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REVIEW ARTICLE

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Research progress on negative pressure wound therapy with instillation in the treatment of orthopaedic wounds

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Abstract
Negative pressure wound therapy with instillation (NPWTi) has the dual function of negative pressure sealing drainage and irrigation, which overcomes the disadvantages of NPWT, such as tube obstruction, inability to apply topical medicine, and poor anti-infection ability. NPWTi has been researched extensively and widely used in various types of wounds, and certain effects have been achieved. A series of parameters for NPWTi have not been unified at present, including the flushing fluid option, flushing mode, and treatment period. This paper reviews the research progress of these parameters for NPWTi and their application in the treatment of orthopaedic wounds.

KEYWORDS
instillation, negative pressure wound therapy, orthopaedic wounds, treatment parameters

Key Messages
- NPWTi has the dual function of negative pressure sealing drainage and irrigation
- setting of treatment parameters for NPWTi has not been unified yet: further research studies are required
- although there are multiple choices of instillation solutions, normal saline is recommended as the first choice; the recommended setting is the intermittent instillation mode and −125 to 150 mmHg, the duration time depends on the type of wound
- NPWTi has been widely used in all kinds of wounds in orthopaedics, such as acute or chronic infected wounds, osteomyelitis, soft tissue injuries, and surgical wound management

1 | INTRODUCTION

Negative pressure wound therapy (NPWT) is a systematic wound treatment that was developed in the 1990s, and it includes vacuum sources, drainage tubes, wound dressings, and semipermeable foils. In 1993, Fleischmann[1] first introduced traditional negative pressure drainage combined with modern wound dressings for wound treatment and achieved remarkable results, namely vacuum sealing drainage (VSD). In 1997, Argenta and Morykwas[2] used porous polyurethane foam as a wound dressing and obtained a better drainage effect, which was called vacuum-assisted closure (VAC). Professor Qiu first introduced the NPWT technique into China in 1994. In recent years, NPWT has been widely used in the treatment of acute and chronic wounds in different departments, such as general surgery, orthopaedics, and burns. Studies[3] have shown that NPWT can effectively promote wound healing by controlling wound infection and inflammation, removing wound exudates, reducing tissue oedema, and promoting granulation tissue formation, angiogenesis, and blood flow perfusion.

Although NPWT has been widely used in clinical practice, some problems obstruct its further development: (a) tube obstruction: wound exudates, bleeding, and necrotic tissue are easily deposited in the tube, resulting in tube obstruction and vacuum failure, especially for wounds with excessive and viscous secretions, such as an infected wound; (b) inability to apply topical drugs: the wound has been sealed during the healing process, which hinders the application of topical drugs, such as anti-infective drugs or growth factor solutions, and may delay wound healing; and (c) weak anti-infection ability: NPWT has an antibacterial function by creating hypoxic and acidulous conditions, although the antibacterial ability is weak and easily leads to anaerobic infection.[4]

In 1998, Fleischmann[5] first proposed negative pressure wound therapy with instillation (NPWTi), which includes three phases: irrigation, dwell, and drainage. Proper use of solution instillation in the process of NPWTi can effectively improve the wound microenvironment, inhibit bacterial growth, and control inflammatory reactions; thus, it has the dual effects of negative pressure drainage and wound flushing. The therapeutic effect is better than that of NPWT only.[6,7] NPWTi has witnessed great progress in recent years and can promote wound healing through wound cleaning, flushing, and non-excision debridement. It can also promote necrotic dissolution or detachment and the removal of necrosis and exudates before and after surgical debridement or when surgical debridement is unavailable.[8]

The effect of NPWTi is affected by many factors, including the setting of treatment parameters. At present, the setting of treatment parameters such as instillation solution and therapy mode has not been unified because strong evidence is lacking. This paper reviews the research progress in setting the treatment parameters of NPWTi and its application in the treatment of orthopaedic wounds.

2 | SETTING OF TREATMENT PARAMETERS FOR NPWTi

NPWTi can be applied to all kinds of wounds, including complex wounds caused by invasive or progressive microbial infection, stagnant growth wounds, diabetic foot ulcers, post-traumatic wounds, and wounds with a large number of sticky exudates. It can also be applied to wounds with osteomyelitis, internal fixation exposure, or orthopaedic implant infection. The setting of NPWTi treatment parameters mainly includes the instillation solutions, instillation mode, etc. At present, international consensus has been reached but standardised guidelines have not been formed. In addition, the setting of treatment parameters should also be adjusted according to the type and condition of the wound and the general condition of the patient.

2.1 | Instillation solutions

2.1.1 | Normal saline

Normal saline is commonly used as a clinical flushing solution, and it is safe, non-toxic, and well tolerated. It can be widely used in all kinds of acute and chronic wounds, which is beneficial to the irrigation and drainage of necrotic tissue and the promotion of granulation tissue production. Leung[9] found that NPWTi with normal saline can effectively promote the growth of granulation tissue in a porcine acute trauma model. Kim[10] found that the effect of NPWTi with normal saline used for infection wounds after surgical debridement was similar to that of NPWTi with antimicrobial solution (0.1% PHMB). Therefore, normal saline is recommended by the international consensus as the first choice of instilled solution for NPWTi.[11,12]

2.1.2 | Antimicrobial solutions

In the clinical practice of NPWTi, a variety of chemical antiseptics have been selected as instillation solutions, including hypochlorous acid solution, sodium hypochlorite solution, silver ion solution, and polyhexamethylene biguanide (PHMB) solution. International consensus recommends antimicrobial solutions such as hypochlorous acid solution, sodium hypochlorite solution, acetic acid solution (0.25% to 1.0%), and polyhexamethylene biguanide (0.1%) + betaine (0.1%) as compatible NPWTi instillation solutions.[12]

Prontosan solution is composed of polyhexamethylene biguanidine (PHMB) (0.1%) and betaine (0.1%), which has broad-spectrum antimicrobial activity. It can significantly inhibit bacterial growth and resist bacterial biofilm activity.[13] It is often used in chronic infected wounds with highly suspected bacterial biofilm formation.

Microcyn and Dermacyn solutions are strong oxidizer solutions, mainly composed of sodium hypochlorite and hypochlorous acid. Sauer[14] confirmed that Microcyn solution could inhibit the growth of *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*. Landsman[15] found that infections are effectively treated in diabetic foot wounds when irrigated with Microcyn solution. Microcyn/Dermacyn solutions are safe and effective instillation solutions for NPWTi. The active ingredient of Dakin's solution is sodium hypochlorite. It has been proven that Dakin's solution exhibits an antimicrobial effect against methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Enterococcus*.[16] Although Dakin's solution is affordable and convenient to use, it is not as commonly used as an irrigation solution because the effect in vivo is limited at present.

Silver ion solution is a broad-spectrum antimicrobial that presents multiple antibacterial mechanisms but does not present antibiotic resistance. Gabriel[17] and Hu[18] both found that NPWTi with silver ion solution has a certain effect on drug-resistant bacteria-infected wounds, thus improving the therapeutic effect. However, more research is needed on silver ion solutions and nanosilver solutions as instillation solutions in the future.

In addition, other antimicrobial solutions are available, including iodine solution, peroxyacid solution, chlorhexidine solution, and oxygen loaded solution, which are used for NPWTi, and reports have noted their therapeutic effects.[19-22]

2.1.3 | Antibiotics

The application of antibiotics as an instillation solution is controversial thus far, although vancomycin, polymyxomycin B, and gentamicin have been reported. Lacking effective evidence for local use, antibiotics are not recommended as NPWTi instillation solutions.[23]

Furthermore, various kinds of growth factor solutions, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), and epidermal growth factor (EGF), have been selected as instillation solutions for NPWTi, and the promotion of wound tissue cell regeneration and repair has been confirmed.[24]

2.2 | Treatment modality

2.2.1 | Negative pressure setting

The appropriate negative pressure setting during the NPWTi period makes the irrigation solution reach the inner layer of the dressing and wound bed, and it avoids air leakage failure and ensures the therapeutic effect. Most studies have shown that a negative pressure setting of −125 mmHg exhibits positive and promising effects.[25,26] Therefore, international consensus recommends that the appropriate setting of negative pressure for NPWTi is −125 to 150 mmHg, which is also consistent with the results of most experimental studies.

2.2.2 | Instillation mode

The instillation mode usually includes the persistent instillation mode and intermittent instillation mode. The persistent instillation mode, known as the period of negative pressure that is always accompanied by irrigation, is not conducive to the delivery of instillation solution to the whole wound, which weakens the effect of irrigation. The intermittent instillation mode has cycles consisting of two phases, namely, the negative pressure phase and instillation and dwell phase, and is termed NPWTi-d, and it allows the solution to permeate into the whole wound freely. Therefore, the intermittent instillation mode of NPWTi is the recommended therapy mode, and the suggested duration of the negative pressure phase is 2 to 3 hours.[27]

When the solution is instilled into the dressing and wound bed, the negative pressure is stopped or reduced, which makes the solution fully infiltrate the wound tissue and exudate. This phase is termed the instillation and dwell phase. However, the capacity and dwell time of the solution are still controversial. The appropriate volume of solution refers to the volume needed when the dressing foam is fully infiltrated and saturated. An excessive volume will cause skin tissue infiltration around the wound edge, while an insufficient volume will affect the irrigation effect. The dwell time is also important, while longer times may produce a toxic effect. Meanwhile, the degradation effect of the instillation solution on the dressing foam is still unknown. It is believed that the best volume should ensure that the solution can fully infiltrate the dressing foam until the sealing film begins to bulge, and the appropriate dwell time is mostly 10 minutes.[12] However, these settings are usually difficult to carry out in clinical practice, and the sealing film is easily damaged because of the high probability of excessive solution or longer dwell time.

2.2.3 | NPWTi duration time

The duration of NPWTi treatment depends on the type of wound and the purpose of treatment. Studies have shown that the duration of NPWTi treatment ranges from a few days to dozens of days: 3 to 14 days for acute non-infectious wounds and 7 to 60 days for chronically infected wounds. It is generally believed that when clinical goals are reached, such as successful wound bed decontamination, stimulation of granulation tissue, preparation for skin grafting or skin flap surgery, and replacement of dressing, NPWTi discontinuation should be considered.

3 | APPLICATION OF NPWTi IN THE TREATMENT OF ORTHOPAEDIC WOUNDS

As an adjuvant wound treatment strategy, NPWTi has been widely used in all kinds of acute and chronic wounds in orthopaedics, such as acute or chronic infected wounds, bone tendon or internal fixation exposed wounds, diabetic foot ulcers, and pressure injuries. It should be noted that the condition of wounds should be fully evaluated before NPWTi application, including the aetiology, vascular condition, and complications. When the wound is prepared for further surgery, it should be repaired as soon as possible, including direct suture, skin grafting, or skin flaps, to avoid delays in wound healing.

3.1 | Acute wound

Open fractures, soft tissue injuries, and necrotizing fasciitis are common acute wounds in orthopaedics. Prevention and control of wound infection and covering the wound as soon as possible are the keys to the treatment of open fractures. NPWTi provides active drainage for the wound, and continuous wound irrigation ensures the continuous cleaning of the wound, thereby avoiding secondary pollution and shortening the treatment time. Mazen[28] reported a case of an open tibia fracture that was treated with NPWTi and skin grafts, and the main goals were achieved, such as preserving the architecture of the leg, achieving bone union, and avoiding infection.

Severe soft tissue injuries often face several problems, such as poor blood supply and wound contamination. Primary closure cannot be achieved because of infection or oedema, and tissue with poor vitality may continue to necrose and exudate. NPWTi can effectively drain wound exudate, necrotic tissue, and toxin and provide coverage and protection for the wound, thereby promoting granulation tissue growth, which creates conditions for secondary wound repair. Ali[29] treated a soft tissue injury of the lower extremity with NPWT and NPWTi and found that the growth of granulation tissue was fast even over the exposed bone despite the presence of non-viable and fibrinous tissue when treated with NPWTi, and the wound was then successfully covered with a skin graft. Omar[30] treated acute soft tissue injuries of the lower extremities with NPWTi with normal saline solution compared with NPWT alone. The results showed that NPWTi could significantly reduce hospitalisation time and accelerate wound healing; however, there was no significant difference in the therapeutic outcome between these two treatments.

Some soft tissue defect wounds cannot be primarily closed because of excessive tension in the wound area, and the wound formed after incision for decompression of osteofascial compartment syndrome is one of these special types. Because of the large skin tension induced by a large area of skin defects and tissue oedema, this kind of wound often experiences delayed closure. NPWT provides temporary wound closure, which is also an ideal method for managing oedema and exudate after incision. DeFazio[31] introduced a traction-assisted NPWT device combined with instillation to repair acute soft tissue defects with delayed reconstruction under tension. The results showed that this method could significantly reduce wound burden and facilitate wound closure, most cases could be repaired directly, and few healed after skin grafting or flap reconstruction.

Necrotizing fasciitis is a severe, widespread, and aggressive soft tissue infection, and prompt surgical debridement is the key to improving the survival rate. Large complex wounds after surgical intervention lead to intractable problems, while necrotic tissue and exudates cannot be drained effectively with the conventional dressing change method, and infection may recur or even be life-threatening. NPWTi provides an innovative method for the treatment of necrotizing fasciitis. Frankel[32] and Reider[33] reported the application of surgical debridement and NPWTi for different areas affected by necrotizing fasciitis and found that it is helpful to remove infectious material, enhance granulation tissue production, and facilitate the development of a healthy wound bed sufficient for reconstruction. Zhang[34] applied NPWTi in the treatment of necrotizing fasciitis and did not observe the recurrence of infection; moreover, all wounds were successfully repaired by skin grafting, sutures, or skin flaps. Thus, the advantages of this method in wound cleaning and wound bed preparation were confirmed.

3.2 | Chronic wound

Chronic orthopaedic refractory wounds are very common and intractable, including chronic infected wounds;

wounds with bone, tendon, or internal fixation exposure; chronic osteomyelitis; diabetic foot ulcers; and pressure injuries. Delayed wound healing is often caused by inflammation, chronic infection, and pathological hyperplasia. NPWTi is an effective method for the treatment of chronic wounds and can effectively remove harmful wound cytokines, improve the wound microenvironment, control wound infection, promote granulation tissue production, and create the conditions for secondary repair.

A retrospective study conducted by Gabriel[17] showed that compared with traditional wound treatment, NPWTi could significantly reduce the wound microbial burden, wound healing, and hospitalisation time when treating multiple types of complex infected wounds. Hu[18] found that wound infection was effectively controlled when treated with NPWTi with silver ion solution, and the length of stay, incidence of complications, and blood inflammation were significantly reduced. Goss[35] confirmed that the application of NPWTi after surgical debridement in chronically infected wounds of the lower extremities can significantly reduce the wound microbial load compared with NPWT alone, and these advantages are conducive to further wound repair. The results of Yang[36] also confirmed that NPWTi can significantly reduce the bacterial load of chronically infected wounds and create conditions for wound bed preparation and closed repair. Having reported all of the above, NPWTi is indeed a good method for the repair of complex infected wounds.

In a retrospective study of the treatment of post-traumatic osteomyelitis, Timmers[37] found that compared with traditional treatments (standard surgical debridement, implantation of sustained-release gentamicin, and long-term intravenous infusion of antibiotics), the application of NPWTi after wound debridement significantly reduced infection recurrence and the number of operations and hospital stay. The reduction of the duration of treatment, the number of operations, the inpatient stay, and the recurrence rate in a post-traumatic osteomyelitis patient group were also confirmed by Jukema,[38] with increasing effectiveness shown for the treatment of the infection.

Diabetic foot ulcers are among the main causes of morbidity and mortality in diabetic patients, and they are caused by a combination of vascular diseases, neuropathy and hindered wound healing. Combining intermittent wound irrigation with NPWT may offer additional benefits compared with NPWT alone, including reduction of wound bed bioburden, promotion of granulation tissue formation, and provision of wound irrigation in a sealed environment; thus, the utilisation of NPWTi in diabetic foot infections is promising.[39] Enodien[40] reported a case of diabetic foot ulcer with severe infection treated with NPWTi with super oxidised solution, which helped to promote wound healing, remove infectious material, and prevent the infection, and wound closure was ultimately achieved.

In the management of sacral and ischial pressure ulcers, compared with conventional NPWT alone, NPWTi has been shown to help irrigate the wound, remove fibrinous debris, and promote granulation tissue formation, which is associated with a decreased number of operative debridements and decreased length of hospital stays.[41] Patients with pressure ulcers in different locations were treated with NPWTi after surgical debridement, followed by wound closure using different local flaps, and the findings indicated its benefits in terms of helping wound bed preparation for secondary healing.[42]

3.3 | Other types of wounds

Tissues such as bone cortex and tendon will be exposed for a long time during orthopaedic surgery, which will increase the possibility of degeneration or necrosis of these tissues and the incidence of wound infection, as well as the improper frequent wound dressing change after surgery. NPWTi can be applied in wound management after orthopaedic surgery, which can effectively improve the healing of operative area wounds and reduce the incidence of postoperative incision-related complications. Hrašovec[43] used NPWTi for postoperative wound treatment after spinal fusion surgery, and healthy granulation tissue with minimal exudate was noted during the course of therapy and complete wound closure was finally achieved. NPWTi has also been proven to promote wound healing after skin grafting. Lee[44] used NPWTi during all phases of wound care as the split-thickness skin graft bolsters in patients with trauma wounds, and excellent graft take without the need for repeat operative intervention was achieved.

A large amount of internal fixation of fractures occurs in orthopaedic surgery, and there is a certain incidence of infection following orthopaedic implants. The conventional treatment is debridement and wound dressing, topical antibiotics, or even removal of the osteosynthetic material; however, the treatment effect is usually unsatisfactory. Patients with postoperative wound infection following fracture repair and internal fixation were treated with NPWTi, and the granulation tissue was found to be sufficient in all cases, no recurrence of infection was noted, and the osteosynthesis material remained in place.[45] Liu[46] discussed the application of NPWTi in the management of wounds with indwelling orthopaedic fixation hardware. NPWTi helps to contract the wound edges, remove infectious material, and promote robust granulation tissue formation.

4 | PROSPECTS

NPWTi provides continuous drainage and irrigation for wounds and removes the exudate and necrotic tissue continuously, and it effectively controls local infection and promotes wound healing.[47] As an improved method of NPWT, NPWTi has been studied and applied widely, and certain promising results have been achieved. Because of its dual advantages of drainage and irrigation, NPWTi is expected to be used in a variety of challenging wounds.[48] However, limitations need to be noted: the efficacy of NPWTi is affected by many factors, such as the wound surface or periwound conditions, general condition of the patient, and setting of treatment parameters. At the same time, most of the existing recommendations for indications and treatment settings of NPWTi refer to the results of case review studies and expert consensus. Therefore, to ensure appropriate patient and wound selection, consistency between the treatment mode and the setting for different types of wounds, and the refinement, standardisation, and individualization of treatment parameters, further randomised and controlled trial research is required.

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CONFLICT OF INTEREST

There are no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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