The Impact of Negative-Pressure Wound Therapy with Instillation Compared with Standard Negative-Pressure Wound Therapy: A Retrospective, Historical, Cohort, Controlled Study

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Background: Negative-pressure wound therapy with instillation is a novel wound therapy that combines negative pressure with instillation of a topical solution.
Methods: This retrospective, historical, cohort-control study examined the impact of negative-pressure wound therapy with and without instillation.
Results: One hundred forty-two patients (negative-pressure wound therapy, $n = 74$; therapy with instillation, 6-minute dwell time, $n = 34$; and therapy with instillation, 20-minute dwell time, $n = 34$) were included in the analysis. Number of operative visits was significantly lower for the 6- and 20-minute dwell time groups (2.4 ± 0.9 and 2.6 ± 0.9, respectively) compared with the no-instillation group (3.0 ± 0.9) ($p \leq 0.05$). Hospital stay was significantly shorter for the 20-minute dwell time group (11.4 ± 5.1 days) compared with the no-instillation group (14.92 ± 9.23 days) ($p \leq 0.05$). Time to final surgical procedure was significantly shorter for the 6- and 20-minute dwell time groups (7.8 ± 5.2 and 7.5 ± 3.1 days, respectively) compared with the no-instillation group (9.23 ± 5.2 days) ($p \leq 0.05$). Percentage of wounds closed before discharge and culture improvement for Gram-positive bacteria was significantly higher for the 6-minute dwell time group (94 and 90 percent, respectively) compared with the no-instillation group (62 and 63 percent, respectively) ($p \leq 0.05$).
Conclusion: The authors' results suggest that negative-pressure wound therapy with instillation (6- or 20-minute dwell time) is more beneficial than standard negative-pressure wound therapy for the adjunctive treatment of acutely and chronically infected wounds that require hospital admission. (*Plast. Reconstr. Surg.* 133: 709, 2014.)
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Negative-pressure wound therapy with instillation combines localized subatmospheric pressure with delivery of a topical solution. Negative-pressure wound therapy has been widely used for decades as an effective adjunctive treatment of acute and chronic wounds.[1–7] Negative-pressure wound therapy with instillation provides an additional dimension to negative-pressure wound therapy, with the ability to deliver a solution to the wound bed in a preprogrammed manner. The interval, duration of negative pressure, solution dwell time, and type of solution can be precisely prescribed.

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To date, there are minimal data examining the efficacy or effectiveness of negative-pressure wound therapy with instillation in the adjunctive treatment of wounds, mostly limited to small case series and uncontrolled studies.[8–17] The purpose of this study was to compare the outcomes for patients who received negative-pressure wound therapy with instillation versus a historical control cohort of patients who received traditional negative-pressure wound therapy without instillation. The variables examined were the (1) the number of operating room visits, (2) length of hospital stay, (3) time to final surgical procedure during the admission period, (4) percentage of wounds surgically closed before discharge, (5) percentage of wounds that remained closed 30 days after discharge, and (6) reduction in microorganisms.

PATIENTS AND METHODS

This is a retrospective, historical, cohort, controlled study comparing negative-pressure wound therapy with negative-pressure wound therapy with instillation. Data were collected from inpatient electronic medical records from a single institution (MedStar Georgetown University Hospital). All patients with infected wounds requiring admission with at least two operative débridements and that received either negative-pressure wound therapy or negative-pressure wound therapy with instillation application at the time of the initial operation, were included in this analysis. An infected wound was defined by clinically evident infection and positive culture results at the time of the initial operation. The need for hospital admission was determined through clinical judgment (e.g., systemic signs of infection, wound quality including the presence of purulence), elevated white blood cell count, and/or radiographic evidence of infection (e.g., cortical erosion, fluid/emphysema). Comorbidities were identified from clinical diagnoses that were designated in the patients' medical records. Negative-pressure wound therapy was compared with negative-pressure wound therapy with instillation using 6 or 20 minutes of dwell time. The negative-pressure wound therapy group was compared with the negative-pressure wound therapy with instillation group for the same 6-month period separated by exactly 1 year. The following criteria were used to exclude patients from the analysis from both the negative-pressure wound therapy and the negative-pressure wound therapy with instillation groups: (1) cultures not taken or documented during sequential operative visits, (2) culture results of no growth at the first operative visit, or (3) an extended hospital stay greater than 30 days because of medical complications unrelated to the infected wound. The primary wound cause was defined as the principal reason for the development of the wound and subsequent infection. Each subject's data were counted once in the analysis.

The device used for negative-pressure wound therapy was the InfoV.A.C. Therapy System (Kinetic Concepts, Inc., San Antonio, Texas) and the negative-pressure wound therapy with instillation device was the V.A.C. Ulta with VeraFlo Instillation Therapy (Kinetic Concepts). The instillation solution used for both negative-pressure wound therapy with instillation groups was Prontosan (B. Braun, Inc., Bethlehem, Pa.). The setting for both the negative-pressure wound therapy and negative-pressure wound therapy with instillation group was −125 mmHg continuous negative pressure. Sufficient volume of instillation was determined by observing foam saturation through a change in color of the foam to a darker black. The dwell time (the period in which the solution is contained in the foam/wound interface while no negative pressure is being applied) was programmed for 6 or 20 minutes. The negative pressure time was 3.5 hours for the 6-minute dwell time group and 2 hours for the 20-minute dwell time group. The application of the foam and drape to the wound surface was performed in a similar fashion for all groups. Negative-pressure wound therapy or negative-pressure wound therapy with instillation was applied at the initial operative visit immediately after the débridement was performed while in the operating room. Negative-pressure wound therapy or negative-pressure wound therapy with instillation was applied at each subsequent operating room visit until the wound was deemed ready for closure or the patient was discharged from the hospital because the infection was determined to be cleared.

Four surgeons performed all surgical procedures as part of the same limb salvage team (P.J.K., C.E.A., J.S.S., and K.K.E.). Operative débridement of nonviable tissue was performed in a similar manner using scalpels, curettes, rongeurs, scissors, and/or hydrosurgical scalpel. The following operative approach sequence was used: (1) predébridement deep wound culture specimens obtained, (2) sharp excisional débridement performed, (3) pulsatile irrigation using 3 liters of normal saline, (4) redraping of the sterile field with new surgical gloves, (5) new surgical instruments

and instrument table used, (6) postdébridement deep wound culture specimens obtained, and (7) application of negative-pressure wound therapy/negative-pressure wound therapy with instillation or closure. Intraoperative wound culture specimens obtained from the deepest margin were sent for qualitative assessment. Improvement in culture results (postdebridement cultures from the first operative visit compared with predébridement cultures from the second operative visit) was defined as a progression to no growth or a decrease in cultured microorganism amount (e.g., heavy growth progressing to scant growth). All patients received parenteral antibiotics at the time of hospital admission, and antibiotic therapy was adjusted to the sensitivities of the bacterial cultures throughout the hospital stay.

The number of operative visits includes any time the patient was taken to the operating room for wound débridement or closure. The length of hospital stay was calculated in days from the date of admission to the date of discharge. The time to final surgical procedure was calculated in days from the date of admission to the date of the final procedure during the admission period. Clinical judgment, laboratory values, radiographic evidence, and qualitative culture results were used by the surgeon to determine whether the wound was ready for closure. Closure was defined as covering the wound by delayed primary closure, skin graft, or flap. A single follow-up time point at 1 month after discharge from the hospital was used to determine whether the wound remained closed. A closed wound was defined by the absence of a break in the skin as determined by the surgeon.

Statistical calculation was performed using StatPlus:mac LE.2009 (AnalystSoft, Inc., Vancouver, British Columbia, Canada). We used multivariate analysis of variance to compare the three treatment arms for the length of hospital stay (days), the time to final surgical procedure (days), and the number of operative visits. We then performed post hoc pairwise comparison using the least significant difference test. Statistical comparisons of percentages (proportional analysis) were performed using Fisher's exact test (two-tailed). The Georgetown University Medical Center Institutional Review Board approved this study.

RESULTS

A total of 142 patients, 74 subjects in the negative-pressure wound therapy group, 34 subjects in the 6-minute dwell time negative-pressure wound therapy with instillation group, and 34 subjects in the 20-minute dwell time negative-pressure wound therapy with instillation group were included in the analysis. Age, sex, body mass index, current smoking status, and medical comorbidities were not statistically different between the negative-pressure wound therapy group and the 6- or 20-minute dwell time negative-pressure wound therapy with instillation groups (Table1). The only difference was a statistically higher percentage of African Americans in the 6-minute dwell time negative-pressure wound therapy with instillation group compared with the negative-pressure wound therapy group ($p = 0.03$).

There was no difference between the negative-pressure wound therapy group and the 6- or 20-minute dwell time negative-pressure wound therapy with instillation group in the primary wound cause. There was a statistically significant difference between the anatomical location of the wound in negative-pressure wound therapy group and the 20-minute dwell time negative-pressure wound therapy with instillation group for the forefoot and hindfoot/heel ($p = 0.04$ and $p = 0.03$, respectively). There was a higher percentage of forefoot wounds and a lower percentage of hindfoot/heel wounds for the 20-minute dwell time negative-pressure wound therapy with instillation group compared with the negative-pressure wound therapy group (Table 2).

There is a statistically significant difference in the following outcomes: (1) length of hospital stay between the negative-pressure wound therapy group and the 20-minute dwell time negative-pressure wound therapy with instillation group ($p = 0.034$; 95 percent CI, 0.27 to 6.86), (2) number of operative visits between the negative-pressure wound therapy group and the 6-minute dwell time negative-pressure wound therapy with instillation group ($p = 0.043$; 95 percent CI, 0.014 to 0.75) and between the negative-pressure wound therapy group and the 20-minute dwell time negative-pressure wound therapy with instillation group ($p = 0.003$; 95 percent CI, 0.19 to 0.93), (3) time to final surgical procedure between the negative-pressure wound therapy group and the 6-minute dwell time negative-pressure wound therapy group ($p = 0.043$; 95 percent CI, 0.065 to 4.04) and between the negative-pressure wound therapy group and the 20-minute dwell time negative-pressure wound therapy with instillation group ($p = 0.0019$; 95 percent CI, 0.39 to 4.36) (Table 3).

The percentage of wounds closed before discharge was significantly higher in the 6-minute dwell

Table 1. Demographics

	NPWT	NPWTi 6		NPWTi 20	
	Value (%)	Value (%)	*p**	Value (%)	*p*†
Age, yr					
Mean ± SD	58 ± 13	63 ± 16		55 ± 17	
Range	18–95	20–88	0.11	18–90	0.43
Male sex	38 (51)	20 (59)	0.54	22 (65)	0.22
Race					
African American	21 (28)	17 (50)	0.03	15 (44)	0.13
Caucasian	39 (53)	16 (47)	0.68	14 (41)	0.30
Hispanic	2 (6)	1 (3)	1.0	0 (0)	
Asian	1 (3)	1 (1)	1.0	1 (3)	1.0
Other	6 (8)	5 (15)	0.32	4 (12)	0.72
BMI, kg/m^2	32 ± 9.14	29.6 ± 6.77	0.17	32.9 ± 8.89	0.63
Current smoker	7 (9)	2 (6)	0.72	1 (3)	0.74
Comorbidities					
Diabetes type 1	7 (9)	2 (6)	0.72	4 (12)	0.74
Diabetes type 2	35 (47)	18 (53)	0.54	16 (47)	1.0
ESRD	22 (30)	12 (35)	0.66	4 (12)	0.05
PVD	27 (36)	10 (29)	0.52	11 (32)	0.83
Autoimmune disease	4 (5)	4 (12)	0.26	3 (9)	0.68
Hemiparalysis	1 (1)	2 (6)	0.23	1 (3)	0.53
History of cancer	6 (8)	2 (6)	1.0	3 (9)	1.0
Kidney/pancreas transplant	3 (4)	1 (3)	1.0	1 (3)	1.0

NPWT, negative-pressure wound therapy; NPWTi 6, negative-pressure with instillation 6-minute dwell time; NPWTi 20, negative pressure with instillation 20-minute dwell time; BMI, body mass index; ESRD, end-stage renal disease; PVD, peripheral vascular disease.
*Comparison of NPWT and NPWTi 6.
†Comparison of NPWT and NPWTi 20.

Table 2. Wound Cause and Anatomical Location

	NPWT	NPWTi 6		NPWTi 20	
	Value (%)	Value (%)	*p**	Value (%)	*p*†
Primary cause					
Ischemic wound	17 (23)	7 (21)	1.0	8 (24)	1.0
Neuropathic wound	16 (22)	6 (18)	0.80	7 (21)	1.0
Decubitus wound	16 (22)	6 (18)	0.80	4 (12)	0.29
Surgical wound	17 (23)	9 (26)	0.81	10 (29)	0.48
Venous	3 (4)	2 (6)	0.65	1 (3)	1.0
Traumatic	4 (5)	2 (6)	1.0	1 (3)	1.0
Other (unclear)	3 (4)	2 (6)	0.65	3 (9)	0.38
Anatomical location					
Forefoot	12 (16)	6 (18)	1.0	12 (35)	0.04
Midfoot	12 (16)	3 (9)	0.38	3 (9)	0.38
Hindfoot/heel	22 (30)	6 (18)	0.24	3 (9)	0.03
Transmetatarsal amputation site	1 (1)	2 (6)	0.23	2 (6)	0.23
Ankle	7 (9)	4 (12)	0.74	3 (9)	1.0
Leg	7 (9)	4 (12)	0.74	6 (18)	0.40
Below-knee amputation site	1 (1)	2 (6)	0.23	0 (0)	
Knee	1 (1)	1 (3)	0.53	2 (6)	0.23
Thigh	3 (4)	1 (3)	1.0	0 (0)	
Back/buttock	2 (3)	2 (6)	0.59	3 (9)	0.32
Abdomen	5 (7)	3 (9)	0.71	0 (0)	
Arm	1 (1)	0 (0)	1.0	0 (0)	

NPWT, negative-pressure wound therapy; NPWTi 6, negative-pressure with instillation 6-minute dwell time; NPWTi 20, negative pressure with instillation 20-minute dwell time.
*Comparison of NPWT and NPWTi 6.
†Comparison of NPWT and NPWTi 20.

time negative-pressure wound therapy with instillation group compared with the negative-pressure wound therapy group ($p = 0.0004$). The overall wound culture improvement was not different between the negative-pressure wound therapy group and the 6- or 20-minute dwell time negative-pressure wound therapy with instillation groups; however, when Gram-negative bacteria, *Corynebacterium*, and yeast were excluded from analysis, there was a significantly greater improvement in

Table 3. Outcomes

	NPWT	NPWTi 6		NPWTi 20	
	Value (%)	Value (%)	*p**	Value (%)	*p*†
No. of OR visits	3.0 ± 0.9	2.4 ± 0.9	0.04	2.6 ± 0.9	0.003
Length of hospital stay	14.92 ± 9.2	11.9 ± 7.8	0.10	11.4 ± 5.1	0.03
Time to final surgical procedure	9.23 ± 5.2	7.8 ± 5.2	0.04	7.5 ± 3.1	0.002
Closed	46 (62)	32 (94)	0.0004	27 (80)	0.08
Remained closed at 1 mo	28 (61)	24 (75)	0.23	14 (52)	0.47
Overall culture improvement	28 (38)	20 (59)	0.06	17 (50)	0.30
Culture improvement with Gram-negative, *Corynebacterium*, and yeast excluded	17 (63)	19 (90)	0.0001	13 (65)	0.77

NPWT, negative-pressure wound therapy; NPWTi 6, negative-pressure with instillation 6-minute dwell time; NPWTi 20, negative pressure with instillation 20-minute dwell time; OR, operating room.
*Comparison of NPWT and NPWTi 6.
†Comparison of NPWT and NPWTi 20.

the 6-minute dwell time negative-pressure wound therapy with instillation group than in the negative-pressure wound therapy group ($p = 0.0001$) (Table 3).

DISCUSSION

To date, this is the most systematic examination of the impact of negative-pressure wound therapy with instillation in the adjunctive treatment of the acutely infected wound in an inpatient setting, and is the only study to compare traditional negative-pressure wound therapy and negative-pressure wound therapy with instillation. Previous publications using negative-pressure wound therapy with instillation use "standard" wound care as the comparator.[14,17] In these studies, it is difficult to determine whether there is any additional benefit from instillation or whether the superior results are simply because of the effectiveness of traditional negative-pressure wound therapy. Although the primary benefit of negative-pressure wound therapy is in the promotion of wound healing and wound bed preparation, there is some evidence that negative-pressure wound therapy may inhibit bacterial growth and reduce infection.[18,19] The use of antiseptic solutions for irrigation of infected wounds has been well established.[20] Our results suggest that adding instillation therapy to negative-pressure wound therapy enhances the effectiveness of both of these treatment modalities.

There are several limitations to this study, including inherent limitations related to the retrospective study design. Comorbidities were identified from the patients' medical records; thus, definitive diagnosis is unconfirmed by diagnostic modalities. For our study, this is less important because both negative-pressure wound therapy and negative-pressure wound therapy with instillation would have been impacted in the same manner. Furthermore, there is the potential for selection bias for the use of negative-pressure wound therapy with instillation and negative-pressure wound therapy. The observed benefit of negative-pressure wound therapy with instillation could have prompted its selective use for wounds that were potentially more infected or when the surgeon suspected that the débridement was inadequate. Contrarily, the negative-pressure wound therapy group could have been biased toward less infected wounds or when the débridement was performed adequately. The retrospective nature of this study makes it impossible to determine whether there was selection bias and the direction and degree of impact on the results.

Although conclusive statements of superior efficacy cannot be made because of a lack of rigid prospective comparative trial design, our approach reflects a "real-world" effectiveness examination of negative-pressure wound therapy with instillation. The important variables of length of hospital stay, number of operating room visits, and time to final closure during the admission period reflect significant clinical and economic comparative effectiveness endpoints. Although the length of hospital stay is heavily influenced by factors unrelated to the wound, the number of operating room visits and time to final surgical closure are less encumbered by these factors.

We found a significantly higher percentage of closed wounds before discharge in the 6-minute dwell negative-pressure wound therapy with instillation group and a strong trend in the 20-minute dwell time negative-pressure wound therapy with instillation group compared with the negative-pressure wound therapy group. Furthermore, there was a statistically significant decrease in time to final surgical procedure for both negative-pressure wound therapy with

instillation groups compared with the negative-pressure wound therapy group. It is possible that the higher percentage of closed wounds and a reduced time to final surgical closure in the negative-pressure wound therapy with instillation groups reflects a bias by the surgeons to close the wounds earlier. However, the percentage closed at the 30-day follow-up did not reflect an inherent bias of premature wound closure because both groups had statistically similar rates of closure. Furthermore, our qualitative culture data suggest that if there had been a bias, there should have been a smaller percentage of culture improvement for the negative-pressure wound therapy with instillation groups compared with the negative-pressure wound therapy group. In other words, a rush to closure would more likely translate to cultures worsening. Although the overall culture data showed no statistically significant difference between the negative-pressure wound therapy and the negative-pressure wound therapy with instillation groups, there was a trend toward greater improvement in favor of the negative-pressure wound therapy with instillation groups. This also suggests that there may be a positive effect of negative-pressure wound therapy with instillation on microorganisms.

We found no difference between the negative-pressure wound therapy with instillation groups and the negative-pressure wound therapy group in overall microorganism improvement, which may reflect the limitations of swab cultures rather than the lack of superior effectiveness of negative-pressure wound therapy with instillation. This includes the lack of consistency in the way the cultures were obtained in the operating room or the fact that swab cultures were selective for a limited number of specific types of bacteria.[21] It is interesting that the 6-minute dwell negative-pressure wound therapy with instillation group but not the 20-minute dwell time negative-pressure wound therapy with instillation group showed a statistically significant culture improvement compared with negative-pressure wound therapy group. Again, this may reflect the limitations of swab cultures.

Polyhexanide has been reported to have positive effects on wound healing, presumably by reducing infection or through biofilm eradication.[22–25] Koburger et al. report that polyhexanide is immediately effective against pathogens in vitro.[26] Furthermore, they report in vitro that the longer the solution is in contact with bacteria such as *Streptococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*, the lower the concentration of polyhexanide that is needed to be effective. Our results suggest that a longer dwell time has no significant bearing on culture improvement. Lee et al. suggest that, in an inoculated agar plate model, polyhexanide is less effective against Gram-negative bacteria compared with Gram-positive bacteria.[27] This is consistent with our results, where we found that excluding Gram-negative bacteria from our analysis yielded a statistically significant difference in culture improvement in the 6-minute dwell time negative-pressure wound therapy with instillation group compared with the negative-pressure wound therapy group. The reason why this was not found for the 20-minute dwell time negative-pressure wound therapy with instillation group is unclear but may again reflect the limitations of swab cultures.

The published literature is not consistent about the most appropriate dwell time, with ranges varying from 1 second to 30 minutes.[13–15] Initially, 6 minutes of dwell time was selected based on reported positive results with shorter durations.[14,15] Furthermore, there was initial concern of longer dwell times increasing the chance of leaks and macerating the surrounding tissue. As these problems did not occur, we progressed to the 20-minute dwell time based on published literature that suggested 10- to 30-minute dwell time.[1,15,17] Fleischmann et al. report 7-day treatment of negative-pressure wound therapy with gravity-fed intermittent instillation for soft-tissue and bone infections using alternating regimens of antibiotic solution (neomycin and bacitracin) with an antiseptic (polyhexanide 0.04%) for 30 minutes of instillation.[13] Lehner et al. report 5 to 30 minutes of dwell time with polyhexanide 0.04% for periprosthetic implant infections, resulting in a salvage rate of 80 percent for acute infections and 86.4 percent for chronic infections.[15] Timmers et al. report using 10 to 15 minutes of dwell time with polyhexanide 0.04% for traumatic bone infections.[17] They report a 10 percent infection recurrence rate using negative-pressure wound therapy with instillation versus a historical control that had a 58.5 percent infection recurrence rate. Furthermore, they report a significantly shorter median duration of hospital stay (36 days versus 73 days) and fewer surgical procedures (two versus five). Our results suggest that there is not an overall difference in using 6 or 20 minutes of dwell time compared with negative-pressure wound therapy. The wide range of dwell times reported in the literature with positive outcomes, and our own findings, suggest that an exact dwell time may not be an important contributing factor

to the overall effectiveness of negative-pressure wound therapy with instillation.

The choice of instillation solution may also play a significant role. We used Prontosan as our choice of instillation solution because of the combined benefit of 0.1% polyhexanide (antimicrobial) and 0.1% betaine (surfactant). Prontosan has a high tolerability profile with in vivo and in vitro benefits at low concentrations and efficacy against a wide variety pathogens.[23] However, many other solutions and combinations of solutions have been reported in the literature, including Dakin's solution, silver nitrate, and mixed antibiotic solution.[11,12,14] Others have suggested that normal saline be used as the instillation solution.[28,29] Perhaps the choice of instillation solution is not as critical as the fact that a solution is being bathed over the wound.

Other factors that may have influenced our results include the duration of negative pressure, volume of instillation solution, and the minimum or maximum duration of therapy. The published literature provides little guidance as to the most appropriate duration of negative pressure, varying from 45 minutes to 6 hours.[9,10] Furthermore, the volume of instillation used varied on the size and location of the wound. It is likely that the subjective determination of "sufficient" volume was inaccurate and the wound was not completely bathed by the instillation solution, which could have changed our results. The volume of instillation used is not generally reported in the published literature, except for two publications where ranges were reported from 3 to 75 ml.[14,17] Establishing the minimum and maximum duration of negative-pressure wound therapy with instillation was not a principal goal of our study and thus was not captured. The literature again reports a wide range from 2 to 60 days.[8,17] Based on our data, we generally used negative-pressure wound therapy with instillation or negative-pressure wound therapy for a minimum of 2 days and a maximum of 10 days.

CONCLUSIONS

Our results suggest that negative-pressure wound therapy with instillation is superior to negative-pressure wound therapy for inpatient adjunctive treatment of the acutely infected wound. However, there are many remaining questions regarding the efficacy and effectiveness of negative-pressure wound therapy with instillation. The data presented in this article add to the body of knowledge regarding this novel technology while simultaneously raising many questions. A robust, prospective, randomized, controlled study is needed to better delineate the most appropriate use of negative-pressure wound therapy with instillation.

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