Negative pressure wound therapy with instillation (NPWTi): Current status, recommendations and perspectives in the context of modern wound therapy.

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Abstract—Introduction of negative pressure wound therapy (NPWT) revolutionized the conception of wound healing. Currently, increasing number of studies confirmed the high efficiency of this therapy in many clinical scenarios. Moreover, some innovations have been introduced in recent years to improve the management of complex and chronic wounds. NPWT with instillation (NPWTi) combines traditional NPWT with application of topical irrigation solutions within the bed of the wound. Bioburden reduction, decreases time to wound closure, promotes granulation and tissue formation. Fewer operative visits are required when using NPWTi compared to standard NPWT. However, there are still questioned aspects of the NPWTi and thus its superiority over standard NPWT has not been fully indicated. Moreover, based on current studies no firm conclusions have been taken concerning the type of instilled solution preferably used, range of dwell-time phase, range of negative pressure and others. The main goal of the publication is to overview and summarize the current state of art concerning NPWTi. Moreover, mechanisms of action, review of the most commonly used instilled solutions are discussed and clinical evidence of NPWTi are described.

Keywords—NPWT, instillation,
potential superiority to the standard NPWT.

We believe that the presented detailed review may help in optimal selection for NPWTi settings for specific clinical indications and scenarios. Moreover, we hope this work may increase researchers’ knowledge and improve the quality of designed experimental studies regarding ongoing research in the field of NPWTi.

II. MECHANISM OF ACTION

The mechanism of action for NPWTi remains the same in regards to the standard NPWT and is the basis for successful outcomes of NPWTi. The applied negative pressure within the surgical wound indicates its multi-dimensional action that positively influences the wound healing process.

The increase of local blood flow influences an enhanced collagen synthesis and promotes mechanisms that stimulate angiogenesis. NPWTi also leads to a decreased local tissue edema, lowers the number of bacteria within the wound and removes inhibitory agents. The use of NPWT positively affects tissue granulation process and maintains a moist wound environment. Additionally, NPWT reduces lateral tension of the wound edge, positively influences the wound contraction and supports a proper wound edge vascularity.11,12

III. CELLULAR AND MOLECULAR CHANGES

Both in vitro and in vivo models showed, that the administration of reticulated open-cell foam (ROCF) generates microstrain at the cellular level which has a direct influence on the elevation of proliferating cells within the wound and enhances vascularity.11,12

At the cellular level, a mechanical strain generated with negative pressure stimulates sensory cells to molecular changes within cells.11 Gravity and hemodynamic forces, as constituents of NPWT, significantly influence the improvement in microenvironmental conditions of the wound bed resulting in an enhanced wound healing.13 Although, some mechanisms of action at the cellular level are still unknown, the conception of cellular mechanotransduction seems to accurately describe the mechanisms of alteration and enhancement of cellular properties with the usage of NPWT through the direct use of administered negative pressure.13

In vitro studies demonstrated that the administration of negative pressure wound therapy positively influences the function and activity of fibroblasts.12 The use of NPWT stimulates proliferation, production and remodeling of fibroblasts, extracellular matrix, as well as increases growth factors production.11,12 The results of in vitro studies were confirmed by in vivo results. Scherer et al. confirmed that cell proliferation expressed as a percentage of Ki67-positive nuclei was significantly greater in NPWT group compared to other groups in mice model.11

IV. BIOFILM

It has been presented that NPWTi significantly influences the reduction of biofilm composed of varying microorganisms within the wound, which is considered one of the main reasons for impaired wound healing.

Based on research studies with an animal model and clinical practice, it was stated that the presence of microorganisms within the wound, their influence on the wound bed, quick replication and tendency to form colonies result in biofilm formation. Bacteria is the most common reason for biofilm formation, however usually within a wound there is a complex biofilm formation by bacteria, fungi and protozoa embedded in a self-produced extracellular matrix of polysaccharides or other extracellular polymeric substance (EPS), cellular debris and exudates.11,12

Consequently, providing a substance to the wound, should by definition remove not only the exudates and cellular debris but also influence the destruction and removal of biofilm bacteria which is a basis for its success.

Mechanical debridement, reduction of biofilm and autolytic mechanisms are considered the most important components of NPWTi action and they are key elements emphasizing the advantage of NPWTi over the standard NPWT.13

The above-mentioned concept and the need for modification of systems and treatment therapy of chronic wounds are associated with the current state of the art, indicating that microbial biofilm is one of the crucial factors impairing healing wound.19-22 Phillips et al. analyzed based on an animal model various antimicrobial solutions on Pseudomonas aeruginosa biofilm.22 Using seven solutions with periodic NPWT instillation, they compare their efficacy versus NPWT alone and NPWT with saline solution. Using NPWT alone (no instillation used), there was no statistical significance in comparison to the untreated control group even though the reduction in total CFUs was observed. All experimental groups using both antimicrobial solutions and saline showed statistical significance in the reduction of CFUs compared to the untreated group. However, in authors’ opinion, in the saline group the reduction in CFUs was rather associated with mechanical removal than other potential mechanisms acting on the bacteria’s biofilm. Comparing the antimicrobial solution groups with the saline groups, all of them except one (S-solution) showed statistical significance in reduction of CFUs.

 Conventionally used lavage, which was initially considered an important element of wound cleansing, has an increased risk of bacteria dispersion within the wound as well as beyond the wound. Allen et al. based on the wound models compared the standard lavage technique and NPWTi and its influence on the degree of bacterial dispersion and cross-contamination using ex-vivo model with fluorescent bacterial particles inoculation.23 Both low-pressure lavage and NPWTi showed comparable effectiveness of wound cleansing (debris reduction >90%). However comparing tissue damage, based on three-dimensional photography, more severe tissue damage was revealed in NPWTi treatment group (P <0.05). The most important is the fact of no evidence for cross-contamination in NPWTi. Gabriel et al. comparing bacterial bioburden reduction in NPWTi group and the control group (standard wound-care therapy) showed statistical significance in the time required to decrease bacterial bioburden (6.0 ± 1.5 versus 25.9 ± 6.6 days respectively).13

It is important to note that regardless of the type of the negative pressure therapy, settings, type of instilled fluid, the
crucial aspect is initial debridement of the wound. Appropriate debridement is necessary to eliminate poorly vitalized and necrotic tissue, all foreign bodies within the wound bed as well as any excessive cellular debris. Currently, there are numerous methods for debridement including lavage, autolytic agents, ultrasound, chemicals and enzymes or surgical procedure. Regular debridement also plays an important role in bacterial biofilm reduction.\(^\text{[25]}\)

V. TISSUE GRANULATION

Leung et al. comparing the standard NPWT versus NPWTi analyzed the acceleration of wound granulation in porcine model. Using the NPWT with instillation and normal saline in 4 cycles of instillation per day (dwell times: 5 or 60 minutes), they demonstrated statistically significant wound filling and collagen deposition within the granulated tissue within a bed wound.\(^\text{[24]}\) Brinkert et al. in a prospective study evaluated the effect of NPWTi used in different clinical scenarios.\(^\text{[25]}\) A total of 131 patients were enrolled to either NPWTi group as the primary method of treatment (n=85; 64.9%) or received NPWTi after a failed standard NPWT therapy (n=46; 35.1%). Granulation of the wound bed was increased in NPWTi group versus standard NPWT. Moreover, significant reduction of wound volume was also shown in NPWTi versus standard NPWT. Dead space of the wound as well as any undermined cavities were granulated more rapidly in NPWTi in comparison to the standard NPWT. Lessing et al. investigated the influence of different application of standard NPWT and NPWTi on granulation of the wound in porcine model.\(^\text{[26]}\) NPWTi with saline (5 minutes of dwell time every 2.5 hours, negative pressure -125 mmHg) and various settings of standard NPWT (intermittent, continuous, dynamic) were applied on dorsal excisional wound for 7 days. At the time of end point, tissue samples were taken for histological examination. In NPWTi group granulation thickness (p<0.05), greater reduction of wound volume (p<0.05) and higher filling rate of the wound (p<0.05) were statistically significant compared to the standard NPWT.

VI. WOUND DRESSINGS

The proper application and arrangement of negative pressure within the wound dressing is guaranteed with the use of reticulated open-cell foam (ROCF). The most commonly used foams on the market are: ROCF-G (V.A.C.® GranuFoam\(^\text{TM}\) Dressing, KCI USA, Inc, San Antonio, TX) or roc ROCF-V (V.A.C. VeraFlo Cleanse\(^\text{TM}\) Dressing System, KCI USA, Inc.). Although pore sizes are comparable in both types of dressings, the different chemical composition of dressings leads to the fact that physical and chemical properties are different in both cases of wound dressings. Therefore, the interactions between the dressing and a wound are also different. ROCF-G is composed of polyether-based polyurethane foam, whereas ROCF-V is made of polyester-based polyurethane foam. ROCF-V is less hydrophobic than ROCF-G, which allows for an easier adherence and distribution of instilled fluid within the wound.

It was confirmed that the less hydrophobic property of ROCF dressing is, the more affinity of fluid adherence within the dressing is observed.\(^\text{[27]}\) Moreover, it is easier to drain the instilled fluid with wound exudate and cellular debris outside the wound. The better susceptibility of ROCF-V for preserving the fluid within the wound dressing also allows for a lower risk of pooling the fluid beneath the dressing and outside the wound, which may contribute to an incidence of a leak and unsealing of the wound dressing.\(^\text{[31]}\) Scanning electron microscopy images showed similar pore size and structure of both ROCF-G and ROCF-V.\(^\text{[23]}\) Comparable results were presented by Lessing et al.\(^\text{[24]}\) The mean value of pore size was estimated to be 400 \(\mu\)m to 600 \(\mu\)m in both ROCF-G and ROCF-V. Lessing et al. using scanning electron microscopy compared mechanical properties of ROCF-G and ROCF-V regarding tension, compression and tearing properties.\(^\text{[20]}\) Moreover, the properties of individual foams were analyzed in both wet and dry conditions. Wet ROCF-V showed statistically better properties under tensile and tear condition than ROCF-G, in both wet and dry circumstances. Comparing fluid distribution, ROCF-V showed better capabilities of accumulating fluid versus ROCF-G. Based on histological analysis, ROCF-V showed increased granulation within the wound in comparison to ROCF-G after 7 days of NPWTi or NPWT alone (P < 0.05).

It is important to note that both dressings ROCF-V and ROCF-G present characteristic to all polymers, a type of plasticizing effect and hydrolytic degradation due to the interaction with instilled fluid; however, ROCF-V has shown weaker above-mentioned properties.\(^\text{[30]}\)

VII. CONTINUOUS- VERSUS PERIODIC- INSTILLATION

Although NPWTi has been used worldwide in many clinical scenarios, there are no firm conclusions and recommendations regarding the optimal type of instillation or a range of dwell time and amount of instilled fluid.

Ryczew et al. described a wound model for the purpose of assessment of optimal fluid distribution within a wound based on two different methods of fluid administration (stained with methylene blue).\(^\text{[33]}\) Using agar-based model, they studied the impact of continuous- and periodic- instillation on two types of designed wounds: 1) a simple wound and 2) a complex tunneled wound. In the model using continuous instillation, 30 ml of fluid/ hour throughout 3.5h was administered using the negative pressure of -125 mmHg. On the other hand, in the model using periodic instillation, 75 ml of fluid in a simple wound model and 120 ml of fluid in a complex wound model were administered and held for 10 min and later repeated (-125 mmHg was set up). Comparing the two types of therapies, an isolated penetration of the fluid within the wound bed in both simple and complex wound was observed in continuous instillation, whereas a regular pattern of wound bed staining was revealed in periodic instillation. Despite the fact that in the above-mentioned study they demonstrated better administration parameters of instillation in the case of periodic instillation, according to some studies the efficiency of continuous instillation was also proven. Independently Lessing et al. and Scimeca et al. demonstrated the effectiveness of continuous instillation even though both used different instilled fluids: saline solution and doxycycline, respectively.\(^\text{[25]}\)
Argenta and Morykwas presented the benefits resulting from the use of intermittent therapy in standard NPWT, emphasizing the better perfusion of both the wound tissue and surrounding tissues.\textsuperscript{21,22} The element of intermittent therapy in NPWTi is unequivocally part of the administered therapy composed of instilled phase with the following dwell time phase, and then with a formation and maintenance of negative pressure. However, it seems that both the benefits of instilled solution and the intermittent pauses of active negative pressure positively influence the effects of treatment with NPWTi.

VIII. INSTILLATION SOLUTIONS

Based on recent International Consensus Guidelines from 2013, the following instillation solutions were approved as efficient for the purpose of instillation: Lavasept\textsuperscript{®} (polyhexanide 0.04%), Prontosan\textsuperscript{®} (polyhexanide 0.1% with betaine) and Microcyn/Dermacyn\textsuperscript{®} (hypochlorous acid solution).\textsuperscript{7} The final consensus was established when more than 80% of expert panelists agreed on the appropriate efficiency of analyzed instillation solution.

However, there are some limitations to these agreements. Firstly, the recommendations are based on a personal opinion of twelve expert panelists’ agreement. Secondly, various studies with different methodologies were included into the consensus such as prospective, randomized, comparative and controlled studies leading to a creation of a bias in the recommendations.

Based on the same consensus other solutions were also evaluated. Despite the fact that they did not meet the agreement criteria, it was stated that other instillation solutions may still be considered in particular clinical scenarios. However, ongoing research and clinical trials are required to confirm its efficiency.

Below, we present the most common instillation solutions used in NPWTi. The mechanism of action of a particular solution was briefly described. Additionally, we indicated their potential disadvantages and described both preclinical and clinical studies regarding the utility of instillation solutions. The most common instilled solutions are summarized in Table 1.

A. Isotonic solutions

Leung et al. by comparing NPWT with normal saline instillation versus standard NPWT in porcine model showed a statistical significance in collagen deposition and tissue granulation within the wound in the experimental group with NPWTi.\textsuperscript{22} Kim et al. conducted a prospective randomized study comparing NPWT instillation with normal saline and antiseptic solution (0,1% polyhexanide plus 0,1% betaine).\textsuperscript{23} There was no statistical significance in any of the analyzed parameters (a number of operative visits, a length of hospital stay, a wound healing rate and a wound healing rate within 30-day follow-up) in comparison to two cohorts of patients. However, the time to final surgical procedure was statistically shorter in the normal saline group (p= 0,038). In authors’ opinion the effectiveness of normal saline utility in NPWTi is comparable to this antiseptic solution.

Brinkert et al. showed a high rate of wound closure in 98% of patients using NPWTi with normal saline in case series of 131 patients.\textsuperscript{29} However, this study has one important limitation. Almost half of the patients (48.8%) received standard NPWT prior to implementation of NPWTi. Thus the firm conclusion suggesting NPWTi as a more efficient therapy is questionable. Fluijeraru et al. in a retrospective case series study proved the efficiency of NPWTi with saline instillation in patients who previously did not recover under the standard therapy as well as in patients with chronic complex wound with no previous NPWT treatment.\textsuperscript{32} In general, in 23 out of 24 patients tissue granulation was achieved and surgical wound closure was possible using either flaps or skin grafts treatment. Phillips et al. and Davis et al. independently proved that Microcyn is a solution composed of hypochlorous acid and sodium salt. Contained hypochlorous acid is similar to the one naturally occurring in humans. In in vitro model, Microcyn reduced the level of P. aeruginosa, E. coli and S. aureus with a statistical significance.\textsuperscript{33,35} Microcyn\textsuperscript{®}/Dermacyn\textsuperscript{®} creates a moist wound-care therapy with the property of rehydration of the necrotic tissue and promoting autolysis. Goretti et al. compared Dermaecyn and diluted povidone iodine in the management of

![Image](image-url)
Table I
THE MOST COMMON SOLUTIONS AND AGENTS USED IN NEGATIVE PRESSURE WOUND THERAPY WITH INSTILLATION

<table>
<thead>
<tr>
<th>Solution class</th>
<th>Study</th>
<th>Solution/ Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotonic solutions</td>
<td>Brinkert et al., 2013</td>
<td>Saline Solution, Lactated Ringer's solution,</td>
<td>1/ availability and low costs</td>
<td>1/ No antimicrobial property</td>
</tr>
<tr>
<td></td>
<td>Flueraru et al., 2013</td>
<td></td>
<td>2/ No sensitization observed</td>
<td>2/ In some studies lower efficiency compared to antiseptic solution</td>
</tr>
<tr>
<td>Hypochlorite-based solutions</td>
<td>Goss et al., 2014</td>
<td>Dakin’s solution,</td>
<td>1/ Availability, simplicity and low costs</td>
<td>1/ potential cytotoxicity</td>
</tr>
<tr>
<td></td>
<td>Wolvos, 2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermacyn™</td>
<td>1/ There are no known drug interactions or contraindications</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2/ Contained hypochlorous acid naturally occurring in human</td>
<td></td>
</tr>
<tr>
<td>Biguanidines</td>
<td>Kim et al., 2014</td>
<td>Polyhexamethylene,</td>
<td>1/ High efficiency in varying type of wounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lehner et al., 2014</td>
<td>Polyhexanide (Lavasept®,)</td>
<td>2/ No sensitization/ interaction observed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polyhexanide plus Betaine (Prontosan®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silver nitrates</td>
<td>Gabriel et al., 2004</td>
<td>0.5% silver nitrate</td>
<td>1/ Broad- bactericidal spectrum</td>
<td>1/ Must be protected from light exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2/ Variety of commercial dressings</td>
<td>2/ Potentially cytotoxic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3/ P. aeruginosa, Enterobacteriaceae or Salmonella resistance was reported</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Fleischmann et al., 1999</td>
<td>Neomycin, Gentamicin, Tobramycin,</td>
<td>Recommended strictly according to bacterial culture results</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wolvos, 2004</td>
<td>Vancomycin, Polymyxin B, Bacitracin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catatonic solutions</td>
<td>Miatasek et al., 2014</td>
<td>Octenidine</td>
<td>Effective in contaminated wounds with multiresistant bacteria</td>
<td>No firm conclusions based on prospective studies</td>
</tr>
<tr>
<td>Insulin</td>
<td>Scimeca et al., 2014</td>
<td>Insulin</td>
<td>1/ Recommended in wounds due to DM</td>
<td></td>
</tr>
<tr>
<td>Anesthetic</td>
<td>Wolvos, 2004</td>
<td>Lidocaine</td>
<td>2/ No influence on systemic glycemia level</td>
<td>No antimicrobial property</td>
</tr>
<tr>
<td>Povidone-iodine solution</td>
<td>Chang 2004</td>
<td>Povidone-iodine</td>
<td>1/ Availability and low costs</td>
<td>1/ contraindicated in patients with hyperthyroidism, dermatitis herpetiformis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cadexomer iodine</td>
<td>2/ Rapid antimicrobial action</td>
<td>2/ Cytotoxicity and sensitization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3/ Tissue staining</td>
</tr>
</tbody>
</table>

postsurgical infected ulcers of the diabetic foot. Patients treated with Dermacyn presented significantly shorter healing time and a higher wound healing rate at 6 months. Landsman et al. evaluated the effect of Microcyn in the treatment of mildly infected diabetic foot ulcers. In comparison to the oral levofloxacin treatment group, Microcyn showed higher clinical success rate of treatment (p= 0.033).

C. Biguanidines

1) Lavasept®/Prontosan®: Both Lavasept®/Prontosan® belong to the group of biguanides composed of polyhexamethylene biguanide. Additionally, Prontosan contains 0.1% betaine which has a comparable mechanism of action to surfactant, reducing the surface tension of a water solution allowing for a better penetration into the wound and to the bacterial biofilm.

Minnich et al. conducted an in vitro study using a solution of 0.1% polyhexanide and 0.1% of betaine. The reduction of 13 tested microorganisms was evaluated after 7, 14, and 28 days. Based on this study, the reduction of S. epidermidis, P. aeruginosa, Serratia marcescens, C. albicans, S. aureus, vancomycin-resistant E. faecalis, P. mirabilis, E. coli, methicillin-resistant S. aureus, A. baumannii, E. cloacae, and E. faecalis was observed confirming the efficiency of 0.1% polyhexanide and 0.1% of betaine for microorganisms reduction. Romanelli et al. in a randomized controlled trial investigated the effect of the utility of polyhexanide and betaine
solution in patients with venous leg ulcers. Using a portable device measuring pH of the wound surface (which correlates with the level of bacterial burden), the authors confirmed the efficacy of polyhexanide and betaine solution in reduction and stability of wound pH level in comparison to the control group (p< 0.05). Hübner et al. evaluated the efficacy of 0.02 and 0.04% polyhexanide (polyhexamethylene biguanide, PHMB) against Pseudomonas aeruginosa SG81 biofilm in in vitro studies. Results achieved in the PHMB group was comparable to 0.1% chlorhexidine digluconate (CHX) in regards to the amount of biofilm and bacterial metabolism in biofilms formed with Pseudomonas aeruginosa. Sibbald et al. conducted a multicenter, prospective, randomized clinical trial comparing the effectiveness of polyhexamethylene biguanide (PHMB) foam dressing and non-antimicrobial foam in the treatment of chronic wounds.

Bacterial bioburden was significantly reduced in PHMB foam group (P = 0.016). In addition, pain reduction was revealed as a statistically significant result at 2 weeks and at 4 weeks of the therapy in the group of PHMB management. Wound size in PHMB was also reduced in comparison to the non-antimicrobial foam.

The efficiency of Lavasept was independently confirmed in clinical practice by a number of authors. Lehner et al., described the utility of Lavasept in 23 patients with infected hip endoprosthesis (19 defined as an early infection and 4 as a late infection). The success rate was 84% in early infection, whereas in late infection 50% of success was reported. Thus in authors’ opinion, NPWTi with Lavasept may be considered as a salvage management for infected endoprosthesis, especially in the early course of an infected hip endoprosthesis.

Köster evaluated the effect of using NPWT with Lavasept instillation in patients with an early periprosthetic infection following a knee endoprosthesis placement. Only in one patient the implant needed to be removed, whereas in the majority of patients implant was preserved. NPWTi was continued from three to nine days. In all except one patient no infection was present at the time of follow-up (between 12 and 34 months postoperatively) confirmed by clinical, radiological and laboratory examination. In authors’ opinion NPWTi with Lavasept reduces the number of surgical revisions, enhances the wound healing and reduction of infection leaving the knee implant in situ.

D. Silver nitrate

Silver nitrate possesses a potential property for a creation of somehow impermeable barrier against microorganisms’ penetration in the bed wound. However, in in vitro models it was observed that silver nitrate (but also nanocrystalline silver) exhibited a cytotoxic effect to cells, therefore playing a key role in the healing processes with the effect on leukocytes and macrophages, as well as fibroblasts and keratinocytes.

In porcine model study presented by Wright et al., slightly different results were observed. An increased apoptosis and decreased level of matrix metalloproteinase may potentially support the process of wound healing. The crucial element making the difference between in vitro and in vivo studies seems to have a potential to bind the ionic silver which is different in organic and inorganic constituents. Gabriel et al. did not observe any side effects of using silver nitrate for wound healing in the fifteen patients that they analyzed. Consequently, the instillation with silver nitrate was continued until the time of confirmed clearance of bacterial bioburden within the wound. Statistical significance was revealed comparing the association between bacterial bioburden and the rate of wound closure in NPWTi group versus moist wound-care therapy (p< 0.001).

E. Povidone-iodine solution

Povidone-iodine solution is a well-known disinfecting agent commonly used in trauma and surgical wounds. Optimal effectiveness of povidone-iodine solution was established with 1:100 dilution. However, solution with 1:10,000 dilution still presents bactericidal activity. Potential disadvantages of povidone-iodine solution are tendency for an irritation to the applied site, cytotoxicity and staining of the tissues. Although in some in-vivo and animal studies the cytotoxicity was observed, these results were not confirmed in humans. Povidone-iodine solution did not negatively influence bed wound healing. Additionally, in comparison to other anti-infective agents (e.g. neomycin), the sensitization rate of povidone-iodine is relatively low. Chang et al. confirmed the efficiency of povidone-iodine solution in spinal surgery indicating a higher surgical site infection rate in the control group (P<0.05).

F. Insulin

The potential positive effect of topical application of insulin on wound healing has been reported in basic science research. However, there are not many studies on insulin instillation in humans, therefore firm conclusions should not be taken. In both rat and rabbit studies, the application of insulin (or combined insulin-zinc therapy) promoted wound healing. Wilson et al. recommended the use of insulin solution for complex and chronic wounds resulting from diabetes mellitus including pressure ulcers and amputation site stumps. Rezvani et al., investigated the use of topical insulin on wound healing in randomized, double-blind, placebo-controlled trial. The mean rate of wound healing was 46.09 mm2/day in the insulin treatment group and 32.24 mm2/day in the control group (P = 0.029). It is important to note that the symptoms of hypoglycemia resulting from the insulin therapy were not observed in any of the patients. Similar results were supported by Greenway et al. indicating that topical insulin is an accelerator of wound healing in humans. Scimeca et al. using NPWTi with insulin in a case report confirmed the efficacy for the treatment of chronic wounds due to emergency amputation at the midfoot level.

IX. CLINICAL INDICATIONS

The review of recent publications concerning NPWTi are summarized in Table 2. In 1988, W. Fleischmann who is considered as a pioneer in NPWT instillation and negative pressure therapy, published...
Table II
TABLE 2. RECENT STUDIES CONCERNING NEGATIVE PRESSURE WOUND THERAPY WITH INSTILLATION

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Type of study</th>
<th>Number of NPWTi patients</th>
<th>Type of instilled fluid</th>
<th>Instill time (sec)</th>
<th>Dwell time</th>
<th>Instillation cycle (hour)</th>
<th>Negative pressure (mmHg) mean (range)</th>
<th>Days of NPWTi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleischmann et al., 1998</td>
<td>Case series</td>
<td>27</td>
<td>Nebacetin (neomycin and bacitracin) plus polyhexanidine</td>
<td>NA</td>
<td>30 min</td>
<td>NA</td>
<td>Od -50</td>
<td>33.5 (30-37)</td>
</tr>
<tr>
<td>Gabriel et al., 2008</td>
<td>Retrospective</td>
<td>15</td>
<td>Silver nitrate</td>
<td>30</td>
<td>1 sec</td>
<td>Every 2 hour</td>
<td>-125</td>
<td>9.8 (5-20)</td>
</tr>
<tr>
<td>Wolfos, 2004</td>
<td>Case series</td>
<td>5</td>
<td>1 or 2% Lidocaine + antibiotic</td>
<td>15-60</td>
<td>5 min</td>
<td>Every 3 hour</td>
<td>-125</td>
<td>15 (5-24)</td>
</tr>
<tr>
<td>Bernstein and Tam, 2007</td>
<td>Case series</td>
<td>5</td>
<td>Polymyxin (500.000 IU) plus Bacitracin (50.000 IU) in 2L of saline</td>
<td>90</td>
<td>5 min</td>
<td>Every 6 hour</td>
<td>-125</td>
<td>NA</td>
</tr>
<tr>
<td>Brinkert et al., 2013</td>
<td>Prospective</td>
<td>131</td>
<td>Saline</td>
<td>20</td>
<td>10 min</td>
<td>Every 6 hour (range: every 4-12 hour)</td>
<td>-125</td>
<td>12,19</td>
</tr>
<tr>
<td>Kim et al., 2015</td>
<td>Prospective, randomized</td>
<td>100</td>
<td>Saline versus 0.1% Polyhexanide + 0.1% Betadine</td>
<td>NA</td>
<td>20 min</td>
<td>Every 2 hour</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gabriel et al., 2015</td>
<td>Retrospective</td>
<td>48</td>
<td>Saline or Prontosan®</td>
<td>NA</td>
<td>1-60 sec</td>
<td>Every 2 hour</td>
<td>-125</td>
<td>NA</td>
</tr>
<tr>
<td>Kim et al., 2015</td>
<td>Retrospective</td>
<td>68</td>
<td>Prontosan®</td>
<td>NA</td>
<td>6 or 20 min</td>
<td>Every 2 or 3.5 hour</td>
<td>-125</td>
<td>NA</td>
</tr>
<tr>
<td>Goss et al., 2015</td>
<td>Prospective</td>
<td>7</td>
<td>0,125% Dakin’s solution (“quarter strength”)</td>
<td>NA</td>
<td>10 min</td>
<td>Every 1 hour</td>
<td>-125</td>
<td>7</td>
</tr>
<tr>
<td>Fluieraru et al., 2013</td>
<td>Retrospective</td>
<td>24</td>
<td>Saline</td>
<td>30</td>
<td>10 min</td>
<td>Every 4 hour</td>
<td>-125</td>
<td>10,1 (6-15)</td>
</tr>
<tr>
<td>Wolfos, 2013</td>
<td>Case series</td>
<td>6</td>
<td>Microcyn or Dakin’s solution (“quarter strength”)</td>
<td>NA</td>
<td>5 or 10 min</td>
<td>Every 2 or 4 hour</td>
<td>From -100 to -125</td>
<td>Jul 54</td>
</tr>
<tr>
<td>Lehner et al., 2014</td>
<td>Prospective, multicenter</td>
<td>32</td>
<td>Lavasept® (n=31), saline (n=1)</td>
<td>&lt;60</td>
<td>19 min (5-30)</td>
<td>From 5 to 40 cycles/day</td>
<td>From -125 to -200</td>
<td>16.3 (9-46)</td>
</tr>
<tr>
<td>Koster, 2009</td>
<td>Case series</td>
<td>10</td>
<td>Lavasept®</td>
<td>Okt 20</td>
<td>10-15 min</td>
<td>NA</td>
<td>NA</td>
<td>03. Sep</td>
</tr>
<tr>
<td>Leffler et al., 2009</td>
<td>Case series</td>
<td>6</td>
<td>Lavasept®</td>
<td>20</td>
<td>20 min</td>
<td>Every 4 hour</td>
<td>-125</td>
<td>NA</td>
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</tbody>
</table>

an initial study concerning the influence of instilled fluid on the wound treatment. Using NPWTi with antiseptic or antibiotic solutions in 27 patients with acute and chronic infections of bone and soft tissue as well as chronic osteomyelitis, they confirmed the efficiency of NPWTi in 26 patients with one recurrence of infection during 3-14 months of follow-up. Gabriel et al. published a retrospective study comparing patients treated with NPWTi and standard moist wound care. The majority of patients were treated with NPWTi due to pressure ulcers, extremity trauma (including bone exposure) and abdominal surgical wounds. In the NPWTi group of treatment the time of required treatment, wound closure, resolution of wound infection and hospital stay were significantly shorter in comparison to the standard method of treatment (p< 0.001). Wolvos also observed that an appropriate, targeted antibiotic (based on the microbiological results) decreased the bacterial burden in the wound. Bernstein and Tam described a case series of patients with post-surgical diabetic foot wounds treated with NPWTi. Based on their initial experience, the application of topical antibiotics positively influences the progress of wound healing in chronic and complex wounds after surgical management in DM patients. In authors’ opinion, NPWTi positively affects the wound fluid viscosity, decreasing inflammatory agents and cellular debris and it also reduces bacterial burden. Brinkert et al. in a prospective study compared the efficiency of NPWTi and standard NPWT in a group of 131 patients treated in three referral orthopedic or surgical centers in France. The most common clinical indication for both NPWTi and standard NPWT was an open fracture (n=46), pressure ulcer (n=27) and non-healing postoperative dehiscence (n=25). Wound closure
was possible to be achieved in 98% of patients treated with NPWTi with the mean duration of the therapy 12.19 days. In the recent prospective randomized study, Kim et al. analyzed the effect of NPWTi on wound healing using two different solutions: normal saline versus antiseptic solution (0.1% polyhexanide plus 0.1% betaine). In the majority, chronic or complex wound was located within the lower extremity in both analyzed groups of treatment. There was no statistical difference between the compared groups of treatment for the number of surgeries, the length of hospital stay, wounds closed/ covered ratio and wounds ratio that remained closed within 30 days of follow up. The only significance was the time to final surgical procedure which was favorable in NPWTi with saline solution group (p=0.038). Based on this study, normal saline and antiseptic solution (0.1% polyhexanide plus 0.1% betaine) demonstrate a similar efficacy. Gabriel et al. compared the standard NPWT and NPWTi with saline or polyhexanide in patients with extremity or trunk wounds. A total of 48 patients treated with NPWTi showed a statistical significance in comparison to the standard NPWT for the time of hospital stay (8.1 vs 27.4 days), duration of the therapy (4.1 vs 20.9 days), time of wound closure (4.1 vs 20.9 days) and mean operating room debridement (2.0 vs 4.4). Goss et al. in a prospective pilot study evaluated the efficacy of the reduction of a wound bacterial bioburden comparing the standard NPWT and NPWTi. Dakin’s solution was used as an instilled bactericidal agent. Chronic venous stasis and diabetic foot ulcer were the most common underlying wound pathologies in both treatment groups with the mean time of wound duration 30 months in the standard NPWT group and 23 months in NPWTi group. At the time of end point (7th day of the therapy), there was no statistically significant difference between these two groups in reduction of bacterial bioburden (CFU/ gram of tissue culture; p=0.43). However, the mean absolute reduction of bacterial bioburden was statistically significant in NPWTi group versus standard NPWT (p=0.016). Fluieraru et al. used NPWTi as the primary method of treatment for extensive undermining deep wounds (n=12) as well as in patients who failed the standard NPWT (n=12). Isotonic saline was used as an instilled fluid with a 10-minute dwell time and 30 seconds of instillation. There was no complication associated with NPWTi. In 23 patients wound closure was achieved using flaps or skin grafts following preconditioning of the wound bed with the use of NPWTi. In all patients, good results of tissue granulation and filling of the wound cavities were observed. Recently, Wolvos published a small case series of patients treated with NPWTi in contaminated, chronic abdominal wounds (n=3) or infected wounds within the lower extremity (n=2) and chest wall (n=1). Wound healing and closure were achieved in all patients using skin graft or surgical closure (primary, secondary or delayed primary). There was no difference in quality and the amount of tissue granulation in patients treated with NPWTi (n=6) and standard NPWT (n=1), even though both groups were small and inconsistent regarding the types of the underlying pathologies of the wound and the degree of the contamination, which is a limitation of the study. In 2011 Lehner et al. published a multi-center prospective observational study concerning the utility of NPWTi in patients following hip and knee replacements with surgical site infection associated with orthopaedic implants. Clinical indication for introduction of NPWTi included infected hip implant (n=20), infected knee implant (n=10) and 2 patients with infected osteosynthesis material. Routinely, polyhexanide was used as an instilled fluid in all but one patient in whom saline was used. Twenty-two patients had an acute infection (<8 weeks after orthopedic implant placement), whereas ten patients had a chronic infection (between 8 and 36 weeks postoperatively). After NPWTi course, an eradication of the wound infection was confirmed in 24 patients (75%), whereas in 6 patients the recurrence of the wound infection was revealed (18.8%) and in 2 patients ongoing wound infection was reported. Koster presented ten patients with an implant-associated infection following a knee implant placement. After a required wound debridement, NPWTi was initialized using Lavasept®. During the observational period of 13-34 months after a completed NPWTi therapy, only in one patient there was a case of a reinfection. Similar results were achieved by Schintler et al., who used NPWTi with Lavasept® in patients with soft tissue infections and necrotizing fasciitis. Additionally, in eight patients bone exposure or septic arthritis were observed. The time of administration of NPWTi ranged from 4 to 18 days. In all patients wound closure was achieved using skin graft, flaps or secondary closure. Leffler et al. described a small case series of 6 patients with osteomyelitis within the lower extremity (n=5) or the upper extremity (n=1) treated with NPWTi. Lavasept® was used as an instilled fluid with the following settings: 20 seconds of instillation with 20-minute dwell time followed by NPWT at -125 mmHg. After the NPWTi therapy, sterile bacterial cultures from the site of an infection were confirmed in all patients. There was no recurrence of a wound infection following a flap reconstruction. Also, they did not observe a flap loss due to the impairment of wound healing.

X. CONTRAINDICATIONS AND WARNINGS

Similarly to the standard NPWT, the list of indications for NPWT with instillation has been recently increased. There has been a tremendous progress in in the field of NPWT as well as NPWT with instillation leading to the fact that this therapy is currently used in many clinical scenarios. However, there are some clinical situations when more attention should be taken. Some solutions should also be avoided as an instillation. Contraindications for NPWTi are exactly the same as for standard NPWT and include: exposed blood vessels or nerves, exposed bowels (or qualified for abdominal NPWT) or anastomotic sites. Solutions containing ocitendine, hydrogen peroxide and other alcohol-based products are contraindicated in NPWT with instillation because of their interactions and potential destructive effect on foam dressings. Certain contraindications are specific to the applied solution. For example, neomycin may be absorbed locally and an increased serum concentration may result in nephrotoxic and ototoxic reactions. Anaphylaxis caused by the local administration of Bacitracin or Polymyxin B or when used as an irrigation was also reported. Although some authors
reported shock, coma or even death related to povidone iodine solution and hydrogen peroxide utility in surgical debridement, generally both local antiseptics seem to be safe and generally recommended for the purpose of wound cleansing.[2][3] Fluid instillation should not be delivered directly to the abdominal or thoracic cavities. Firstly, a potential retention within the human cavity may decrease the body temperature. Secondly, instilled fluid may be retained within the body cavities and may not be properly suctioned. Thus, the cases with a present bacterial inflammation may lead to intra-abdominal/ intrathoracic abscesses formation, despite the proper maintenance and application of negative pressure. However, D'Hondt et al. recently described a case report of NPWTi use in a patient treated with open abdomen management following a pancreatic surgery.[3] Due to a failure of previous therapy (included abdominal NPWT), NPWT with gentamicin and metronidazole (based on antibiogram results) was implemented. Instillation time was set for 20 seconds with 10 minutes of dwell time and a negative pressure of -125 mmHg. During the 12-day no local or systemic side effects of NPWTi were observed and the eradication of B. fragilis, P. aeruginosa and Lactobacillus was confirmed based on abdominal cultures. It is important to note that described patient developed frozen abdomen. Thus, possibly the retention of instilled fluid is minimized by the granulated tissue preventing it from pooling the solution directly through the entire abdominal cavity. Based on our experience, we agree with the authors that NPWTi may serve as an important alternative when the standard open abdomen therapy fails. However, further research and clinical trials are required to evaluate the safety and efficiency of NPWTi in open abdomen. Because of the above mentioned reasons, NPWT with instillation should be avoided in clinical situations with unexplored wound or a potential tunnel drained into body cavities. NPWTi should not be placed over skin flaps or grafts with a potential risk of failure and problems with adapting and healing of the skin flaps or grafts.

XI. CONCLUSIONS

Based on current knowledge supported by clinical trials, NPWTi is found as an important alternative to standard NPWT in many clinical scenarios. Moreover, in some publications the superiority of NPWTi over standard NPWT was highlighted. Further studies regarding both basic science as well as clinical trials are needed to establish the firm conclusions concerning the efficiency of NPWTi.

From practical point of view, in authors’ opinion it is important to share experience and collect data from varying institutions in different clinical indications to create firm conclusions and form guidelines for NPWTi.

REFERENCES


BOBKIEWICZ et al.: NPWTI IN WOUND THERAPY

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