Photodynamic Therapy Associated With Mesalt® In The Treatment Of Hypergranulation In Diabetic Foot Ulcer

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Introduction

Diabetic foot ulcers (DFUs) are a significant source of morbidity in adults with diabetes mellitus (DM).[1] The standard treatment for DFU care includes regular follow-ups by specialized professionals for ulcer assessment, cleaning and debridement, removal of calluses, selection of dressings and off loading devices to control exudation and maintain a moist environment, as well as infection control.[2] However, in people with DM, this standard treatment has often proven insufficient to achieve healing in a satisfactory timeframe.[3]

The delay in healing may be partly due to DM itself, as this disease impairs the three phases of healing (inflammatory, proliferative and remodelling),[4] and also because most DFUs have polymicrobial cultures, with the presence of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus spp*., *Streptococcus*, *Escherichia coli* and *Enterococcus spp.*, which delay the healing process.[5] Furthermore, colonization by these microorganisms can prolong the wound's inflammatory phase and trigger excessive granulation, also known as hypergranulation which delays the healing process.[6]

Clinically, hypergranulation is identified as a friable, red, shiny, soft tissue that extends beyond the level of the surrounding skin and physically impedes the migration of epithelial cells to the wound bed.[7] The exact mechanism in which this cell migration better works remains unclear in the literature. However, it is still accepted that ulcers usually do not heal appropriately when hypergranulation tissue is present, as it becomes difficult for epithelial tissue to migrate across the wound surface. In this sense, contraction is generally interrupted or delayed.[8]

Despite being an important phenomenon in the healing process, hypergranulation is underexplored in the literature and its treatment is marked by controversy. Currently, there is a range of treatment reports, such as silver nitrate, 20% sodium chloride, and topical corticosteroids, among others.[6] With the advent of new adjunct technologies for wound treatment, other options should be tested in the treatment of hypergranulation. Therefore, in this study, we opted for the antimicrobial photodynamic therapy (PDT) associated with Mesalt® (Mölnlycke)*, a technological dressing specifically designed to treat excessive granulation.

PDT involves a light source (Laser or LED) that transfers energy to a photosensitizer, such as methylene blue, which reacts with intracellular substrates to form free radicals that interact with molecular oxygen to form reactive oxygen species.[9] This energy transfer to molecular oxygen produces singlet oxygen, which acts as an essential element in the PDT oxidative process, producing an antimicrobial effect.[9] Mesalt® is a dressing made from soft nonwoven, viscose/polyester material impregnated with sodium chloride, which is released when in contact with moisture. Sodium chloride gradually reduces hypergranulation and absorbs exudate, creating a hypertonic environment in the ulcer bed.[10]

The relevance of this study is grounded in its use of an adjunct technology in association with an innovative dressing for treating hypergranulation in people with DFUs, aiming to reduce infectious agents, promote tissue repair in a timely manner, and prevent infection and further complications such as amputation. Thus, this study aims to describe the use of PDT associated with Mesalt® in the treatment of hypergranulation in people with DFUs using a descriptive study of a single case study.

Methods

The study setting was the vascular surgery outpatient clinic of the Hospital Beneficência Portuguesa, located in the city of Ribeirão Preto, in the state of São Paulo, Brazil. The clinic operates from Monday to Friday by vascular surgeons and residents, as well as a research nurse from the graduate program at the doctoral level of the School of Nursing at the University of São Paulo, Ribeirão Preto campus, who provide nursing assessments and laser treatments at this setting.

The case study was conducted from October 2023 to January 2024. The participant was a 62-year-old woman who was living with DFU with a great amount of exudate for three months, which led to the developed of hypergranulation.

For data collection and measurement of baseline variables, a semi-structured instrument was used, including sociodemographic and clinical data of the participant (age, gender, occupation, birthplace, marital status and income), and an assessment of risk factors (associated systemic diseases, duration of DM and medications).

The ulcer assessment was conducted using the Bates-Jensen Wound Assessment Tool (BWAT), validated for Brazilian Portuguese, which allows for practical, objective and conclusive application to monitor the healing progress of wounds.[11] The scale evaluates the lesion based on 13 parameters: size, depth, edges, sloughing, type and amount of necrotic tissue, characteristics and amount of exudate, edema and perilesional induration, colour of the perilesional skin, quality of granulation tissue, and epithelialization. Each item is scored from one to five, where one indicates the best condition and five indicates the worst condition of the wound.[11]

In each assessment, the lesion was measured using the Imito® smartphone application. Additionally, at the initial moment, blood was collected to evaluate glycated hemoglobina (A1C), and the Ankle-Brachial Index (ABI) was assessed on the same day as the first treatment session.

The ABI was measured using a Portable Vascular Doppler (DV 610 MegaMED) for locating arterial pulses, employing a transducer with a frequency of 10 MHz with a high sensitivity level and a sphygmomanometer to measure systolic pressure. With the participant in a supine position, and after five minutes of rest, systolic pressure measurements were collected from the dorsalis pedis artery and the brachial artery bilaterally. The result was obtained by calculating the ratio between the highest pressure in the dorsalis pedis artery at the ankle and the highest pressure in the brachial artery of the upper limb, thus obtaining the ABI.

Additionally, a tissue biopsy was conducted to evaluate the microorganisms present in the lesion. The procedure was performed in the outpatient clinic and the sample was stored in a sterile plastic collector and labelled. Then it was promptly sent to the hospital's Microbiology Laboratory for identification of microorganisms present in the tissue, following the BrCAST standardization guidelines.

For PDT procedure, a 1% methylene blue solution was used, formulated upon request by a registered pharmacist. This photosensitizer was applied to the lesion (0.5 cm from the edge and central portion) with the aid of a disposable 3 mL pipette; the amount used depended on the size of each lesion (0.5 ml for lesions up to 4 cm^2 and 1 ml for areas above 4 cm^2). After application, a five-minute absorption period was observed, timed using a smartphone.

Following this period, light irradiation was performed using the Therapy EC equipment from DMC (ANVISA Registration 80030819013), with a wavelength of 660 nm, a dose of 9 Joules, and an irradiation time of 90 seconds per point (following manufacturers recommendations).[12] The point technique was used in contact, with a standardized distance of 1 cm between points around the lesion and 0.5 cm from the lesion's edge, ensuring that the entire extent of the ulcer received light irradiation. It is important to note that this procedure was reported as painless by the patient (pain scale 0-10).

The data were organized using a printed data collection instrument and analyzed by the researcher, being described narratively, with sequential images to illustrate the healing progress.

Ethical principles were respected, with the ethical approval of the study granted by the Research Ethics Committee of the School of Nursing of Ribeirão Preto at the University of São Paulo, under opinion no. 5.802.182, and consent was recorded through the signature of the Informed Consent Form (ICF).

Results and Discussion

The patient, a 62-year-old female, was married and originally from a city in the state of Sao Paulo, Brazil. She lived with her husband and a youth child, with a lower income rate. The diagnosis of diabetes was made 34 years ago, and she has been using insulin therapy since then. Her glycated hemoglobin level (A1c) was 7.3%. During the assessment of the Ankle-Brachial Index,

she exhibited normal circulation in both lower limbs. The DFU started in August 2023 on the left hallux, shortly after amputation at the same site. Inadequate care and footwear probably led to the formation of a new ulcer. The DFU had a circular shape and was being treated with collagenase, using dressing changes performed at home by family members. The left foot (with the lesion) was dry, and both feet had positive protective plantar sensitivity as assessed with a 10 g monofilament.

On October 6, 2023, the initial evaluation of the case was conducted. The lesion exhibited partial loss of skin thickness, involving both the epidermis and dermis, with a small amount of devitalized tissue and hypergranulation. It presented moderate to high exudate with serous characteristics and the lesion area measured 6.1 cm^2 (3.5 cm in height and 2.6 cm in width) (Figure 1). A biopsy identified the presence of *Staphylococcus aureus*, though no signs or symptoms of infection were observed.

Figure 1 – 1st evaluation (Oct 6, 2023)

In the second and third evaluations, conducted on October 11 and 18, respectively, there was slight improvement in lesion size and drainage; however, hypergranulation persisted (Figures 2 and 3). Given the limited response to the initial treatment approach, a revised protocol was implemented.

Figure 2 – 2nd evaluation (Oct 10, 2023)

Figure 3 - 3rd evaluation (Oct 18, 2023)

This new care planning approach involved self-management by the patient's sister-in-law, who was trained by the first author, a nurse specialized in wound care. The protocol included daily wound cleansing with normal saline and the application of wet gauze with 20% sodium chloride over the wound bed for five minutes, followed by Mesalt® as a secondary dressing. This method was selected to help reduce the amount of exudate through the hypertonic effect of sodium chloride. Sodium chloride (20%) has a hypertonic effect when used on wounds, meaning that it has a higher concentration of solutes compared to normal body fluids. This hypertonic effect can help reduce the amount of exudate in the wound, decrease tissue tension and allow the wound edges to close together.[13] Weekly follow-up occurred at a wound care clinic, where PDT was performed and Mesalt® was reapplied as the secondary dressing.

Following the implementation of this new approach, the lesion showed significant improvement. On October 25, 2023, there was a noticeable reduction in both exudate and hypergranulation tissue. By the following evaluation on November 1, 2023, the ulcer area had decreased to 3.9 cm^2 (2.9 cm in height and 2.1 cm in width) (Figure 4).

Figure 4 - 5th evaluation (Nov 1, 2023)

Improvement continued progressively. On November 8, 2023, the lesion size reduced further to 3.6 cm^2, measuring 2.7 cm in height and 1.9 cm in width. At this point, the exudate was serosanguineous (thin and watery) and reduced in quantity (Figure 5). On November 17, 2023, the ulcer continued to reduce in size, now measuring 2.4 cm^2 (2.3 cm in height and 1.5 cm in width) (Figure 6).

Figure 5 – 6th evaluation (Nov 8, 2023)

Figure 6 – 7th evaluation (Nov 17, 2023)

Figures 7 and 8 illustrate the final stages of the healing process. On December 14, 2023, during a home visit, substantial healing progress was noted, with the lesion area reduced to 0.5 cm^2 (1.1 cm in height and 0.7 cm in width), and physiological moisture present. Daily use of a hydrogel with alginate dressing was recommended solely for moisture maintenance, accompanied by a single session of laser therapy on December 14 (2 J, punctual, red-light laser). Complete healing of the ulcer was achieved on January 4, 2024, marking two months and 29 days since initial treatment.

Figure 7 – 8th evaluation (Dec 14, 2023)

Figure 8 – 9th evaluation (Jan 4, 2024)

Source: Maria Girlane S. A. Brandão

Table 1 provides a summary of the treatment protocols used in this clinical case, including the type of dressing, application period, frequency of change, rationale for choice, and observed effects.

Table 1: Treatment protocol applied for the management of hypergranulation in diabetic foot.

Treatment Protocol	Application Period	Frequency of secondary dressing change	Rationale for Choice	Observed Effects
Cleaning with 0.9% saline solution + weekly PDT + calcium alginate	1st evaluation (Oct 6, 2023) until two weeks after the protocol start	Daily	Control of exudate, promoting a physiologically moist environment for healing	Slight improvement after two weeks, with high exudation and hypergranulation still present
Cleaning with 0.9% saline solution + gauze moistened with 20% sodium chloride (5 min) + weekly PDT + Mesalt®	3rd evaluation (Oct 18, 2023) until 8th evaluation (14/12/2023)	Daily	Reduce exudate level and hypergranulation through hypertonic effect	Significant improvement in the lesion, with reduced exudate and absence of hypergranulation by the 8th evaluation
Laser therapy every 15 days + Hydrogel with alginate	After the 8th evaluation (Dec 15, 2023) until 9th evaluation (Jan 4, 2024)	Daily	Maintain moisture and support healing with laser therapy	Small amount of exudate, with complete healing by the 9th evaluation

Discussion

The amount of exudate plays a crucial role in the healing process, helping to maintain a moist environment in the wound bed, which is essential for cell migration and new tissue formation. It also provided good hydration for the granulation tissue.[14] However, when exudate levels are moderate to high, excessive moisture hinders healing, promoting the formation of hypergranulated tissue, which can delay healing.[6]

Hypergranulation is a significant phenomenon in wounds, particularly in DFUs, but its therapeutic approach remains contradictory. This highlights the importance of conducting studies that seek effective solutions for hypergranulation management, as it can impede the healing process and lead to complications.[15]

Considering the exudate level, treatment was initiated with calcium alginate, a highly absorbent dressing derived from algae, suitable for wounds with moderate to high exudate levels.[16] However, in this case it was not as effective as we expected, which led the team to discuss the need for another approach approach. In DFU, it is essential to choose a dressing that can absorb excess exudate and maintain a physiologically moist environment.[17]

Observing that the patient had *Staphylococcus aureus* in the microbiological analysis and knowing that high levels of bacteria can promote chronic inflammation and increase exudate production, the need for an adjuvant therapy with antimicrobial action was considered. Therefore, we introduced the photodynamic therapy (PDT) in combination with calcium alginate. PDT was selected due to its antimicrobial potential, acting through the production of reactive oxygen species that help eliminate *S. aureus* and reduce the bacterial load in the wound.[9,18,19]

However, after two weeks of using the new treatment protocol (i.e., PDT + calcium alginate), wound progression continued to be limited, with sustained moderate exudate and the presence of hypergranulation. Given this, 20% saline solution was introduced to the treatment protocolo this cliente. For this product, it is important to allow it to sit on the wound bed (wet gauze) for five minutes after cleaning with 0.9% saline solution. A daily dressing with 20% sodium chloride (Mesalt®) was also chosen to help control exudate and hypergranulation.

Another study also showed that the healing process showed satisfactory progress after the application of the hypertonic solution (20%), with improvement in hypergranulation. Mesalt® contains mainly two components: 20% sodium chloride, which provides a hypertonic environment for the wound, and absorbent polyester fibre, capable of absorbing a large amount of secretion. The hypertonic nature of the Mesalt® dressing plays a vital role in the healing process in wounds with hypergranulation by effectively absorbing exudate, thereby preventing excessive moisture accumulation, which can exacerbate excessive granulation.[20]

In fact, after implementing this new treatment protocol, the DFU showed substantial improvement, with a reduction in exudate levels and hypergranulation. The combination of a dressing that promotes a hypertonic environment and PDT has a great potential to accelarate healing. In line with findings of Cesar and colleagues[21], our study supports that PDT also aided DFU treatment, with notable reductions in wound size and exudate levels.

After the resolution of hypergranulation and exudate controle, it was decided to use hydrogel with alginate to maintain physiological moisture levels in the wound bed. The hydrogel is a dressing that hydrates the wound bed, accelerates the healing process and promotes tissue ephitelization.[22] In addition, laser therapy was applied biweekly to support the maintenance of granulation,[23] intentionally limiting its frequency to avoid overstimulation of the granulation tissue, which could lead to recurrency of hypergranulation. This strategic use of laser therapy allowed for controlled granulation without risking excessive tissue growth, aligning to promote balanced and sustained wound healing.

These findings collectively emphasize the importance of an integrated treatment approach combining PDT with hypertonic dressings, such as Mesalt,® to optimize wound healing outcomes. In

summary, the association of PDT and hypertonic dressings (in this case, Mesalt®) provided a promising therapeutic strategy for managing hypergranulation in a clinical case of DFU. Future studies should continue to explore the effectiveness of these modalities and their impact on various wound characteristics to establish standardized protocols for clinical practice.

Conclusion

Hypergranulation in foot ulcers among individuals with diabetes is detrimental to healing and can lead to negative outcomes due to delays in the tissue repair process. In this case study, the combination of an antimicrobial adjuvant technology (PDT) with a 20% sodium chloride dressing (Mesalt®) facilitated progressive improvements in the clinical aspects of the ulcer. Additionally, hydrogel with alginate dressings were employed as the wound bed and exudation evolved throughout the healing process. These variations necessitate careful management, as different wound conditions may require dressings with distinct mechanisms of action. The decrease in hypergranulated tissue and complete healing further support the potential of the protocol used in this clinical case. We recommend that further studies on this topic be conducted to enhance the scientific evidence regarding the effectiveness of combining PDT and hypertonic dressings in the treatment of hypergranulation in individuals with DFUs.

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