A Comparison of Collagenase to Hydrogel Dressings in Maintenance Debridement and Wound Closure

Catherine T. Milne, APRN, MSN, CWOCN; Armann Ciccarelli, MD, FACS; Mandie Lassy, BSN

Abstract: The role of maintenance debridement in wound healing has been well described, yet little is known regarding comparative methods and associated outcomes with this process when using collagenase or hydrogel. Objective. Evaluation of maintenance debridement and wound closure with collagenase compared to hydrogel in institutionalized adults with pressure ulcers from time of necrotic tissue removal up to 84 days from enrollment. Methods. This second phase of a rollover evaluation enrolled only subjects who successfully completed phase 1 (previously reported) from time of necrotic tissue debridement. Subjects received daily dressing changes with either hydrogel or collagenase followed by a standard semiocclusive dressing to evaluate wound-healing parameters and wound closure from initial enrollment to day 84. Investigators blinded to randomization evaluated weekly wound photographs using a digital planimetry software package for wound-healing parameters. Additionally, Pressure Ulcer Scale for Healing (PUSH) Tool and wound bed scores (WBS) were monitored. Results. Eleven of 13 subjects from the collagenase group entered into phase 2, with 4 of the 14 subjects from the hydrogel group. One subject from each group was eliminated within the first week of phase 2. All subjects ($n = 3$) in the hydrogel group reached complete epithelialization with a mean of 32.6 days. Nine of 10 subjects in the collagenase group reached complete epithelialization with a mean of 45 days. An independent samples $t$ test showed no statistical significance between the 2 groups ($P = 0.121$) in days to healing. A Fisher’s exact test performed on the primary endpoint of complete epithelialization also demonstrated no significant difference in outcomes between the groups ($P = 0.99$). Mean WBS at the onset of phase 2 was 13.7 (range 12-16), and the PUSH Tool mean score was 1.0 (range 0-3). In aggregating phase 1 and phase 2 data, a difference in the closure rates at the end of the study, 69% (collagenase) vs 21% (hydrogel), was statically significant ($P = 0.0213$) using a Fisher’s exact test. Conclusion. Facilitating maintenance debridement by either collagenase or hydrogel can be used to complete wound closure when used in conjunction with a validated predictive wound-healing tool that closely monitors therapy. This study showed statistical significance in favor of collagenase when evaluating closure rates from the onset of the pressure ulcer.
Wound bed preparation (WBP) is an established concept in chronic wound management. Addressing the relationship between necrotic tissue, exudate, and bacterial and cellular dysfunction leads to optimal outcomes. Execution of WBP includes eliminating necrotic tissue, bacterial burden, biofilms, edema, and exudate, while promoting the formation of granulation tissue. Debridement is one essential step in accomplishing these goals.

Concepts related to debridement have evolved with increased understanding of WBP. Initially considered the removal of visible, nonviable tissue, debridement is further elucidated into 2 distinct phases: initial debridement and maintenance debridement. Initial debridement is defined as “the removal of necrotic, damaged, and/or infected tissue.” However, despite removal of visibly necrotic tissue, phenotypically altered senescent fibroblasts and keratinocytes, coupled with accumulating extracellular matrix materials and substrates that may contribute to bioburden, need ongoing removal from the wound bed. Maintenance debridement offers a continuous removal of cellular burden not visible to the naked eye and frees the wound bed from these obstacles to healing. Falanga’s review of in vitro studies suggest that maintenance debridement may recruit functional cells to the chronic wound. Maintenance debridement can be achieved via mechanical, enzymatic, or autolytic means; though there is little literature that associates these concepts in vivo. Regardless, incorporating this key concept in clinical practice is paramount to optimizing wound outcomes.

The clinical setting in which maintenance debridement occurs often influences decision-making regarding treatment, as resources, patient populations, and expertise in wound management may differ. Clinicians often change from one therapeutic modality to another when the wound appears to be free from necrotic debris upon visual assessment. A less-skilled clinician often equates the absence of necrotic tissue with wound health, failing to appreciate the pathophysiological processes occurring at the cellular level.

Many skilled nursing facilities have adopted predetermined wound protocols, as standardization has been shown to improve wound healing outcomes. Many protocols provided by wound care vendors strongly encourage changing from an active debridement process, such as an enzymatic agent, to a product that provides corrective moisture balance when visible, non-viable tissue has been removed. Collagenase has not been traditionally accepted in clinical practice for use beyond the removal of necrotic tissue, though in vitro work suggests collagenase may play a role in reducing formation of biofilms and bacterial proliferation, and enhance keratinocyte proliferation and migration. While comparison of hydrogel dressings and enzymatic debriding agents on wound healing have been done using swine, there are no reports in the clinical area, or, specifically, the long-term care setting, where these agents are extensively used.

The aim of this 2-phase study was to evaluate the outcomes of both hydrogel and collagenase on initial debridement of nonviable tissue and impact on the maintenance debridement phase of wound bed preparation. The results of phase 1, examining initial debridement, have been published. This manuscript reports the time from complete debridement of visible, nonviable tissue to epithelialization from phase 2.

**KEYPOINTS**

- Execution of wound bed preparation includes eliminating necrotic tissue, bacterial burden, biofilms, edema, and exudate, while promoting the formation of granulation tissue. Debridement is one essential step in accomplishing these goals.
- Collagenase has not been traditionally accepted in clinical practice for use beyond the removal of necrotic tissue, though in vitro work suggests collagenase may play a role in reducing formation of biofilms and bacterial proliferation, and enhance keratinocyte proliferation and migration.
- While comparison of hydrogel dressings and enzymatic debriding agents on wound healing have been done using swine, there are no reports in the clinical area, or, specifically, the long-term care setting, where these agents are extensively used.

**Methods**

The study protocol was approved by the local Institutional Review Boards of the long-term care facilities from which patients were recruited. Patients or their legal representatives were asked to sign a written informed consent prior to entering phase 1. Inclusion and exclusion criteria for phase 1 have been reported, and salient details have been reproduced (Table 1). Subjects were rolled over to phase 2 if complete debridement of all visible, nonviable tissue was complete by day 42, with continuance of pressure redistribution or offloading recommendations, and adherence to dietary intake recommendations. The primary outcome of this evaluation was to determine the number of days needed to achieve epithelialization, capped at 84 days. Secondary outcomes in-
In the presence of wound depth, after application of the assigned agent, the wound was then filled to the depth equal to that of the surrounding wound tissue with gauze dampened with normal saline, so that there was no excess moisture noted when pressure from the clinician’s hand was applied. The wound was then covered with a semi-occlusive dressing (CoverSite, Smith and Nephew, Largo, FL).

Dressing changes, performed by the nursing staff at the long-term care facility, occurred on a daily basis and as needed if the dressing integrity was lost due to dislodgement or incontinence. Weekly subject evaluations, including subject and wound assessment, as well as wound photographs, were conducted by the same investigator. Wound photos were evaluated for wound healing parameters using calibrated digital wound measurement software (Pictzar, BioVisual Technologies, Elmwood Park, NJ) by 2 designated investigators blinded to randomization. In addition, each weekly photograph was assigned a wound bed score (WBS)\(^\text{14}\) or a Pressure Ulcer Scale for Healing (PUSH) Tool score,\(^{15-17}\) as each of these tools has shown reliability and validity in monitoring and predicting wound healing. Nursing staff at each facility were trained by one investigator in the wound dressing procedure. Other methods of debridement were not performed during phase 2.

### Table 1. Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age &gt; 18 years</td>
<td>• Steroid use &gt; 5 mg daily</td>
</tr>
<tr>
<td>• Presence of at least 85% necrotic nonviable tissue on a pressure ulcer between 1 cm(^2) and 64 cm(^2)</td>
<td>• Inability to cooperate with offloading recommendations</td>
</tr>
<tr>
<td>• Hydrogel or collagenase dressing naïve on study pressure ulcer</td>
<td>• Ankle-brachial index &lt; 0.85 if the pressure ulcer was located on the lower extremity</td>
</tr>
<tr>
<td>• No current use of parenteral or oral antibiotics except for urinary tract suppressive therapy</td>
<td>• Presence of callus requiring sharp or surgical debridement within 3 days prior to enrollment</td>
</tr>
<tr>
<td>• Hemoglobin A1C (HbA1c) &lt; 7.9%</td>
<td>• Medical instability as deemed by the investigator</td>
</tr>
<tr>
<td>• Currently receiving adequate pressure redistribution to the affected area via devices such as a group 2 or 3 specialty bed, and a static air wheelchair cushion if out of bed, and/or an offloading device if the pressure ulcer was located on the lower extremity</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Compliance with nutritional interventions per registered dietician</td>
<td>• Participation in another clinical trial or wound dressing evaluation in the 30 days prior to enrollment</td>
</tr>
<tr>
<td>• No allergies to collagenase or hydrogel</td>
<td></td>
</tr>
<tr>
<td>• No allergies to semiocclusive secondary dressing</td>
<td></td>
</tr>
<tr>
<td>• Written informed consent</td>
<td></td>
</tr>
</tbody>
</table>

Inclucluded the portion of patients with complete wound closure by 84 days, and the evaluation of changes in wound measurements on a weekly basis.

Randomization occurred after informed consent was obtained to reduce selection bias. Subjects were assigned to either collagenase (Santyl Ointment, Healthpoint, LTD, Fort Worth, TX) or hydrogel (SoloSite Gel, Smith & Nephew, Largo, FL). Successful completion of phase 1 was determined by visual assessment by 1 investigator, and confirmed by wound photography using calibrated digital wound measurement software (Pictzar, BioVisual Technologies, Elmwood Park, NJ) by investigators blinded to randomization category. Subjects remained on the same assigned agent when rolling over into phase 2.

Each dressing change consisted of the following: normal saline irrigation with a device providing 4-15 psi (Irrimax, Weston, FL) followed by application of the assigned therapeutic agent, “nickel thick,” to the entire wound bed.

**Keypoints**
- Subjects were assigned to either collagenase or hydrogel.
- Successful completion of phase 1 was determined by visual assessment by 1 investigator, and confirmed by wound photography using calibrated digital wound measurement software by investigators blinded to randomization category.
- Subjects remained on the same assigned agent when rolling over into phase 2.
- Dressing changes, performed by the nursing staff at the long-term care facility, occurred on a daily basis and as needed if the dressing integrity was lost due to dislodgement or incontinence.

**Results**

Twenty-seven subjects consented to participate over an enrollment period of 1 year. Thirteen subjects were randomized to the collagenase group; 14 were randomized to the hydrogel group. Data analysis was performed by SPSS. Using Student’s t test, there were no significant differences in groups for age, gender, age of wound, or percentage of nonviable tissue at the time of enrollment (\(P < \)
More than half of the pressure ulcers (55.5%) were related to devices such as splints, braces, ill-fitting wheelchair arm rests, or prostheses. Wound size was statistically different; overall the collagenase group presented with larger wounds ($P < 0.004$) when entering phase 1.

Eleven of the 13 subjects from the collagenase group, and 4 of the 14 subjects from the hydrogel group, entered the portion of the study reported in this paper. One subject from each group was eliminated within the first week of phase 2.

All subjects ($n=3$) in the hydrogel group reached complete epithelialization with a mean of 32.6 days. Nine of the 10 subjects in the collagenase group reached completed epithelialization with a mean of 45 days. An independent samples t test showed no statistical significance between the 2 groups ($P = 0.121$) in days to healing.

At the time of complete debridement, 7 patients had stage 3 pressure ulcers (4 collagenase; 3 hydrogel) with the remaining 6 patients having stage 4 pressure ulcers (6 collagenase; 0 hydrogel). Significance in wound pressure ulcer stage was noted using Chi-Squared analysis, with the collagenase group having greater severity ($P = 0.03$). All subjects ($n=3$) in the hydrogel group reached complete epithelialization with a mean of 32.6 days. Nine of the 10 subjects in the collagenase group reached completed epithelialization with a mean of 45 days. An independent samples t test showed no statistical significance between the 2 groups ($P = 0.121$) in days to healing. A Fisher’s exact test performed on the primary endpoint of complete epithelialization also demonstrated no significant difference in outcomes between the groups ($P = 0.99$). The WBS mean at the onset of phase 2 was 13.7 (range 12-16) and the PUSH Tool mean score was 1.0 (range 0-3). Intent-to-treat closure rates were statistically significant ($P = 0.0213$) at the end of the study: 69% (collagenase) vs 21% (hydrogel) using a Fisher’s exact test. (Figure 1).

Weekly reductions in wound sizes occurred at a greater rate in the collagenase group ($P = 0.009$) as compared to subjects receiving hydrogel using a Fisher’s exact test.

**Discussion**

Hydrogels, which are composed of hydrophilic polymers in a dimensional matrix, are frequently used after the removal of visible necrotic material to provide moisture to the wound bed. By providing an exogenous source of moisture, the body’s own physiological mechanisms to achieve wound repair can occur in the optimized environment. Maintenance debridement is achieved via moisture-facilitated cell migration in the absence of desiccation and thermal insulation. Intrinsically enzymes recruited by the moist wound bed environment provided by hydrogel are selective in the protein degradation. This passive method of debridement has been shown to be slow and associated with anaerobic bacteria. Hydrophilic components and water content of hydrogels vary,
making general comparisons between this class of topical wound treatment and other, nonhydrogel treatments difficult. However, hydrogels have been shown to be superior to moist saline gauze dressings. Hydrogels have shown efficacy in wound healing and now have replaced wet-to-dry dressings as the product category for which to compare outcomes. Bale et al compared 2 amorphous hydrogels and found little difference in time to debridement between them. Eisenbud et al in their review of physiological interaction of hydrogels with the wound bed suggested that one particular hydrogel offered no clinical benefit over any other hydrogel.

Collagenase ointment, a metalloproteinase made from the bacteria Clostridium histolyticum, has been studied extensively with regards to its ability to degrade eschar in the clinical setting, though not for maintenance debridement. Herman and Shi et al have shown in vitro ability of collagenase to promote fibroblast proliferation, keratinocyte migration, and growth factor preservation. Falanga first suggested the clinical utility of collagenase in performing maintenance debridement. The ability of collagenase to debride eschar from the edge of the wound while simultaneously promoting angiogenesis and reepithelialization, thus allowing a smaller wound to be managed at the time of complete eschar removal, was postulated. This may be considered a beneficial “edge effect” of collagenase. The results of this study suggest maintenance debridement begins at the time of initial application of collagenase, lending support to the findings of Margolis et al for predictive significance of wound healing with edge migration.

At day 84, there was complete epithelialization in 9 of the 13 intent-to-treat subjects assigned to the collagenase group, which clinically supports previous works by Riley and Herman, Herman and Shi et al. As collagenase in vitro avoids non-denatured collagen and other protein degradation, growth factors are preserved. Accumulation of nonviable cellular debris and remaining denatured collagen in the wound bed, invisible to the naked eye, promotes the prolongation of the chronic wound state. This study suggests collagenase may impact this accumulation. Additional studies with larger subject numbers are warranted.

In the intent-to-treat hydrogel group, slower closure rates suggest that no edge effect with fibroblast proliferation and keratinocyte migration occurred. As hydrogel success is related to the host’s ability to mount the physiological response for wound healing, the quick epithelialization time in the study suggests this group may have improved regardless. This may have influenced the nonstatistical significance between the primary outcome comparing days to healing. Further studies with larger subject numbers should be performed to confirm these findings.

The prognostic ability of both the WBS and PUSH Tool to predict complete wound closure supports the previous works in this area. Upper quartiles of the WBS favor wound closure in pressure ulcers with a score of less than 14, as do PUSH Tool scores. Until biological markers that correlate with wound health are routinely available at the bedside, the use of these instruments can provide reliable objectivity to the clinician in guiding treatment decisions. Given cost considerations in the current health care economic climate, changing therapies without objective measurements that support prognostic capability based on wound visualization may not be cost-effective.

Of the patients in the rollover analysis reported here, it is important to recognize that the continuum of data from phase 1 and phase 2 provides information on the clinical management of pressure ulcers in long term care. This was addressed by assigning these patients to identical clinical pathways with the only difference being the choice of debridement, enzymatic vs autolytic. In this case, the proportions healed (9 of 13 for collagenase; 3 of 4 for hydrogel) in this intent-to-treat group, encompassing both phases of the evaluation, were assessed at 84 days after the initiation of therapy (Figure 1). In this study, there is a statistically significant difference in the healing rates of 48 percentage points between the collagenase and hydrogel groups.

Limitations of this study include the small number of enrolled patients that entered into phase 2. Further exploration into the area of maintenance debridement with

---

**Key Points**

- Falanga first suggested the clinical utility of collagenase in performing maintenance debridement.
- The ability of collagenase to debride eschar from the edge of the wound while simultaneously promoting angiogenesis and reepithelialization thus allowing a smaller wound to be managed at the time of complete eschar removal was postulated. This may be considered a beneficial “edge effect” of collagenase.
- In the intent-to-treat hydrogel group, slower closure rates suggest that no edge effect with fibroblast proliferation and keratinocyte migration occurred. As hydrogel success is related to the host’s ability to mount the physiological response for wound healing, the quick epithelialization time in the study suggests this group may have improved regardless.
these and other agents is required. These results cannot be generalized to all hydrogels owing to their different chemical compositions. Generalizations cannot be made in populations with wounds caused by other etiologies or outside the long-term care setting.

**Conclusion**

Pressure ulcer healing continues to be a challenging issue for clinicians in the long-term care setting. In a frail population within a financially stressed health system, this study adds to the evidence base that facilitating maintenance debridement, either by collagenase or hydrogel, can be used to complete wound closure when utilized in conjunction with a validated predictive wound healing tool that closely monitors therapy.

**References**


