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PRS GLOBAL OPEN

ORIGINAL ARTICLE
Reconstructive

Negative Pressure Wound Therapy with Instillation and Dwell Time Using Antiseptic Solution in Chronic Limb-threatening Ischemia

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Background: Chronic limb-threatening ischemia (CLTI) is a severe peripheral artery disease with rest pain and lower limb ulceration. After revascularization, limb ulceration treatment should be completed quickly before restenosis. We aimed to investigate the effect of negative pressure wound therapy with instillation and dwell (NPWTi-d) using an antiseptic solution (AS) versus a saline solution (SS) in CLTI. There is no research limited to CLTI on this topic.

Methods: All patients underwent revascularization and surgical debridement. NPWTi-d was applied after surgical debridement. We evaluated wound tissue cultivation from pre- and post-NPWTi-d, length of NPWTi-d, and laboratory data pre- and post-NPWTi-d. All data are presented as the median, interquartile range. For univariate analysis, nonnormally distributed data were examined using the Wilcoxon rank sum test between the two groups of NPWTi-d (AS and SS group). A *P* value of less than 0.05 was considered statistically significant.

Results: Forty-eight CLTI patients participated. The SS group included 24 patients (19 men, five women, average age 68.8 years) and the AS group included 24 patients (16 men, eight women, average age 67.4 years). The comorbidities included 23 and 19 patients with diabetes mellitus and hemodialysis in the SS group, and 22 and 16 patients in the AS group, respectively. There were no adverse events in either group. Both groups reduced the number of bacteria. The AS group required shorter NPWTi-d time ($P = 0.02$).

Conclusion: The AS group was able to shorten the treatment duration in CLTI.
(Plast Reconstr Surg Glob Open 2024; 12:e5578; doi: 10.1097/GOX.0000000000005578; Published online 5 February 2024.)

INTRODUCTION

Chronic limb-threatening ischemia (CLTI) is a severe peripheral artery disease with rest pain and limb ulceration. Patients with CLTI should take revascularization. After balloon angioplasty for infrapopliteal lesions, the restenosis rate is high.[1] After revascularization, limb ulceration treatment should be completed quickly before restenosis.

Limb ulceration treatment includes several methods. Recently, a wound hygiene concept was suggested[2] that deals with biofilm management. There are four steps for daily wound treatment. One of the steps is cleansing the wound and periwound skin. The antiseptic or surfactant solution was used in cleansing.

Negative pressure wound therapy (NPWT) promotes wound granulation tissue, improves edema, and decreases the wound size, but it does not work when the wound has little necrotic tissue and mild infection. So, NPWT with instillation and dwell time (NPWTi-d; V. A. C. VERAFLO Therapy; 3M) is a beneficial tool after surgical debridement procedures. NPWTi-d helps remove necrotic and turbid tissue containing proinflammatory mediators.[3] NPWTi-d is applied to the wound earlier than NPWT in the wound with necrotic tissue and infection. NPWTi-d usually uses saline solution (SS), but it does not have antibacterial property. There are some studies on NPWTi-d with antiseptic solution (AS), but there is no significant difference between SS and AS in hard-to-heal ulcers.[4,5]

The application of NPWTi-d with AS was considered for treating CLTI only among patients with difficult-to-treat ulcers in this study to investigate the effect of NPWTi-d using AS versus SS on CLTI. The purpose of

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Received for publication August 23, 2023; accepted December 15, 2023.

DOI: 10.1097/GOX.0000000000005578

Disclosure statements are at the end of this article, following the correspondence information.

this study was to confirm that NPWT with AS shortens the treatment period and reduces overall cost of treatment.

METHODS

The study was performed at the Limb Salvage Center, Kasukabe Chuo General Hospital, Saitama, Japan. The study was approved by the hospital's research ethics committee (approval no: 2212-3). This study was a retrospective nonrandomized trial. The study procedure was explained, and written informed consent was obtained from all participants between April 2019 and March 2023. The inclusion criteria were as follows: (1) patients who had endovascular treatment and surgical debridement; (2) those with mild and moderate ulceration, as classified by the Infectious Disease Society of America; (3) patients who used a suitable off-loading device. Exclusion criteria were as follows: (1) patients who were unwilling to be involved in the study; (2) patients who were pregnant; (3) patients aged below 20 years; (4) patients who were unable to continue treatment due to other factors.

Prontosan (B. Braun Medical Supplies Sdn. Bhd.: Prontosan) was used as AS. Prontosan includes polyhexanide and betaine. Polyhexanide is a highly effective broad-spectrum antimicrobial that is active against gram-negative and gram-positive bacteria and yeast, including methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, vancomycin-resistant *Enterococci*, among others.[6] Betaine is a gentle effective surfactant that is able to penetrate, disturb, clean, and remove biofilm and wound debris.

All patients underwent revascularization and surgical debridement. NPWTi-d was applied after confirming the hemostasis for surgical debridement. The setting items of NPWTi-d were as follows: negative pressure was −75 mm Hg or −125mm Hg depending on pain and ischemia levels. The amount of irrigation depended on the ulcer area, and dwelling time was 15 minutes. NPWTi-d was changed thrice a week. NPWTi-d was terminated when good granulation grew, and it was determined that the wound could be closed. After NPWTi-d, the wound was closed by skin grafting or epithelialization in all cases.

The evaluation points were wound, ischeia and foot infection (WIfI) classification pre-NPWTi-d, wound tissue cultivation pre- and post-NPWTi-d, length of NPWTi-d, and laboratory data (C-reactive protein: CRP and white blood cell: WBC) pre- and post-NPWTi-d (ΔCRP = pre-CRP – post-CRP, ΔWBC = pre-WBC – post-WBC). The wound bed tissue cultivation was observed in pre- and post-NPWTi-d.

All data are presented as median values and interquartile ranges (IQRs). Fisher exact test was used to examine differences by sex between the two NPWTi-d groups (ie, AS and SS groups). For univariate analysis, nonnormally distributed data were examined using the Wilcoxon rank sum test between the AS and SS group. Statistical data were analyzed using the statistical software R, version 4.0.3, R foundation for Statistical Computing (Vienna, Austria). A *P* value of less than 0.05 was considered statistically significant. The findings were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

Takeaways

Question: The effect of NPWTi-d with antisepitic solution on CLTI.

Findings: Compared with saline solution and antiseptic solution (AS), AS has a shorter treatment duration.

Meaning: The combination of NPWTi-d and AS solution is effective for CLTI.

RESULTS

Table 1 shows the characteristics of 48 CLTI patients. The SS group and AS group each had 24 patients. The SS group had a median age 68.8 years, 19 men and five women. Twenty-three patients with diabetes mellitus, and 19 patients required hemodialysis for chronic renal disease. The AS group had median age 67.4 years, 16 men and eight women. Twenty-two patients with diabetes mellitus, and 16 patients required hemodialysis for chronic renal disease. The blood sugar levels of all diabetes mellitus patients were adequately controlled. Each hemodialysis session for all hemodialysis patients was stable. There were no significant differences in the patient characteristics between the SS group and AS group. There was no significant difference between wound and ischemia, but there was a significant difference in foot infection in WIfI classification.

Table 2 shows the laboratory data of each group. The median glycosylated hemoglobin (HbA1c) levels were less than 8.0% in both groups. The prealbumin and albumin levels were within the normal range in both groups. The level of brain natriuretic peptide was significantly different between the two groups ($P = 0.046$).

All patients achieved wound closure in the end. There were no adverse events with NPWTi-d. Table 3 shows the results of treatment. No significant differences in outcome was observed between the SS and AS groups in the reduction of bacteria count ($P = 0.25$) and laboratory data (ΔCRP and ΔWBC) (both $P = 0.40$). Compared with the SS group, the duration of NPWTi-d was shorter in the AS group ($P = 0.02$).

DISCUSSIONS

The study aimed to identify the utility of NPWTi-d with AS for CLTI treatment. The treatment period was found to be shorter for AS than that for SS.

Table 1. Patient Characteristics

	SS	AS	*P*
Age (y), median [IQR]	72.5 [77.0–60.5]	66 [75.3–62.0]	0.32
Sex (male:female)	19:5	16:8	0.33
Diabetes mellitus (n)	23	22	0.28
Hemodialysis (n)	19	15	0.11
WIfI classification			
W (median)	2.04	1.92	0.22
I (median)	0.33	0.38	0.42
fI (median)	0.92	1.21	0.036
Wound closed			
Skin graft (n)	15	10	—
Epithelization (n)	9	14	—

Table 2. Laboratory Data

Laboratory Data, Median [IQR]	SS	AS	*P*
Albumin (g/dL)	2.6 [2.90–2.38]	2.6 [3.0–2.20]	0.41
CRP (mg/dL)	4.4 [6.58–2.23]	4.7 [7.04–2.40]	0.31
Post-CRP (mg/dL)	1.9 [2.79–0.66]	2.0 [4.29–0.5]	0.14
HbA1c (%)	6.1 [7.8–5.65]	6.4 [9.3–5.6]	0.20
WBC (10 × 3/μL)	100 [111.5–98.8]	86.5 [98.75–62]	0.43
Post-WBC (10 × 3/μL)	92.5 [105–63]	71 [89.5–65.5]	0.13
Hb (g/dL)	9.6 [10.1–8.75]	10.5 [11.23–9.15]	0.12
Brain natriuretic peptide (pg/mL)	382 [778.2–264.2]	648 [1427.4–423.68]	0.046
Prealbumin (mg/dL)	13 [15.85–10.15]	15.5 [18–10.4]	0.43

Table 3. Results of Bacteria Count Using NPWTi-d Term and Laboratory Data

	SS	AS	*P*
Bacteria reduction (n)	11	11	0.42
Duration of NPWTi-d (average days)	16.8	11.3	0.02
ΔCRP	2.32	2.60	0.40
ΔWBC	6.42	4.96	0.40

NPWT is an effective measure for hard-to-heal ulcers. There are several types of NPWT available worldwide. NPWTi-d has functions of irrigation and dwelling. It is a unique method to reduce bioburden. Normally, SS solutions are used with NPWTi-d, but SS alone is inadequate for biofilm removal in the wound hygiene concept. Thus, antiseptic and surfactant solution, such as Prontosan, is used due to their effectiveness in biofilm removal. We used prontosan as AS for this study. Prontosan is a wound irrigation solution that has bactericidal and antiseptic effects. Prontosan-soaked gauze pads were applied to the affected area for 15 minutes, followed by gently wiping the wound area and surrounding skin to facilitate removal of surface debris and contaminants, biofilm, and devitalized tissue. With proper utilization, a wound bed preparation can be achieved. Currently, Prontosan is the only AS that can be used in our country, and comparisons with other solutions will be made in the future once other AS options become available.

Prontosan with NPWTi-d is effective against biofilm. The combination with NPWTi-d gives the impression that there are more merits than using SS. Several studies have compared SS and AS as irrigation solutions for NPWTi-d, but no difference has been observed in the treatment of hard-to-heal ulcers.[7] Thus, in general, NPWTi-d is most often combined with SS.[8] Several studies work on hard-to-heal ulcers (CLTI, diabetic foot ulcer, venous ulcer, pressure ulcer, among others), and there are few studies that focus on one disease like out study.[9–11]

Our results indicate that AS can shorten the treatment period of CLTI and is more useful than SS ($P = 0.02$). There was no case of restenosis in the studied cohort. However, patients with CLTI generally develop restenosis after revascularization. Therefore, it is likely that patients included in this study may develop restenosis if they are administered the same treatment as other patients. This highlights the importance of performing an early treatment of CLTI. This result benefits from reduced cost of revascularization and shorter treatment duration. In short, overall cost of treatment might be reduced.

NPWT is a semi-occlusive wound dressing environment and can cause infection if residual infection exists. In contrast, NPWTi-d removes infectious wastes, adding a topical wound solution to the wound bed and allowing it to remain for a set period. The mechanism reduces the number of bacteria on the wound bed by automated topical wound solution distribution and removal.[12,13] It can improve the wound, and its use may reduce the number of surgical debridements and shorten the duration of treatment.[14,15]

The present study has several limitations. First, the current study was a non–randomized controlled trial and, therefore, requires consideration of various biases. Future studies should use a randomized design to confirm these findings. Second, we did not investigate to what extent it is useful for infection, ischemia, and wound size. The setting configurations of NPWTi-d could also play a role, particularly, in dwelling time. Dwelling time is set at 15 minutes, which is currently the general usage time of Prontosan. In addition, there is a possibility that the selection of AS has a therapeutic effect. It is believed that a more detailed study will be necessary in the future.

CONCLUSIONS

CLTI treatment with NPWTi-d is one of the good measures. Regardless of the solution used with NPWTi-d, we observe reduction in the number of bacteria and facilitation of wound closure. However, in this study, using AS with NPWTi-d shortened the treatment duration. Thus, choosing AS along with NPWTi-d is a simple and safe method for CLTI treatment.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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