TECHNICAL ARTICLE

Negative pressure wound treatment with polyvinyl alcohol foam and polyhexanide antiseptic solution instillation in posttraumatic osteomyelitis

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ABSTRACT

In a retrospective, case–control cohort study an assessment was made of the clinical outcome of patients with osteomyelitis treated with a new modality of negative pressure wound therapy, so called negative pressure instillation therapy. In this approach, after surgical debridement, a site of osteomyelitis is treated with negative pressure of at least 300 mmHg applied through polyvinyl alcohol dressing. The polyvinyl alcohol foam is irrigated through the tubes three times a day with a polyhexanide antiseptic solution. In 30 patients (14 males; mean age 52 [range, 26–81]) admitted between 1999 and 2003 with osteomyelitis of the pelvis or lower extremity, we assessed time to wound closure, number of surgical procedures and rate of recurrence of infection as well as need for rehospitalizations. For comparison, a control group of 94 patients (males, 58; mean age 47 [range, 9–85]), matched for site and severity of osteomyelitis, was identified in hospital records between 1982 and 2002. These patients underwent standard surgical debridement, implantation of gentamicin polymethylmethacrylate beads and long-term intravenous antibiotics. In the Instillation group the rate of recurrence of infection was 3/30 (10%), whereas 55/93 (58.5%) of the controls had a recurrence ($p < 0.0001$). Moreover, in those treated with instillation the total duration of hospital stay was shorter and number of surgical procedures smaller as compared with the controls (all $p < 0.0001$). We conclude that in posttraumatic osteomyelitis negative pressure instillation therapy reduces the need for repeated surgical interventions in comparison with the present standard approach.

Chronic-infected wounds, with little tendency to heal spontaneously, pose a continuing challenge in medicine. Despite various options for treatment of such infected wounds, e.g., repeated surgical debridement and antibiotic therapy, the condition cannot always be treated effectively and can result in prolonged and multiple hospitalizations. In some cases a final solution to cope with such wounds, e.g., a severe posttraumatic osteomyelitis, may be a disabling amputation.

The process of wound healing is complex and normally proceeds through at least three stages.[1] The first, catabolic stage occurs directly after the noxe and in a traumatic wound lasts from day 1 to day 5. The second stage lasts about 2 days, from day 5 to day 7, and is called the proliferation or anabolic phase. During this phase, fresh granulation tissue will grow into the wound area. The last stage of wound healing, the recovery stage, occurs when the ingrowth of fibroblasts creates scar tissue. This final stage may last until day 21 of the recovery. The normal process of wound healing may be disturbed at each stage by local or systemic infection, be delayed by underlying conditions such as diabetes mellitus or by exogenous factors such as smoking. If the wound becomes colonized by bacteria or even infected, production of lytic enzymes and toxins by microorganisms and the host inflammatory reaction impairs wound healing and spontaneous wound closure will be delayed even further. Many of these factors play a role when the infection progresses to involve underlying bone, resulting in osteomyelitis. The current standard surgical approach to osteomyelitis, i.e., repeated debridement of necrotic tissue, lavage, sequestrectomy, or bone resections, complemented by antibiotics, will in many cases not succeed in curing the infection or prevent prolonged or recurring hospitalization.[2–5] Even after wound closure, there remains a risk of recurrence of infection, which may lead to rehospitalization and a prolonged time of disability.

In this study we investigated whether negative pressure therapy (NPT) with use of polyvinyl alcohol (PVA) foam in combination with intermittent instillation of polyhexanide antiseptic solution can aid the recovery of osteomyelitis of the pelvis and leg, chronic nonhealing soft tissue infections, and selected acute traumatic wounds. To this

end, consecutive patients presenting with these conditions were treated by this method and the results were compared with the outcome in a historical control group of patients with osteomyelitis at identical sites and of similar severity.

MATERIALS AND METHODS

The NPT with polyhexanide antiseptic solution, which is now called the V.A.C-Instillation® therapy (Negative Pressure Instillation therapy [NPIT]),[6] consists of a sterile, open-cell foam connected through incorporated tubing to a vacuum source. The wound, foam, and connecting tubing are sealed through an adhesive polyurethane (PU) film (Kinetic Concepts Inc. [KCI], San Antonio, TX), which is semi-permeable to skin vapor. Because of this semi-permeable closed system, a controlled subatmospheric pressure can be applied to a wound and thus a moist but controlled wound chamber is created, with excess fluid being removed by suction. For NPT, two types of foam are used: a ''black'' PU foam (V.A.C.® GranuFoam®, KCI) or a ''white'' PVA foam. The advantage of the PVA foam in comparison with the PU foam for use in traumatology is defined by its physical characteristics. The PVA foam has a finer structure, with a smaller pore size (60–270 vs. 400–600 μm for the PU foam) and therefore, less ingrowth of surrounding tissue into the foam is observed during VAC therapy, despite extensive contact with the surrounding tissue. Thus, in contrast to PU foam,[7] changing and replacing PVA foam is not painful, will rarely cause bleeding and does not traumatize the wound when dressing changes are performed.

In this study, before NPT was applied to the wound, the wound had to be surgically cleaned through an extensive debridement.[4] Following this procedure, the PVA foam was cut to fit the wound size and placed inside the wound. The wound with the foam and incorporated tubing was sealed off with a PU film and was connected to a dedicated, specially adjusted electrical vacuum therapy unit with a fluid reservoir. The subatmospheric pressure applied to the wound was at least 300 mmHg and could be adjusted to a maximum of 600 mmHg. The PVA foam was changed the first day after the debridement, and subsequently every 3–4 days. Most changes were performed in the traumatology ward and need not be performed on the operating theatre. During dressing changes, deep wound swabs were taken, put in Stuart's medium and cultured to assess bacterial colonization. The NPIT was ended if two consecutive swabs, taken a few days apart, were either sterile or showed skin bacteria only, or when enough new granulation tissue had grown into the wound to permit surgical wound closure. Alternatively, if spontaneous wound closure occurred during therapy, NPIT was ended.

To maintain optimal contact between foam and surrounding tissue, which likely is pivotal to the success of NPIT treatment, the foam is instilled two to three times daily. This instillation is necessary to keep the pores in the foam patent and the tubing free of obstruction. The instillations prevent disturbances in fluid suction and corresponding subatmospheric pressure application to the wound's surface. For instillations, use was made of polyhexanide/macrogol 4000—containing antiseptic solution (Lavasept® solution 0.2%, B. Braun Melsungen AG, Germany, containing 0.04% polyhexanide). The combination of NPT and instillations was described first by Fleischmann and colleagues[6,8] and was shown to be effective in the treatment of infected wounds.[9–11] For instillation of the foam, 3–10 mL of polyhexanide antiseptic solution per tube is used, depending on the length of the tubing and on the size of the foam. The solution is administered until the foam becomes completely saturated; during instillation, the vacuum device is switched off for approximately 10–15 minutes. Throughout this period, the so-called ''hold phase,'' the antiseptic fluid remains in the foam and wound area. Next, the vacuum unit is switched on again, the fluid with debris from the tubing and foam is drained and the preprogrammed subatmospheric pressure is restored. In case of osteomyelitis, in addition to the NPIT, the standard approach includes the administration of antibiotic drug(s) with confirmed activity against the etiological microbial agent. For about 2 weeks, the antibiotics are given intravenously. For instance, in case of a methicillin-sensitive *Staphylococcus aureus* infection, patients are treated with 6 g flucloxacillin intravenously. Next, a switch is made from intravenous to oral administration of the drugs provided that oral resorption of the antibiotic is adequate (e.g., serum flucloxacillin $>$ 10 mg/mL 1–3 hours after 1 g taken orally on an empty stomach). Antibiotic therapy is administered for 6 weeks at a minimum, with stopping made dependent on normalization of local abnormalities (including x-ray evaluation) and normalization of indirect measures of inflammation like erythrocyte sedimentation rate and number of blood leukocytes. In a particularly severe case of osteomyelitis, antibiotic therapy often was prolonged for 12 weeks.

NPIT patient cohort and controls

Consecutive patients who presented to the Leiden University medical Center with osteomyelitis of the pelvis and leg, between March 1999 and February 2003 and were treated in the Department of Traumatology with NPIT were enrolled in this prospective treatment group study. Patients with osteomyelitis were included as they received at least one hospital admission in combination with surgical debridement before NPIT because of an underlying recurrent osteomyelitis of the pelvis or lower leg. For each osteomyelitis patient treated with NPIT we identified historical case controls among patients admitted to the Department of Surgery or Department of Orthopedic Surgery between January 1982 and December 2002 with a diagnosis of recurrent osteomyelitis of pelvis or lower extremity, as documented in the hospital diagnosis registry, which underwent at least one admission for recurrence of osteomyelitis of the pelvis or lower leg, including surgical procedure in the past. The patients in the historical control group received the standard medical approach consisting of surgical debridement, repeated as often as felt necessary by attending physicians, systemic administration of antibiotics with confirmed activity against the etiologic microbial agent and implantation of gentamicin beads at the site of osteomyelitis. Futhermore, it should be noticed that in the period January 1999–February 2003 (period of 4 years), patients suffering osteomyelitis who were admitted to the Department of Orthopedic Surgery (prospective treatment group) were treated with the standard approach, while patients admitted to the Department of Traumatology were treated with NPIT. In both groups an etiologic microbial agent was

identified in the infected wound, by deep wounds swabs and/or bone culture taken before treatment during first surgical debridement. Culture swabs were put in Stuart's medium and cultured according to standard microbiological methods. In all cases, treatment was stopped when either two consecutive swabs taken within a few days had become sterile or when enough new granulation tissue had formed to permit surgical wound closure.

In the cases and controls we extracted, from the medical records, demographic characteristics, location, severity, and culture characteristics of the osteomyelitis, duration of hospitalization, number and duration of hospital stay(s) related to the present medical condition, the number of surgical procedures, the number of clinical and microbiological recurrences and any relevant comorbidity the patient may suffer. For our (retrospective) nonrandomized, open-label cohort study including data analysis no approval of our Institutional Review Board was needed, because NPT is an established therapy.

Statistical analysis

For analysis of the results obtained in this study, SPSS version 13.0 was used as statistical software. *p*-values < 0.05 were considered significant. For comparison of mean values between groups Student's *t* test was used. For comparison between distribution of variables in each group χ^2 test for correlation was used.

RESULTS

Baseline characteristics of NPIT patients and controls

In 4 years, we treated 59 patients (30 males; mean age 53 [range, 2–94] years) with NPIT (Table 1). Thirty-three patients were treated for osteomyelitis. We matched the osteomyelitis patients with 94 controls (58 males; median age 46.6 [range, 9–85] years) (Table 3). In cases the cause of osteomyelitis was posttraumatic because of various types of injuries or trauma in the past. In controls the principal cause of osteomyelitis was posttraumatic (84.0%), tumor surgery (8.5%), hematogenous (4.3%), or other (3.2%), with areas affected: lower leg (68.1%), femur/pelvis (29.8%), and other (2.1%).

In the total NPIT group, a total of 72 bacterial species (13 patients had two bacterial species isolated from the wound) were identified, including *S. aureus* (40.3%), *Enterobacter cloacae* (12.5%), and *Pseudomonas aeruginosa* (9.7%), the latter two being common microorganisms colonizing chronic wounds, whereas *S. aureus* and streptococci are common isolates in osteomyelitis.[5] Therefore, a different distribution of microorganisms in the NPIT group for treatment of osteomyelitis was observed, with 38 bacterial species identified with more *S. aureus* species (50%) and more non-common isolates (39.3%) (Table 2A) than in the total group, most likely related to the facts that *S. aureus* is often isolated in case of osteomyelitis and many noncommon isolates could be observed as many patients had an extensive history of antibiotic treatments, before admission to our hospital.

Scope of this study was primarily focused on treatment of osteomyelitis, therefore, from this point microbiologic considerations are only used for patients treated for osteomyelitis.

In all controls, an etiologic agent was cultured from the initial culture. Microbiological examination revealed 108 bacterial specimens (83 patients with one bacterial specimen causing infection, eight patients with two, and three patients with three bacterial infestations). Principal bacterial specimens as cause of osteomyelitis were *S. aureus* (67.6%), *P. aeruginosa* (5.6%), *Streptococcus* sp. (4.6%), Gram-negative stains, and other bacterial species (22.2%) (Table 2A). Although there are methodological limitations to this study (a prospective treatment group compared with a historical control group), in our opinion new information about treatment of posttraumatic osteomyelitis is provided and. First of all, no statistical significant difference in appearance of the two most important cultured bacterial specimens over the time could be detected (*S. aureus* and *P. aeruginosa*) between the groups could be

In a motorcycle accident, a 38-year old male suffered a Gustilo II-degree open fracture of the lower leg complicated by compartment syndrome. After unreamed tibial nail osteosynthesis and a 4-compartment fasciotomy, the postoperative course was complicated by chronic osteomyelitis. Despite removal of the nail and reaming of the medullary canal. the local placement of gentamicin-PMMA beads, recurrent exacerbations of the chronic osteomyelitis and discharging fistulae were formed. After four years, a tibial fistula still produced putrid secretion and *S. aureus* was isolated in deep wound swabs. An MRI examination of the tibia showed an extended osteomyelitis of the medullary canal in the distal third of the tibia, spanning a distance of 14 cm (*Figure 2)*. A surgical debridement of the fistula was performed in surgery that included extensive reaming and lavage of the distal tibia. Next, NPIT with a 12 cm long PVA foam, inserted in the medullary canal in combination with polyhexanide antiseptic solution instillation, was applied and changed twice weekly. In addition, the patient received flucloxacillin intravenously (6 grams/day) for 6 weeks. Only after 31 days, swabs of the intramedullary canal became sterile. The medullary canal defect was filled with autologous bone taken from the ventral iliac crest and a mesh graft done covering the autologous bone transplant. Seven years after NPIT Therapy, the soft tissues are closed and there has not been a recurrence of the osteomyelitis (*Figures 3, 4a, 4b)*.

Figure 1. Case study.

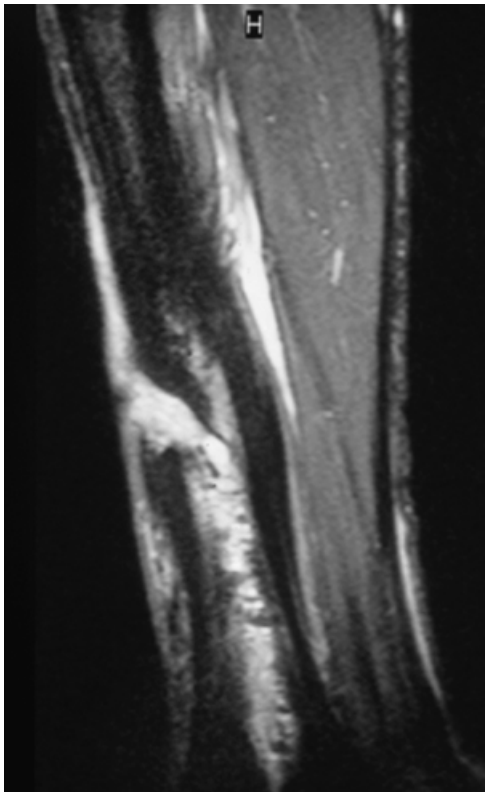


Figure 2. Magnetic resonance imaging of the left tibia showing fistulating osteomyelitis of the medullary canal.

observed ($p = 0.153$, Table 2A). In the period January 1999–February 2003 (4 years) patients suffering osteomyelitis who were admitted to the trauma department were treated with TNIP, while their counterparts treated in the orthopedic department were treated with standard therapy. The recurrence rate of osteomyelitis in the TNIP group was 10%, but the recurrence rate in the prospective control group was still $> 50\%$.

Comparison of treatment effect in NPIT patients and controls

Sterile wound swabs were obtained in 35 (59.3%) of 59 treatment courses, whereas, in another 17 (28.8%) patients

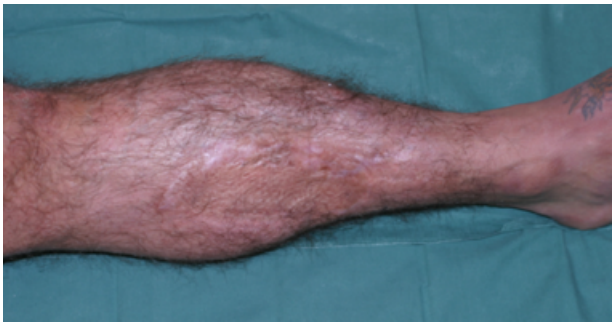


Figure 3. Left leg after a 5-year follow-up without clinical signs of osteomyelitis.

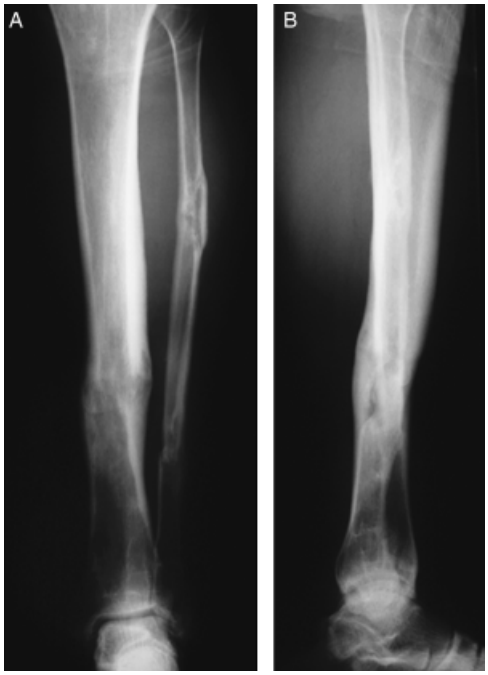


Figure 4. (A, B): Five years follow-up: x-rays of the left tibia without signs of osteomyelitis.

in whom clinical signs of infection of the wound had vanished, bacteria known to colonize the skin (e.g., coagulase-negative staphylococci) were repeatedly cultured but no longer the pathogens held responsible for the infection. Thus, the wound infection had been treated successfully in the first treatment episode in 52 (88.1%) of the 59 patients.

The average time until an infected wound had become sterile or yielded skin bacteria only amounted to 12 (range, 3–38) days (Table 1). Also, in the three patients with fresh traumatic injuries at high-risk sites such as the pelvis, no infection occurred after start of NPIT. A small percentage of wounds failed to become sterile ($n=7$; 11.9%), yet enough new granulation tissue was formed to permit surgical closure of the wound. Principal surgical closure techniques were delayed primary closure ($n=32$; 51.6%) and split-thickness skin grafting ($n=25$; 40.3%). In five patients (8.1%), spontaneous secondary wound healing occurred.

During a 43–89 month follow-up period of patients treated with NPIT, three patients had a recurrence of the infection, caused by the identical bacterial species cultured in the first episode. All these patients suffered of osteomyelitis. The recurrence rate of clinical infection in the group of patients with osteomyelitis was three in 30 (10%). The average time to recurrence was 8 months. None of the patients treated for indications other than osteomyelitis suffered a relapse of infection.

After surgical closure of the wound, one patient, aged 78 years, died due to underlying condition unrelated to the wound (i.e., a cardiac insufficiency). Furthermore, five patients died during follow-up, after apparent successful treatment of the wound. None of the deaths were related to the primary indication for which NPIT had been applied: e.g., one patient died as result of an accident, one

Table 1. Treatment indications and characteristics of negative pressure instillation treatment group

Diagnosis	Infected region(s)	No. of treatments (M/F) $N=62$	Mean age (years) (range)	Mean duration of therapy (days) (range)	Mean time until sterile wound swabs/skin bacteria (days) (range)
Osteomyelitis	Tibia/fibula, femur, pelvis, ankle, foot, patella, rib	33 (17/16)	52.3 (26–81)	22.4 (6–60)	11.4 (3–38)
Soft tissue infection	Femur, tibia/fibula, ankle	13 (3/10)	69.1 (33–94)	18.5 (6–52)	10.7 (3–29)
Trauma wound	Tibia/fibula, femur, ankle	12 (7/5)	36.3 (2–92)	21.1 (6–41)	12.2 (4–27)
Necrotizing fasciitis	Head/neck, thorax, femur	3 (3/0)	55.0 (47–68)	19.3 (9–34)	22.0 (7–37)
Pilonidal sinus	Peri-anal region	1 (1/0)	33	19.0	4.0

M, male; F, female.

patient died of an underlying hematological disorder, whereas three patients died due to myocardial infarction in combination with severe diabetes.

Table 2A. Bacterial specimens cultured prior to negative pressure instillation therapy vs. historical control group for the diagnosis of osteomyelitis

Overall distribution	Negative pressure instillation group (%)	Historical control group (%)	*p*-value
Bacterial species (number/%)			
Staphylococcus aureus	19 (50)	73 (67.6)	0.153
Pseudomonas aeruginosa	3 (7.9)	6 (5.6)	
Streptococcus sp.	1	5	
Other Gram-negative stains	2	4	
Other	13	20	
Total	38	108	

To determine whether NPIT had shortened hospital stay and reduced the risk of recurrent exacerbations of infection in osteomyelitis cases, a comparison was made between the NPIT and a historical control group. Controls were identified as described before from the electronic hospital information system including the bacterial specimens causing the osteomyelitis (Table 2B). Patients and controls did not differ with respect to age, sex, or underlying medical conditions (Table 3).

In the osteomyelitis control group ($n=94$), the median duration of hospital stay was 27.3 (range, 3–196) days. Fifty-five patients (58.5%) had to be rehospitalized at least once because of a recurrence of the osteomyelitis. The median number of hospitalizations amounted to 2.0 (range, 1–25) per patient. When taken together, the median cumulative duration of hospital stay in this group was 73 (range, 6–419) days. Related to these recurrences, many patients underwent multiple surgical interventions (median, 5.0 per patient; range, 2–42), varying from the removal of osteosynthesis material to extensive debridement of the wound and the local application of gentamycin polymethylmethacrylate (PMMA) polymer chains.

The cases and controls did not differ in the duration of the first hospital stay ($p=0.624$); however, due to the high number of rehospitalizations because of recurrences in the control group, the cumulative duration of hospital stay

Table 2B. Distribution of bacterial species according to number of recurrences of osteomyelitis

	Negative pressure instillation group		Historical control group		
	No recurrence (%)	1 recurrence (%)	No recurrence (%)	1 recurrence (%)	> 1 recurrence (%)
Bacterial species (number/%)					
Staphylococcus aureus	17 (48.6)	2 (66.7)	31 (77.5)	16 (61.5)	26 (61.9)
Pseudomonas aeruginosa	2 (5.7)	1 (33.3)	0 (0.0)	2 (7.7)	4 (9.5)
Streptococcus sp.	1 (2.9)	—	2 (5.0)	1 (3.8)	2 (4.8)
Other Gram-negative stains	2 (5.7)	—	1(2.5)	2 (7.7)	1 (2.4)
Other	13 (37.1)	—	6 (15)	5 (19.3)	9 (21.4)
Total	35	3	40	26	42

Table 3. Osteomyelitis group characteristics and comparison: negative pressure instillation vs. historical control group

Group characteristics	Negative pressure instillation group	Historical control group	*p*-value
No. of patients	30	94	—
Sex (M/F)	14/16	58/36	0.868
Median age (range)	52 (26–81)	47 (9–85)	0.146
Comorbidity (%) (DM, Sm, CVD, PULM†)	18 (60.0)	54 (57.4)	0.354
Location (%)			
Lower leg	16 (53.3)	64 (68.1)	
Femur/pelvis	12 (40.0)	28 (29.8)	0.228
Other	2 (6.7)	2 (2.1)	
Treatment characteristics			
Median no. of hospital admissions	1 (1–2)	2 (1–25)	< 0.0001
Median no. of operations (Range)	2 (1–4)	5 (2–42)	< 0.0001
Mean no. of operations per admission (Range)	2.3 (1–4)	2.4(1–7)	0.577
Median duration of hospital stay (days) (Range)	36 (15–75)	27.3 (3–196)	0.624
Median duration of total hospital stay per patient (days) (Range)	36 (15–75)	73 (6–419)	< 0.0001
Recurrence of osteomyelits (no.) (%)	3 (10)	55 (58.5)	< 0.0001

†DM, diabetes mellitus; Sm, smoker, CVD, cardiovascular disease; PULM, pulmonary disease.

was much higher in the control group with 73 (range, 6–419) days vs. 36 (range, 15–75) days in the NPIT group which was statistical significant different ($p < 0.0001$; Table 3). Also, by consequence, the number of surgical interventions was significantly higher in the control group (five vs. two in the NPIT group [$p < 0.0001$]). Overall, three recurrences (10%) occurred in the NPIT group while 55 recurrences (58.5%) were observed in the control group ($p < 0.0001$). Furthermore, the time to a first recurrence differed significantly between the groups, as illustrated in the Kaplan–Meier curve for recurrence-free survival (Table 6).

DISCUSSION

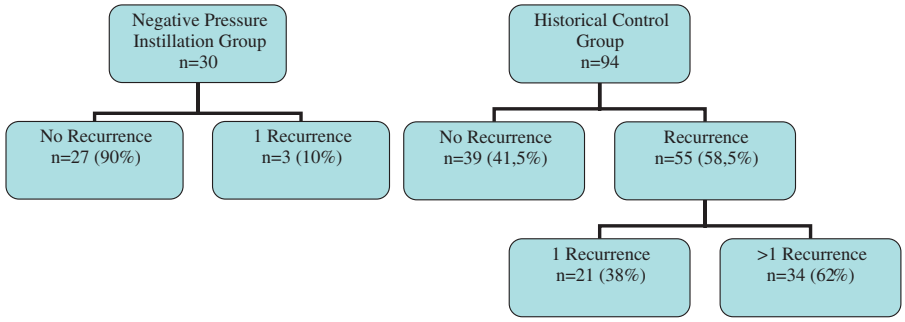
The present findings indicate that NPT in combination with intermittent Instillation technique (NPIT), by means of polyhexanide antiseptic solution, is a valuable new modality to treat posttraumatic osteomyelitis. In 1993, NPT was introduced as a new treatment modality to support impaired wound healing and is at present day widely used for wounds with low tendency to heal, including wounds compromised by poor vascularization or infection.[12] A recent study by Armstrong et al.[13] reported that NPT is a useful technique for the treatment of wounds following the amputation of a diabetic foot. Our present findings confirm and extend these findings by showing that NPT results in a higher percentage healed wounds and a lower recurrence rate of infection in posttraumatic osteomyelitis, thus precluding the need for multiple surgical interventions and likely even (multiple) amputations.[14–16]

The assumed working mechanisms of NPT are diminishment of interstitial edema, increase of capillary blood flow, and significant decrease of bacterial growth inside the wound.[17–22] Furthermore, during NPT growth of granulation tissue into the wound is observed as a response to the mechanical force of suction. The basics of the response of tissue to external stimuli and its possible clinical

Table 4. Osteomyelitis: recurrence and time to recurrence in accordance to location

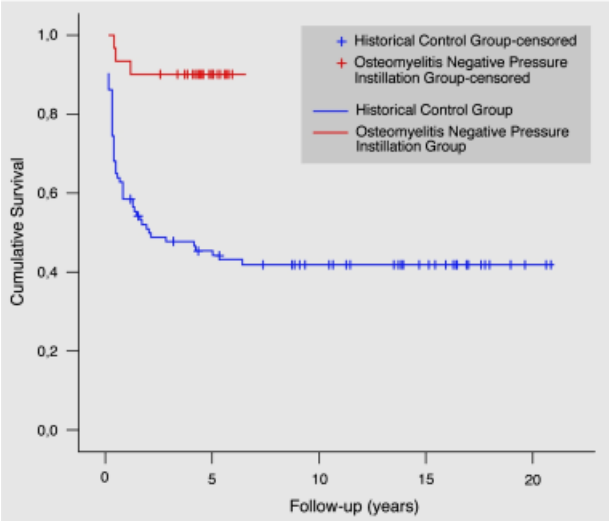
				Mean time to recurrence (months)		
	Negative pressure instillation group (n=30) (%)	Historical control group (n=94) (%)	*p*-value	VAC-instillation group	Historical control group	*p*-value
No recurrence	27	39		—	—	
Lower leg (%)	15 (55.6)	22 (56.4)	0.896			
Femur/pelvis	10 (37.0)	15 (38.5)				
Other	2 (7.4)	2 (5.1)				
1 Recurrence	3	21		8.3	15.8	0.493
Lower leg	1 (33.3)	12 (57.1)	0.151	5.5	12.7	0.522
Femur/pelvis	2 (66.7)	9 (42.9)		14	19.9	0.804
Other	—	—		—	—	
> 1 Recurrence	—	34		—	10.2	
Lower leg		30 (88.2)			7.6	
Femur/pelvis		4 (11.8)			29.7	
Other		—			—	

Table 5. Osteomyelitis recurrence: negative pressure instillation versus historical control group



Odds ratio for VAC-instillation group vs. historical control group: 0.08.

Table 6. Kaplan–Meier curve: survival function for recurrence in both groups (osteomyelitis of the pelvis and leg)



relevance was first described by Thoma[23] in a vascular model and later supported by Ilizarov[21] in a canine bone model. The newly formed granulation tissue resulting from this tension–stretch effect is highly vascularized and shows a high capillary density.[18] This highly vascularized state of the newly formed granulation tissue provides stable wound healing and scar formation, which could strengthen local defense against recurrence of infection. The influence of the PVA foam in this process is supported by the observation of these foams being infiltrated by bloodcells, predominantly granulocytes.[20] The level of negative pressure and type of foam to be used also has an influence on the capillary blood flow as was observed in our cutaneous blood flow study in which a negative pressure of 300 mmHg increased cutaneous blood flow to nearly three times with use of PVA foam and 5.5 times with use of PU foam.[24] These findings, together with the observations carried out in this study might permit and do support that a higher pressure can be used for optimal clinical efficacy (Note: the manufacturer's recommended standard negative pressure setting in NPT therapy today is 125 mmHg and the maximum negative pressure setting of the standard NPT machines can be raised up to 200 mmHg).

The positive effect of NPT on wound healing with use of the PVA foam might be enhanced by use of flushing the foam with an antiseptic solution. This instillation technique was first described by Fleischmann and colleagues[6,8] In this study, polyhexanide antiseptic solution was used for this purpose, as it demonstrates very low tissue toxicity as compared with other antiseptic agents.[9–11] Instillation physically flushes the foam, preventing blockage of the foam and tubing, and therefore a stable distribution of the negative pressure on the foam-wound interface is maintained. Furthermore, the polyhexanide solution has a local antiseptic effect, promotes wound contraction and has an effect on wound microcirculation that might enhance the antibacterial effect of NPT.[25,26]

To reach the conclusion concerning the efficacy of NPT in posttraumatic osteomyelitis of the pelvis and lower leg, we compared characteristics of cases with those of historical controls. Some potential pitfalls that may affect complete recruitment of patients and individual classification of cases and controls need to be considered. Inclusion criteria were that each control individual should have at least one recurrence of osteomyelitis with a surgical procedure in the past. Although we performed a thorough check of the electronic hospital registry including the OR and departmental diagnosis registry, it could be possible that not all eligible patients might have been included. Although some of the controls were treated in the 10 years before starting NPT, the standard approach to osteomyelitis had not changed during this period, and etiologic microbial pathogens and culture methods did not differ in those treated before and after introduction of NPT (Table 2A). Since 1999, at our institution in the department of trauma surgery, osteomyelitis patients are treated by surgical procedure and NPIT, but on the other hand, in the department of orthopedic surgery osteomyelitis patients were treated by standard therapy. During this period, the recurrence of osteomyelits was still more than 50% in the orthopedic department and on the contrary, the recurrence

rate in the trauma department was decreased to 10% in favor of the NPIT Group. Although the prospective NPIT treatment group during a period of 4 years was compared with a historical control group of 20 years, in a period of 4 years the historical controls (1999–2002) were treated with standard care in the orthopedic department. In the same period patients with the same indication (osteomyelitis with one recurrence) were treated with NPIT. If in this period (1999–2002) the orthopedic control group is compared with the trauma NPIT group, the recurrence of osteomyelitis was also reduced to 10% instead of $>$ 50% in the controls. Moreover, cases and controls did not differ in demographic characteristics, location of osteomyelitis and underlying medical conditions. Taking the mean time to the first recurrence into account, there was no statistical difference between both groups; however, in the NPIT group no further recurrences were observed during the follow-up time up to 89 months (Tables 4–6). In this study, the mean time for treatment of osteomyelitis of the pelvis and the leg for the NPIT group was 36.4 days per admission and not statistically different from the Historical Control Group (Table 3). Therefore, we might conclude, that this new treatment modality is beneficial for patients suffering osteomyelitis of the pelvis and leg, since the time for in hospital treatment is not prolonged and the risk of a recurrence can be reduced (Tables 3, 4, and 6). This treatment is different from the present standard of care for posttraumatic osteomyelitis, which often consists of repeated surgical interventions combined with intravenous antibiotics and subsequent oral antibiotic drug treatment.[2–5,27]

In conclusion, although there are methodological limitations to this prospective treatment group compared with historical controls (partially historical likely biased cohort study), a NPIT approach can be recommended in combination with surgical debridement for treatment of osteomyelitis and a controlled randomized trial should be performed to definitely add this indication to the manufacturers' guidelines[17] and clinical practice. The present findings suggest that this technique can be used as an adjunct after surgical debridement and in future might even replace standard treatment such as lavage, removal of necrotic bone, systemic or local antibiotic therapy (i.e., gentamycin PMMA beads), or the use of saline-wet-to-moist dressings for recurrent fistulas.[2–4,18,19,27–29] However, as the basic mechanisms of NPT in wound healing are not yet fully understood, more research in this area is needed and is currently an issue of investigation in our research group.

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