Application of hyaluronic acid and collagenase ointment in the treatment of chronic wounds: a case series




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Wound bed preparation is an important concept that encompasses the importance of debridement. The use of proteolytic enzymes is one method of wound debridement. Collagenase is a naturally occurring proteolytic enzymes which is also available as a commercial product which is used for debridement. Collagenase has been shown to be useful for debridement due to its ability to degrade collagen and elastin. This case series reviews eight patients with chronic wounds of different etiologies including diabetes mellitus (n=6), bullous cellulitis (n=1), thigh abscess (n=1). All patients had sloughy, necrotic tissue in the wound bed. Wounds were evaluated using the TIMES concept before cleansed with polyhexamethylene biguanide with betaine (PHMB) solution. Patients were assessed for pain using the Visual Analog Pain Score during each visit. Hyaluronic acid and collagenase (hyaluronic acid sodium salt 0.2% + collagenase) ointment was applied to the wound. Barrier cream was applied to protect the surrounding periwound area. A polyurethane foam dressing was used as the secondary dressing. Patients were followed-up twice a week until the wound was clean and granulating. In this case series, the combined action of hyaluronic acid and collagenase ointment demonstrated a reduction in healing time while improving healing quality although there was limited change seen in relation to pain. There were no adverse events reported. The limitation in this study is that only 8 cases were chosen and this number is a small sample size compared to the population.

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Wound healing consists of four phases including: haemostasis, inflammation, proliferation and tissue remodeling (Gosain and DiPetro, 2004). When any of these phases are disrupted, wound healing can be delayed resulting in impaired tissue repair (Landen et al, 2016). Wound bed preparation has become the gold standard model for proper wound assessment. To facilitate wound bed preparation, a group of wound care experts developed the mnemonic TIMES (T=tissue, I=inflammation/infection, M=moisture imbalance, E=epidermal margin, S=surrounding skin); which was created in 2002 and was updated in 2016 (Vera, 2016). Another wound care guideline, DIME (D=debridement/devitalized tissue, I-infection/inflammation, M=moisture balance, E=wound edge preparation and wound depth), has evolved to include a holistic patient-centred approach to wound care. D in DIME represents devitalized tissue of the wound that need to be debrided (Sibbald et al, 2008). By definition, debridement is the removal of foreign matter or devitalized, injury and infected tissue from the wound (Whiteside and Moorehead, 1999). Debridement techniques include but not limited to surgical, mechanical, autolytic or enzymatic methods in this study. Surgical debridement is removal of devitalized tissue in the presence of underlying infection using sharp

instruments. However, it is not recommended in severely compromised patients as anesthesia may be required. Mechanical debridement is a non-selective type of debridement as it will remove both devitalized tissue and debris as well as viable tissue. Mechanical debridement is often limited by pain associated with the procedure (Ramundo et al, 2009). Autolytic and enzymatic debridement are selective debridement methods as they are design to remove only necrotic / sloughy tissue. Existing evidence suggests that enzymatic debridement is superior compared to autolytic as it is quicker.

Proteolytic enzymes have been used for wound debridement for many years. One of the proteolytic enzymes widely used for debridement is collagenase (Claeys et al, 2010). Collagenase can be made by the body as part of its normal immune response which is also available as a manufactured enzyme. Collagenase has been shown to be useful for debridement due to its ability to degrade collagen and elastin (Cortivo et al, 2011; Onesti et al, 2016). Collagenase degrades fibrinous and necrotic tissue hence it contributes to wound bed preparation. In addition, collagenase preserves peri-lesional skin and healthy tissue (Onesti et al, 2013). Collagenase used in combination in hyaluronic acid (HA), particularly collagenase derived from *Vibrio alginolyticus*, has been shown to promote cell proliferation in healing wounds (Cortivo et al, 2011; Onesti et al, 2016).

Hyaluronic acid is an endogenous compound synthesized by the plasma membrane and can be found in extracellular tissues. HA is believed to play a role in the inflammation and granulation phases of healing (Onesti et al, 2013). In addition, Roehrs et al (2016) proposed that HA helps maintain a moist environment and thus assist cell migration into the wound bed.

Hyalo4® Start is an enzymatic debriding ointment for topical application that is composed of sodium hyaluronate 0.2% from bacterial fermentation and bacterial collagenase derived from non-pathogenic *Vibrio alginolyticus*. Hyalo4® Start is designed in line with the principles of wound bed assessment and preparation (TIMES) and can be tailored according to individual wound needs. It creates a moist environment and prepares the wound bed to promote natural healing. Collagenase used is 99% pure and the absence of non-specific proteases ensures specific action leaving the peri-lesional site intact (Hyalo4® Start Product Insert8, 2016).

Objective

To evaluate the efficacy of hyaluronic acid and collagenase ointment in wound bed preparation.

Methodology

This case series included eight patients with chronic wounds of different etiologies, i.e. diabetes mellitus (n=6), bullous cellulitis (n=1),

Case study 1

- A 70-year-old male: diabetes mellitus, hypertension, dyslipidemia, benign prostatic hyperplasia and bullous cellulitis.
- Diabetic foot ulcer on the right, on the dorsal and lateral heel. Wound presented with slough 70% and granulation tissue 20% with heavy yellowish exudate. Dry skin was seen at the periwound area.

Total duration: 54 days of treatment

Before: 16th July 2019		After: 5th September 2019	
Wound A	Wound B	Wound A	Wound B
			
Total wound area			
63.8 cm^2	7.5 cm^2	20 cm^2	4 cm^2
Pain score			
3		0	

Case study 2

- A 56-year-old female
- Bullous cellulitis on right dorsal foot. Ultrasound revealed heterogeneous subcutaneous hypoechoic collection over lateral aspect representing an early abscess. Wound presented with moderate slough 50%, granulation tissue 25%

Total duration: 44 days of treatment

Before: 17th July 2019	After: 29th August 2019
	
Total wound area	
30 cm^2	9.8 cm^2
Pain score	
1	1

Case study 3

- A 48-year-old male: diabetes mellitus, hypertension. History of Ray's amputation of 3rd right toe
- Left lateral diabetic foot ulcer. Wound presented with exposed tendon, sloughy tissue 50% and granulation tissue 10%

Total duration: 46 days of treatment

Before: 25th July 2019	After: 5th September 2019
	
Total wound area	
96 cm^2	51 cm^2
Pain score	
0	0

thigh abscess (n=1). Patients were included in the evaluation if their wounds were sloughy or necrotic tissue (more than 50%). For this study, wounds were evaluated by using the TIMES framework before cleansing with polyhexamethylene biguanide with betaine (PHMB) solution. Patients were assessed for pain using the Visual Analog Pain Score of 1 to 10 on each visit. Hyaluronic acid and collagenase (hyaluronic acid sodium salt 0.2% + collagenase) ointment was applied to the wound as per standard of care. A barrier ointment was applied to the surrounding periwound area. Polyurethane foam was used as the secondary dressing. Patient follow-up was twice a week until the wound was clean and granulating. A 2-layer compression bandage was applied for chronic venous ulcers patients and diabetic foot ulcers were offloaded using paddings.

The trial was conducted in accordance with the guidelines set in the Declaration of Helsinki and approval by hospital review board. Informed consent and permission to use clinical images and case details for publication/research purposes were obtained prior to the evaluation.

Case study 4

- A 48-year-old male: diabetes mellitus, hypertension. History of ray amputation of 3rd left toe
- Left lateral diabetic foot ulcer. Wound presented with exposed tendon, sloughy tissue 50% and granulation tissue 10%

Total Duration: 48 days of treatment

Before: 25th July 2019	After: 10th September 2019
	
Total wound area	
72 cm^2	4 cm^2
Pain score	
1	0

Case study 5

- A 69-year-old female: diabetes mellitus, hypertension and dyslipidemia
- Initial wound on 4th left toe followed by severe infection, which resulted in extensive wound debridement and amputation of 4th and 5th toes. Wound presented with thick sloughy tissue 50%, granulation tissue 40%. Maceration tissue was seen at the periwound area

Total Duration: 41 days of treatment

Before: 25th July 2019	After: 3rd September 2019
	
Total wound area	
158 cm^2	98 cm^2
Pain score	
3	0

Case study 6

- A 75-year-old female: diabetes mellitus
- Diabetic wound on 2nd right toe. Wound was sloughy 70% with granulation 20% tissue and epithelization 10% of skin surrounding the wound

Total duration: 10 days of treatment

Before: 25th July 2019	After: 3rd September 2019
	
Total wound area	
3 cm^2	1.2 cm^2
Pain score	
1	1

Case study 7

- A 52-year-old male: diabetes mellitus and hypertension. History of ray amputation of 1st and 2nd toes followed by 4th and 5th toes of the left foot
- Infected left diabetic foot ulcer. Wound with slough 50%, granulation 50%. Maceration tissue seen in periwound and tunneling seen about 4 cm at 12 o'clock

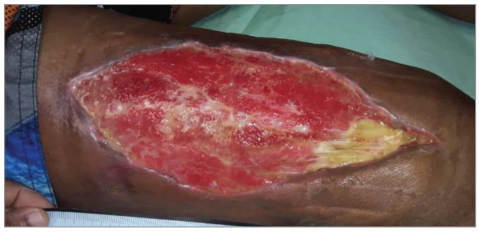
Total duration: 16 days of treatment

Before: 15th August 2019	After: 30th August 2019
	
Total wound area	
19.5 cm^2	7.5 cm^2
Pain score	
0	0

Case study 8

- A 62-year-old male: diabetes mellitus
- Ruptured right thigh abscess. Wound presented with slough and fibrin 50%, granulation 50%, exposed tendon and dry periwound

Total duration: 58 days of treatment

Before: 25th July 2019	After: 17th September 2019
	
Total wound area	
175.8 cm^2	75 cm^2
Pain score	
0	0

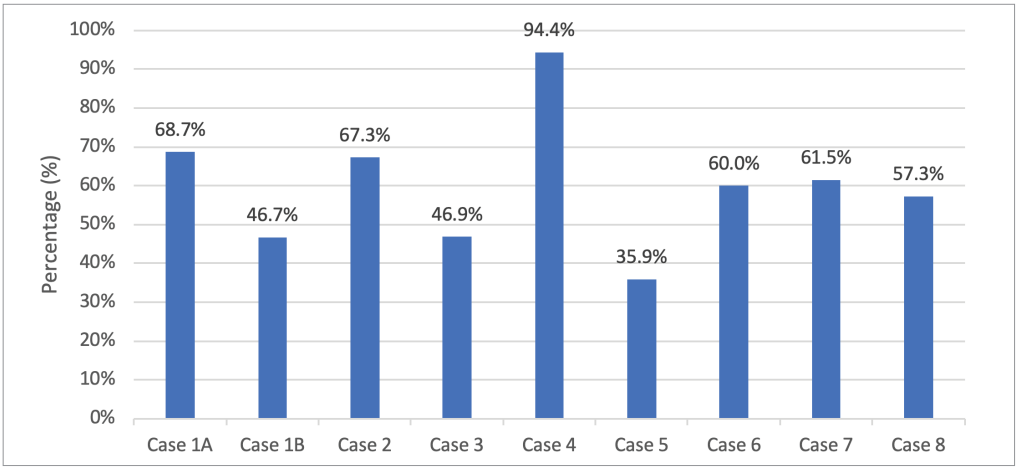


Figure 1. Overall reduction in wound size at the end of treatment.

Please note that in case 4, rthe eduction of wound size was affected by the closing of the wound with sutures as the wound was granulating and epithelizing. Wound size reduced 48.8% (from 72 cm^2 to 36.8 cm^2) prior to suturing and reduced a further 76.5% (from 17 cm2 to 4 cm^2) afterwards.

Discussion

All cases showed improvement in the wound bed whereby there was a reduction in the slough and necrotic tissues as well as reduction in wound size. Case 5 took a longer period as it was a case of plantar aspect ulcer which required proper offloading. The plantar aspect ulcers usually take a longer time even with standard of care.

The results of this case series are similar to that reported in previous studies whereby application of the Hyalo4® Start ointment resulted in improved healing (Onesti et al, 2013; Onesti et al, 2016; Scalise et al, 2017). In all of the case series presented in this study, there was a reduction in the amount of slough until the wound was clean and granulating.

There was also a decrease in wound size treated with Hyalo4® Start, with up to a 69% reduction in the total area of wound size. The patient in Case 4 who had experienced the 94.4% reduction in wound size was unique as the wound was sutured to oppose the edges after experiencing improvement in healing after beginning treatment with the Hyalo4® Start ointment.

Collagenase from *Vibrio alginolyticusis* effective towards the native collagen, or type 1 collagen, which is responsible for eschar's "anchoring" on the bottom of the lesion (Cortivo et al, 2011). Besides that, hyaluronic acid facilitates the migration of fibroblasts and endothelial cells in the natural process of re-epithelialization. Hyaluronic acid moderates the inflammatory phase, by acting as a scavenger of the free radicals and activation a negative feedback (Cortivo et al, 1996; Onesti et al, 2013).

There was limited change in the pain score for the patients observed in these cases. A possible explanation for this is that a majority of these patients were diabetic and were likely to have had a degree of diabetic neuropathy. Due to this, their pain scores were low. Another explanation could be due to the pain-relieving properties of HA which induces activation of the -opiod receptor. (Zavan at al, 2013).

A limitation in this study is that only 8 cases were chosen and this number is a small sample size compared to the population. More studies are needed to verify these results.

Conclusion

In this small case series, the combined action of hyaluronic acid and collagenase ointment showed clinically significant improvements in wound debridement and wound closure. The evidence seems to indicate that hyaluronic acid and collagenase ointment can help to reduce healing time while improving healing quality. WAS

Declaration of interest: EP Plus Group supplied the hyaluronic acid and collagenase ointment (Hyalo4® Start) used for this study. The author has no conflicts of interest to declare.

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