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Management of Acute and Chronic Wounds Using Negative Pressure Wound Therapy With Instillation: A Retrospective Review of a 100-Patient Cohort in Padova, Italy

--Manuscript Draft--

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Abstract:	The presence of debris covering a wound surface significantly impedes progression toward closure. Negative pressure wound therapy, in conjunction with instillation and dwelling (NPWTi-d) of topical wound solutions, is a versatile tool that can be applied to various wound types to promote wound healing. At a [blinded] in Padova, Italy, NPWTi-d has been incorporated into wound management plans that included debridements and antibiotic therapy, as necessary, for a diverse population of patients suffering from open wounds, including those that are acute, chronic, and infected. We performed a retrospective analysis of 100 patients who underwent NPWTi-d and report on key healing outcomes observed in subgroups differentiated by sex, wound aetiology, initial wound size, and topical instillation solution. The patient population was 53 males and 47 females, ranging in age from 22 to 95 years old. Wound types included vascular ulcers, surgical wounds, dehiscences, and trauma, and they were located on different areas of the body. NPWTi-d with 0.05% sodium hypochlorite, normal saline, or 0.25% acetic acid was implemented with a dwell time of 3-10 minutes, followed by a negative pressure cycle length of 2-3.5 hours at -75 to -125 mmHg. Dressings were changed approximately every 3 days. After a median of 11 (range: 1-35) days, wound surface area significantly decreased ($P < .0001$), the percent of infected wounds declined from 72% to 46%, and wound closure was achieved in 91% of cases. A significant reduction of wound surface area was detected in both sexes, small and medium wounds, vascular ulcers, surgical wounds, dehiscences, trauma wounds, and pressure ulcers ($P < .05$). This effect was detected in wounds regardless of topical instillation solution ($P < .001$). In conclusion, NPWTi-d is a valuable asset under a variety of circumstances, able to achieve a range of therapy goals based on individual patient needs.

Suggested Reviewers:	Luis Fernández, MD Christus Trinity Mother Frances Hospitals thebigkahuna115@gmail.com Has published on NPWT with instillation in multiple wound types.
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Question	**Response**

Dear Editor,

Regarding to the reviewers' comments, we answered to all their request and in particular:

1) we provided new references
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Sincerely,

Prof. Franco Bassetto

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Dear Editor,

I am submitting our manuscript titled, “Management of Acute and Chronic Wounds Using Negative Pressure Wound Therapy With Instillation: A Retrospective Review of a 100-Patient Cohort in Padova, Italy,” for your consideration for publication in *Wounds*. This manuscript describes the benefits of negative pressure with instillation across multiple wound types, as observed in our clinical setting. The final manuscript has been seen and approved by all authors, who accept full responsibility for the design and conduct of the study, had access to the data, and controlled the decision to publish.

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Management of Acute and Chronic Wounds Using Negative Pressure Wound Therapy With Instillation: A Retrospective Review of a 100-Patient Cohort in Padova, Italy

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Abstract

The presence of debris covering a wound surface significantly impedes progression toward closure. Negative pressure wound therapy, in conjunction with instillation and dwelling (NPWTi-d) of topical wound solutions, is a versatile tool that can be applied to various wound types to promote wound healing. At a [blinded] in Padova, Italy, NPWTi-d has been incorporated into wound management plans that included debridements and antibiotic therapy, as necessary, for a diverse population of patients suffering from open wounds, including those that are acute, chronic, and infected. We performed a retrospective analysis of 100 patients who underwent NPWTi-d and report on key healing outcomes observed in subgroups differentiated by sex, wound aetiology, initial wound size, and topical instillation solution. The patient population was 53 males and 47 females, ranging in age from 22 to 95 years old. Wound types included vascular ulcers, surgical wounds, dehiscences, and trauma, and they were located on different areas of the body. NPWTi-d with 0.05% sodium hypochlorite, normal saline, or 0.25% acetic acid was implemented with a dwell time of 3-10 minutes, followed by a negative pressure cycle length of 2-3.5 hours at -75 to -125 mmHg. Dressings were changed approximately every 3 days. After a median of 11 (range: 1-35) days, wound surface area significantly decreased ($P < .0001$), the percent of infected wounds declined from 72% to 46%, and wound closure was achieved in 91% of cases. A significant reduction of wound surface area was detected in both sexes, small and medium wounds, vascular ulcers, surgical wounds, dehiscences, trauma wounds, and pressure ulcers ($P < .05$). This effect was detected in wounds regardless of topical instillation solution ($P < .001$). In conclusion, NPWTi-d is a valuable asset under a variety of circumstances, able to achieve a range of therapy goals based on individual patient needs.

Introduction

For an open wound, the presence of devitalized tissue and slough can be a contributing factor that prolongs the inflammatory response and delays wound healing.[1] Due to its viscous texture, slough can be difficult to separate from healthy tissue. One method by which slough and soft infectious materials can be gently removed from the wound bed is negative pressure wound therapy with instillation and dwell time (NPWTi-d), which is a tool that enables the automated delivery of topical solutions to remove exudate and debris from the wound surface.[2] Desired therapy outcomes of NPWTi-d can include wound cleansing, promotion of granulation tissue growth, and wound bed preparation for closure.[3-5] In this study, we examine the use of NPWTi-d in a heterogeneous cohort of patients receiving care for various wound types at a hospital in Padova, Italy, and we report key healing outcomes in each wound category.

Methods and Materials

This study is an observational retrospective review of 100 patients with wounds managed with NPWTi-d (V.A.C. VERAFLO™ Therapy; 3M Company; San Antonio, TX) from January 2013 to December 2017. Deidentified data were collected from medical records from a single institution [blinded]. Patient consent to treatment was acquired in accordance with institutional and governmental guidelines. No other informed consent or ethical approval have been required.

Application of NPWTi-d was prescribed in accordance with patient features, wound characteristics, and current institutional practice. Negative pressure settings ranged from -75 to -125 mmHg, with a dwell time of 3-10 minutes and a cycle length of 2 to 3.5 hours (**Table 1**). Initially, normal saline was instilled in 30 cases, acetic acid in 20 cases, and 0.05% sodium hypochlorite in 50 cases (this concentration is the only one that is present in our hospital, no possibility to use Daikin solution 0.125%) **(Table 1)**. Acetic acid (0.25%) was chosen for patients who initially presented with signs of infection with

Pseudomonas spp (abundant blue-green exudate). Sodium hypochlorite 0.05% was used for patients with complex wounds or signs of infection with non-*Pseudomonas* species (only serosanguinous exudate was present). Normal saline was selected for patients with simple wounds, delicate skin, or previous reaction to topical antiseptic solutions. In 2 patients, acetic acid was later changed to 0.05% sodium hypochlorite solution; one patient experienced discomfort as a result of the initial application of acetic acid, and the other was switched after the bacterial swab cultures confirmed the clearance of *Pseudomonas spp*. In one patient, instillation with 0.05% sodium hypochlorite was changed to normal saline after evidence of skin irritation. Dressing changes were performed every 72 hours (even if it was on the weekend), or as necessary. Swab samples were collected for microbial testing before and after application of NPWTi-d. Debridements and administration of culture-specific antibiotics for 7 days were performed as necessary. In order to avoid bias, we excluded patients treated with specialty reticulated open-cell foam dressing with through holes.

For statistical analysis, the data were divided into subgroups based on sex, instillation solution, wound size, and wound aetiology. Microsoft Excel (Microsoft Corporation; Redmond, Washington, USA) was used for all descriptive statistics. Statistical analysis for significance of wound surface area reduction was performed using a Wilcoxon Signed-Rank test using SAS (SAS Institute; Cary, North Carolina, USA), with significance defined as a *P*-value less than .05.

Results

Patient and Wound Characteristics

The study population included 100 patients; 53 were male and 47 were female. The mean age was 63 (range: 22-95) years old. The most common comorbidities among patients were diabetes (40.0%), peripheral vascular disease (36.0%), hypertension (35.0%), and coronary disease (24.0%; **Table 2**).

Wounds managed with NPWTi-d fell into 8 different categories based on aetiology, with the most common wound types being peripheral vascular ulcer (28.0%), surgical wound (21.0%), and dehiscence (16.0%; **Table 3**). Nearly two-thirds (61.0%) of the wounds were located on a lower extremity, with the second most common wound location being the pelvic area (23.0%).

Treatment Outcomes

Wound management with NPWTi-d continued for a median duration of 11 days, ranging from 1 to 35 days. The patient treated only for 1 day stopped the therapy because of a general deterioration of his health unrelated to NPWTi-d; no improvement in wound healing has noticed. Overall, the wound surface area decreased in 75 (75.0%) patients throughout the duration of NPWTi-d. In the remaining 25 (25.0%) patients there was no difference in surface area. These 25 patients presented without a common wound aetiology: 10 peripheral vascular ulcers, 7 traumatic wounds, 3 dehiscences, 2 surgical incisions, 1 diabetic foot ulcer, 1 radiodermatitis injury, and 1 peripheral gangrenous wound with sepsis. In the entire 100-patient population, the median wound surface area decreased from 45.0 cm^2 before NPWTi-d to 35.0 cm^2 after NPWTi-d ($P < .0001$; **Table 4**). This decrease in surface area remained significant in both men and women ($P < .0001$), and when the population was divided into subgroups initially receiving instillation with 0.05% sodium hypochlorite ($P < .0001$), acetic acid ($P = .0002$), or normal saline ($P < .0001$). A significant decrease was also observed in small (<250 cm^2; $P < .0001$) and medium (250-500 cm^2; $P = .031$) wounds. There was a non-significant decrease in the median surface area of large wounds (>500 cm^2; $P = .250$) from 888 cm^2 to 594 cm^2 before and after NPWTi-d, respectively. All the large wounds were positive for Gram-negative bacteria, no other common features were present. A significant reduction in wound area was observed in 5 wound types: peripheral vascular ulcer, surgical wounds, dehiscence, trauma, and pressure ulcer ($P < .05$; **Table 4**).

Prior to the initiation of NPWTi-d, bacterial infections were detected in 72 (72.0%) cases (**Table 5**). Of these, more than one microbe was detected in 33 (45.8%) cases and multi-drug resistant organisms were detected in 11 (15.3%) cases. At the conclusion of NPWTi-d, in conjunction with the appropriate administration of systemic antibiotics for 7 days, qualitative swab analyses of 46 (46.0%) cases were positive for bacterial persistence. The largest difference was seen in surgical wounds (preoperatively positive for *Morganella morganii* and/or *Pseudomonas aeruginosa*) which declined from 71.4% to 19.0%, all of which achieved closure by the end of the study. The subgroups with the highest infection rate after antibiotics and NPWTi-d were wounds treated with acetic acid (70.0%), peripheral vascular ulcers (75.0%), and pressure ulcers (71.4%); the closure rates for these groups were 90.0%, 89.3%, and 92.9%, respectively (**Table 5**).

Wound closure was achieved in 91 (91.0%) patients (**Table 5**). Of these, 39 (42.8%) were closed by skin grafts, 24 (26.4%) were closed by local flaps, 23 (25.3%) were closed via surgical revision or sutures, and 5 (5.5%) were closed using free flaps. In 3 patients, wound healing was complicated by a general deterioration of the patient's health. Two wounds remained recalcitrant, and amputations were performed in 4 patients. Among patients whose wounds were positive for bacteria persistence at the conclusion of NPWTi-d with antibiotics, the closure rate was 91.3%. In these patients, we performed hydrosurgical debridement and treatment with a two-step porcine dermal substitute for 14 days prior to final reconstruction.

Case Study

A 41-year-old man with paraplegia resulting from spinal tuberculosis presented to the Department of Plastic Surgery with multiple pressure ulcers. The patient was cachectic and showed ulcers in the trochanteric (**Figure 1**), ischiatic, and calcaneal areas. The stage-4 trochanteric ulcer underwent debridement involving the coxofemoral joint (**Figure 2**) with immediate reconstruction using

a tensor fascia lata myocutaneous flap (**Figures 3 and 4**). Unfortunately, the flap suffered partial necrosis and dehiscence (**Figure 5**). Analysis of bacterial swab cultures detected the presence of *Pseudomonas aeruginosa*. Debridement was performed to completely remove the necrotic tissues, and systemic antibiotics were administered during the course of NPWTi-d, which was initiated with instillation of 80 cc of acetic acid, followed by a 10-minute dwell time and 3.5-hour cycles of negative pressure at -125 mmHg (**Figure 6**). After 17 days, swab analysis was negative for bacterial presence, and 3 days later a debridement and flap revision were performed (**Figure 7**). The wound remained closed and stable upon follow-up 6 months later (**Figure 8**).

Discussion

In this cohort of 100 patients, we identified NPWTi-d as a versatile tool that could be used to cleanse a diverse range of wound types at various locations on the body. In the first publication reporting its use in 2004, it was suggested that NPWTi-d could be used to benefit cases in which wounds are covered with slough or exudate that was preventing advancement to the next stage of wound healing.[6] This proposal was subsequently supported by a study by Gabriel et al, comparing 15 patients with complex, open, infected wounds receiving NPWTi-d and 15 control patients with matching wounds receiving standard moist wound care; although both groups received appropriate antibiotics, the NPWTi-d group had a shorter number of days to infection clearance and wound closure.[7] As reported in these and other publications, NPWTi-d may sometimes be used after an initial application of conventional NPWT was unable to effect the wound status.[8] Multiple studies have been conducted examining the advantages NPWTi-d has over NPWT, as part of a treatment plan with debridement and antibiotics particularly in infected wounds . A retrospective, historical, cohort-control study by Kim et al comparing the outcomes of 142 patients with infected wounds receiving conventional NPWT or NPWTi-d with a polyhexanide solution observed that the NPWTi-d group had a reduced number of operative

room visits, shorter length of hospital stay, shorter time to final surgical procedure, and higher rate of closure.[2] Likewise, a retrospective cohort-control study by Gabriel et al examining differences among 82 patients with infected or critically colonized extremity and trunk wounds receiving NPWT or NPWTi-d using saline or a polyhexanide solution found that the NPWTi-d group had a reduced number or operating room debridements, shorter hospital stay, shorter length of therapy, and shorter time to wound closure.[9] Despite these results, we note that NPWTi-d is not indicated for the treatment of infection, per the manufacturer's instructions. However, literature seems to suggest NPWTi-d is a valuable asset in the management of complex wounds, especially those that are contaminated or in need of cleansing. In 2014, Goss et al performed a single-center prospective randomized trial in which quantitative cultures were taken preoperatively, postoperatively, and after 7 days treatment with NPWTi-d or traditional NPWT. The authors reported a mean absolute reduction in bacteria equal to $10.6x10^6$ bacteria per gram of tissue in NPWTi-d group and a mean absolute increase in bacteria equal to $28.7x10^6$ bacteria per gram of tissue in traditional NPWT group.[10] Also, Yang et al reported the observation in a randomized clinical trial that there was a significant 43% reduction of quantitative biofilm-protected bacteria in colonized leg and foot ulcers managed with NPWTi-d with 0.125% sodium hypochlorite without systemic antibiotics, compared to a mean 14% increase among wounds managed with NPWT.[11] In our patient population, we utilized NPWTi-d in conjunction with antibiotic therapy for 7 days when infection was detected, per international consensus guidelines for use of NPWTi-d in infected wounds.[12;13]

In this present study, there was a significant decrease in wound surface area for the majority of patients receiving NPWTi-d, and we were able to achieve a 91% closure rate. NPWTi-d was also effective in delivering wound healing support using three different types of solutions, which were selected based upon the wound characteristics and patient features. Wound surface area decreased in all major wound types, and in medium and small wounds. Although there was no significant reduction in patients with

very large wounds, the sample number was very small in this subgroup and may not reflect outcomes of NPWTi-d usage in the general population. Additionally, the goals of therapy for large wounds may be different than that for medium or smaller wounds; large wounds often require prolonged, multi-step treatment plans to facilitate the creation of a healthy wound bed. In the current study, 100% of the large wounds were closed, either using a local flap or skin graft.

Within the different wound subgroups, the initial infection rate before NPWTi-d varied from 41.9% to 100%. After administering appropriate antibiotics, debridement, and NPWTi-d, the proportion of infected wounds declined in all groups. We did observe that the effect was not the same in all wound subgroups, which may indicate that some wounds (eg, peripheral vascular ulcers and surgical wounds) gain a stronger benefit from NPWTi-d than others. However, even among wounds that were positively indicated to be infected at the conclusion of NPWTi-d, the closure rate was high (91.3%). Additionally, we observed similar positive outcomes (significant reduction in wound area and high closure rate) between wounds undergoing NPWTi-d with normal saline and topical antiseptic solutions (ie, sodium hypochlorite and acetic acid). This suggests that the mechanism of NPWTi-d – removing infectious slough and materials away from the wound site, instilling a topical cleansing solution across the wound surface, and applying negative pressure onto the wound bed – may be able to promote wound healing regardless of infection status. According to the literature,[3,5] in our experience we didn't note a combination between a specific wound and a particular topical solution. Even in this case, it seems that the mechanism of NPWTi-d may be enough to stimulate wound healing regardless used specific topical solution (salin or antiseptic), but further studies are required.

Limitations

This study is limited in that there is no comparative control group: all patients received NPWTi-d at a single healthcare center. Also, the patients varied widely in age, comorbidities, and wound aetiology

and location – they were not subcategorized as complex or high-risk wounds as in previously published studies. A final limitation could be found in the wide variance of NPWTi-d settings, although in our experience these differences do not produce significantly different outcomes, even taking into account the possibility that a single-day application or a low intensity (eg, -75 mmHg) may lower efficacy. However, we propose that the diversity of our patient population and therapeutic regimen may provide insight into how NPWTi-d may benefit the typical patient requiring wound management.

Conclusions

In summary, we reviewed the records of 100 patients who underwent NPWTi-d at a single healthcare center and reported on the utility of NPWTi-d to promote wound healing under a variety of circumstances. Over the course of NPWTi-d, the patients were able to meet important healing milestones, including reduced wound surface area, improve bacteria bioburden control, and wound closure. NPWTi-d provided biomechanical support, delivered sterile and antiseptic topical solutions to the wound surface, and laid the groundwork from which concurrent therapies could provide additional benefit. In our experience, the presence of excessive exudate, highly adherent slough, and positive swab have been fundamental for choosing NPTWi-d. Considering these results, NPWTi-d has presently become one of our most used treatments expexiallt in the management of patients affected by chronic or acute ulcers that are infected or at high risk of infection.

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Figure Legends

Figure 1. Initial presentation of a trochanteric pressure ulcer.

Figure 2. Surgical debridement of the coxofemoral joint.

Figure 3. Harvesting the tensor fascia lata myocutaneous flap.

Figure 4. Initial closure of trochanteric wound using myocutaneous flap.

Figure 5. Partial flap necrosis and dehiscence.

Figure 6. Application of NPWTi-d after debridement of necrotic tissues.

Figure 7. Wound appearance after 20 days of NPWTi-d.

Figure 8. Closed wound stable at 6-month follow-up.

Table 1. NPWTi-d Settings

Setting	**N=100**
Negative pressure (median, range)	125 (75-125) mmHg
Solution (n, %)	
0.05% sodium hypochlorite	50 (50.0%)
Normal saline	30 (30.0%)
0.25% acetic acid	20 (20.0%)
Dwell time (median, range)	10 (3-10) minutes
Cycle length (median, range)	3.5 (2-3.5) hours

Table 2. Patient Characteristics

Characteristics	**N=100**
Age (± sd, years)	62.8 ± 16.1
Sex (n, %)	
Male	53 (53.0%)
Female	47 (47.0%)
Comorbidity* (n, %)	
Diabetes	40 (40.0%)
Vascular disease	36 (36.0%)
Hypertension	35 (35.0%)
Coronary disease	24 (24.0%)
Paralysis	17 (17.0%)
Steroid use	9 (9.0%)
Obesity	8 (8.0%)
Cachexia	7 (7.0%)
Previous radiotherapy	5 (5.0%)
None	16 (16.0%)

sd, standard deviation; *patients could have more than one comorbidity

Table 3. Wound Characteristics

Characteristics	**N=100**
Etiology (n, %)	
Vascular ulcer	28 (28.0%)
Surgical wounds	21 (21.0%)
Dehiscence	16 (16.0%)
Trauma	14 (14.0%)
Pressure ulcer	14 (14.0%)
Wound with radiodermatitis	4 (4.0%)
Diabetic foot ulcer	2 (2.0%)
Wound with gangrene and sepsis	1 (1.0%)
Location (n, %)	
Lower limb	61 (61.0%)
Pelvic	23 (23.0%)
Thoracic	7 (7.0%)
Abdomen	5 (5.0%)
Upper limb	4 (4.0%)

Table 4

Table 4. Changes in Wound Surface Area after NPWTi-d in Each Subgroup

Subgroup	n	Before NPWTi-d (cm^2; Median, Q1, Q3)	After NPWTi-d (cm^2; Median, Q1, Q3)	P value
Total	100	45.0 (20.5, 120)	35.0 (16.0, 99.5)	<0.0001
Sex				
Male	53	40.0 (20.0, 100)	28.0 (14.0, 66.0)	<0.0001
Female	47	50.0 (25.0, 180)	36.0 (21.0, 144)	<0.0001
Instillation solution				
Sodium hypochlorite	50	40.0 (20.0, 85.0)	24.0 (14.0, 64.0)	<0.0001
Acetic acid	20	82.5 (25.5, 257)	79.5 (21.5, 221)	0.0002
Normal saline	30	47.5 (25.0, 120)	35.5 (21.0, 72.0)	<0.0001
Wound area				
Large (>500 cm^2)	4	888 (798, 1140)	594 (384, 900)	0.250
Medium (250-500 cm^2)	7	375 (300, 450)	256 (238, 414)	0.031
Small (<250 cm^2)	89	40.0 (20.0, 80.0)	28.0 (15.0, 60.0)	<0.0001
Wound type				
Vascular ulcer	28	44.0 (22.5, 133)	3.50 (0.00, 14.0)	<0.0001
Surgical wounds	21	50.0 (40.0, 100)	36.0 (24.0, 66.0)	<0.0001
Dehiscence	16	42.0 (18.0, 192)	25.5 (11.0, 180)	0.0002
Trauma	14	40.0 (18.0, 120)	34.0 (18.0, 105)	0.0156
Pressure Ulcer	14	42.0 (20.0, 80.0)	29.5 (16.0, 72.0)	0.0001
Other	7	50.0 (18.0, 64.0)	36.0 (12.0, 64.0)	0.1250

NPWTi-d, negative pressure wound therapy with instillation and dwell time

Table 5

Table 5. Subgroup Infection Status and Closure Rate

	Infected before NPWTi-d (n, %)	**Infected after NPWTi-d* (n, %)**	**Closed (n, %)**
Total	72 (72.0%)	46 (46.0%)	91 (91.0%)
Sex			
Male	40 (75.5%)	25 (47.1%)	49 (92.5%)
Female	32 (68.1%)	21 (44.7%)	42 (89.4%)
Instillation solution			
Sodium hypochlorite	36 (72.0%)	21 (42.0%)	44 (88.0%)
Acetic acid	20 (100.0%)	14 (70.0%)	18 (90.0%)
Normal saline	16 (53.3%)	11 (36.7%)	29 (96.7%)
Wound area			
Large (>500 cm^2)	3 (75.0%)	1 (25.0%)	4 (100.0%)
Medium (250-500 cm^2)	5 (71.4%)	3 (42.9%)	6 (85.7%)
Small (<250 cm^2)	64 (71.9%)	42 (47.2%)	81 (91.0%)
Wound type			
Vascular ulcer	26 (92.9%)	21 (75.0%)	25 (89.3%)
Surgical wound	15 (71.4%)	4 (19.0%)	21 (100.0%)
Dehiscence	10 (62.5%)	6 (37.5%)	16 (100.0%)
Trauma	6 (42.9%)	4 (28.6%)	10 (71.4%)
Pressure Ulcer	11 (78.6%)	10 (71.4%)	13 (92.9%)
Other	4 (57.1%)	1 (14.3%)	6 (85.7%)

NPWTi-d, negative pressure wound therapy with instillation and dwell time; *Culture-specific antibiotics were administered as needed throughout the course of NPWTi-d.

Figure 1

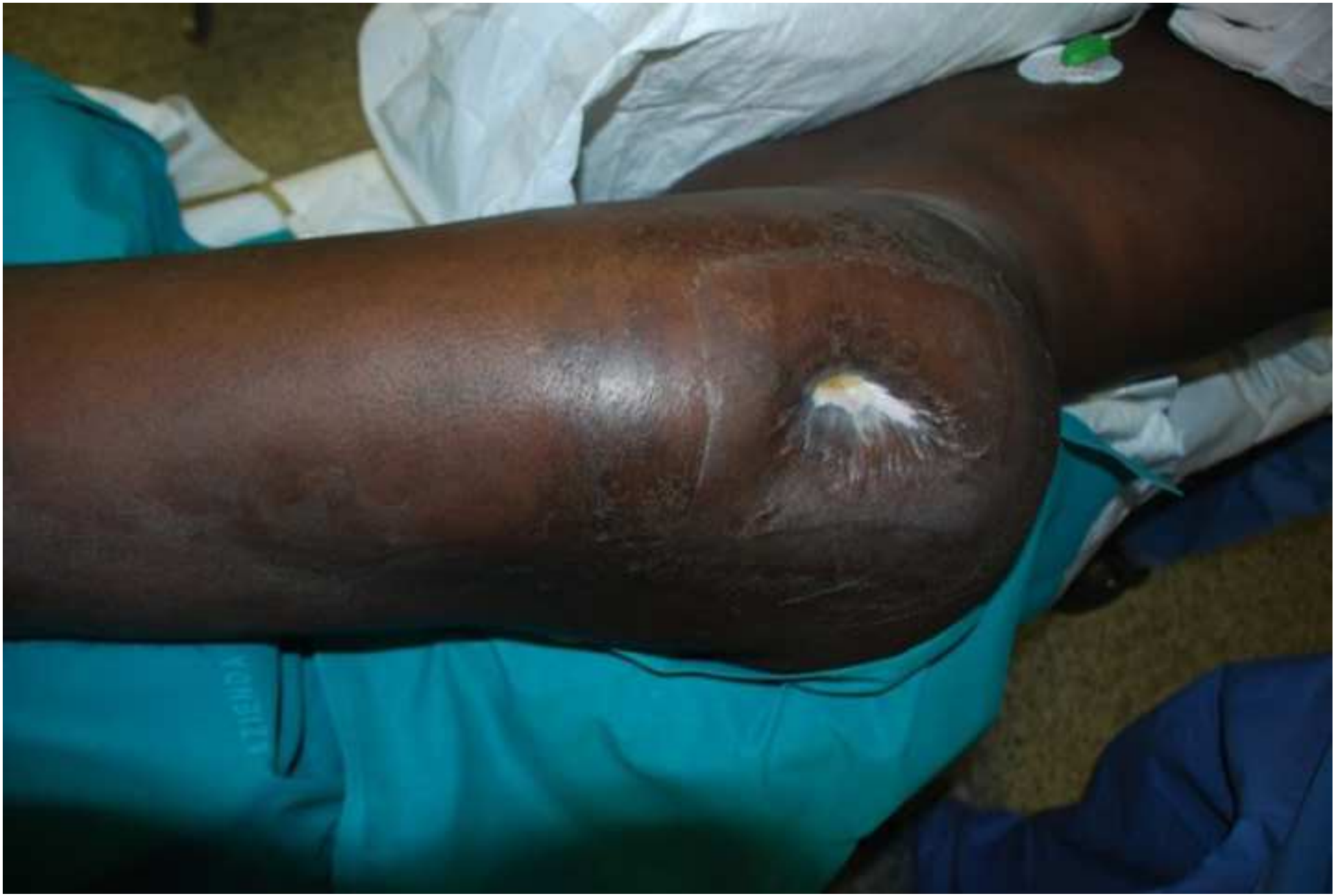

Figure 2

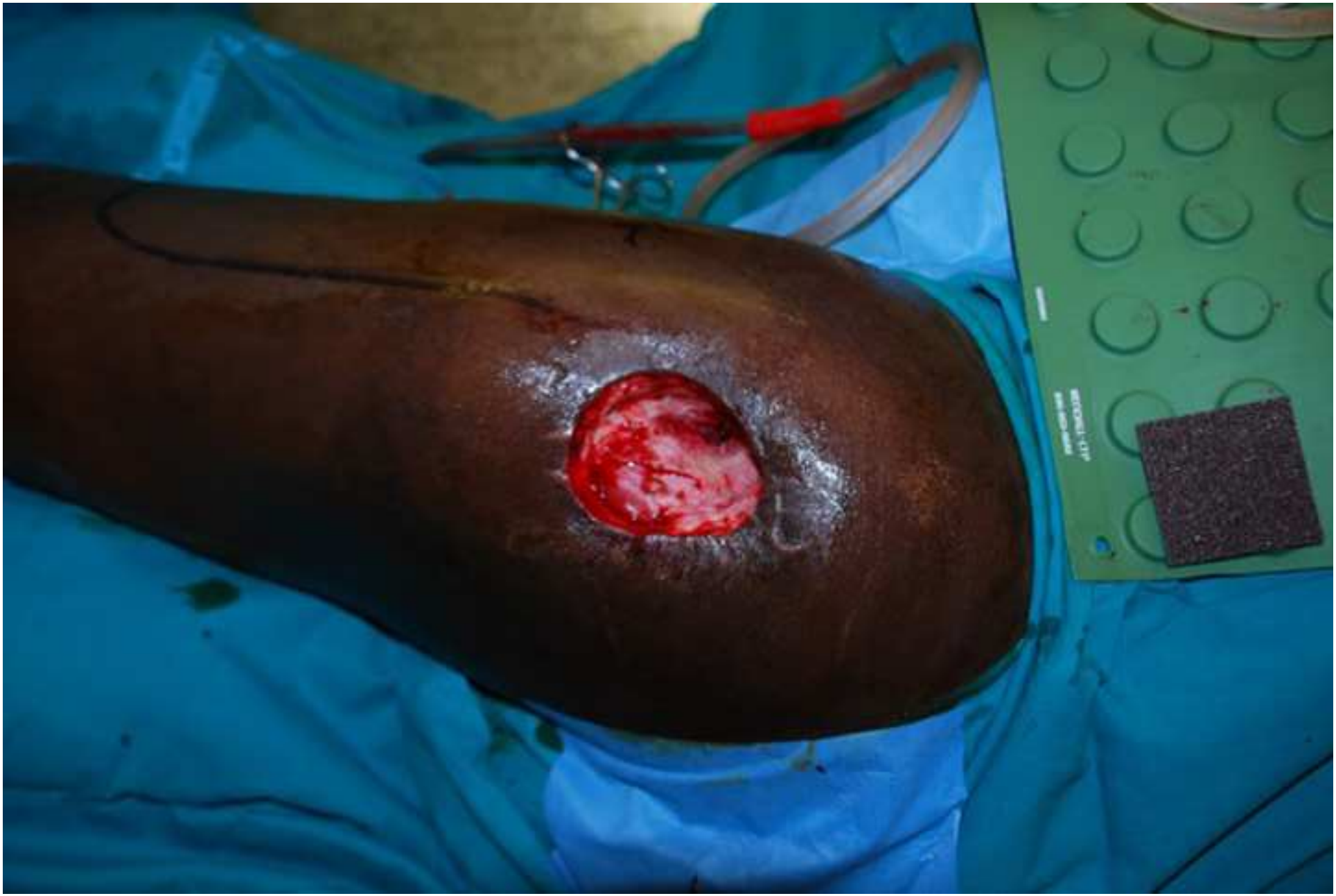

Figure 3

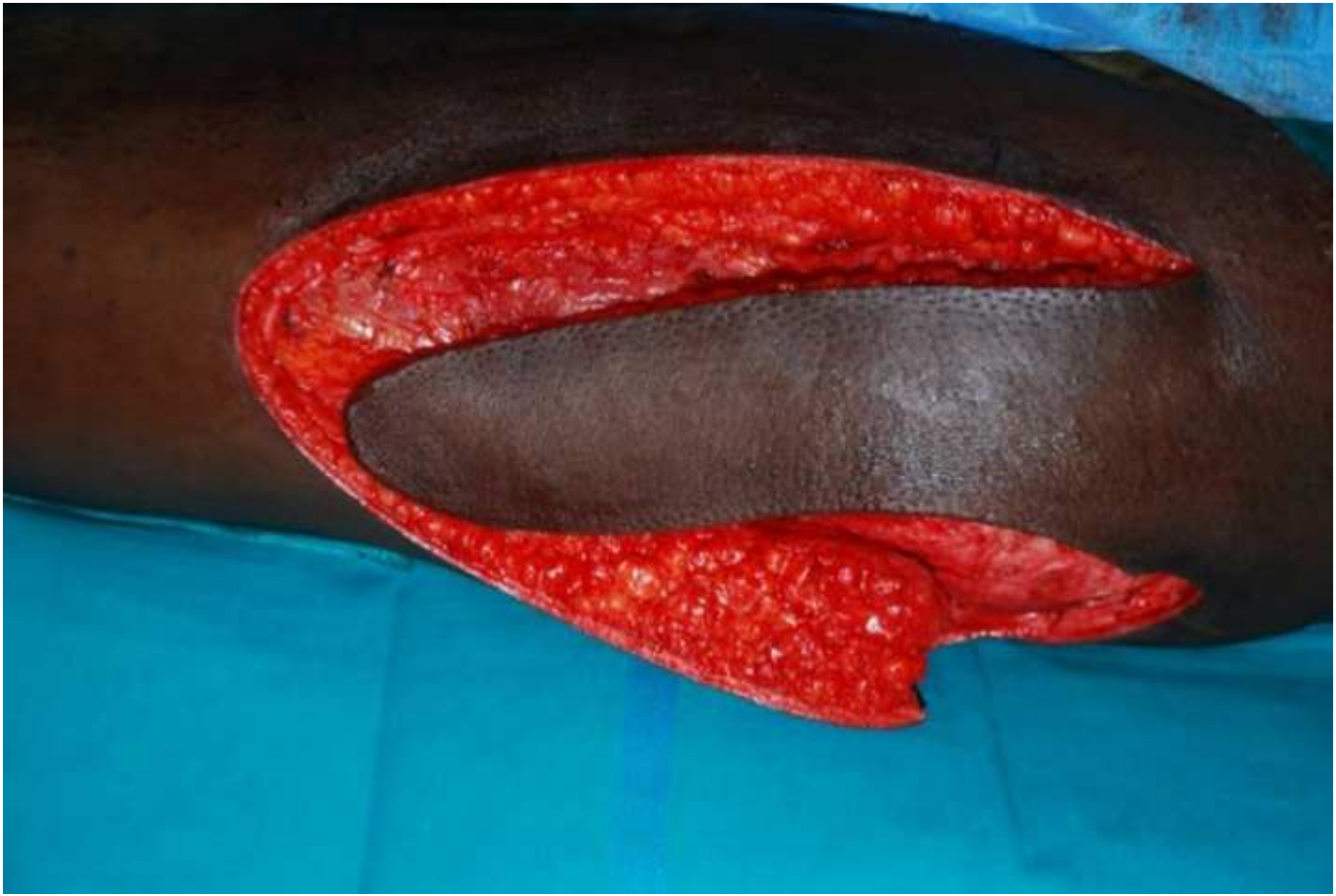

Figure 4

Figure 5

Figure

Figure 7

Figure 8