

TREND ARTICLE

Use of collagenase ointment in conjunction with negative pressure wound therapy in the care of diabetic wounds: a case series of six patients

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Background: Diabetic wounds with additional comorbidities are costly, time intensive, and difficult to heal. Often, multiple modalities may be necessary to achieve wound resolution, relying on the synergistic advantage of each therapy to affect wound healing. The selectivity of *Clostridium* collagenase is physiologically effective at degrading non-viable collagen fibers while preserving living collagen tissue. Additionally, negative pressure wound therapy (NPWT) has long been used to aid wound healing while concurrently depreciating biological wound burden time.

Methods: Six patients were selected from those appearing to our university based limb salvage service. Inclusion criteria included patients with a recurrent mixed fibrotic and granular wound base, in which NPWT was indicated, without exclusion criteria. Patients enrolled were administered clostridial collagenase ointment at each regularly scheduled NPWT dressing change. Patients were followed until healing, with visual representations of wound progression and time to full healing recorded.

Results: Tandem application of these therapies appeared to expedite wound healing by clearing degenerative fibrous tissue and expediting wound granulation without additional complication. Unfortunately, not all patients were able to reach full healing; with two patients experiencing ulcer recurrence, likely a result of their significant comorbid nature.

Conclusion: In our experience, we have noticed a specific subgroup of patients who benefit greatly when collagenase enzymatic debridement therapy is combined with NPWT. It is our belief that this combination therapy combines the molecular clearing of non-viable collagen with the wound granulation necessary to advance complex wounds to the next step in healing despite the current paucity in literature discussing this specific pairing.

Keywords: *diabetes; ulcers; wound healing; negative pressure wound therapy; collagenase*

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Diabetic foot ulcers are a grave complication of diabetes mellitus, occurring with a predicted lifetime risk as high as 25% (1, 2). Neuropathic foot ulcerations precede approximately 85% of lower limb amputations in the diabetic population (3, 4) and are well linked to significant patient morbidity (5, 6). Over the last decade, the economic cost of diabetes has skyrocketed, estimated at \$174 billion in 2007 and over \$245 billion in 2012 (7); 25–50% of the costs related to inpatient diabetes care may be directly related to diabetic foot ulcers (DFU) (8). It should therefore come as no surprise that some

33% of the direct costs of diabetes and its complications are linked to the treatment of foot ulcers (4, 9).

In the last two decades, the use of negative pressure wound therapy (NPWT) has become ubiquitous for the promotion of granulation tissue after significant tissue loss or wound debridement (10, 11). Apelqvist et al. established that post-amputation patients with diabetes who received NPWT drastically reduced their cost to the system; this population demonstrated lower resource utilization and fewer clinic visits, dressing changes, and surgical procedures when compared to those who only receive standardized

moist wound therapy (12). In some cases, however, NPWT may not be enough. In a subset of patients who present with chronic non-healing wounds, underlying comorbid conditions such as nutritional deficits, drug therapy, or aging skin may cause an impairment of endogenous collagenase production and therefore lead to an insufficiency in autologous dead tissue removal.

The targeted proteolytic activity of clostridial collagenases isolated in the 1950s by bioscience pioneers Mandl, Seifter, Harper, and colleagues was demonstrated to deliver targeted disruption of types I, II, III, IV, and V collagen while maintaining the integrity of viable tissue in wounds (13). In the chronic wound, both viable and denatured collagens are the major constituents of the wound eschar and thus selective debridement is essential in the health of the wound (14). Selective degradation remains superior to non-selective methods due to the risks associated with disruption of viable wound tissue such as fibrinolysis and increased bleeding (13).

In this article, we present six cases from our inpatient hospital service where tandem utilization of collagenase enzymatic debridement with NPWT was complicit in wound progression to the next stage of ulcerative healing.

Methods and materials

Patient care in this series (Table 1) was guided by the following parameters. Following sharp debridement, irrigation, and measurement, the patient's wound is windowed-out using forceps or a tongue depressor. Santyl collagenase ointment 250 units/g (Smith and Nephew, London, UK) is then spread evenly over the entire wound base. Note, it is advisable to make every attempt to prevent excess Santyl application to gloves or the periwound area, as it may compromise the subsequent drape adherence. Regular Santyl application continues until healthy granular tissue replaces all fibrotic slough. In some cases, NPWT therapy may continue after Santyl application is no longer indicated.

Due to availability, the KCI V.A.C.UltTM Negative Pressure Wound Therapy System (Kinetic Concepts

Incorporated, San Antonio, TX) was preferred during patient admissions. It was also preferred in instances of larger wounds or those requiring increased drainage. During all KCI V.A.C.UltTM application, the supplied black sponge is used and sealed at a continuous 125 mmHg of continuous pressure. Smaller more superficial wounds received the SNaP[®] 125 mmHg NPWT system (Spiracur Inc., Sunnyvale, CA) with the supplied blue foam. All NPWT systems were applied to manufacturer specifications and changed at least three times per week with reapplication of Santyl at each instance. For high risk cases these changes would be done twice per week by a wound care nurse and patients would be seen once per week by a podiatrist.

Case series

Case #1

Our initial patient was a 66-year-old male with a medical history significant for coronary artery disease, acute left ventricular dysfunction, heparin-induced thrombocytopenia, and peripheral vascular insufficiency. He was transported from Colorado to our facilities in Tucson for emergent treatment of bilateral dry gangrene of the forefoot on November 7, 2013 (Fig. 1). Initially, a right Chopart and left transmetatarsal amputation (TMA) were performed in the operating room. The left extremity was allowed to heal by secondary intention in attempts to avoid a more proximal TMA.

Following bilateral surgery, the left extremity became deeply fibrotic and remained gangrenous, at which time the patient enrolled in 3 weeks of larval tissue debridement therapy (Fig. 2). This was followed by a repeat surgical debridement on December 11, 2013 (Figs. 3a and b), where intraoperative inspection exhibited a mixture of fibrotic and granular tissue base. The presence of stagnant tissue debris over a granulated wound base warranted collagenase administration in addition to NPWT. Therefore, tandem therapy was initiated and the patient was kept

Table 1. Patient demographics

	Initial wound size (cm ³) (initial)	Initial wound locations	Status of last follow up	Vascular interventions during therapy
Case #1	Left: 5.3 × 5.6 × 3.2 Right: 5 × 5 × 3	Left and right plantarly	Left remains healed. Right has reopened.	None
Case #2	7 × 11 × 1	Left dorsal and plantar	Status post metatarsal head resection with extensor tenotomies.	Initial revascularization performed 1/10: Angioplasty with stent on 7/23.
Case #3	1.3 × 0.1 × 0.5	Left hallux	Healed	None
Case #4	1 × 1.4 × 0.1	Right heel	New wound lateral left foot. Prior wounds remain healed.	None
Case #5	4.1 × 1.6 × 0.4	Left plantar metatarsal head	Healed	None
Case #6	1.7 × 0.8 × 0.5	Left hallux, plantar	Healed	None



Fig. 1. Sixty-six-year old male presented to our facility with a significant history of vascular insufficiency and an emergent case of bilateral gangrene of the forefoot. Upon arrival, patient was immediately taken to the operating room and received a right Chopart amputation and left trans-metatarsal amputation.

in-house for 1 week. In this time, the burden of fibrotic sloughage decreased and areas absent of healthy wound tissue rapidly granulated. With this resolution, the patient was released to a skilled nursing facility on January 6, 2014 (Fig. 4).

During follow-up, the patient presented from nursing care with significant purulence from the left foot wound prompting the resumption of advanced wound care. Conjoined collagenase/NPWT using a KCI V.A.C. was reinstated, with progressive improvement in healing noted. After a month of tandem therapy, sufficient granulation prompted split-thickness skin graft (STSG) application via the SALSA Spike (Fig. 5), which was applied with full incorporation (15). The patient was administered a custom shoe, and is now currently ambulatory on the left extremity.

Following the initial bilateral surgeries of this patient's gangrenous wounds, the right extremity was treated as a separate entity. The emergent right Chopart amputation mentioned above resulted in an eschar covering the right plantar surface. Due to a patient allergy, betadine was unable to be utilized, so other modalities to facilitate drying were attempted upon discharge to skilled nursing facility. Unfortunately, after 2 weeks of patient follow-up, two deep wounds divided by an island of skin were noticed beneath the superficial eschar. During the application of a STSG for the left limb on February 19, 2014, the right limb eschar was debrided and a rotational flap attempted to close the irregular right plantar wound.

Postoperatively this wound dehiscd, leading to further ulceration and continued disrepair. At this point, collagenase and NPWT were initiated to promote healing of the wound, and the tandem therapy was reinstated following an additional right incision and drainage on April 2, 2014. Follow-up was noted as progressing well on May 20, 2014 (Fig. 6). As of September 28, 2014, wounds



Fig. 2. Following emergent amputation and debridement, the left extremity was allowed to close by secondary intention and became deeply fibrotic and gangrenous. At this time the patient was enrolled in 3 weeks of larval debridement therapy to reduce the presence of degenerative tissue.

of the right plantar foot are healed (Fig. 7), with wounds of the left nearly healed (Fig. 7).

Case #2

Our second case discusses a 55-year-old male with a history of poorly controlled diabetes, peripheral neuropathy, a hemoglobin A1c >16, multiple lower extremity ulcerations, and Fournier's gangrene. He presented to our hospital service on January 8, 2014, with left shoulder pain as well as a painful Wagner stage 3 left foot ulcer. The lower extremity ulcer demonstrated significant edema, erythema, and absent palpable pulses on examination. He concurrently had a left shoulder non-union fracture with swelling, warmth, and pain. This was to be later confirmed as secondary to an abscess. The patient was admitted for sepsis with positive blood cultures for gram positive cocci, and was administered broad spectrum IV antibiotics.

Magnetic resonance imaging of the left foot confirmed cellulitis overlying a deep soft tissue abscess accompanied by osteomyelitis of the left fifth metatarsal base. The wound was circumferential and at high risk for systemic involvement. The presentation and nature of this wound elicited numerous suggestions from other services for proximal amputation. Two days following admission, the



Fig. 3. After 1 month of inpatient therapy, the patient was again taken to the operating room for bilateral debridement. (a) represents the preoperative status of the patient's wounds. (b) represents the intraoperative status of the wounds following staple removal (right) and debridement of yellow, fibrous tissue (left). Postoperatively, the patient was initiated on routine Santyl and negative pressure wound therapy treatments, and kept in house for 1 week.

patient underwent left foot incision and drainage with debridement to the level of the tendon and fifth metatarsal resection (Fig. 8).

Following surgery, two separate instill NPWT were placed, one on the dorsal surface and one on the plantar surface of the wound. The NPWT systems were changed three times per week during this admission, and the patient was kept under tight glycemic control. On January 15, 2014, the patient again underwent surgical incision and drainage (Fig. 9) and due to the significant size and circumferential nature of the postoperative wound the dorsal and plantar aspects were treated separately. NPWT therapy was applied to all exposed wounds, with collagenase product applied to the partially fibrotic dorsal, medial, and lateral wound surfaces.

On January 22, 2014, purulent discharge was noted from the eschar at the distal plantar forefoot, and the patient underwent further surgical debridement. Following debridement of the plantar wound, NPWT was reestablished in

tandem with collagenase gel application. By February 12, 2014, significant wound granulation warranted a STSG (Fig. 10) to dorsal, medial, and lateral wound surfaces utilizing white foam NPWT to promote graft anchoring and wound drainage. Plantarily, black foam was utilized with collagenase therapy to promote granulation and to aid in clearing the deep, non-viable, and fibrotic tissue which remained.

Due to the healthy wound base prepared by the use of tandem NPWT and collagenase enzymatic debridement, the dorsal STSG healed well, exhibiting fully granulated tissue without subsequent purulence, erythema, and only mild pain. The plantar wound eventually achieved granulation sufficient to warrant a second skin graft, this time to the plantar facet of the wound, on March 17, 2014 (Fig. 11). Unfortunately, before complete healing seemed likely (Fig. 12), the patient was lost to



Fig. 4. Following significant healing as a result of week-long Santyl and negative pressure wound therapy, the patient was taken to the operating room for a third debridement and irrigation, and was released to a skilled nursing facility.



Fig. 5. During split-thickness skin grafting of the left plantar foot, the right extremity was debrided of plantar eschar and closed with a rotational flap. The SALSA 'Spike' technique was used to secure the skin flap using two 0.45 Kirschner wires. This is a strong, inexpensive and versatile solution to secure fasciocutaneous flaps when local soft tissue anchoring alone may not be possible.



Fig. 6. Postoperatively, the right wound dehiscd and after repeated use of Santyl with negative pressure wound therapy and surgical debridement the wounds presented as pictured on 5/20/14.

follow-up. During this time, the patient experienced a reversal of progress and as of August 22, 2014, is currently status post multiple metatarsal head resections with extensor tenotomies.

Case #3

This 39-year-old male presented to the emergency department on November 10, 2013, with an ulcer of the left hallux and associated abscess for which he was admitted

the next day. On November 16, 2013 he underwent debridement of non-viable soft tissue and bone with a first hallux interphalangeal joint (IPJ) arthroplasty. Debrided tissue was determined to be acute osteomyelitis of the left distal hallux with cellulitis of the distal foot confirmed via radiograph. He was discharged on antibiotic therapy of ertapenem for 2 weeks through a peripherally inserted central catheter.

The patient returned to the emergency department on November 24, 2013, due to significant purulent drainage from the wound with associated edema, skin ulceration, and necrosis of the underlying muscle. It is thought that upon closure of the skin a significant enough void remained to provide a nidus for infection. As a result, the wound became deeply fibrotic with resulting eruption and wound dehiscence. A second debridement was performed, and following this operation, collagenase debridement with NPWT was instituted. The use of NPWT during the second closure provided support for the cavitation created by the debridement of necrotic tissue. Collagenase therapy reduced fibrous tissue burden and allowed for the growth of healthy tissue. Rapid granulation secondary to collagenase/NPWT therapy allowed for subsequent delayed primary closure with great success. The patient healed his wound by December 6, 2013, and



(a)



(b)

Fig. 7. With 4 months of continued Santyl and negative pressure wound therapy, the wounds continued to close, and as of 9/8/14 the patient presented with a closed right wound (a) and nearly closed left (b).



Fig. 8. Preoperative presentation of a left, cellulitic, soft tissue abscess overlying the fifth metatarsal, extending both plantarly and dorsally. Magnetic resonance imaging of the left foot confirmed osteomyelitis of the bone, and the patient was taken to the operating room for emergent incision and drainage.

returned to full ambulation by his January 23, 2014, visit. As of July 22, 2014, the patient remains healed, and has not returned.

Case #4

Our service was consulted in November 2013 for a malodorous right heel eschar. The patient is a 70-year-old woman with a history of peripheral vascular disease, hypertension, diabetes mellitus type 2, Alzheimer's, prior left lower extremity angioplasty, and left great toe amputation. She was brought to the operating room where a partial calcaneotomy was performed due to osteomyelitis. The wound was intended to heal via primary closure, however due to altered mental status; the patient was unable to comply with the request to keep her incision site offloaded. This resulted in dehiscence with significant wound fibrosis.

A collagenase/NPWT combination was applied on November 15, 2013, to facilitate adequate granulation and enzymatic debridement of the non-viable fibrotic tissue. The patient was administered a multipod boot, which allowed her to ambulate and maintain compliance with adequate offloading. Wound health quickly precipitated, and the patient was allowed to upgrade to a Charcot restraint orthotic walker, which facilitated even



Fig. 9. Following 1 week of postoperative negative pressure wound therapy, the patient again underwent surgical incision and drainage of both the plantar (Fig. 8) and dorsal wounds (Fig. 9). Postoperatively, negative pressure wound therapy was applied to all wounds, with collagenase product applied to the partially fibrotic dorsal, medial, and lateral wound faces.

greater ambulation with offloading. As of May 6, 2014, the patient's heel wound has completely healed and the patient is able to ambulate uninhibited. Unfortunately, new wounds on her left foot were noted on July 29, 2014; however, her healed wounds remain resolved at this time.

Case #5

On November 11, 2013, a 45-year-old male returned to our clinic for evaluation of a wound caused by a prominent plantar left second metatarsal head. This patient was well-known to our podiatric service and has been treated for numerous infections of chronic non-healing wounds, and has undergone multiple limb salvage procedures. It was found that as a result of biomechanical changes due to a previous limb salvage attempt he developed this prominence, associated wound, and a sub metatarsal head adventitial bursa (Fig. 13). He therefore underwent a second metatarsal exostectomy with bursa excision and wound debridement.



Fig. 10. One month following the initial operative incision and drainage, significant wound granulation accumulated as a result of the persistent tandem use of Santyl and negative pressure wound therapy. This prompted the use of a split-thickness skin graft to the dorsal, medial, and lateral wound surfaces. After 1 month of continued postoperative care, the dorsal graft healed well.

On November 22, 2013, collagenase alone was applied during postoperative dressing changes to facilitate enzymatic debridement of remaining non-viable tissue. The patient failed to appear at the weekly scheduled follow-up but returned on December 5, 2013, presenting with incision dehiscence (Fig. 14). Fibrous slough was noted upon suture removal, and there was low suspicion for wound infection at that time. Empiric antibiotic therapy was initiated, and NPWT with a total contact cast (TCC) therapy was utilized. Cast changes were subsequently performed every 3 days, and over-the-counter gentian violet was administered to reduce NPWT maceration.

Due to decreased healing and persistent fibrosis, collagenase was added to NPWT therapy on December 19, 2013 (Fig. 15). With 1 month of concomitant collagenase, NPWT, and TCC therapy, full healing of the plantar wound was noted on January 10, 2014. As of February 4, 2014, the patient presented as healed, and has not needed to return to the clinic.

Case #6

This 41-year-old patient presented to our podiatry service on December 2, 2013, with a painful blister below the left great toe and was associated with swelling, erythema,



Fig. 11. Two months following the initial operative incision and drainage, the plantar wound achieved sufficient granulation to warrant a split-thickness skin graft.

fever, and chills. Patient had a longstanding history of insulin dependent diabetes mellitus, and upon examination, the wound was erythematous, tender, edematous, purulent, and malodorous. His white blood cell count was elevated to a level of 15.6, and radiographs revealed prominent soft tissue swelling, air within the soft tissue about the great toe IPJ, and osseous fragmentation of the distal phalangeal base.

Due to clinical and radiologic evidence of acute soft tissue infection with osteomyelitis, the patient underwent



Fig. 12. During follow-up this appeared to be progressing towards healing, however, due to this patient's significant comorbid state, the patient's deteriorated and he required multiple metatarsal head resections with extensor tenotomies.



Fig. 13. Patient presented to our clinic for evaluation of a wound secondary to a descended left second metatarsal head remnant of a previous limb salvage attempt. This patient was taken to the operating room for a second metatarsal exostectomy with bursa excision and wound debridement. Postoperatively, the patient was managed with collagenase enzymatic debridement to perpetuate the removal of non-viable tissue.

beside incision and drainage. An IPJ resection of the left hallux was performed the next day without complication. The patient was discharged home with a TCC and NPWT on December 11, 2013. The patient was seen in our clinic for regular NPWT changes and follow-up. On February 14, 2013 the patient returned with a full dehiscence of the surgical incision. Significant fibrotic tissue was present within the resected space, and the resultant infection and swelling led to tissue necrosis and the disruption of suture lines.

Due to the evolved nature of the wound, including fibrosis, the patient was started on a weekly regimen of collagenase debridement, NPWT, and TCC. He continued this regimen for 2 months with weekly office visits for equipment checks, cast changes, and reapplication of collagenase. By February 4, 2014, the wound was free from fibrotic tissue and noted to have a fully granular base. On March 26, 2014, the patient presented as fully healed and able to ambulate without complication. He has not needed to return to the clinic since resolution.

Discussion

Diabetic wounds with numerous comorbidities are costly, time intensive, and difficult to heal. Numerous modal-



Fig. 14. Unfortunately, the patient was non-adherent to scheduled follow-ups, and after 1 month, presented with significant dehiscence of the surgical wound. The patient received empiric oral antibiotic therapy, debridement, negative pressure wound therapy, and was placed in a total contact cast. Gentian violet was also administered to the wound sites to reduce maceration caused by prolonged negative pressure therapy inside the cast.

ities are often necessary for successful resolution of these wounds, including the regular use of overlapping therapies. In our experience, we have noticed a specific subgroup of patients who benefit greatly when collagenase enzymatic debridement therapy is combined with NPWT. In conjunction with the available scientific evidence, it is our belief that this combination therapy combines the molecular clearing of non-viable collagen with the wound granulation necessary to achieve satisfactory wound healing in the difficult to resolve case.

Full thickness debridement of chronic wounds has been the mainstay of wound healing therapy for decades. Frequent and regular debridement has been shown to improve healing rates of DFU's and venous leg ulcers, due to the ability of debridement to revert a previous chronic wound back to an acute status (16). Essential to this transition is the removal of decaying necrotic tissue, the majority of which is comprised of collagen dense connective tissue. The selectivity of *Clostridium collagenase* is physiologically attributed to the mucopolysaccharide sheaths present on intact collagen, a barrier *clostridial collagenase* is unable to bypass and disrupt (14). In this way, *clostridial collagenase* is effective at specifically degrading



Fig. 15. After 2 weeks of post-dehiscence management, and due to the presence of persistent fibrosis, collagenase debridement was re-initiated in tandem with the continued negative pressure wound therapy and total contact cast. Within 1 month of concomitant usage, full healing of the plantar wound was noted, and confirmed again at the 1 month follow-up.

non-viable collagen fibers, while preserving living collagen tissue in the wound to aggrandize healing (17).

Enzymatic debridement has also demonstrated superiority over mechanical debridement by reducing neutrophil infiltration and periwound inflammation while improving rates of full thickness closure (13). Selective degradation remains superior to non-selective methods such as mechanical debridement due to the risks associated with disruption of the viable wound tissue and fibrin and the increased risk for extended bleeding (13). Promotion of cell migration in addition to the specificity of collagen debris degradation strongly supports the use of *Clostridium* collagenase in chronic wounds that require serial debridement.

However, it is clear that no single exogenous agent can effectively mediate the multifarious components of difficult to heal diabetic wounds. In conjunction with debridement of necrotic wounds, granulation of the exposed wound area is often necessary to achieve resolution. Numerous publications link the use of NPWT to improved granulation formation, decreased healing times, and lowered cost of treatment when compared with standard dressings (18–20). However, the molecular mechanisms behind its success are still undefined.

It is possible that the subatmospheric conditions present in NPWT accelerate wound healing by invoking increased cellular migration to the wound site (21). In addition, the use of intrawound gauze or foam appears to be critical to the rapid regranularization of wound sites, demonstrating a general trend for increasing success rates when used (22, 23). Additionally, Armstrong et al. demonstrated similar wound healing outcomes in a multi-center randomized controlled study comparing SNaP wound care system with the KCI wound VAC product (24). In our experience, collagenase therapy is equally efficacious with either NPWT product, and no significant difference in time or ability to heal was noted with use of either device.

It is important to note that the use of collagenase with heavy metal ions, especially with transition metals that feature iron (Fe^{++}), silver (Ag^{++}), or nickel (Ni^{++}) is contraindicated as these ions significantly inhibit collagenase activity (13). Therefore, when deciding what dressings to use with any collagenase therapy, materials containing Iodine or Silver should be avoided as they have an inhibitory effect on enzyme performance. In addition, pH regulation should be considered, especially because dual therapy with NPWT has the potential to create an environment unsavory for collagenase activity.

The nature of these case reports demonstrate new experiences in which NPWT and conjunctive enzymatic debridement were utilized to aggrandize wound healing. There are, of course, several weaknesses inherent in a report of this format. A small sample of six individuals was presented in this report, without control comparison. Additionally, therapies were applied based on clinical judgment, and in varying types and severity of wounds. The remaining strength is the discovery that collagenase/NPWT tandem treatment has been safely utilized in wounds of varying etiologies, severity, and treatment modality. One of the more difficult attributes of the selection of patients involved in this report is the varying severity and treatment modalities of comorbidities. Different aspects of comorbidity and concomitant therapy may influence the outcome of wound healing. Although acknowledged, there were no significant changes in comorbidity therapies other than glucose control and systemic antibiotics that would have drastic impact on wound cellular make-up including fibrosis, nor the effects of tandem therapy on a distal lower extremity wound to promote granulation or decrease fibrous burden.

Conclusion

Over the past three decades, investigative research has elucidated extensive details regarding the cellular regulation of cutaneous wound healing, and has demonstrated that isolated treatment modalities alone cannot effectively mitigate the multiform complications of wound healing (25). It is our understanding that many care centers across

the nation pair NPWT with collagenase therapy, yet it remains previously unreported. Due to its cost-effectiveness and ease of application, reporting this tandem treatment regimen will allow it to gain wider integration into treatment algorithms, thus improving wound healing outcomes.

Conflict of interest and funding

The authors have not received any funding or benefits from industry to conduct this case series.

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