. Other wound care was also performed during this time, including cadexomer iodine gel and pad, but the deep cavity still showed no signs of healing. NPWT was started at week 5 to improve local microcirculation and increase the amount of granulated tissue. After 2 weeks of NPWT treatment without significant improvement, PRP therapy began and was performed each week.

After 2 weeks of PRP treatment, a 25% reduction in wound volume was recorded. At this point, the wound steadily improved and after 2 more weeks of PRP treatment and 7 weeks of collagen maintenance (a total of 19 weeks from admission), the wound closed. Figure 3 shows the treatment progression timeline.

**Case 4.** A 56-year-old woman presented to the wound center with an open post-surgical wound on her left breast. The wound was the result of the surgical removal of an infected breast implant. The patient had been diagnosed with breast cancer 3 years previously, at which time she underwent prophylactic bilateral mastectomy, and a course of chemotherapy and radiation. One year
after her mastectomy, she had breast implants inserted and did well for the next 2 years. Two weeks prior to presentation at the wound center, the patient noticed signs of an infection in the left implant—local swelling, redness, and fever. No culture was taken to identify the specific pathogen(s), but the acute infection was treated with a course of oral antibiotics; the infected implant was then removed. The resultant wound measured 2.6 cm x 0.3 cm x 1.5 cm with tunneling (6.8-cm) at the 4 o’clock position, and undermining (3.9-cm) at the 9 o’clock position.

Treatment course. PRP therapy was initiated in the second week after admission and was repeated weekly for the following 4 weeks. After 2 weeks of this therapy, a 50% reduction in the wound was noted. During the next 2 weeks of treatment, no improvement in wound dimensions, tunneling, or undermining was achieved. Two courses of weekly NPWT was applied, followed by 4 weeks of PRP therapy. At week 10 of treatment (11 since admission), wound volume had reduced by 75%. One more PRP treatment was applied, and then maintenance with standard treatment was continued. At 15 weeks, all tunneling and undermining had dissipated. Figure 4 shows the treatment progression timeline.

Discussion

In this 4-patient case series, the use of both NPWT and PRP in various combinations had a positive effect on wound healing rates (Figure 5). Treatment courses in these cases included weekly applications of either PRP or NPWT at some time during the patient’s stay in the clinic. These treatments were sufficiently spaced (7 days apart) to prevent NPWT from removing activated platelet-rich plasma platelet releasate, growth factors, and fibrin scaffolding from the wound bed. The decision on the appropriate length of each treatment and the variation in treatment was made based on the clinical condition of the wound and the effect of the previous treatment. Criteria used for wound condition included the amount of granulating tissue and the level of tissue “vascularity,” which was assessed before and after each debridement. Hypervascular tissue showing multiple new microvessels has a red, beefy appearance and has a tendency to bleed easily for prolonged periods. PRP therapy was considered appropriate for wounds with hypervascularization, and was applied until hypervascular granulating tissue was significantly reduced. NPWT was initiated and continued until a positive change in tissue quality was achieved if the wound showed a pale, avascular appearance and tended not to bleed during debridement. When signs of infection were noticed, a tissue culture was obtained and an appropriate oral course of antibiotics was prescribed.

The data analysis has shown that there was a significant change in wound volume (20%–50%) 2–6 weeks after beginning one or both of these treatment modalities. In the first three cases, the advanced wound care began with NPWT. After lack of significant progress, PRP was added. In the fourth case, the first treatment was PRP where there was initial improvement after 2 weeks of therapy but then after 2 more weeks, the healing did not progress so NPWT was initiated. In these 4 cases, using NPWT and PRP treatments alternately resulted in successful wound healing. None of these patients’ wounds have reopened after 2 years.

Topical application of autologous PRP may play an important role in complicated, limb-threatening wounds. Wound volumes decreased after the first application in most cases, with continued wound contraction observed weekly until complete wound healing was achieved.

Conclusion

This case series illustrates positive clinical outcomes that are possible when using alternating treatment combinations of PRP and NPWT. These cases represent some of the more recalcitrant wounds that we see—all of the wounds exhibited tunneling or sinus tracts. No serious adverse events were noted with either treatment, and patients expressed no discomfort during the treatments. None of the wounds in these cases have reopened after 2 years.

Other clinical data have shown the significant effects platelet growth factors have on wound healing in enriched hypervascular environments. The use of NPWT to promote healing of open wounds has considerable support in the literature as well. Previously
reported data, along with the results from this case series, suggest that larger trials may support both efficacy and safety of this alternating treatment regimen. Such trials would need to establish more precise standards and treatment protocols and offer clinical guidelines to optimize the combined therapy.

References