

A Prospective, Randomized, Comparative Study of Collagenase and Papain-Urea for Pressure Ulcer Debridement

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Abstract: *Objective:* To evaluate and compare the ability of two commercial chemical debridement ointments to effectively remove devitalized tissue and promote granulation in pressure ulcers requiring debridement. One of the test agents was an enzymatic formulation (collagenase) and the other a formulation of papain and urea. *Design:* This study was a prospective, randomized, parallel group, tri-center, open-label, clinical trial with a two-week screening period to stabilize the wound and an evaluation period of four weeks in duration. *Setting:* The patients who participated in the trial were nursing home residents in northern New Jersey. *Participants:* Twenty-eight patients were randomly assigned to ulcer treatment with either collagenase debriding ointment ($n = 12$) or papain-urea debriding ointment ($n = 14$). Two patients dropped out early due to unrelated treatment issues. *Measurements:* Wounds were treated once daily until complete debridement or four weeks. The major outcome of nonviable (necrotic) tissue reduction (determined by planimetry) was assessed weekly by intention to treat. The amount of nonviable tissue, degree of wound granulation, and overall wound response were evaluated weekly using a visual scale. Wound area measurements were performed by morphometric analysis of perimeter tracings. *Results:* The papain-urea debriding ointment was significantly more effective ($p < 0.0167$) than the collagenase ointment in reducing the amount of necrotic tissue at each of the three prospectively determined weekly evaluations. Development of granulation tissue in wounds treated with papain-urea was significantly enhanced as compared to wounds treated with collagenase. Epithelialization generally correlated with the development of a granulating wound bed as determined by visual assessment. However, the general increase in the amount of epithelial tissue associated with the papain-urea-treated wounds did not predict a significantly different rate of reduction in the actual wound area. *Conclusion:* This study evaluated the effects of papain-urea and collagenase on pressure ulcer debridement in a relatively small population (26 patients) of nursing home residents. Although the papain-urea debriding ointment exhibited some clear advantages over the collagenase debriding ointment, a strong scientific conclusion cannot be made.

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Research studies have demonstrated that devitalized tissue present in pressure ulcers enhances bacterial growth, reduces resistance to infection, delays the formation of granulation tissue, and impedes reepithelialization.^{1–6} Debridement is necessary for healing and is considered a cornerstone of pressure ulcer care.^{6–8} Surgical or sharp debride-

ment describes the use of surgical instruments, such as scissors, scalpels, dermatomes, or curettes, to remove devitalized tissue. This is the fastest type of debridement, but it is invasive, may require anesthesia and/or hospitalization, and must be performed by a qualified professional. Mechanical debridement may include the use of wet-to-dry gauze dressings, hydrotherapy, irri-

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gation, and dextranomer bead therapy. Mechanical debridement does not discriminate between viable and nonviable tissue. Autolytic debridement is a form of chemical debridement but does not involve treating the wound with a therapeutic agent. It is the process by which the wound bed clears itself of devitalized tissue and cellular debris by phagocytic cells and endogenous proteolytic enzymes present in the wound or in wound fluid. Autolytic debridement usually requires the use of a moist environment provided by an occlusive wound dressing. The debridement of pressure ulcers by autolysis is not as predictable as with venous ulcers and may take as long as 60 days.⁸⁻¹⁰ Chemical debridement is the application of topical agents (enzymatic or nonenzymatic) that chemically disrupts or digests devitalized extracellular proteins present in the wound. Most of the research work in the field of chemical debridement has dealt with the use of enzymes with proteolytic action.¹¹ However, other chemical agents that denature proteins have also been shown to be useful for the debridement of wounds either as sole agents¹² or when used in combination with enzymes.¹³⁻¹⁵ Among chemical agents used for the debridement of pressure ulcers, the enzyme collagenase has been the most studied in the clinical setting. In general, good to excellent results have been reported when collagenase was compared to an inactive vehicle. However, when collagenase was compared to other active agents or debridement formulations, there were conflicting results.¹⁶⁻²⁰ Three pressure ulcers studies and two pooled chronic wound studies reported enhanced removal of devitalized tissue when collagenase was compared to the petrolatum vehicle or heat-inactivated placebo.¹⁶⁻²¹ When collagenase was compared to autolytic debridement with a hypertonic gel, it was reported that autolysis was superior for pressure ulcer debridement.²⁰ In another study comparing collagenase to fibrinolysin/deoxyribonuclease (DNase) and streptokinase/streptodornase and standard of care control in patients with leg ulcers, no statistically significant differences in debridement and healing were observed between the treatments.^{15,21}

Papain-urea is the combination of a proteolytic enzyme (papain) and a chemical agent (urea),

which, together, act as humectants and agents that render the nonviable proteins within necrotic tissue more susceptible to the proteolytic action of papain. Papain-urea has an advantage over other enzymatic debridement agents in that it is active over a wide range of pH, from 3 to 12. In contrast, collagenase has an optimal activity in a pH range of 6 to 8.²²⁻²⁶ *In-vitro* studies (using heat-denatured porcine skin as the substrate) comparing papain alone and the papain-urea combination demonstrated quantitatively that the combination is approximately two times more effective than the enzyme alone.^{22,32} More recently, using an experimental animal model of debridement, it was shown that papain-urea treatments produced better outcomes (debridement and wound healing) than collagenase or the fibrinolysin/DNase combination.²³ Clinical trials examining the efficacy of papain-urea have been consistently positive, but for the most part, the studies have not been comparative or controlled and have involved the treatment of a wide variety of pooled chronic and acute wounds rather than a more comprehensive examination of the effectiveness on necrotic pressure ulcers.^{13,24-26}

The primary purpose of this study was to evaluate and compare the ability of two commercial chemical debridement ointments to effectively remove devitalized tissue in pressure ulcers requiring debridement. We chose to examine only one wound type and to conduct the study in the nursing home setting where a more conservative approach to debridement is often desirable.

When pressure ulcers are first assessed, the overall damage to the skin and subcutaneous tissues cannot be determined, and the effects of a test agent may be confused with the course of pressure ulcer development. Therefore, an important design element of this study was to evaluate wound debridement after the condition of the pressure ulcer was stable.

Methods

Materials. Collagenase-Santyl[®] (Knoll Pharmaceutical Company, Whippany, New Jersey; currently marketed by Smith and Nephew, Inc., Largo, Florida) is an ointment containing 250 bacterial collagenase units per gram of white petrola-

tum USP. The collagenase is isolated from *Clostridium histolyticum* in a partially purified form. The collagenase is indicated for debriding chronic dermal ulcers and severely burned areas. Collagenase is stable at room temperature and is supplied sterile in 15g and 30g tubes. Collagenase was purchased from the nursing home pharmacy or from Medical Services Group, Inc. (MSG), Wayne, Pennsylvania.

Accuzyme® Papain-Urea (Healthpoint, Ltd., Fort Worth, Texas) is a hydrophilic ointment containing papain (8.3×10^5 units of papain USP activity per gram) and urea (100mg per gram). It is indicated for debridement of necrotic tissue and liquefaction of slough in acute and chronic wounds. Papain-urea is stored in a cool place (8 to 15 degrees C or refrigerated). Papain-urea is supplied in 15g and 6g tubes. Papain-urea debriding ointment was provided by Healthpoint, the sponsor of the study.

Study design. The study was a prospective, tri-center, parallel-group, comparative trial. Eligible patients greater than 18 years old were randomly assigned to receive either collagenase debriding ointment or papain-urea debriding ointment after completing either a one- or two-week screening period to stabilize the wound and institute physical and supportive therapies. The patients were followed for four weeks for analysis of efficacy endpoints prospectively set at two, three, and four weeks. Patients were entered into the study after an institutional review board-approved informed consent was obtained. Patients who qualified to participate in the study were assigned to either the collagenase debriding ointment or the papain-urea debriding ointment groups according to a computer generated-randomization schedule.

Screening for enrollment. Upon identifying the target ulcer, the wound and devitalized tissue were assessed and measured. The wound was cleansed with normal saline, and in order to avoid mechanical debridement, the wound was

dressed with a nonadherent primary dressing (Adaptic®, Johnson & Johnson Medical Inc., Arlington, Texas) and moist-to-moist saline gauze. Dressing changes were performed once daily or p.r.n. (*pro re nata*, according to needs). No other topical agents or dressings were used throughout the screening period. At the end of the screening period, if the target pressure ulcer and area of necrosis were stable (< 20% increase in size) or improving (decrease in size), the patient was advanced into the randomization phase of the trial.

Patient population and disposition. In total, 29 patients were randomized for the trial and 28 were enrolled; of these, 26 patients who met the

Table 1. Patient demographics and wound characteristics

Parameter	Papain/Urea	Collagenase
Patient		
n	14	12
Male	6	5
Female	8	7
Age in years (range)	76 (25–97)	74 (21–101)
Wound		
Stage 2	2	2
Stage 3	3	2
Stage 4	4	6
Unstageable	5	2
Baseline size (SD)	9.8cm ² (8.25)	9.9cm ² (10.66)
Nonviable Tissue		
Slough	7	8
Eschar	7	4
Baseline area (SD)	6.6cm ² (6.07)	4.4cm ² (4.24)
Baseline area % (SD)	70.2 (26.10)	66.7 (32.94)

Table 2. Mean percent nonviable tissue areas and *p*-values*

Treatment	Parameter	Week 1	Week 2	Week 3	Week 4
Papain-Urea	Mean (%)	23	9	2	1
	SD	23	9	3	3
	n	14	11	9	8
Collagenase	Mean (%)	86	85	62	75
	SD	46	51	39	68
	n	12	12	9	8
			<i>p</i> = 0.0001	<i>p</i> = 0.0007	<i>p</i> = 0.0053

* Values expressed as percent nonviable tissue surface area relative to baseline (Day 0)

established inclusion and exclusion criteria produced treatment data sets that were determined to be evaluable. One, patient #3, was incorrectly assigned, so this patient number was skipped. Two patients, #14 and #19, randomized to the collagenase group, met the initial inclusion criteria but did not produce data for the final evaluable data set, leaving a total of 12 evaluable patients in the collagenase debriding ointment patient data set and 14 patients in the papain-urea debriding ointment data set. All wounds were pressure ulcers defined as follows: a wound over a bony prominence in a mobility-compromised individual caused by pressure, shear, friction, or excessive moisture. The target pressure ulcer could be either full thickness or partial thickness and may involve muscle or bone. To enroll the patient, the pressure ulcer must, in the opinion of the investigator, require debridement. A pressure ulcer requiring debridement must have nonviable tissue attached to the base of the wound. If the pressure ulcer was located on the feet, appropriate vascular studies (ankle to brachial index [ABI] of > 0.75 or a normal pulse volume recording [PVR]) were obtained in order to exclude arterial disease. Exclusion criteria were as follows: clinical signs of infection, cellulitis, osteomyelitis, inadequate nutrition, uncontrolled diabetes, and other clinically significant medical conditions that would impair wound healing inclusive of renal, hepatic, hematologic, neurologic, or immunological dis-

ease. Patients receiving corticosteroids, immunosuppressive agents, radiation, or chemotherapy within one month prior to entry into the study were also excluded. Patient demographics and wound characteristics of the two randomization groups are presented in Table 1.

Treatment protocol and follow up. Wound cleansing with sterile normal saline, without preservative, was performed before application of the test agent. There were no forceful irrigation techniques and no other cleansing agents utilized. The same dressing technique was used throughout the study. It consisted of moist saline gauze that was lightly fluffed and covered with sufficient dry gauze to create a moist environment. If the wound was covered with thick hard eschar, the surface was crosshatched with a #10 scalpel blade to allow more surface contact and assist in penetration. If the wound was infected, the infection had to be resolved prior to enrollment. Wound infection was determined by clinical assessment. Manufacturer suggestions concerning dosage and administration were followed in accordance to the package inserts whenever possible.

Treatment with the study medication was performed once daily. Using a tongue depressor, enough study medication (approximately the thickness of a nickel, 2mm) was applied over the entire surface of the nonviable tissue. If the dressing came off or became soiled, only one addition-

al application of the test agent was allowed. If necessary, additional dressing changes were permitted, but no more than two applications per day of the test agents could be performed.

Appropriate support surfaces, such as dynamic air mattress replacement systems, low air-loss beds, air-fluidized beds, alternating pressure mattress overlays, and wheel chair cushions, were provided to all the study patients. Support surface selection was performed by the investigational team and was dependent on the location of the wound and needs of the individual patient according to the Agency for Health Care Policy and Research clinical practice guidelines for the treatment of pressure ulcers. Patients confined to bed were repositioned from supine onto right and left 30-degree oblique positions every two hours using pillows and foam wedges whenever possible. Written turning schedules and diaries were kept for all the study patients.

Study evaluations. One investigator or clinical study coordinator at each site (study personnel) performed all evaluations. All study personnel practiced the evaluation procedures (tracing and clinical wound assessments) in the same five patients prior to starting the trial. Interrater reliability was 91 percent for clinical evaluations and 94 percent for the tracing. Patients were evaluated prior to starting the screening phase and once weekly during screening for a minimum of one week. Upon randomization and prior to treatment, patients were evaluated (baseline). Initially, since it was not known how fast debridement would occur with either of the test agents, evaluations were performed once daily for the first week and twice weekly for three weeks. As the study progressed, it was observed that the daily evaluations were not necessary, as there were no significant changes in wound status. Subsequently, evaluations were performed at least once weekly throughout the four-week study period. At each evaluation, the nonviable tissue type was described as follows: adherent yellow/gray/white slough, adherent soft black eschar, or firmly adherent hard black eschar. The line of demarcation between nonviable and viable tissue was measured, and the percentage of the wound covered with nonviable tissue was estimated. Wound evaluation included overall wound condition,

wound edges (undermining), wound odor, wound pain, wound exudate, peripheral tissue induration, edema, erythema, amount of granulation, and amount of reepithelialization. Nonviable tissue was evaluated clinically by estimating the percentage of the wound base that was covered and quantitatively (objectively) by measuring the area of nonviable tissue from surface tracings. Ulcer healing (epithelialization) was also evaluated clinically and by comparing the surface area of wound tracings. The surface area of the wound and the nonviable tissue attached to the wound base were determined by computerized planimetry of surface tracings made with an acetate transparent film. Maximal length, width, and depth of the wound were also recorded at each evaluation. The primary efficacy endpoint was resolution of nonviable tissue (debridement, determined by both clinical evaluation and area covered by nonviable tissues as a percentage of baseline). Other efficacy endpoints included the presence of granulation tissue (determined by clinical assessment) and overall wound score.

Statistical analysis. Summarized numerical parameters were evaluated using GraphPad InStat version 3.01 for Windows NT (GraphPad Software, San Diego, California). The baseline wound size, area covered by nonviable tissue, and the percent of wound area covered by nonviable tissue were compared using a two-sample *t*-test.²⁷ Due to missing data points (e.g., patients not available for a weekly assessment) and large difference in the variance between the two groups of data points, the Mann-Whitney U-test²⁸ was employed for the planimetric data. Similarly, the clinical assessment measures were all compared using the same nonparametric analysis. When conducting repeated measures (weeks 2, 3, and 4), as we prospectively determined to do, it is necessary to perform a Bonferonni adjustment on the *p*-value required to demonstrate a statistical difference. Taking this into consideration, it was necessary for a calculated *p*-value to be < 0.0167 in order to denote a significant difference between the two groups.

Results

Patient demographics were not different

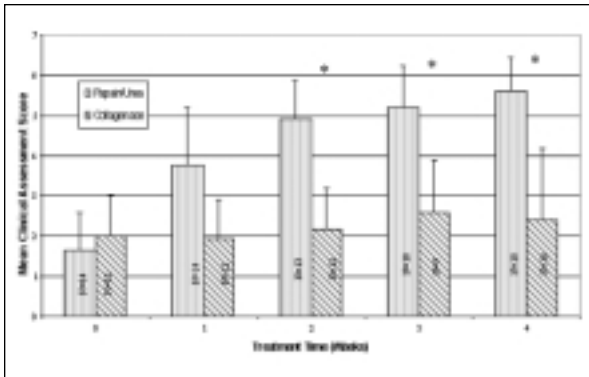


Figure 1. Reduction of nonviable tissue by clinical evaluation.^{ab}

^aVisual score includes both fibrin slough and eschar

^bA score of:

- 1 = 76–100% wound covered with nonviable tissue
- 2 = 51–75% wound covered with nonviable tissue
- 3 = 26–50% wound covered with nonviable tissue
- 4 = 11–25% wound covered with nonviable tissue
- 5 = 0–10% wound covered with nonviable tissue
- 6 = no necrotic tissue

*Indicates a statistically significant difference between means for collagenase and papain urea at $p < 0.0167$.

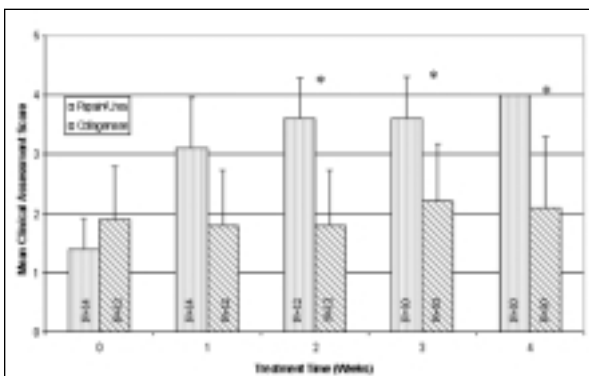


Figure 2. Degree of granulation tissue by clinical evaluation.^a

- ^a 1 = no granulation present
- 2 = < 25% of wound
- 3 = 25–74% of wound filled
- 4 = 75–100% of wound filled

*Indicates a statistically significant difference between means for collagenase and papain urea at $p < 0.0167$.

between the collagenase and papain-urea treatment groups. In addition, there were no significant ($p > 0.05$) differences between the two groups with respect to baseline ulcer size and amount of nonviable tissue (Table 1). Treatment with both debriding ointments was easy and con-

venient. The application of either the collagenase or papain-urea ointments was not associated with any pain or discomfort. Folliculitis was observed in one patient with collagenase but was determined (by the investigator) to be the result of tape irritation and not caused by the study agent.

Treatment with the combination of papain-urea proved more effective than collagenase alone for the debridement of pressure ulcers by both clinical evaluation and planimetry (measurement of nonviable tissue). When scores were compared with the collagenase debriding ointment, at each of the weekly evaluations (weeks 2–4), the papain-urea debriding ointment was observed to be significantly ($p < 0.0167$) more effective in dissolving nonviable tissue at all three time points of the study (Figure 1). Similarly, the reduction in the area of nonviable tissue covering the wounds over time was significantly greater ($p < 0.0167$) for the papain-urea group at all three weekly (weeks 2, 3, 4) evaluations (Table 2). Visual scores showed that the presence of granulation tissue (Figure 2) was significantly ($p < 0.0167$) greater for the papain-urea ointment-treated wounds than the mean granulation scores at weeks two to four for the collagenase ointment-treated wounds.

The epithelialization data indicated that there was an increase in the amount of epithelial tissue that generally corresponded to the development of the granulation tissue. However, the general increase in the amount of epithelial tissue associated with the papain-urea-treated wounds did not predict a significantly different rate of reduction in the actual wound area. The data indicated that the papain-urea treatment did not yield a significant difference in the wound area, as determined by planimetry, relative to the collagenase treatment over the four-week period of the study. Similarly, excluding the amount of granulation tissue and the decreased amount of nonviable tissue, there was no significant difference in the overall wound condition.

Discussion

In pressure ulcers requiring debridement where there is no acute infection, one must consider the overall treatment goals of the patient when selecting a method of debridement.²⁹ In the nursing

home setting when a more conservative approach to debridement is desirable, the use of chemical debridement methods have become accepted and are considered a safe and effective alternative to surgical or mechanical debridement.^{29,30}

The authors compared two chemical debridement methods, an enzymatic agent alone (collagenase) and a combination of an enzyme with a chemical agent (papain and urea). To the authors' knowledge, this is the first time that collagenase has been compared to another chemical debridement formulation in pressure ulcers. Debridement studies in pressure ulcers are generally difficult to conduct, because it is troublesome to know at what stage of necrosis the wound is when treatment is initiated. Upon initial evaluation of a pressure ulcer, it is impossible to determine the full extent of the tissue damage. In order to perform a valid evaluation of debridement, it is necessary to first address the physical and supportive needs of the patient. Then, frequently evaluate the wound until the wound is stable and there is a line of demarcation between the nonviable and viable tissues. Only patients whose target pressure ulcers were stable or improving (after the screening phase) were advanced onto the treatment phase of the trial.

In a study with a relatively small patient population, strong scientific conclusions cannot be made. However, taking into consideration the difficulty of conducting a study of frail elderly pressure ulcer patients in the nursing home setting and the absence of randomized trials, the results of even small controlled studies are of value. In this study, papain-urea proved to be significantly more effective than collagenase for pressure ulcer debridement. Papain-urea also appeared to be more effective in promoting granulation tissue than collagenase. But because wound granulation tissue was only evaluated clinically, it cannot be determined whether there was an increase in granulation tissue production resulting from the treatment or that more granulation was visible after debridement. Our findings are consistent with debridement studies conducted using both animal and *in-vitro* models that have compared collagenase with papain-urea. Hebda, et al., found that papain-urea was more effective than collagenase and

fibrinolysin/DNase in the debridement of both experimental excision and burn wounds.²³ In two separate studies using different *in-vitro* models for debridement, Hobson, et al.,³¹ and Levenson, et al.,¹² demonstrated that the combination of an enzyme (papain) with a mucolytic nonenzymatic agent (urea) was significantly more effective than enzymatic agents alone (collagenase or DNase/fibrinolysin).

The package insert for the collagenase debridement ointment recommends the use of a topical antibiotic powder prior to collagenase application when there is wound infection. However, in order to evaluate the debriding agents only, the use of antiseptic agents and topical antibiotics were not permitted in this trial. It is possible that the use of a topical antibiotic in addition to a chemical debriding agent could lower the wound's bacterial burden. Whether a lower bacterial burden favorably affects debridement or healing of pressure ulcers is not known. In a previous debridement study of pooled chronic wounds, collagenase combined with neomycin was similar to collagenase alone.¹⁸

Initially, it was the authors' intent to conduct this trial in a double-blind manner, but obvious differences in the physical appearance of the test agents combined with the difficulty of controlling for this factor in the nursing home setting made this goal unrealistic. The length of time that a debridement ointment should be used has not been determined. A four-week evaluation period was chosen because it was felt by the investigators that this was ample time for a debridement formulation to demonstrate its efficacy.

Papain-urea is in a white hydrophilic ointment, whereas collagenase debriding ointment has a petrolatum vehicle and is considerably more hydrophobic. Differences in the hydrophilic nature of the ointment vehicles between these two formulations may be of importance, since hydrophilic formulations have been shown to be more effective in releasing enzymes than hydrophobic formulations.³²

In the authors' experience, it appears that both papain-urea and collagenase may be slightly more effective when the substrate is eschar as opposed to fibrin slough. The composition of pressure ulcer eschar is very different than that of

slough. Pressure ulcer eschar is either a hard or soft black nonviable layer composed mainly of elements that make up skin and muscle tissue, such as collagens, keratins, elastic fibers, proteoglycans, and fat. Perhaps treating pressure ulcers with a chemical or enzymatic debridement ointment earlier (before the eschar dissolves) may lead to faster overall debridement and complete granulation.

Sharp, surgical debridement is often considered the standard of care for pressure ulcers requiring debridement. The results of this study demonstrate that chemical/enzymatic debridement with papain-urea was a safe and effective alternative to surgical debridement. Furthermore, in certain patients where a more conservative (or palliative) approach is desired, topical treatment with chemical/enzymatic agents could be a better alternative without pain or increased risk to the patient.

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