Original Article

Wound Care for Calciphylaxis: A Novel Approach for Wound Management with Negative Pressure Wound Therapy with Instillation and Dwell Time

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ABSTRACT

Introduction: Calciphylaxis is a serious life-threatening skin condition, which mainly affects dialysis patients. The mortality rate is reported to be as high as 50–80%, mainly due to severe wound infection. Thus, appropriate wound care is critical for its management, but still there is no consensus on the optimal method for this purpose.

Materials and methods: The purpose of this study was to provide an insight into the treatment of calciphylaxis wounds by describing our case series. Retrospective data analysis was performed using data on calciphylaxis patients and their wounds. All patients were treated with the same protocol, including application of negative pressure wound therapy with instillation and dwell time (NPWTi-d) by our multi-disciplinary wound care team.

Results: In the study period, nine wounds in seven patients with calciphylaxis underwent our treatment. On the first day of NPWTi-d, each wound was covered with 35.2% of necrotic tissue, on average. The mean duration of the therapy was 27.8 days, and later, good granulation and reduction of necrotic tissue was achieved in all cases. None of the cases showed clinical infection during treatment, and complete resolution was achieved in seven of the nine wounds.

Conclusion: Our approach was useful for facilitating healing of calciphylaxis wounds without causing infection even with a high presence of necrotic tissue. NPWTi-d was beneficial in terms of gentle debridement and suppression of bacterial growth, in addition to promotion of good granulation.

Key words : calciphylaxis, dialysis, NPWTi-d, wound care

Introduction

Over the past years, the number of patients with end-stage renal disease (ESRD) has been increasing worldwide. Japan is one of the countries with the highest number of dialysis patients, given its aging population^{1,2)}. A dialysis patient has

many negative factors for wound healing, which result in long hospitalization, low quality of life, and high overall mortality^{3,4)}. This trend has a negative impact not only on public health but also on medical economics, as it is posing challenges to wound care surgeons.

Calciphylaxis, or recently known as calcific uremic arteriolopathy, is a life-threatening skin condition that mostly

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affects patients on long-term dialysis, with 1%–4% prevalence in this population^{5,6}. Calciphylaxis is clinically characterized by the development of painful, purplish, mottled skin lesions (livedo reticularis) that eventually resemble and progress to non-healing ulceration with a large extent of necrotic tissue^{7,8}. Pathologically, calcification of the tunica media of medium-sized to small vessels and intimal hyperplasia are often found in combination with fibrosis and thrombosis, causing obliteration of the vessels. This pathological change causes ischemic tissue bed and has distinctive clinical manifestations⁹. Recently, the incidence rate has been reported to be increasing, but still, it is considered that a large number of patients is missed or misdiagnosed^{9,10}. The mortality rate is reported to be as high as 50%–80%, but an evidence-based treatment strategy is still lacking^{9,11,12}.

The main cause of death is uncontrollable sepsis as a result of infection that mostly occurs in the wounds^{9,11}. Therefore, appropriate wound care is critical in the management of calciphylaxis, but is particularly challenging. Firstly, calciphylaxis develops as a result of defects in the surrounding microcirculation; hence, surgical debridement itself can cause wound damage, trigger further ulceration and necrosis, and even create a focus of infection^{8,13,14}. Therefore, surgical intervention needs to be performed with extreme caution. Secondly, these wounds heal poorly and may even deteriorate, and the remaining necrotic tissue acts as a reservoir for microorganisms, which puts the patient at a high risk of infection regardless of the wound care modality used¹⁵. Previous reports have stated that even though debridement was performed carefully and antibiotics were administered, 44% of the patients with calciphylaxis wounds treated by conventional negative pressure wound therapy (NPWT) developed wound infections and half of them died of sepsis afterward^{7,16–21}.

Advances in devices and techniques for wound care have led to the recent introduction of NPWT with instillation and dwell time (NPWTi-d), which involves automated, volumetric-controlled instillation and dwelling of a topical solution to the wound. Unlike conventional NPWT, NPWTi-d is expected to be useful for complex wounds with large amounts of necrotic tissue and exudate^{22,23}. This article describes our wound management approach with NPWTi-d and determines its effectiveness for calciphylaxis. This is the first case series treated with an NPWTi-d device for such indications. This study also evaluated the wound healing process.

Materials and methods

Study design

A retrospective review was conducted on patients with calciphylaxis who were treated from August 2017 to October

2018 at our institutions. The study was approved by the hospital's ethical committee and was conducted in accordance with the 1975 Declaration of Helsinki Principles. Informed consent was obtained from each patient. The patients were diagnosed using a set of diagnostic criteria⁶, based on clinical manifestations and supported by histopathological examination of deep skin and subcutaneous tissue after debridement. The records of patients and wound characteristics, treatment regimens, and outcomes were analyzed. Follow-up was conducted at outpatient clinics or via contact with the hospitals to which the patients were transferred.

Treatment protocol

All wounds were treated with the same protocol by our multi-disciplinary wound care team, which consisted of plastic surgeons, a nephrologist, a vascular surgeon, and wound care nurses. After admission, the dialysis membrane and dialysis protocols were appropriately adjusted with a target Kt/V value of > 2.0. We surgically removed all black eschar and the slough demarcating the granulation tissue. Postoperatively, we confirmed that there was no clinical sign of infection such as redness, swelling, and purulent discharge, and then applied an NPWTi-d device (V.A.C.UltTM wound therapy system; KCI, San Antonio, TX). Normal saline was used as the instillation solution and the wound dressing was changed 2–3 times per week. The continuous negative-pressure was set low at -75 mm Hg to avoid progression of local ischemia. The instillation volume was set manually to bathe the entire wound surface by monitoring the foam color as it changed to a partially dark color. The negative pressure time was set as 2.5 hours except for patients who had discomfort with frequent bathing. Detailed settings of the device for each wound are listed in Table S1 (supplemental material). During each dressing change, slough and fibrinous tissue were debrided, only if demarcating granulation tissue was present, at the bedside using a QoustickTM wound therapy system (Arobella Medical, LLC, Minnetonka, MN), scissors, and sharp curettes. When the wound was covered with good granulation tissue and/or the wound condition was considered to be constant by the plastic surgeon, the NPWTi-d device was stopped and skin grafting was performed. Pain management consisted of oral medication (e.g., tramadol, gabapentin, loxoprofen sodium hydrate, and acetaminophen) and/or continuous sciatic nerve block with ropivacaine hydrochloride hydrate as needed. Low-density lipoprotein apheresis (LDL-A) and hyperbaric oxygen therapy (HBOT) in a sealed chamber were also performed according to the patient's condition.

Calculating the area percentages in the wound

For the evaluation of wounds, clinical photographs taken before and after NPWTi-d were examined. Two plastic surgeons blinded to all clinical information coded the wounds

Table 1. Patient demographics at admission

Demographics	
Patients, n	7
Male, n (%)	3 (42.9)
Mean age (range)	67.6 (54–77)
Comorbidities, n (%)	
ESRD on HD	7 (100)
CVD	5 (71.4)
DM	4 (57.1)
IgA nephropathy	2 (28.6)
Mean duration of HD (range), years	9.4 (4–23)
Wounds treated, n	9
Lower leg	8
Thigh	1
Wounds area, n	
< 25 cm ²	3
25–50 cm ²	4
50–75 cm ²	2

CVD: cardiovascular disease, DM: diabetes mellitus, ESRD: end stage renal disease, HD: hemodialysis

using the Procreate™ digital illustration App (Savage Interactive Pty Ltd., North Hobart, Australia) as follows: good granulation, red (R255, G0, B0); necrotic tissue (eschar and slough), blue (R0, G0, B255); and other wound lesion, green (R0, G255, B0). Each coded area was then calculated as a percentage of the whole wound using ImageJ software (National Institutes of Health, Bethesda, MD).

Scoring bacterial growth

Wound cultures were taken before and after NPWTi-d using the Levine method where a culture swab is rolled over 1 cm² of each wound and exudate is collected²⁴. Bacterial growth is then scored as follows: (-), no growth; (1 +), below one-third of the culture dish; (2 +), one-third to two-thirds of the culture dish; or (3 +), over two-thirds of the culture dish.

Results

Nine calciphylaxis wounds in seven patients (three men and four women) were identified during the study period. The mean age was 67.6 (range, 54–77) years. All patients had ESRD and had been on hemodialysis (HD) for a mean period of 9.4 (range, 4–23) years, with five having cardiovascular disease (CVD) and four, diabetes mellitus. The mean Kt/V value was 0.96 (range, 0.75–1.1) at admission. Two patients continued taking warfarin for cardiac comorbidities during treatment for calciphylaxis. All wounds were located on the

lower extremity (lower leg or thigh), and in two patients, the wounds were located on both lower legs and each wound was treated (the clinical characteristics are summarized in Table 1).

At the time of first application of the NPWTi-d device, each wound was covered with 35.2% (range, 4.3%–84.0%) of necrotic tissue, on average, even after surgical debridement, and with 44.6% (range, 2.8%–86.3%) of granulation layer, on average. The NPWTi-d device was applied for mean of 27.8 (range, 10–54) days. After NPWTi-d, good granulation was achieved with a mean coverage area of 73.2% (range, 42.0%–92.6%), and the remaining necrotic tissue covered 13.0% (range, 1.7%–37.8%) of the wound area, on average. Skin grafting was performed in all cases. Postoperatively, the skin graft did not heal completely in some cases, so conservative wound therapy was performed. Complete resolution of seven wounds (the exception being case 8 and case 9) was achieved during 6 months of follow-up. With case 8, skin graft had healed but small ulcers recurred during follow-up. Although some improvement was observed in case 9, the patient died because of worsening heart failure during treatment. No clinical infection was reported throughout the treatment (wound evaluation, treatment regimens, and outcomes are listed in Table 2).

As for wound culture throughout NPWTi-d, bacterial growth was suppressed in 66.7% (6/9) of the cases including case 9, which was positive for methicillin-resistant *Staphylococcus epidermidis* before NPWTi-d, but showed no bacterial

Table 2. Wound evaluation, treatment regimens, and outcomes

Case	Wound evaluation before NPWTi-d			Wound evaluation after NPWTi-d		Concurrent therapy (times)	Wound outcome	Follow-up (months)	Mortality
	Necrotic tissue (%)	Good granulation (%)	Duration of NPWTi-d (days)	Necrotic tissue (%)	Good granulation (%)				
1	7.7	82.5	21	1.7	92.6	HBOT (20), LDL-A (10)	Healed	14	Alive
2	4.3	86.3	10	2.3	87.5	-	Healed	14	Alive
3	52.3	9.2	28	9.7	72.7	HBOT (20), LDL-A (10)	Healed	13	Alive
4	14.2	68.6	27	5.2	91.5	HBOT (20), LDL-A (10)	Healed	12	Alive
5	84.0	2.8	54	19.5	42.0	HBOT (24), LDL-A (7)	Healed	8	Alive
6	35.1	44.6	46	13.5	70.9	HBOT (40), LDL-A (10)	Healed	7	Alive
7	23.6	65.2	19	18.8	73.7	HBOT (40), LDL-A (10)	Healed	6	Alive
8	47.8	38.1	28	8.7	80.3	HBOT (20), LDL-A (10)	Improved	6	Alive
9	47.8	4.0	17	37.8	48.0	HBOT (18), LDL-A (10)	Improved	3	Dead

HBOT: hyperbaric oxygen therapy, LDL-A: low-density lipoprotein apheresis, NPWTi-d: negative pressure wound therapy with instillation and dwell time

Table 3. Bacterial growth before and after NPWTi-d

Case	Before NPWTi-d	After NPWTi-d
1	<i>Serratia marcescens</i> (1 +)	<i>Serratia marcescens</i> (1 +), MRSA (1 +)
2	(-)	(-)
3	(-)	(-)
4	(-)	(-)
5	(-)	<i>Staphylococcus aureus</i> (3 +)
6	<i>Enterococcus faecalis</i> (2 +), <i>Stenotrophomonas maltophilia</i> (1 +)	<i>Enterococcus faecalis</i> (3 +), <i>Stenotrophomonas maltophilia</i> (1 +)
7	<i>Klebsiella pneumoniae</i> (3 +)	<i>Klebsiella pneumoniae</i> (3 +)
8	(-)	(-)
9	MRSE (2 +)	(-)

MRSA: methicillin-resistant *Staphylococcus aureus*, MRSE: methicillin-resistant *Staphylococcus epidermidis*, NPWTi-d: negative pressure wound therapy with instillation and dwell time

growth afterwards (the results are shown in Table 3).

Figs. 1, 2, and 3 show the wound-healing process of three patients in the present series.

Case presentation (Case 5)

A 73-year-old man with a 4-year history of HD-dependent ESRD presented with a 2-month history of painful ulceration with black dry eschar on his Achilles tendon. The lesion had occurred as painful dark-purplish cutaneous nodule at the beginning, and then the size radically progressed. He also had a history of IgA nephropathy, CVD, and warfarin use. His foot skin perfusion pressure value was 59/54 mmHg. After admission, adjustment of HD protocols, HBOT, and LDL-A were performed. As general anesthesia was considered risky

because of his cardiac function, debridement was performed several times at his bedside. NPWTi-d was applied on his wound that was covered with 84.0% of necrotic tissue and 2.8 % of granulation tissue. After 14 days of NPWTi-d application, the necrotic tissues were reduced to 68.2% but most of them were still adhered especially on the tendon and bone surface. After 54 days of NPWTi-d application, good granulation was achieved to 42.0%, and the percentage of necrotic tissue decreased to 19.5%. Sheet skin grafting was then performed, and postoperatively the graft healed well. At the 8-month follow-up, he showed no recurrence and could walk by himself.

Fig. 1. Clinical presentation of case 5.

- (A) Appearance of the lower leg at admission.
- (B) At the time of NPWTi-d application.
- (C) NPWTi-d day 54.
- (D) Six months after skin grafting.

Fig. 2. Clinical presentation of cases 6 and 7.

- (A) Appearance of the both lower legs at admission.
- (B) Appearance of the right lower leg (case 6) at admission.
- (C) At the time of NPWTi-d application.
- (D) NPWTi-d day 46.
- (E) Seven months after skin grafting.

Discussion

Our case series presents the details of successful treatment for calciphylaxis by our team. To the best of our knowledge, this is the first reported use of NPWTi-d for this indication. Our wound management for calciphylaxis is summarized as follows: We performed surgical debridement taking caution to avoid damage to the wound bed, and then an NPWTi-d device was applied after confirming that there was no clinical

infection. During the NPWTi-d dressing change, we performed gentle bedside debridement, and after good granulation was achieved, we closed the wound by skin grafting. Currently, there is no consensus on wound care in the management of calciphylaxis, and how to prevent infection and facilitate healing is being discussed^{12, 25}. We believe that appropriate use of an NPWTi-d device could be a good solution for the problems in calciphylaxis wound care in mainly two areas:

Firstly, NPWTi-d has an advantage of facilitating removal

Fig. 3. Clinical presentation of case 8.

(A) Appearance of the lower leg at admission.

(B) At the time of NPWTi-d application.

(C) NPWTi-d day 28.

(D) Four months after skin grafting. Small ulcers recurred during follow-up.

of necrotic tissue within the wound without causing excessive damage. An important feature of NPWTi-d is the “instillation and dwelling,” which allows uniform distribution of solution across the wound bed and facilitates debridement by loosening, solubilizing, and detaching dry fibrin, wet slough, and other infectious material^{26, 27}. Previous studies have reported that NPWTi-d contributed to fewer trips to the operating room for debridement than conventional NPWT^{28, 29}. In the present series, we believed aggressive debridement would cause wound damage, so mild debridement was performed. Further, the wound deteriorated and the necrotic tissue increased daily postoperatively. Thus, each wound was covered with a large extent of necrotic tissue, with a highest coverage of 84.0% at the time of NPWTi-d application. After NPWTi-d, the percentage of necrotic tissue markedly decreased to 13.0%, on average, without any concomitant progression of skin lesions. With cases 5 and 6, there were greater amounts of necrotic tissue around exposed tendon and bone surfaces, so it took rather longer to prepare the wound bed with NPWTi-d. The NPWTi-d application was gentle on the patients so the pain during therapy could be controlled.

Secondly, unlike conventional NPWT, the mechanism by which NPWTi-d works limits bacterial activity, expedites clearance of infection, and reduces the risk of recurrence of infection^{26, 30}. The presence of slough, which may act as a macroscopic biofilm within chronic wounds, also has the potential for acting as a reservoir for microorganisms, and carries an extremely high risk of infection for calciphylaxis wounds¹⁵. Despite the high amount of necrotic tissue in this series, none of the patients developed clinical infection during treatment. The wound culture score confirmed suppression of bacterial growth in 66.7% of the wounds, including one case that was positive for methicillin-resistant *S. epidermidis* before NPWTi-d, but showed no bacterial growth afterwards.

It is well known that NPWT improves vascularity in an

open wound bed, which promotes the healing process. Recent studies showed that NPWTi-d is more effective in inducing good granulation than conventional NPWT^{30, 31}. The “dwelling” is thought to help dilute and solubilize infectious materials, facilitating removal of factors that negatively affect wound healing³¹. In the present study, good granulation was achieved in 73.2% of the wound area, on average, and skin grafting could be performed on all wounds.

Local wound care is not enough and the best possible therapy should be considered for this complicated, high-mortality skin condition. As suggested in recent reports, we also conducted a multidisciplinary approach including adjustment of dialysis protocols, HBOT, and LDL-A^{32, 33}. Further, with recent studies, appropriate adjustment of dialysis protocols is estimated to improve not only the patient’s general condition but also vascular condition and wound healing process¹⁰. We support the recommendation of increasing dialysis intensity in the management of calciphylaxis.

This study has all of the limitations of an uncontrolled case series, and a large, controlled clinical study is needed. We emphasize that NPWTi-d should be discontinued if any sign of wound infection is evident. In conclusion, NPWTi-d was useful in promoting healing of calciphylaxis wounds without causing infection even with a high presence of necrotic tissue. We hope that our experience offers better insights on the management of calciphylaxis.

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Conflicts of interest

None.

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