Economic and Clinical Benefit of Collagenase Ointment Compared to a Hydrogel Dressing for Pressure Ulcer Debridement in a Long-Term Care Setting

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Abstract: Introduction. The purpose of this study is to determine the cost-effectiveness of collagenase ointment relative to autolysis with a hydrogel dressing when debriding necrotic pressure ulcers in a long-term care setting. Methods. A Markov decision process model with 2 states (necrotic nonviable wound bed transitioning to a granulated viable wound bed) was developed using data derived from a prospective, randomized, 6-week, single-center trial of 27 institutionalized subjects with pressure ulcers that were ≥85% necrotic nonviable tissue. Direct medical costs from the payer perspective included study treatments, wound treatment supplies, and nursing time. Clinical benefit was measured as “granulation days” and was derived from the time-dependent debridement rates of the alternative products. Results. The average cost per patient for 42 days of pressure ulcer care was $1,817 in 2012 for the collagenase group and $1,611 for the hydrogel group. Days spent with a granulated wound were 3.6 times higher for collagenase (23.4 vs 6.5) than with the hydrogel. The estimated cost per granulation day was >3.2 times higher for hydrogel ($249) vs collagenase ($78). Conclusions. In this economic analysis based on a randomized, controlled clinical trial, collagenase ointment resulted in a faster time to complete debridement and was more cost-effective than hydrogel autolysis for pressure ulcers in a long-term care setting. Even though collagenase ointment has a higher acquisition cost than hydrogel, the clinical benefit offsets the initial cost difference, resulting in lower cost per granulation day to the nursing home over the course of the 42-day analysis.

Key words: collagenase ointment, hydrogel dressing, pressure ulcer debridement, debridement cost-effectiveness

Chronic wounds pose significant clinical and economic challenges to health systems, providers, patients, and society. A successful multidisciplinary treatment process for the management of chronic, indolent, or nonhealing wounds incorporates wound bed preparation (WBP). A seminal component of WBP is debridement, which may include autolytic, surgical,
biologic, mechanical, and enzymatic techniques. The recommended debridement approach varies with the wound, potential for infection, the patient’s clinical and demographic characteristics, and time, as well as available medical expertise, knowledge, and resources within the patient location. Moreover, it is increasingly important to also consider the cost-effectiveness of treatment options in the management of chronic wounds.

Within the long-term care or nursing home setting, the use of autolytic and enzymatic debridement methods have long been accepted as effective strategies for wound management, and both methods are considered simple, safe, and practical. These techniques are more efficacious than nonselective, mechanical debridement using wet-to-dry dressings; more cost-effective; and less painful for the patient. Compared with bedside sharp debridement, autolytic and enzymatic methods do not require a physician’s technical skills, a significant advantage since physician availability may be limited within the long-term care setting.

Autolytic debridement using hydrogels, which are comprised of hydrophilic polymers within a dimensional matrix, are designed to create a moist wound bed environment, facilitating the body’s intrinsic enzymes to break down necrotic or nonviable tissue. Enzymatic debridement with a selective debriding agent, such as collagenase ointment (derived from Clostridium histolyticum), has been used for removal of necrotic tissue from chronic cutaneous wounds and burns.

A prospective, randomized study of 27 nursing home residents, Milne et al., found a statistically significant clinical benefit (time to complete necrotic tissue debridement) for collagenase ointment compared with hydrogel dressing. Given the acquisition cost difference between collagenase ointment and hydrogel dressing, there is a need to assess the relative cost-effectiveness of the 2 alternatives.

**Key Points**
- Within the long-term care or nursing home setting, the use of autolytic and enzymatic debridement methods have long been accepted as effective strategies for wound management, and both methods are considered simple, safe, and practical.
- Given the acquisition cost difference between collagenase ointment and hydrogel dressing, there is a need to assess the relative cost-effectiveness of the 2 alternatives.

To the authors’ knowledge, only a few studies have evaluated the cost of collagenase vs hydrogel treatment. All found that collagenase was more cost-effective than hydrogel therapy. However, the study conclusions are of limited economic use because the cost data are 10 or more years old, were conducted in countries with notably different health care systems than the United States, or efficacy data were derived by expert panels rather than clinical trials. Consequently, there is a need to address the cost-effectiveness of these therapies using randomized clinical trial data and current cost estimates. Therefore, a Markov decision process model was developed to assess the cost-effectiveness of collagenase enzymatic debridement relative to hydrogel autolytic debridement for the treatment of pressure ulcers in a long-term care setting.

**Material and Methods**

**Study and model design.** Decision analysis is a well-accepted methodology for comparing costs and benefits based on probability of events. A 2-state Markov state-transition model (Figure 1) was developed using Microsoft Excel 2007 to compare the cost and outcomes of collagenase ointment (Santyl® Ointment, Healthpoint Biotherapeutics, Fort Worth, TX) with hydrogel autolysis (SoloSite™ Gel, Smith & Nephew Inc, St. Petersburg, FL). Markov models are particularly well-suited to emulate clinical pathways where events and costs transition over time.

The clinical and resource utilization data for the Markov model were derived from a US-based, prospective, randomized, 6-week trial, described by Milne et al. The 42-day clinical study was conducted in a single long-term care center among 27 institutionalized subjects with pressure ulcers that had ≥ 85% necrotic nonviable tissue, randomly assigned to receive daily dressing changes with either hydrogel (n = 13) or collagenase (n = 14) followed by a standard semioclusive dressing. The 2 treatment groups in the clinical study were statistically similar at baseline with respect to age, gender, age of the wound, percent of nonviable tissue, and prealbumin levels. The only observed difference...
between the 2 groups at baseline was that wound size was statistically larger ($P < 0.004$) in the collagenase group compared to the hydrogel group, at 12.3 cm$^2$ versus 7.9 cm$^2$, respectively.

To improve reliability and reduce variability of the clinical trial results, a single investigator performed the initial and weekly wound evaluations, including taking wound photographs. Consistent with typical clinical practice within the long-term care setting, neither sharp debridement nor cross-hatching of the wound bed was performed for either agent. Dressing changes (ie, normal saline irrigation, study drug application, semiocclusive dressing) were performed daily, or more frequently as needed, by investigator-trained nursing staff.

The primary clinical study outcome was time to complete debridement of wound or 42 days, whichever came first. Wound assessment by 2 blinded primary study investigators was conducted using calibrated, noninvasive wound measurement planimetry software (PictZar®, BioVisual Technologies, Elmwood Park, NJ). Digital planimetry results in more accurate wound measurements compared with standard manual (length x width) measurements, which may overestimate wound area by approximately 40%.

The Markov model estimated the number of granulated wound bed days and cost per patient for 42 days of pressure ulcer care for collagenase compared with hydrogel. Outputs from the Markov model were then used to derive a cost-effectiveness ratio for each product, defined as the cost per granulation day.

Model Inputs

**Time horizon.** The time horizon for the model was 42 days. Costs associated with occlusive wound dressings (ie, supplies, nursing time) continued to accrue for the entire trial duration, regardless of whether full wound debridement was achieved or not.

**Wound states.** The 2 Markov states used in the analysis were: State 1, a necrotic nonviable wound bed potentially transitioning to State 2, a granulated viable wound bed.

**Transition probabilities.** The transition probabilities (the likelihood of moving from one health state to another) for wound progression were derived from the clinical trial. Milne et al. found that 11 of the 13 subjects (85%) treated with collagenase achieved a fully debrided wound bed by day 42 of therapy. Among hydrogel-treated subjects,
4 (29%) of 14 achieved a debrided viable wound bed by day 42. The difference in achieving full debridement by day 42 was statistically significant (Pearson’s chi squared test, $P < 0.003$) between the 2 groups.

Figure 2 shows the relationship between the proportions of patients achieving a debrided wound bed as a function of time for collagenase vs hydrogel, using data derived from the clinical trial.\(^3\) Achievement of wound bed debridement was faster and occurred in a greater proportion of patients with collagenase than with hydrogel. The equations describing the necrotic to granulation state transitions across time are:

Collagenase probability of debridement = \(\ln(1.1 + [0.032 \times \text{Days of Therapy}])\)

Hydrogel probability of debridement = \(\ln(1.0 + [0.008 \times \text{Days of Therapy}])\)

Clinical outcomes definition. Clinical benefit for the cost-effectiveness analysis was measured as “granulation days,” and was defined as the average number of days spent in debrided granulated wound bed within the 42-day episode of care, with higher values indicating greater benefit conferred. Granulation days for the 2 comparators were calculated using the following formula, in which $GD = \text{cumulative granulation days for therapy X (collagenase or hydrogel)}$; $PDW = \text{probability of achieving a debrided wound}$; and $t = \text{time in days}$:

$$GD_x = \sum_{t=1}^{42} PDW_t$$

Economic outcome definition. The perspective of the analysis was that of the payer, and only direct medical costs of care were considered. Economic outcomes included resource utilization and associated costs for nursing time, collagenase ointment, hydrogel dressing, secondary semiocclusive dressings, wound irrigation, and wound care kits. Resource use estimates were derived from the clinical trial or provided by the lead clinical study investigator.\(^3\) Associated costs were based on standard costs references (see Table 1). All costs were reported in US dollars, and no cost or outcome discounting was performed due to the short time horizon (ie, 42 days). A cost-effectiveness analysis was performed assessing the average per-patient cost per granulation day for each of the debridement modalities. The average per-patient cost of therapy was calculated using the following formula, in which $CC_x = \text{cumulative cost of wound therapy X}$; $R_t = \text{resources used at time t}$; $C = \text{cost of resources}$; and $t = \text{time in days}$:

$$CC_x = \sum_{t=1}^{42} R_t C$$

Results

As shown in Figure 3, the average cost per patient for 42 days of pressure ulcer care was $1,817 for the

<table>
<thead>
<tr>
<th>Resource</th>
<th>Mean Quantity</th>
<th>Mean Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santyl Ointment 30 grams</td>
<td>1.26 tubes/42 days</td>
<td>$222.92/42 days</td>
</tr>
<tr>
<td>Solosite Gel 90 grams</td>
<td>1 tube/42 days</td>
<td>$17.40/42 days</td>
</tr>
<tr>
<td>Nursing Time</td>
<td>15 minutes/day</td>
<td>$9.30/day</td>
</tr>
<tr>
<td>CovRSite Dressing</td>
<td>1/day</td>
<td>$2.21/day</td>
</tr>
<tr>
<td>Irrimax Irrigation System</td>
<td>1/day</td>
<td>$21.39/day</td>
</tr>
<tr>
<td>Wound Care Kit</td>
<td>1/day</td>
<td>$4.17/day</td>
</tr>
</tbody>
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collagenase group and $1,611 for the hydrogel group, a difference of $206. The average number of days a patient spent with a granulated wound during the 42-day episode of care was 3.6 times greater for those treated with collagenase than for patients treated with hydrogel (23.4 vs 6.5) (Figure 4).

Cost-effectiveness. A cost-effectiveness ratio was derived for each product based on the estimated total costs per patient and the clinical benefit conferred, based on the number of days with a granulated wound bed during the 42-day treatment period (Table 2). The collagenase group had an estimated average wound care cost of $1,817 per patient while the average cost of wound care was estimated at $1,611 in the hydrogel group resulting in an incremental cost of $206 dollars in the collagenase group. The average numbers of granulated wound bed days were estimated at 23.4 days in the collagenase group and 6.5 days in the hydrogel group, resulting in an incremental effect of 17 additional granulation days in the collagenase group. Although patients treated with collagenase had wound care costs that were approximately 13% higher than those treated with hydrogel, the clinical benefit in terms of granulated wound beds was 260% higher, resulting in a more favorable cost-effectiveness ratio for collagenase. The estimated average cost per granulation day was more than 3.2 times higher for hydrogel ($249/ granulation day) than for collagenase ($78/ granulation day), indicating that the higher acquisition cost of collagenase was offset by its greater effectiveness.

The incremental cost-effectiveness ratio (ICER) is defined as the difference in cost ($206) divided by the difference in effect (17 granulation days). The ICER provides an estimate of the additional cost necessary to gain an additional granulation day (Table 2). The ICER indicates that for every $12.00 spent on collagenase the patient gained an additional granulation day compared to hydrogel autolytic therapy. Although it may be difficult to conceptualize the clinical and economic impact of the $12.00 ICER, the implications are explained in the discussion section of this article.

Discussion

In today’s health care environment, a product’s value must encompass the therapeutic benefit as well as total cost of care, not just the simple acquisition cost of the drug treatment. The results of this economic analysis conclusively show that although collagenase ointment has a higher acquisition cost compared with a hydrogel dressing, the superior efficacy of collagenase offsets the acquisition cost difference over 42 days of care. Specifically, the cost of collagenase therapy was 13% higher than the cost of autolytic therapy with a hydrogel dressing. However, the therapeutic effect of collagenase was 3.6 times greater than hydrogel dressing when assessing the cumulative time patients experienced a granulated viable wound bed. Patients administered collagenase ointment had an estimated mean of 23.4 days with a completely granulated wound bed compared with 6.5 days for patients using hydrogel-based dressings. Taking the total therapy costs and clinical outcomes together, this analysis demonstrates that the cost per unit of clinical benefit for collagenase ointment is approximately one-third that of the hydrogel dressing ($78 vs $249 per granulation day), indicating a better cost-effectiveness profile for collagenase. These results establish a compelling argument for the clinical value of collagenase ointment for the treatment of necrotic pressure ulcers in a long-term care setting.

Intuitively, the incremental cost-effectiveness ratio may be a difficult economic concept to grasp in regard to its clinical and economic implications. The practicing clinician will want to know the benefit of spending an additional $12.00 just to obtain an additional granulation day where the wound is free of necrotic tissue. The answer lies in the chronology of pressure ulcer outcomes. If one

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Estimated Total Costs per Patient</th>
<th>Incremental Cost</th>
<th>Days with Granulated Wound Bed&lt;sup&gt;a&lt;/sup&gt; (Effect)</th>
<th>Incremental Effect</th>
<th>Incremental Cost-Effectiveness Ratio</th>
<th>Average Cost-Effectiveness Ratio</th>
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<tbody>
<tr>
<td>Collagenase</td>
<td>$1,817</td>
<td>$206</td>
<td>23.4</td>
<td>17</td>
<td>$12/Granulation Day</td>
<td>$78/Granulation Day</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>$1,611</td>
<td>--------</td>
<td>6.5</td>
<td>--------</td>
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*Derived from Milne et al<sup>3</sup>
makes the logical clinical assumption that earlier granulation of the wound bed results in earlier closure of the wound then the value of purchasing an additional granulation day via enzymatic debridement becomes apparent. In this study the daily cost of wound care, excluding the autolytic or enzymatic dressings, was estimated at $37.07. The daily cost included nursing labor costs, semiocclusive cover dressing costs, irrigation solution costs, plus the costs associated with gloves and gauze. If you assume a 1:1 relationship between granulation days gained and wound closure days gained, then for every $12.00 spent on collagenase ointment there is a potential net benefit of $25.07 for each wound closure day gained across the course of therapy ($37.07 - $12.00 = $25.07) due to cost savings from averted wound care.

This research involves an economic assessment of debridement alternatives, not wound healing. Theoretically, it is possible that collagenase ointment could facilitate the closure of pressure ulcers to such a degree that acquisition costs are recovered to the extent that collagenase pays for itself or even provides a cost savings relative to autolytic debridement. The authors acknowledge, however, that pressure ulcers in the long-term setting have considerable potential for chronicity and further study is necessary to test this hypothesis about improved wound closure and cost-savings.

There are a small number of published economic analyses7,14,15 comparing collagenase with hydrogel dressing and the results are consistent with the current study’s clinical and cost-effectiveness findings. Mosher et al7 found that collagenase therapy resulted in a higher likelihood of achieving a clean wound bed and a lower cost of treatment over 1 month than autolysis ($611 vs $921, respectively [1999 US dollars]) among Medicare patients with pressure ulcers. Specifically, collagenase was estimated to be 1.3 times more cost-effective than autolysis. It is important to note the effectiveness outcomes for this study were derived from expert panels, although the results were consistently favorable for collagenase. Another study by Müller et al14 found that wound healing of grade IV pressure ulcers located on the heel was achieved 4 weeks earlier with collagenase than with hydrogel (10 weeks vs 14 weeks, respectively). Average costs were 54% higher with hydrocolloidal dressing, leading to a better cost-effectiveness ratio for collagenase (cost savings of $899 [1998 Dutch guilders] per successfully treated patient). The analysis was based on 24 hospitalized patients in the Netherlands and data were derived from a clinical trial. A study conducted in Germany compared 5 treatments for pressure and venous leg ulcers using Monte Carlo simulation and found that a hydroactive wound dressing plus an enzymatic debridement ointment was more cost-effective than the alternatives (ie, gauze, impregnated gauze, or calcium alginate), due to a reduction in duration of treatment and personnel costs.15

The current study builds upon earlier analyses7,14,15 using currently available products and costs, with clinical inputs derived from a randomized controlled clinical trial, and also reflects an important perspective of the nursing home population. However, results from decision modeling are only as robust as the data inputs, and, therefore, should be interpreted in light of certain limitations.

The clinical data used in this analysis were derived from a clinical trial3 conducted in a single center, with a relatively small patient sample; thus, the results may not necessarily generalize to other hydrogel dressings, health care settings, age groups, or wounds of other etiologies. However, because the difference in clinical benefit was substantial for collagenase compared with hydrogel, and it was this clinical benefit that was the primary driver of improved cost-effectiveness ratio for collagenase, it is reasonable to conclude that larger enrollment results would not produce markedly different results from an economic value perspective.

**Key Points**
- The clinical data used in this analysis were derived from a clinical trial conducted in a single center, with a relatively small patient sample.
- The results may not necessarily generalize to other hydrogel dressings, health care settings, age groups, or wounds of other etiologies.

**Conclusion**

In this economic analysis based on a prospective, randomized, clinical trial of necrotic pressure ulcer therapy occurring in a long-term care setting, collagenase ointment demonstrated its cost-effectiveness relative to autolysis with a considerably less-expensive hydrogel dressing. Based on the clinical trial, a larger proportion of collagenase patients achieved complete wound bed debridement compared to the hydrogel group over the course of therapy. The improved outcomes associated with collagenase therapy translate into a superior cost-effectiveness ratio relative to autolytic debridement with the hydrogel dressing. Despite the higher acquisition cost of collagenase ointment, its clinical benefit offsets its initial cost difference.
In a long-term care setting, treatment of necrotic pressure ulcers with collagenase ointment results in a lower cost per granulation day gained compared to autolysis with a hydrogel dressing. However, the authors’ conclusions must be interpreted with caution because they are based on the clinical notion that granulation always leads directly to wound closure and, in chronic wounds, that assumption may not always hold true.

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Previous Presentation
These data were previously shared by Curtis Waycaster, RPh, PhD. Poster presented at: American Professional Wound Care Association’s APWCA2011 National Clinical Conference; March 31-April 3, 2011; Philadelphia, PA.

References