

Using Angiogenesis in Chronic Wound Care with Becaplermin and Oxidized Regenerated Cellulose/Collagen

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For most of the last century, chronic wound care was a practice of passive techniques, designed to prevent the progression of the wound. The last decade, however, has seen a change in active wound care. These advanced techniques focus on improving the wound at the molecular level to accelerate wound healing. Successful modalities include tissue-engineered products, hyperbaric oxygen, negative pressure therapy, electrical stimulation, and recombinant growth factors [1–7]. This shift in the treatment of wound care saw the development of a recombinant human platelet-derived growth factor (rh PDGF-BB), approved by the Food and Drug Administration (FDA) for nonhealing diabetic ulcers in 1997 [8,9]. Now commonly used for treatment, becaplermin (REGRANEX) stimulates granulation and increases the incidence of complete wound closure [2,8–10]. Another development was found to protect growth factors and granulation tissue by inhibiting wound proteases [11]. This product is oxidized regenerated cellulose (ORC)/collagen (PROMOGRAN). Used together, an optimal environment for wound healing can be created.

Angiogenesis

Angiogenesis is simply the growth of new capillary blood vessels. The medical community is using what they know of angiogenesis to produce

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medications that stimulate or inhibit these molecular roles. Antiangiogenesis is the motivation behind many cancer-fighting treatments, just as angiogenesis is the factor behind many healing therapies. The focus of this article is how becaplermin and ORC/collagen are used to stimulate angiogenesis in chronic wound care.

Phases of wound healing

To emphasize the role of angiogenesis in wound healing, one must first look at the naturally occurring process of wound repair in a healthy individual. The three phases of wound healing are codependent and overlapping.

Phase I (inflammatory phase) occurs at time of injury and continues for approximately 5 days. Injury immediately kicks off the events that lead to clotting. A temporary increase in permeability of the vascular wall allows neutrophils, platelets, and plasma proteins to enter the wound. With the initial injury, cell membranes release vasoconstrictors that limit hemorrhaging. Platelets then release multiple chemokines that help stabilize the wound with clot formation. The second part of this phase starts when the platelets release growth factors that draw polymorphic neutrophils (PMNs) into the wound, initiating early inflammation. For about 48 hours, the PMNs keep the wound clean and prevent infection by killing bacteria and removing foreign debris. After 48 hours, the PMNs recruit macrophages into the wound to replace them slowly as the primary inflammatory cell. Both cells, the PMN's and macrophages, are releasing growth factors as they continue to maintain a clean wound [12,13].

Phase II (proliferation phase) occurs from day 4 to approximately day 21. This phase overlaps the first phase. It is characterized by epithelialization, angiogenesis, granulation tissue formation, and collagen deposition. Fibroblasts, recruited by growth factors, lay down new collagen that works with new blood vessel growth (codependent), allowing epithelial cells to traverse the wound, forming granulation tissue [12,13].

Phase III (maturation phase) overlaps phase II and can last for more than a year. It is characterized by wound contraction, resulting in a smaller amount of apparent scar tissue, as compared with the original wound size. The collagen is continually reorganizing during this time to get maximal tensile strength [12,13].

Growth factors

Growth factors are a large family of proteins designed to promote cell proliferation and migration. About 20 growth factors have been identified that stimulate angiogenesis [2]. Among these are platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and the transforming growth factors [1].

One of the first cells in the wound is the platelet. Platelets are responsible for releasing many growth factors into the wound, including PDGF, which is unique because of its multiple roles in stimulating endothelial cells and stabilizing the new vasculature [14]. PDGF is released by platelets, macrophages, and monocytes, where it then binds to its receptor on the surface of endothelial cells. Binding activates signals that begin cell proliferation, migration, invasion, tube formation, and vascular survival [15–17].

PDGF promotes the release of the other growth factors including VEGF and FGF [2,18,19]. Studies have shown that when PDGF is combined with either VEGF or FGF, more functional blood vessels result [3,20].

Another way that PDGF impacts vascular stabilization is through its ability to recruit smooth muscle cells and pericytes to newly forming blood vessels [21–24]. This concept is important because diabetic ulcers have shown a diminished expression of PDGF [2,25]. One of the primary reasons becaplermin is so helpful in stimulating healing in diabetic wounds is that, in a sense, it serves as a type of gene-based therapy. Gene-based therapies offer the theoretic advantage of sustained local expression of growth factors to target tissues [1,26]. Later in this article, the important role of becaplermin in diabetic wound healing due to PDGF concepts is discussed.

Proteases

In the early inflammatory phase of wound healing, a family of enzymes called proteases is introduced into the wound. They are expressed transiently at the tip of newly forming blood vessels to facilitate vascular growth [2,27]. In normally healing wounds, proteases assist in tissue remodeling and removal of necrotic tissue. Chronic wounds have an excess of protease activity. When this level becomes abnormally elevated, proteases may destroy growth factors, inhibit angiogenesis, and break down granulation tissue [27]. Because of this phenomenon, controlling protease activity has become a key factor in managing a chronic wound.

Becaplermin

Becaplermin is the first, and currently only, recombinant angiogenic growth factor to become FDA approved and is widely used by wound care specialists [1,8,9]. Because it is a peptide drug, it needs to be stored in the refrigerator to prevent heat degradation. This drug attaches to the PDGF receptors in the wound bed to start angiogenesis. It is a gel that is applied topically and is easy for patients to use at home.

Through four multicenter, randomized, parallel-group clinical trials that evaluated the effects of once-daily topical becaplermin gel in 922 patients who had nonhealing diabetic foot ulcers of at least 8 weeks' duration, clinical efficacy was established [28]. These patients were randomly assigned to a standardized regimen of good wound care alone, or good wound care plus

becaplermin gel or a placebo gel of sodium carboxymethylcellulose. Treatment continued for 20 weeks or until the wound healed, with the primary endpoint of complete healing, defined as 100% epithelialization with no drainage. Becaplermin gel significantly increased the incidence of complete healing compared with the placebo gel (50% compared with 35%), based on an analysis of patients with a baseline ulcer area common to all trials, representing 95% of all patients [1,28].

Oxidized regenerated cellulose/collagen

ORC/collagen is a medical dressing composed of freeze-dried ORC and bovine collagen [29]. This dressing binds and neutralizes destructive proteases in chronic wound fluid. Once the proteases are neutralized, they undergo an alteration of their protein configuration, which makes them inactive. The dressing then binds directly to growth factors and is capable of releasing them back into the wound over time while keeping the proteases inactive [30], which helps to protect PDGF and other growth factors like FGF and VEGF from destruction related to overly high levels of these proteases in the wound.

An important study documenting the efficacy of ORC/collagen dressings was performed, *in vitro*, by incubating exogenous PDGF with plasmin, a protease present in chronic wound fluid, in the presence of ORC/collagen. The PDGF activity was retained and showed the protective effect of this dressing [2,30]. An additional study incubated exogenous PDGF in chronic wound fluid for 24 hours at 37°C with either ORC/collagen or a standard gauze dressing [30]. Only the ORC/collagen group demonstrated significant recoverable PDGF activity after incubation. These studies support a mechanism by which ORC/collagen promotes angiogenesis by protecting growth factors [2].

Use of the ORC/collagen dressing is quite simple. It is cut to the size of the wound bed and gently pressed to the base. This dressing is followed in application by a secondary dressing to help maintain the moist wound environment. Once the ORC/collagen is affixed as described, it begins to absorb drainage, and over a period of days it dissolves and is completely reabsorbed into the wound.

Recognizing its ease of use and potential indications in wound care, recent advancements in ORC/collagen have taken place. One such advancement includes the introduction of ORC/collagen impregnated with silver (Promogran prisma). Quickly becoming the popular dressing of choice for infected or potentially infected wounds, silver products provide antisepsis to the chronic wound.

Becaplermin and oxidized regenerated cellulose/collagen combined

Creating regimens of care for chronic wounds using becaplermin and ORC/collagen includes many options. In the authors' clinic, they combine

the use of becaplermin with ORC/collagen to enhance growth factor efficacy. Combining them is designed to

- Deliver a potent growth factor to stimulate wound granulation
- Optimize the growth factor's effect by protecting it from degradation by proteases

The authors have developed a protocol implementing the optimal methods of treating the patient with becaplermin and ORC/collagen.

Wound evaluation

The evaluation of all chronic wounds includes assessment for presence of infection, determination of primary cause, assessment of nutritional status, and assessment of macrovascular and microvascular disease. Any suspicion that a cutaneous malignancy, vasculitis, or thromboembolic cause may be present requires a biopsy to be performed before initiating treatment. This step is very important because becaplermin accelerates angiogenesis in all cells, thus facilitating growth in malignant cells.

Initiation of treatment

If several weeks of routine conventional management of the acute wound have not resulted in improvement, or in the case of a chronic wound, the authors select an advanced modality to accelerate closure. Because granulation tissue is needed universally, they consider becaplermin for almost every patient. Their experience has shown that the earlier becaplermin treatment is initiated, the faster wound closure is achieved, regardless of wound cause.

Additionally, the use of ORC/collagen is generally optimal for almost every patient who has such wounds. The only patients not considered are those with known allergies to any related collagen products. Also, for patients who have a high potential for infection, the addition of ORC/collagen with silver provides an added antiseptic benefit.

Debridement

Prior to adding either becaplermin or ORC/collagen to the wound care regimen, the wound base must first be prepared. Appropriate, sharp debridement is essential to the successful use of becaplermin [31]. In the authors' clinic, sterile debridement is achieved by first cleansing the wound with an antiseptic surgical soap. Debridement is performed by the physician with a number 15 scalpel blade, an iris scissors, or a curette to remove necrotic tissue or fibrinous slough, before initiation of growth factor therapy. When debridement is performed properly, it will produce some minor local bleeding at the wound bed. This bleeding can stimulate angiogenesis in response to the new accumulation of platelets and also by exposing the cellular receptors so that PDGF can activate vascular endothelial cells. Additionally, it serves to remove senescent cells that do not respond to growth

factors, allowing the wound margins to close by changing a chronic wound into an acute wound.

Although sharp debridement is optimal for use with becaplermin, other options can be considered. For patients who are unable to tolerate sharp debridement, or for those with a large amount of adherent eschar, enzymatic debridement is an option. It is necessary first to score the eschar with a 15 blade to allow the enzymatic cream or ointment to start degrading the necrotic tissue.

Becaplermin

Next, the use of becaplermin, the first advanced modality, is implemented. Only a small amount of becaplermin is necessary to treat the entire wound surface. A small amount of the gel should be applied to a cotton-tipped applicator and spread thinly onto the wound surface, allowing the rh PDHF-BB (becaplermin) to come into direct contact with the exposed receptors.

Oxidized Regenerated Cellulose/collagen

ORC/collagen is the next layer to be applied. The ORC/collagen is cut to the size of the wound bed before application, which allows it to fit into the base of the wound and come into contact with all the growth factors and proteases. The same technique is also used for the ORC/collagen with silver. It should be gently pressed to the base of the wound to allow the material to conform to the concavity of the wound bed. An additional method involves applying a second layer of the becaplermin atop the ORC/collagen, which promotes a sustained release effect as the ORC/collagen is resorbed into the wound. Finally, the focus turns to coordination of dressing changes.

Dressing changes

The original clinical trials for becaplermin involved twice-daily dressing changes, using saline to rinse the wound, as recommended by the package insert [2]. This high frequency of dressing changes is often impractical for patients and reduces patient compliance. In their clinic, the authors have seen positive results using less frequent dressing changes, once daily or every other day. Again, this frequency depends on the individual wound and the amount of drainage present. It is always necessary to maintain a moist wound environment on which hydrogels can be added below the ORC/collagen to maintain moisture. Some wounds have the potential of becoming too moist, leading to maceration of healthy tissue and an increase of bacterial bioburden, increasing the risk for infection. In these instances, it is recommended that the patient be treated instead with ORC/collagen with silver. If ORC/collagen with silver is used, it is necessary to rinse with sterile water to avoid neutralizing the silver ions. To help with excess moisture, one could also add an alginate or foam dressing after the ORC/collagen to absorb the excess drainage.

Added benefits

Using this treatment gives patients added benefits; not only does it accelerate healing and wound closure but is also cost effective. When a patient heals more quickly, he/she spends less money on dressing supplies and, for some patients, less on visiting nurses, which is always a major concern for patients and the health care industry as a whole. Another benefit is an increase in patient compliance. When patients are seeing improvement in their wound healing, they are more likely to continue with it. As all nurses are well aware, it is impossible to have successful healing without the patient being compliant with the wound care process.

Summary

Angiogenesis is part of the normal process of wound healing. Several factors help to regulate this healing process. Chronic wounds have defects in this normal process related to the underlying cause of the wound, whether diabetic, venous, or other. To bridge the defects in this process, science has been able to control part of the molecular process of angiogenesis, or new blood vessel growth, through the use of recombinant growth factors. Becaplermin has demonstrated its ability to provide that much-needed bridge to promote healing, dramatically improving patient wound outcomes. Becaplermin is currently the only FDA-approved growth factor for chronic wound healing, and as it bridges the gap of healing to promote angiogenesis it thus encourages an increase in granulation tissue.

Granulation tissue is required for wounds to heal, so becaplermin has a wide potential in the management of various wounds [2]. Becaplermin can be used alone or in combination with various other modalities, such as bioengineered tissue equivalents and negative pressure therapy. To enhance the applied growth factor effects, ORC/collagen can be applied with becaplermin to maximize the potential of both these products. With the recent advancement in biologically active dressings like ORC/collagen, one can control wound proteases and promote angiogenesis, thereby achieving the maximum benefit for patients and their healing wounds.

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