Topical Negative Pressure in Wound Care
Effectiveness and guidelines for clinical application

Chantal M. Moues-Vink

Topical Negative Pressure Therapy in Wound Care
Effectiveness and guidelines for clinical application

Topicale negatieve druktherapie als wondbehandeling
Effectiviteit en richtlijnen voor klinisch gebruik

Proefschrift

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Jan Hugo de Wit

A thousand days to learn
Duizend dagen om het te leren…

What is success? To laugh often and much; To win the respect of intelligent people and the affection of children; To earn the appreciation of honest critics and endure the betrayal of false friends; To appreciate beauty; To find the best in others; To leave the world a bit better, whether by a healthy child, a garden patch or a redeemed social condition; To know even one life has breathed easier because you have lived; That is to have succeeded.

Waldo Emmerson Ralph (1803 - 1882).
American Transcendentalist philosopher, essayist, poet and writer

Contents

Summary, conclusions, closing remarks and perspectives

CHAPTER I

Introduction and outline of the thesis

Introduction

Health economics of wounds

The aim in the treatment of any type of wound is to achieve normal and timely healing. Complicated wound healing may affect functional ability and almost always involves appearance or "looks" despite reconstructive measures. Recent figures on either the incidence of wounds or the total cost of wound care in the Netherlands are not available.

A reporting system to the public health inspection authority (the so-called quality indicators) was introduced by the Dutch government in order to create more transparency on hospital-related complications in 2003. Since then, complication registration is obligatory in every hospital. This resulted in the registration of the cost of illness in a small group of patients with pressure ulcer wounds. The cost for the pressure ulcer group alone ranges from a low estimate of $362 million to a high estimate of $2.8 billion (1). The cost for the diseases of skin and the subcutis was estimated at € 886 million (1.3% of the total health care costs) in 2005 (2). These figures reflect only the direct costs. They neither reflect the pain, frustration, economic loss nor impaired quality of life of the patients and their families, nor the burden on the health care system in general.

Etiology

Skin wounds are a heterogeneous and complex group of disorders with a wide variety of causes (Table 1). Wound healing progresses through well-recognized, pathophysiological stages. Wounds that do not heal as expected are considered to be chronic. Although there is no consensus on the definition, most wounds are called acute if they are present only

Table 1. Classification of Skin Wounds

Acute	Chronic
Traumatic wounds	Pressure wounds
• Burns; chemical, electrical, radiation, thermal	• Decubitus ulcers
• Laceration/skin tear	• Neuropathic ulcers
• Penetrating trauma; explosion, bites , gunshot wound, puncture	Inflammatory wounds
• Surgical cuts; deep/superficial	• Autoimmune disorders
• Blunt trauma; contusion, avulsion, traction, crush	• Primary cutaneous disorders
	Vascular insufficiency wounds
	• Venous insufficiency
	• Arterial insufficiency
	• Mixed arterial/venous insufficiency
	Malignant wounds
	• Primary cutaneous malignancies
	• Secondary cutaneous malignancies
	Miscellaneous wounds
	• Burns
	• Radiation injury
	• Frostbite
	• Vasculitic ulcers
	• Insect bites

for a short period of time before intervention (< 4 weeks to a maximum of 6 weeks) and show signs of normal wound healing (3). There are two types of tissue injury: full and partial thickness. Partial thickness injury is limited to the epidermis and superficial dermis, with no damage to the dermal blood vessels. Healing occurs by regeneration of epithelial tissue. Full thickness injury involves loss of the dermis, extends to deeper tissue layers, and disrupts dermal blood vessels. Chronic wounds are defined as those present for more than one month to 6 weeks prior to intervention without any tendency of normal wound healing. These wounds either require a prolonged time to heal, do not heal completely, or recur frequently (4). Research on chronic wounds emphasized that numerous factors such as deficiencies in local-/systemic growth factors, changes in extracellular matrix (ECM), diminished fibroblast function, decreased antimicrobial activity of leukocytes, biofilms and disturbance of macro- and microcirculation are responsible for slowing down the healing of these wounds (5, 6).

Phases in wound healing

The body's response to wounding of any kind is a complex and highly orchestrated sequence of cellular and biochemical changes. Successful wound healing involves a series of overlapping phases: (i) coagulation and inflammation, (ii) cell proliferation and repair of the ECM and (iii) the remodeling phase (7). These phases are distinct, but overlap in time during the healing process (Figure 1).

The **inflammatory phase** is characterized by hemostasis and inflammation. After a tissue injury, the damaged cells release thromboxane A2 and prostaglandin 2-alpha, potent vasoconstrictors so that further bleeding is limited. The initially responding cells and platelets

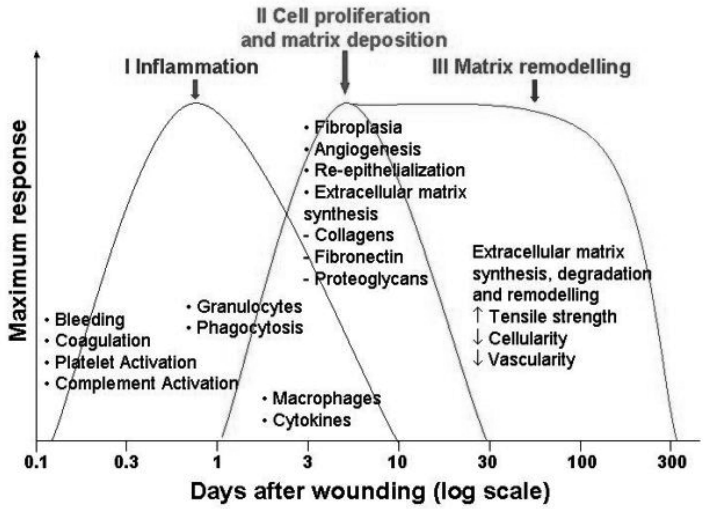

Figure 1. Phases of wound healing
Enoch S, Price P. www.worldwidewounds.com/2004/august/Enoch

release multiple chemokines (e.g. epidermal growth factor (EGF), fibronectin, fibrinogen, histamine, platelet-derived growth factor (PDGF), serotonin, and von Willebrand's factor which trigger coagulation and formation of the clot. Hereafter, vasodilatation of the capillaries occur secondary to local histamine release and the cells of inflammation are able to migrate to the wound bed. Platelet degranulation also activates the complement cascade, specifically C5a, which is a potent chemo-attractant for neutrophils. Neutrophils and macrophages enter the wound site. Neutrophils act primarily to prevent and respond to infection, whereas macrophages release inflammatory mediators such as cytokines, enzymes and growth factors, which clear the wound of devitalized tissue (phagocytosis), and set the stage for cellular regeneration (8, 9).

The **proliferative phase** begins after two or three days and lasts for several weeks. Cell migration, proliferation, new capillary formation and synthesis of ECM components are the principal steps in this anabolic stage of wound healing. This stage is marked by a predominance of fibroblasts, endothelial cells and keratinocytes. Fibroblasts secrete growth factors and both fibrous and non-fibrous components of ECM that lead to tissue regeneration. The damaged proteins must be degraded by matrix metalloproteinases (MMPs) in order to buildup new healthy ECM (10). Tissue inhibitors of metalloproteinases (TIMPs) bind to MMPs at the moment that the degrading function of the MMPs is required to fade out in order to proceed to the proliferative phase. A failure in this regulation has been suggested to affect not only wound healing (11, 12), but also other pathologic conditions such as cardiovascular disease (13), inflammatory, fibrinogenic diseases, and tumor growth and invasion (14-16). Endothelial cells form the new blood vessels that are also necessary for tissue regeneration (8). Epithelial cells proliferate and migrate over the newly vascularized ECM (granulation tissue) to form the epithelial layer (9).

The final phase is the **remodeling phase**, in which intact skin replaces scar tissue. This phase is characterized by continued cycles of new cellular component formation and degradation of the scar by proteases. The wound reaches maximum strength in one year. Collagen deposition continues for a prolonged period, but the net increase in collagen deposition plateaus after 21 days (8, 17). Wounds that heal properly, progress through these phases in an orderly fashion. Non-healing wounds often remain "arrested" in one of these phases, usually showing continued inflammation or proliferation (8). The initial debridement of a chronic wound often temporarily speeds up wound healing followed by a healing arrest eventually returning to the poor state before therapy started (18). This detrimental effect can be explained by some common features of all chronic wounds; (i) the effects of aging on the proliferating cell, both by intrinsic (diabetes) and extrinsic mechanisms (smoking, sun exposure) (ii) repeated ischemia-reperfusion injury, and (iii) bacterial colonization with the accompanying inflammatory response. Treatment approaches logically have to address all three of these aspects of chronic wounds (19).

Clinical manifestations and diagnosis

Conventional treatment of wounds incorporates common principles for all wounds along with specific treatment strategies targeted at specific types of wounds and overall clinical status of the patient. This approach should include adequate good quality care, that is effective, efficient and regards the specific needs of the patient (20). Optimum management of wounds starts with a good medical history of the patient as well as an extensive inquiry into the background of the wound (Figure 2). In the field of venous leg ulcers (Phlebology), one is able to establish an accurate diagnosis on clinical criteria alone in up to 75% of the skin wounds. However, specialized testing such as blood flow measurement is necessary in the remaining cases (21). Basic clinical observations such as hypo/hypertrophic skin, pigmentation, smoker's breath, blood tests (oxygenation, infection, nutrition) and physical examinations (pulses) are often ignored or forgotten and blind ultra-sophisticated topical treatment is started in the hope that remission will be simple and complete. However, a chronic wound is neither simple nor there is a simple therapy.

Open wound management

The mainstay of wound management is thorough debridement, which is the *sine que non* of contaminated wounds. An open wound invariably becomes colonized by bacteria because there is no protective skin barrier to prevent bacterial adherence to the exposed tissue. Although colonization does not preclude healing, it can be significantly delayed when there is clinical infection (22). Clinical infection implies bacterial invasion into the deeper layers of the surrounding tissue. Infection of a wound site alters the normal healing process by disrupting and prolonging the inflammatory phase (23) with subsequent increased levels of cytokines and MMPs and lower numbers of growth factors in the wound. The inflammatory infiltrate reduces fibroblast proliferation and thus lowers ECM synthesis and deposition and the macrophages are inhibited to direct the formation of granulation tissue and neo-vascularization. If this condition is not dealt with effectively then the end result would be a wound that is "arrested" at this stage of healing and becomes a chronic wound.

Topical wound treatment

Although wound management is a part of every medical and paramedical discipline, it is only recently that wound management seems to have progressed beyond ancient remedies and beliefs (24). Increased understanding of the biology of wound healing and new technological innovations have led to major advances in wound care. Major changes were introduced at the end of the nineteenth century with the identification of the cellular components of the wound and continued with the investigation of inflammation and the introduction of the concept of moist wound healing (25). These concepts led to the rapid expansion of local wound dressing categories in the last two decades of the 20th century. Recent advances in technology combined with better understanding of the mechanisms of wound healing

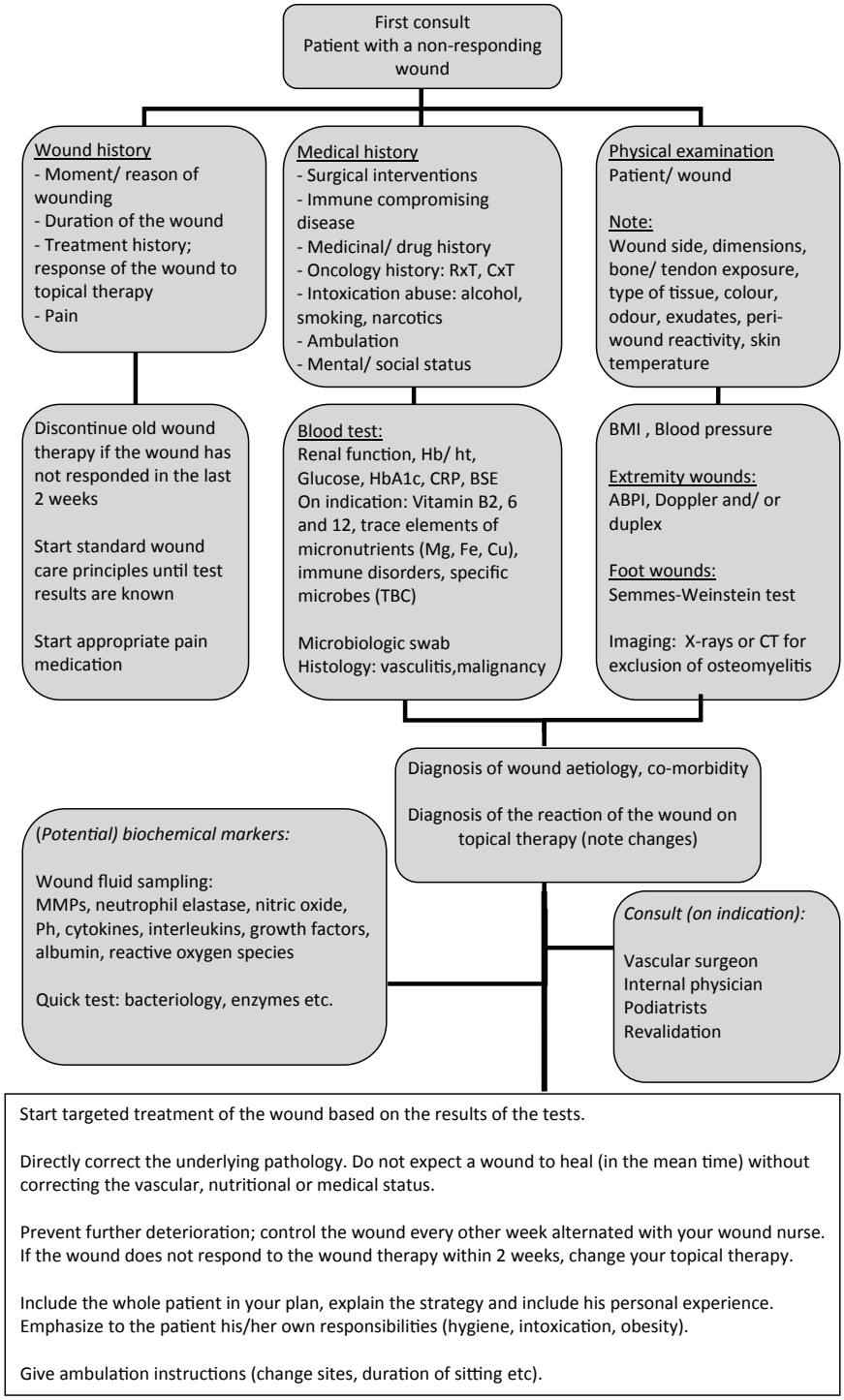

Figure 2. Flow chart of wound diagnosis

have resulted in the development of advanced wound healing modalities such as hyperbaric oxygen, topical growth factors, bioengineered skin and tissue equivalents, and topical negative pressure (TNP) therapy. Surgical decision taking has shifted from an acute setting towards strategically planned operations. It has become possible to treat some wounds more conservatively than initially planned while others can be closed with sophisticated flaps at a better stage in the wound healing process within this surgical plan.

Research

The large number of factors that contribute to wound healing and the high degree of variation in wound characteristics and patient status may lead to numerous potential confounding factors in attempts to measure treatment efficacy. As a result of these multiple confounding factors, it is difficult to interpret outcomes from single-arm trials that lack a control group, since improvement could have been due to factors other than the specific intervention that was being investigated. A concurrent control group is necessary to permit the correct evaluation of the treatment efficacy. Randomized assignment to treatment group maximizes the likelihood that confounding factors are equally distributed across treatment groups. Unfortunately, less than optimal results are often achieved when translating the results from randomized clinical trials (RCTs) into routine practice. This is not surprising firstly, because the efficacy of the treatments within a RCT is measured under tightly controlled conditions often performed by specialized wound care personnel. Secondly, in every day practice many patients receive the treatment with a product that would not have met inclusion/exclusion criteria of an RCT. And third, measurement of outcome and effect are mostly based on subjective inter-/and intra observer variable parameters. In addition, in daily wound management, many clinicians rely on the product to achieve a healing outcome without first employing all of the necessary components of good wound healing principles and practice. The problem with translating clinical efficacy from RCTs into actual efficiency in the clinical setting is a commonly encountered problem in wound care (26).

Outline and aims of this thesis

Wounds in need of reconstructive surgery are often large, with extensive soft tissue loss caused by de-gloving injuries, infection, dehiscence, donor site defects after reconstruction and de-bulking of invasive tumors, or full thickness ulceration in pressure sores. These situations leave patients in debilitating circumstances with wounds that require labor-intensive treatment. Direct reconstruction after admission to the hospital is in most of these cases not possible because of the condition of the patient and/or the extensiveness of the wounds. The first stage is to optimize the condition of the wound through aggressive debridement in order to remove necrotic tissue, foreign material and potentially harmful bacteria (27). Wounds may be allowed to heal by secondary intention forming granulation tissue later to be covered with artificial or natural skin grafts, local or distant tissues, pedicle flaps or

micro-vascular free tissue transfer. Choice of therapy during this period is mainly based on the physicians' and nurses' hands on experience with certain products and their initiative to try new modalities. The work-up of complex full thickness wounds has become easier by the incorporation of TNP therapy into wound management programs (Figure 3, appendix). Surgical decision making has shifted from an acute setting to a strategically planned operation. Within this surgical plan, it has become possible to treat some wounds more conservatively than initially planned, whereas others can be closed with sophisticated flaps at a better stage in wound healing or at a better time.

The aim of this thesis was to investigate whether TNP therapy is superior to conventional therapy (moist gauze) for the treatment of full thickness wounds after debridement. TNP therapy has already been introduced as a novel technique for wound management a decade ago and has evolved since than faster then any other new technique. Physicians, nurses and wound specialists were enthusiastic and clinical case studies piled up without serious research. However, a new technique can only be deemed acceptable if it is save, offers an equal or better treatment, if it is easy to master and if it is cost-efficient. When we started this research only little was known about these parameters. This thesis predominantly focuses on the role of TNP in wound healing as well as its impact on clinical practice.

Chapter 2 provides a review of the literature on the history of topical wound therapy in general and highlights some of the meaningful landmarks (i.e. asepsis/antisepsis, fundamental cellular research, antibiotics/antimicrobials, moist wound healing and chemical and physical processes of wound healing) that have been incorporated into the actual guidelines for the major developments in wound management.

The results of a prospective clinical randomized trial are described conducted at the Department of Plastic and Reconstructive Surgery in which we evaluated and compared the clinical effects (**Chapter 3**) and the costs (**Chapter 4**) of TNP therapy with conventional (moist gauze) therapy in the management of full thickness wounds.

Two mechanisms are focused on in the investigations in **Chapters 5** and **7**. The bacteriological influence of TNP therapy on the wound environment is described in **Chapter 5**. The effect of TNP therapy on the biochemical and cellular microenvironment of the wound bed is dealt with in **Chapter 7**.

The aim of the study described in **Chapter 6** was to determine the most appropriate bacterial sampling method for predicting bacterial wound contamination and post-operative complications in contaminated acute and chronic full thickness wounds before surgical closure.

In **Chapter 8**, a literature review, which focuses on the role of TNP in wound healing, the mechanism of action and the implication for clinical practice is given.

The international vacuum assisted closure consensus document which was compiled by us and a selected group of international expert opinion leaders in TNP therapy is described in **Chapter 9**.

The studies described in this thesis are summarized in **Chapter 10** and potential directions for future studies are addressed.

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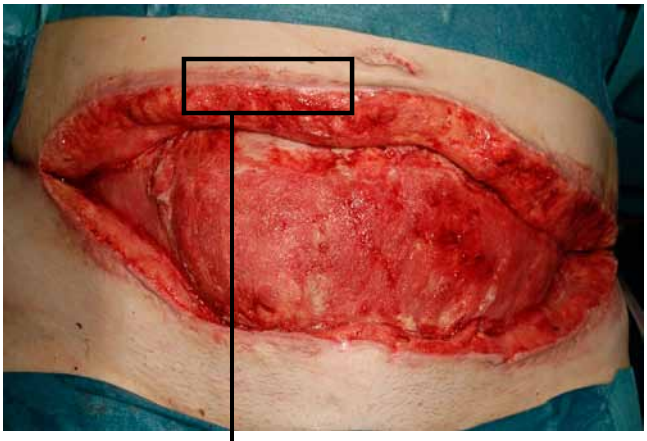
Appendix



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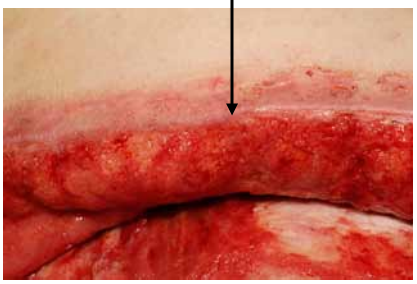

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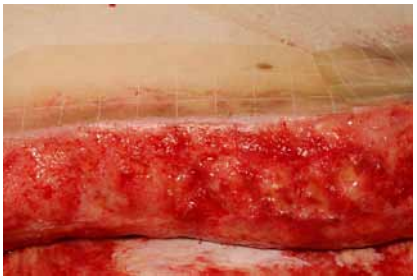

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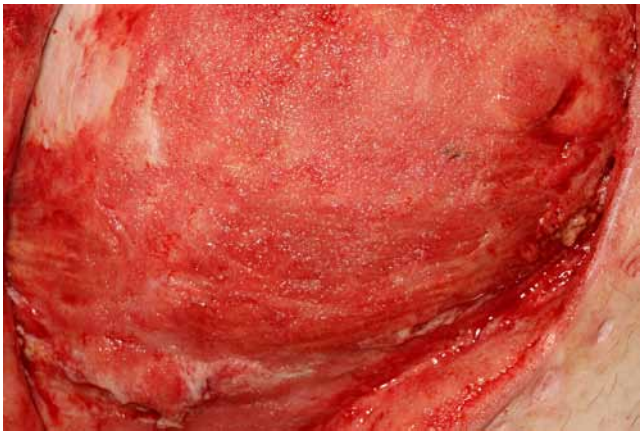


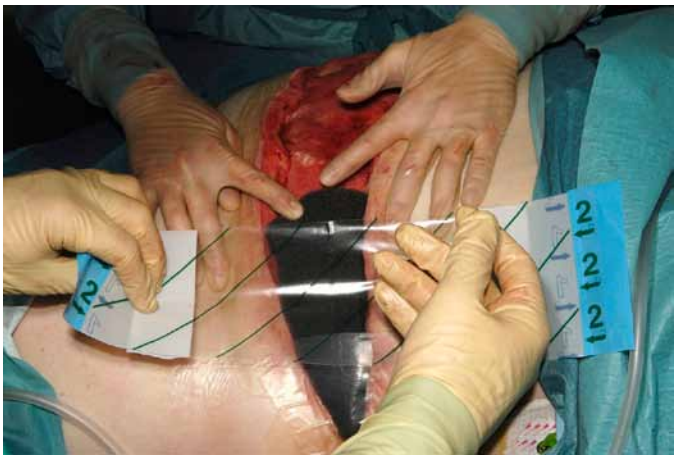
Figure 3

A. Dehiscent wound due to infection after abdominoplasty.

B. Superficial skin damage due to maceration and sensibility to foil adhesives.

C. Protection of the surrounding skin using hydrocolloids.

D. Healthy appearing granulation tissue covering abdominal fascia after 4 days of TNP therapy.



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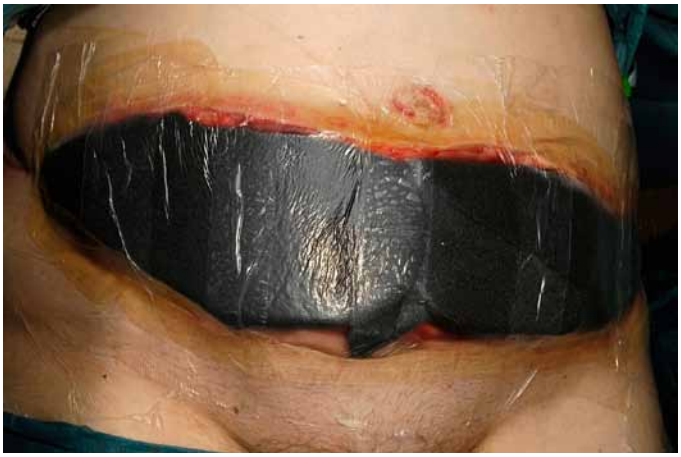

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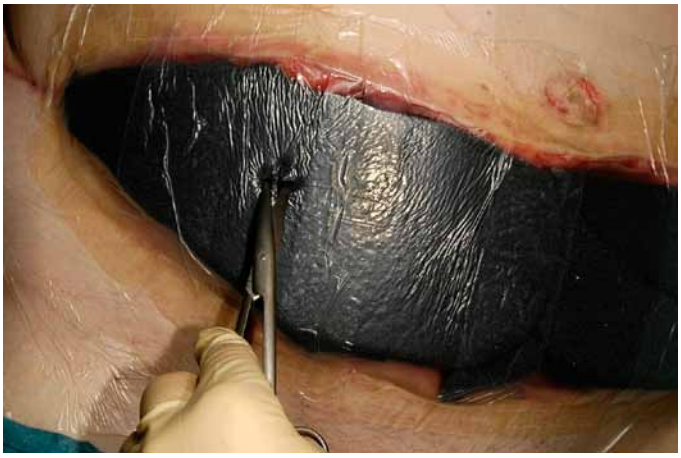

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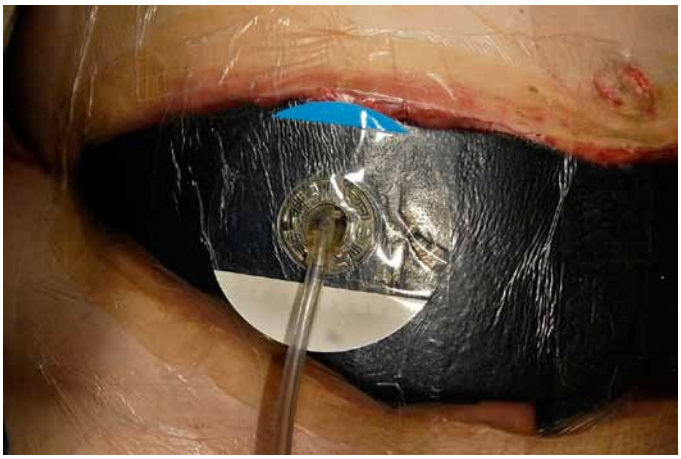
E. Diminishing wound size by cutting smaller sized black foam sponges. Transparent foil is cut in smaller sizes to make the procedure easier.
F. Completed coverage.
G. Cutting out foil for the placement of a traction pad.



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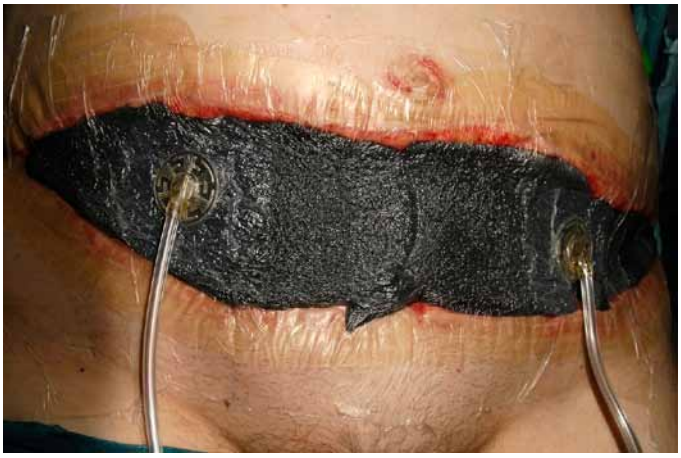

J

H. Do not place the traction pad directly on the skin to prevent pressure ulcers.

I. Use two traction pads in case of large wounds.

J. Apply the vacuum, sponges collapse without manually pressing the sponge.

CHAPTER II

Five millennia of wound care products; what is new? A literature review

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Abstract

The first wound and wound treatments were described five millennia ago. Since then, various principles of wound care have been passed on from generation to generation. In contrast to large numbers of general technological inventions over the last 100 years, progress beyond ancient wound care practices is a recent phenomenon. It is essential to know the historical aspects of wound treatment (both successes and failures) in order to continue this progress and provide future direction. A survey of the literature shows that concepts such as "laudable pus" persisted for hundreds of years and that lasting discoveries and meaningful progress did not occur until grand-scale manufacturing and marketing started. Landmarks such as understanding the principles of asepsis/antisepsis, fundamental cellular research findings, knowledge about antibiotics/antimicrobials, moist wound healing, and the chemical and physical processes of wound healing have provided the foundation to guide major developments in wound management, including available evidence-based guidelines. Although research regarding interaction of basic wound management principles remains limited, the combined efforts of global research and clinical groups predict a bright future for improved wound management.

An ancient background

Knowledge of the biology of wounds and wound healing, together with inventions and innovations of new wound care products, has proliferated throughout time. The earliest civilizations of Mesopotamia, Arabia, Egypt, and Greece left fascinating records of their medical practice — ie, the clay tablets, Sanskrit documents (2000 BC), Smith papyrus (1650 BC), Eber's papyrus (1550 BC) and Homer's writings (800 BC) (see Figure 1). Medical practices of those eras were founded predominantly on empirical beliefs and magic; physicians made decisions based on observation, judgment, and experience. However, wound management during the early Egyptian civilization resembles current approaches. Treatments consisted primarily of wound closure through suturing or open wound therapy in diseased wounds with debridement followed by (though probably not intentionally) antibacterial therapies (1).Ulcerating lesions were bound with figs containing papain (2). Only recently have these agents been found to remove the fibrous slough present on wounds. Wine, vinegar, and hot water were used to cleanse the wounds. After cleansing, dry powders consisting of a mixture of metals (mercury, zinc, silver, and copper) were used to prevent inflammation (1) (see Table 1). Copper

Table 1. Topical products and their presumed mechanism of action

General Group	Action	Presumed mechanism of action	Products
Antiseptic	Kill or inhibit the growth of various micro-organisms on the external surfaces of the body	Cell destruction	Plants (i.e. *Pistacia terebinthus*), hydrogen peroxide, alcohol, iodine, mercury, silver, chlorhexidine, sodium hypochlorite Slow release antiseptics: Iodine compounds, silver-releasing compounds, silver sulfadiazine
		Creation of an acidic environment	Wine, vinegar, acetic acid, carboxy acid
Antimicrobial	Inhibition of bacterial repopulation	Exact mechanism unknown	Myrrh and frank incense, vegetables, plants
		Acidic environment	Sugar, honey
		Alkaline environment	Maggots
		Osmolytic effect	Sugar, honey
		Inhibition of bacterial synthesis, or disruption of the cell membrane	Topical antibiotics
		Drainage of exudate, bacteria or toxins	Topical negative pressure therapy (TNP)
		Stimulation of the immune response	Honey
		Creation of hypoxic environment	Semi/occlusive dressings, TNP
		Creation of hyperoxic environment	Hyperbaric oxygen
		Digestion and ingestion	Maggots
Debridement	Removal of nonviable tissue	Mechanical	Wet-to-dry gauze, ultrasound-assisted wound debridement, whirlpool, irrigation or pulsed lavage
		Chemical	Sodium hypochlorite, hydrogen peroxide
		Enzymatic	Honey, papain, maggots, collagenase
		Autolytic	Hydrogels, hydrocolloids, honey
Wound closure	Facilitate wound closure	Creation of a moist environment increases angiogenesis, stimulates of fibroblasts and induces re-epithelization,	Semi-occlusive dressings, occlusive dressing, alginates, collagen, honey, silver-releasing compounds, TNP, hyperbaric oxygen

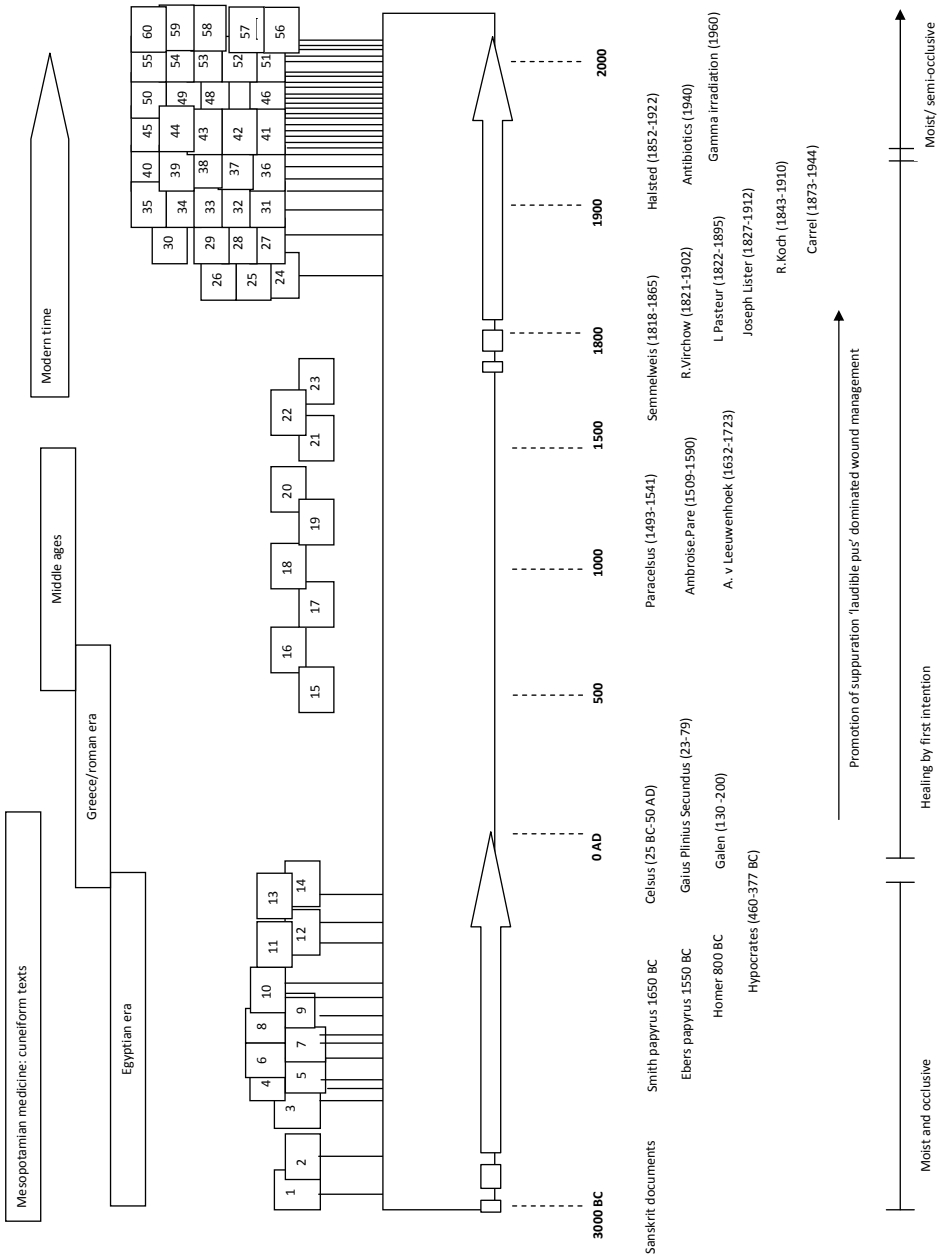

Figure 1. Timetable showing the events, important inventions, and leading historical opinion makers in wound care. The numbered boxes refer to the invented wound care products that can be found in numeric order in the key to follow.

was found on the island of Cyprus in great amounts and because of its bright blue color, it was used to "paint" ugly wounds (1,3). Interestingly, the reaction of copper with wine and vinegar results in the formation of a strong antibacterial compound (copper acetate)(4). Silver was used as an ingredient in plasters to cover open wounds, as well as to purify the drinking water of monarchs of ancient dynasties (5). Strips of linen soaked in grease, honey, oil, and lint were used to cover the wound surface (1). A literature review by Aldini et al. (6) notes that it is now known that using lint to pack and fill the wound space might create an oxygen-poor environment that could stimulate angiogenesis; combining the aforementioned products not only prevented the linen from sticking to the wound base (ie, creating a nonadherent dressing), but also was a potential practical solution to diluting the strong osmolytic honey. The Egyptians may have been the first — unknowingly — to employ the "moist wound healing" principle (7). Additionally, treatments included application of natural products such as plants and vegetables (eg, *Pistacia terebinthus* — antiseptic; *Alchemilla vulgaris* — tannine,

Key to Figure 1

1. Cleansing of the wound with wine, vinegar, beer, hot water
2. Metal powders: copper, silver, zinc
3. Fresh meat
4. Lint with honey, grease, and oil
5. Covering with mud
6. Leaves (plants)
7. Figs bound on wound surface
8. Aromatic resins; myrrh, frankincense
9. Onion and garlic
10. Adhesive bandages prepared with gum
11. Warmth, sunlight
12. Grease on wool
13. Bread and wheat as poultices
14. Seaweed
15. Mercury
16. Boiling oil
17. Red-hot iron pokes for hemostasis
18. Yolk of egg, oil of roses, and terpentine
19. Silver nitrate
20. ~17th century: electric stimulation of wounds
21. ~17th century: "sympathetic" powder: moss scrapings from a dead man's skull mixed with powdered mummy's flesh.
22. Almond oil
23. Gold leaves on smallpox lesions
24. 1800: Cotton wool as surgical dressing (Gamgee)
25. 1839: Iodine
26. ~1849: Hypochlorite hand scrubbing
27. 1860: Carbolic acid
28. 1899: Zinc oxide plasters
29. ~ From 1887: Mustard plasters
30. Belladonna plasters
31. Carbolated sterile dressings
32. Impregnated iodoform dressings
33. Metallic antisepsis; mercuric bichloride
34. 1895: Silver foil
35. 1903: Light therapy
36. 1910: Reintroduction of Sodium hypochlorite on wounds
37. 1914-1918: Tulle grass (paraffin dressing) (Lumiere)
38. ~ 1919: Organic mercurials; mercurochrome
39. 1921: Band-aid
40. ~ 1930: Topical antibiotics: sulfonamides
41. ~ 1943: Topical penicillin
42. 1945; Chlorhexidine
43. ~ 1950: Topical corticosteroids
44. 1954: Aerosol spray dressing containing bacteriostatic agents
45. 1960: Hyperbaric oxygen for the treatment of wounds
46. 1961: Impermeable film
47. 1962: Polyvinyl alcohol sponges
48. 1968: Silver sulfadiazine/povidone-iodine and cadexomer iodine
49. ~ 1974: Zinc sulfate paste
50. ~ 1975: Water vapor permeable polyurethane films
51. ~ 1980: Hydrocolloids
52. ~ 1980: Hydrogels
53. ~ 1980: Alginates
54. ~ 1980: Foams
55. ~ 1980: Polyether urethane foams
56. ~ 1993: Vacuum-assisted closure wound therapy
57. 1997: Topical growth factors
58. 1998: Tissue engineered skin
59. 2001: Matrix- metalloproteinase modulators
60. Gene therapy

anti-stringent; *Symphytum officinale* — allantoine, antibacterial) (8, 9) (see Table 1). Seaweed, which contains iodine, was used for sunburns (10).

Greek medical practice greatly resembled the Egyptian approach with a few key exceptions. An important change was the shift toward promoting pus instead of preventing inflammation. Another change in wound management was introduced by Hippocrates (460 BC–377 BC) who advocated the concept of dry wound therapy (11) to promote healing by first intention and emphasized careful observation of the patient, the recuperative powers of nature, and a high standard of ethical conduct as incorporated into the Hippocratic Oath. Although questioned by many great inventors, dry wound therapy and stimulating the formation of "laudable pus" (pus bonum et laudable) remained the therapy of choice far into the 19th century (12).

The Roman era produced the first science-based medical manuscript (*De Medicina*), written by Celsus (13) (25 BC–50 AD). He described the four fundamental signs of infection — rubor, calor, dolor, tumor — which are still used today. Furthermore, Celsus addressed the importance of thorough wound cleansing: "Clean the wound of old blood because this can cause infection and change into pus, which inhibits wound healing". Despite these astute observations, the "laudable pus" and "dry wound" strategy did not change during the following millennium.

Middle Ages until 18th century

Wound debridement (*remove a bridle*, originally meaning wound incision) was reintroduced around the 16th century (14). After debridement, wounds were treated with red-hot iron pokes, cleaned with boiling oil, and covered with suppuration-provoking substances. Paré (1509–1590) condemned the treatment of wounds with hot oil after serendipitously experiencing the positive effect of a mixture of egg yolk, oil of roses, and turpentine on wound healing (4). Paré also reinvented ligation of vessels and in the battle of St. Quentin (1557) he observed and recorded that maggots frequently infested suppurating wounds; unfortunately, this observation did not result in a new treatment modality. Many of Paré's published works provide cutting-edge insights regarding nutrition, pain, and debridement, as well as psychological counsel for wounded persons — advanced thoughts, considering the time (15). Silver nitrate was invented and used in the treatment of skin ulcers, compound fractures, and suppurating wounds (draining pus) (16). From the 17th and 18th centuries forward, anatomists and scientists offered a number of good ideas; however, they were chastised by their colleagues.

18th century toward the present

Cells

The invention of the microscope in the 17th century and the findings of Leeuwenhoek (1632–1723) (protozoa and animalcules) and Malpighi (1628–1694) (epidermal structure) did not facilitate progress in wound healing treatments until a century later when scientists began to focus on the more fundamental cellular level. In 1839, Schleiden and Schwann formulated the so-called "Cell Theory" based on their microscope findings. In 1858, Virchow (1821–1902) discussed his ideas on the formation, proliferation, and regeneration of cells. Understanding of tissue and cell culturing leaped forward when Carrel (among others including Harrison, Jolly, and Burrows), introduced *in vitro* technology, cultivating adult tissue and organs outside the body (17). Reverdin (1842–1929) achieved a clinical breakthrough when small graft islets were placed onto wounds, a process he called "epidermal grafting" (18). Skin grafts became the first widely used form of tissue engineering, progressing from autografts in animal and human subjects to allografting tissue from one person to another (19,20). At the end of the 19th century, the first tissues were cultured using skin placed in a culture medium derived from ascites and preserved at room temperature until re-transplanted several days to months later (21). Interestingly, the researcher thought it represented the beginning of over-the-counter products for wound therapy. However, another 100 years elapsed before these ideas were developed further.

Antisepsis/asepsis

In the same period, another group of researchers focused more on the interaction of cells and the animalcules. Semmelweis (1818–1865), Pasteur (1822–1895), and Koch (1843–1910) provided evidence about the relationship between germs and disease. Pasteur's studies on contamination of wine and beer by airborne yeast clearly stimulated certain investigators to recognize that these "diseases" were due to the invasion of foreign micro-organisms. In England, Lister (1827–1912), impressed by Pasteur's work, began to systematically sterilize his instruments and bandages and sprayed phenol solutions in his operative field (22) (see Table 1). He came upon this idea when a chemist friend explained how he had solved the problem of putrefaction odors of the public water system in Carlisle, Scotland for that city's local council (23). Mortality rates associated with surgical procedures decreased significantly from 45% to 15% after using carbolic acid as a spray in operating theatres (1, 23). However, Lister encountered great resistance and hesitance because a clear connection between micro-organisms and disease had not yet been established.

The demands of war

During wartime, surgeons, once-hesitant to institute the practice, returned to using full-strength phenol to address complications in patients developing gangrene due to invasive

infections (12). Use of hydrogen peroxide, another popular antiseptic, declined after reports of air emboli formation; Carrel (1873–1944) introduced a method that required extensive opening of the wound followed by bathing the wounded area with Dakin's solution (sodium hypochlorite combined with boric acid) (24). One month before the introduction of Dakin's solution, Smith introduced Edinburgh University Solution of Lime (EUSOL), which Dakin criticized as being toxic at any dilution. Iodine, first described by Davis in 1839, was used during the American Civil War (1863) and World War I to treat wounds and scrub hands before surgery (25). Interestingly, iodine had been used during Napoleon's Egyptian campaign (1798–1801) — soldiers were treated with high concentrations of iodine as found in extracts of seaweed and other marine plants (10) (see Table 1).

At the turn of the century, Halsted (1852–1922) advocated the use of silver foil dressings as an antiseptic for infected wounds (26). These dressings were used extensively until just after World War II (16,27). Chlorhexidine was discovered in 1946 and introduced into clinical practice in 1954, predominately as an antiseptic for washing hands and as a surgical scrub (28). However, its application in wounds has been limited largely to irrigation. Acetic acid was used in wounds infected with Gram-positive and Gram-negative bacteria (eg, *Pseudomonas aeruginosa*) (24) a remnant of the ancient wine-and-vinegar cleansing strategy. Additional antiseptics used included boric acid, alcohol, hexachlorophene, thimerosal, gentian violet, and permanganate (see Table 1). Concern regarding the possible side effects was tempered by the sheer number of wounded soldiers. After the war, medical personnel heeded the *in vitro* research that indicated these agents were cytotoxic to human cells and many appeared to have an adverse effect on wound healing — thus, clinicians were increasingly reluctant to use many of these antiseptics (29-31). The discussion on the toxicity of these agents, started in 1914 by Fleming, still continues today, almost 100 years later.

Antibiotics/antimicrobials

Fleming's discovery of penicillin (1928) and the development of oral antibiotics (1940) that provided potent and pathogen-specific antimicrobial agents revolutionized clinical therapy and marked the demise of many former remedies. Topical application of antibiotic ointments increased, especially in burn care. However, after the emergence of antibiotic-resistant strains of pathogens, alternative treatments became imperative (32) In 1949, iodophores (povidone iodine and cadexomer iodine, also known as slow-release antiseptics) were developed and proved to be safer and less painful to use than the early iodine products that caused irritation and skin discoloration, as well as pain (10,24,33) In 1968, Fox (34) introduced another slow-release antiseptic, silver sulfadiazine (SSD), which combines the antiseptic properties of silver and sulfonamide to provide a broader-spectrum and safer antibiotic. Initially, silver nitrate was used. Although complications such as discoloration and irritation of the skin and possible toxicity reduced silver's popularity, SSD and silver-releasing dressings remained in use (4). Various and emerging silver-coated dressings use metallic silver, inorganic silver

compounds, or organic complexes as their source of silver combined with dressing components such as polyurethane, alginates, carboxymethyl cellulose, knitted fabrics, and activated charcoal (5) (see Table 1).

The age-old use of honey, sugar, and maggots was re-introduced. All were popular throughout the centuries but remained in the background after the introduction of antibiotics. Several studies reported the three-fold benefits of honey on wounds: antibacterial (and deodorizing), debriding, and promotion of wound healing. The enzymatic action of glucose-oxidase on glucose and molecular oxygen leads to the production of hydrogen peroxide and gluconolacton, which have an antibacterial effect (35-42) (see Table 1). The effectiveness of honey as an antimicrobial agent varies according to factors such as floral origin, viscosity, and geographic location. Currently, various wound treatments are commercially available in tubes, impregnated dressings, or as components in innovative dressings (honey and alginate). Sugar in powder form is used in traditional medicine in Brazil where sugar production is high (43); several case studies describe the use of sugar in modern medicine (44). However, until today, sugar has not received a place in the standard wound management.

In 1829, Napoleon's surgeon-in-chief, Baron Larrey, reported that when maggots were found in battle injuries, they prevented the development of infection and accelerated healing (45). Zacharias, a confederate medical officer (surgeon) during the American civil war (1861–1865) was the first Western physician to intentionally introduce maggots into wounds (46). The benefits of maggot therapy on wounds have been found to be three-fold: debridement (elimination) of necrotic tissue, microbial killing, and stimulation of granulation tissue (46-50) (see Table 1). Today, the bio-industry is flourishing and produces sterile larvae, primarily of the common green bottle fly *Lucilia sericata*.

Moist wound healing

Understanding of asepsis and antisepsis was an important step in wound healing. However, the paradigm of dry wound healing or exposing the wound to air remained part of many treatments. One exception was reported in the early 19th century, when good healing results in burns were achieved by immersing the wound in water. However, this concept was not accepted as a standard of care. Little progress was made in this area (with the exception of the invention of tulle gras and paraffin-impregnated gauze in 1914) until the 1960s when studies compared dry and moist wound healing. Winter's historical study (1962) demonstrated that partial-thickness wounds in domestic pigs re-epithelialized more rapidly under occlusive dressings (51); the same result was reported *in vivo* in humans 1 year later (52). The basic concept behind moist wound healing is that the presence of exudate (*ex* + *sudare*, to sweat) in a wound will provide an environment that stimulates healing through the delivery to the wound of a range of cells and cytokines necessary for wound repair. These findings eventually led to the development of three generations of occlusive dressings. The first generation comprised impermeable foils without adhesive layer, described in a study by Garb (53) in

1960; such dressings allow exudate to accumulate beneath the dressing, causing the foil to swim off the wound. The second generation of foils, semi-permeable polyurethane films with an adhesive layer, were introduced in the 1970s (see Table 1). The third-generation foils (hydrophilic polyurethane films, polyether urethane) had an even higher permeability so the adhesive layer, which could destroy the newly formed epithelium, became redundant (54).

Hydrocolloids, initially manufactured for the preservation of fruits (reducing moisture loss and surface wounding), were introduced into clinical practice in the 1980s (55). According to product descriptions and the experience of wound care providers, hydrocolloids are designed for use in partial- and full-thickness wounds with or without necrotic tissue and have been found to be especially useful on areas such as heels and sacral ulcers that require contouring (see Table 1).

Foam dressings were developed during the 1980s as an alternative to hydrocolloids and are designed to protect and to absorb fluid without product breakdown but they require fixation. Foam dressings may be impregnated or layered in combination with other materials and are indicated for partial- and full-thickness wounds (see Table 1). Around the same period, hydrogels (amorphous formulations of water, polymers and other ingredients) were introduced. They are designed to provide moisture to a dry wound and are indicated for partial- and full-thickness wounds, wounds with necrosis, minor burns, and radiation tissue damage. The high moisture content serves to re-hydrate wound tissue (see Table 1).

Alginates, the next innovation in the treatment of exuding wounds, were designed to absorb exudate and provide calcium to the wound area. When alginates come in contact with wound exudate, they form a biocompatible gel that provides a moist healing environment (see Table 1). Although the products may be relatively new, the idea and basics behind alginates have a long history. In 1881, Stanford, a chemist working on brown algae, discovered alginic acid, a new group of seaweed-derived chemicals (56). After World War II, Blaine, an army major, investigated tissue reactions to alginates. He discovered that alginates had the above-mentioned properties. More recently (2007), a review (57) of the literature on the efficacy of modern dressings in healing chronic and acute wounds by secondary intention was conducted. The review included 99 studies — 89 randomized controlled trials (RCTs), three meta-analyses (one came from one of the selected systematic reviews), seven systematic reviews, and one cost-effectiveness study. The authors concluded that hydrocolloid dressings are superior to saline gauze or paraffin gauze dressings for the complete healing of chronic wounds and that alginates were better than other modern dressings for debriding necrotic wounds. Hydrofiber and foam dressings, when compared with other traditional dressings or a silver-coated dressing respectively, reduced time to healing in acute wounds (57,58).

Present and future

Recently, more than a century after the first description of the fundamental cellular world, tremendous progress has been made in exploring the cellular and molecular mechanisms responsible for wound healing. Research on chronic wounds emphasized that not one but numerous factors (ie, deficiencies in local and systemic growth factors, changes in extracellular matrix [ECM], diminished fibroblast function, decreased antimicrobial activity of leukocytes, biofilms, and disturbance of macro- and microcirculation) are responsible for slowing down healing in chronic wounds (59,60). These findings triggered the pharmaceutical industry to develop products that tackle specific aspects of these processes; thereby, narrowing their therapeutic spectrum.

Growth factors

Topical gels containing growth factors were introduced in the early 1980s after clinical studies demonstrated a possible beneficial effect of autologous platelet-derived growth factors (PDGF) (61). Further development of these gels resulted in the first commercially available product containing recombinant human PDGF (rhPDGF) in 1997 (62). US Food and Drug Administration (FDA) approval was based on several RCTs (63-65) in which rhPGDF healed more wounds by week 20 of care than the placebo gel/standard care. Currently, the FDA notes evidence of an increased risk of death from cancer in patients who had repeated treatments but because of known risks associated with diabetic foot and leg ulcers that do not heal, potential risk should be weighed against benefit for each individual patient (66).

Gene therapy using adenoviral vectors that transiently express PDGF also were tested as a therapeutic modality for treating difficult-to-heal wounds (67). Because high doses of growth factors were necessary to achieve minor healing effect, it was assumed that endogenous proteolytic enzymes probably degrade exogenously applied growth factors.

This led to the development of matrix metalloproteinase (MMP)-modulating products that reduce proteolytic enzymes by physically entrapping and mechanically inhibiting their activity. Although these modern categories can not be seen as a panacea, positive results with rhPDGF were reported in neuropathic diabetic ulcers (68) and in venous leg ulcers with an ECM-modulating product (69). However, it must be noted that efficacy of these treatments was measured by specialized wound care personnel under tightly controlled conditions. The conditions for their use are often not ideal when these therapies are used in routine practice.

Tissue engineering/skin substitutes

The term *tissue engineering* was coined at a National Science Foundation meeting in 1987 (70). It had taken a long route from the late 19th century. Skin substitutes can be categorized into three groups: temporary, semipermanent, and permanent. Temporary skin substitutes are placed on either a partial- or full-thickness wound and remain until the wound is healed.

Semipermanent material remains attached to an excised wound and is eventually replaced by autologous skin grafts. Permanent skin substitutes incorporate an epidermal or dermal component, are designed to replace autologous skin grafts, and can be categorized as acellular/synthetic bilaminates, collagen-based composites, and culture-derived tissue. In 1998, the first tissue-engineered skin consisting of a bilayered construct of neonatal foreskin fibroblasts, keratinocytes, and bovine collagen gained FDA approval (70,71) and was shown to improve healing of venous stasis, diabetic (72), and arterial insufficiency wounds (73) in studies comparing its use with local wound care consisting of gauze with saline solution. No comparison has been made between the use of tissue-engineered and autologous skin graft treatment. Recent research (74) has examined genetically modified epidermal cells that can be used to engineer three-dimensional skin substitutes, which when transplanted, can act as *in vivo* "bioreactors" for local or systemic delivery of therapeutical proteins.

Stem cells

Research also is investigating the differential capacities of stem cells and how to influence and enhance their capabilities. This is facilitating development of scaffolds and stem cell markers (75).

Wound bed preparation

In 2000, renewed interest in wound debridement led to introduction of *wound bed preparation*, a term coined at a meeting of the European Tissue Repair Society (76). Wound bed preparation infers a more prolonged maintenance debridement phase along with the correction of the biological micro-environment (77) — the focus shifting from application of sophisticated dressings. Many agents can be used to facilitate debridement — from saline soaks to maggots and dressings that enhance wound autolysis (see Table 1). However, surgical debridement should be performed first if possible (78) unfortunately, the lack of suitable equipment and fear of removing healthy tissue are common reasons for abandoning this technique and turning to alternative methods. Also, sharp debridement can be performed only by physicians or specially trained registered nurses (of whom there are few). The initial debridement of a chronic wound often temporarily speeds up wound healing but may be followed by a healing arrest, eventually returning the wound to its poor pre-therapy state (79). Explanations for this negative spiral address the phenotypically abnormal fibroblasts that seem to exist in chronic wounds (80), the degenerative wound fluid that blocks or slows down the proliferation of cells, and biofilms of organized bacterial communities that thwart successful healing if not eliminated. In order to heal the wound, repeated removal of detrimental factors (after addressing and correcting underlying pathology) should precede implementation of improved wound care products and/or devices. To date, terms such as wound bed preparation and their affiliated meanings remain untested concepts/theories.

Biophysical stimulation

Other newer technologies thought to support biological pathways involved in tissue repair comprise biophysical stimulation such as vacuum-assisted wound closure, hyperbaric oxygen (HBO), and pulsed electromagnetic fields (81-83) (see Table 1).

Negative pressure. Draining wounds after surgery is a long-established surgical practice made more feasible with the introduction of suction drainage and later the evacuation glass bottle (84). A series of five articles, the "Kremlin papers" (85), was published in the Russian literature in the 1980s. Negative pressure (-75 mm Hg to -80 mm Hg) was used in combination with aggressive debridement to significantly reduce bacterial counts in purulent wounds (86). In 1989, Chariker et al. (87) discussed their experience utilizing topical negative pressure (TNP) in seven patients with incisional or cutaneous fistulae. A moist gauze was placed over the wound surface and a flat drain placed over the gauze and covered with a bio-occlusive dressing. The drain was connected to an existing vacuum line such as a standard hospital wall suction source with continuous pressure set at approximately -60 mm Hg to -80 mm Hg. This method became known as the Chariker-Jeter technique. In the early 1990s, suction drainage using Redon-drainage tubes combined with foam dressings as the interface was proposed as a new therapeutic concept to achieve wound healing (88-90). In 1993, a commercially available vacuum-assisted closure device (the V.A.C.® Therapy System, KCI, San Antonio, TX) was introduced by Argenta and Morykwas; its efficacy was validated through several animal models using -125 mm Hg pressure (82,83). Additional medical manufacturers/suppliers provided TNP systems, including the patented Versatile 1™ Wound Vacuum System using the Chariker-Jeter (8) approach (Blue Sky Medical Group Inc, Carlsbad, CA). The most important difference between the two negative pressure systems is in the interface used (polyurethane/-and polyvinylalcohol foam versus gauze, respectively). Topical negative pressure therapy removes wound exudate by active suction, changes the bacterial environment (81), and indirectly manages the micro- and macro environment of the wound by increasing circulation/oxygenation. Experimental studies, clinical experience, and the latest RCTs have shown enhanced granulation tissue formation (91) and wound bed preparation (92); increased wound area reduction (81,91); increased cell division, possibly induced by increased tension (93); decreased local and interstitial tissue edema and increased perfusion of the (peri-) wound area (94); and a significant modulation of bacterial species (81). At the recent Third World Union of Wound Healing Societies' (WUWHS) meeting, a consensus document of best practice was presented for use of vacuum-assisted wound closure (95). This document, prepared by a working group of experts, included recommendations based on several large retrospective and cohort studies and seven RCTs, as well as several smaller studies.

Positive pressure. Wound environment also may be changed by positive pressure (HBO). Generally, wounds with increased oxygen tension at the wound site following HBO may benefit from this therapy; however, it is still debated if evidence is sufficient to support HBO

use in larger populations (96, 97). Further research is needed to clarify the exact mechanism of this treatment (98, 99) (Table 1).

Other adjunctive therapies

Findings of transcutaneous voltage differences between skin surface and deeper skin layers (100) have resulted in the development and use of several devices that manipulate current to stimulate wound healing. Direct current, low-frequency pulsed current, high-voltage pulsed current, bio-electrical stimulation (101), and pulsed electromagnetic fields (102) have been used with varying degree of success. Other adjunctive devices still under evaluation include infrared heat lamps, noncontact radiant therapy, radiant therapy, laser photostimulation, light therapy, ultrasound (103), and intermittent pneumatic compression.

Despite recent advances in wound care, the challenge of managing chronic wounds remains compounded by a lack of consensus on clearly defined wound care principles. Many organizations have developed guidelines for the assessment and treatment of wounds (Table 2). These groups often examine the available literature and compile the findings into a set

Table 2. Overview of recent evidence based guidelines

Guideline	Source
AAWC Conceptual Framework of Quality Systems for Wound Care, AAWC Content-Validated Venous Ulcer Guideline	www.o-wm.com/article/6393
The Association for the Advancement of Wound Care: Summary algorithm for venous ulcer care with annotations of available evidence.	www.guidelines.gov
The Wound Ostomy and Continence Nurses Association: Guideline for management of wounds in patients with lower-extremity venous disease.	www.guidelines.gov
The Wound Ostomy and Continence Nurses Association: Guideline for prevention and management of pressure ulcers	www.guidelines.gov
Paralyzed Veterans of America: Pressure ulcer prevention and treatment following spinal cord injury	www.guidelines.gov
Best Practice Statement: Care for the Older Person's Skin Minimising Trauma and Pain in Wound Management Compression Hosiery	www.wounds-uk.com
Wound Healing Society Prevention Guideline	*Wound repair regen 2008*, 16(2)
1. Guidelines for the prevention of venous ulcers	Page 147-150
2. Guidelines for the prevention of pressure ulcers	Page 151-168
3. Guidelines for the prevention of diabetic ulcers	Page 169-174
4. Guidelines for the prevention of lower extremity arterial ulcers	Page 175-188
Wound Healing Society Clinical Treatment Guidelines	*Wound repair regen 2006*, 14 (2)
1. Guidelines for the treatment of venous ulcers	Page 649-662
2. Guidelines for treatment of pressure ulcers	Page 663-679
3. Guidelines for the treatment of diabetic ulcers	Page 680-692
4. Guidelines for the treatment of arterial insufficiency ulcers	Page 693-670
Registered Nurses of Ontario: Risk Assessment and Prevention of Pressure Ulcers	www.rnao.org/bestpractices
Pressure Ulcer Prevention: National Guideline Clearinghouse (NGC) Guideline Synthesis	www.guideline.gov
Nursing Standard of Practice Protocol: Pressure Ulcer Prevention & Skin Tear Prevention	www.consulgerirn.org/topics
SOLUTIONS® wound care algorithm	www.guidelines.gov

of guidelines. Because few guidelines have been validated, not every hospital follows the same protocol. Each patient must be comprehensively assessed and treatment plans must be individualized.

Conclusions

In the last two decades, enhanced understanding of the biology of wound healing and technological improvements have led to numerous improvements in wound care. Although clinicians have outgrown the ancient way of decision-making that was based on empirical and magical beliefs, old habits never die. Many healthcare professionals continue to treat and dress wounds according to age-old practices, despite the fact that new research shows this may not be the best treatment modality for the patient. The choice of therapy still depends largely on high-quality marketing, expert opinion, and gut feeling rather than on scientific evidence.

Because evidence-based medicine has become the new paradigm, the number of international guidelines for the assessment and treatment of wounds has slowly increased. Some of the components of these guidelines are somewhat limited by lack of Level A support but this situation should improve as more rigorous studies are conducted to address existing research gaps. Evidence-based medicine represents the integration of best research results with clinical expertise and patient values. In other words, without diminishing the importance of the opinion of experts in the field, more solid and large RCTs comparing old to new standards of care are needed. In addition, healthcare workers must be aware of the persuasive power of their industrial partners and products. More training on product specifications, proper use, and the need for a broad biopsychosocial patient approach is warranted. The medical doctor and his companion in battle — the qualified, registered wound nurse — should be alert to withstand the Siren's song of industry and address the patient's interest first.

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CHAPTER III

Comparing conventional gauze therapy to vacuum-assisted closure wound therapy: A prospective randomised trial

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In this manuscript the term Vacuum-assisted closure wound therapy (in short VAC or Vacuum therapy) is used. After introduction of other negative pressure devices besides the V.A.C. device, we have decided to use the general nomenclature: Topical negative pressure therapy (TNP).

Abstract

Background: Vacuum-assisted closure wound therapy (vacuum therapy) has been used in our department since 1997 as a tool to bridge the period between debridement and definite surgical closure in full thickness wounds. We performed a prospective randomised clinical trial to compare the efficacy of vacuum therapy to conventional moist gauze therapy in this stage of wound treatment.

Methods: Treatment efficacy was assessed by semi-quantitative scoring of the wound conditions (signs of rubor, calor, exudate production and fibrinous slough/necrotic tissue) and by wound surface area measurements. Tissue biopsies were performed to quantify the bacterial load. Besides this, the duration until 'ready for surgical therapy' and complications encountered during therapy and postoperatively were recorded.

Results: Fifty-four wounds were included (vacuum n=29, conventional n=25). With vacuum therapy healthier wound conditions were observed. Furthermore, a tendency towards a shorter duration of therapy was found, which was most prominent in late-treated wounds. In addition, the wound surface area reduced significantly faster with vacuum therapy. Surprisingly, these results were obtained without a decrease in the number of bacteria colonising the wound. Complications were minor, except for one case of septicaemia and one case of increased tissue necrosis, which compelled us to stop vacuum therapy.

Conclusions: For the treatment of full-thickness wounds, vacuum therapy has proven to be a valid wound healing modality.

Introduction

Wounds of patients in need of reconstructive surgery are frequently large with extensive soft tissue loss caused by degloving injuries, infection, dehiscence, donorsite defects after reconstruction of invasive tumours, or full-thickness ulceration in pressure sores. These situations leave patients in debilitating circumstances with wounds that entail labour-intensive treatment. Direct reconstruction after admission to the hospital is, in most of these cases, not possible due to the condition of the patient and/or the extensiveness of the wounds. The first stage is to optimise the condition of the wound through aggressive debridement in order to remove necrotic tissue, foreign material and infecting bacteria (1, 2). Following this, treatment consists of topical dressing applications until the wound shows healthy, vascularized tissue. Choice of therapy during this period is mainly based on the physicians' and nurses' experience with certain products and their initiative to try new modalities. One of the more recent modalities is vacuum-assisted closure wound therapy, in short vacuum therapy. Drainage of wounds after surgery is a long established surgical practice since the introduction of suction drainage and later the evacuated glass bottle (3). However, it was not until the early 1990s that suction drainage, using Redon-drainage tubes combined with foam dressings, was proposed as a new therapeutic concept to achieve wound healing (4-6). In the same period a commercially available vacuum-assisted closure device was introduced by Argenta and Morykwas, of which the efficacy was validated through several animal models (7). Treatment of a diversity of chronic and acute wounds using this device followed, and promising clinical results were described (8-14). Unfortunately, nearly all of the studies were either case reports or non-randomised trials. As reviewed by Evans and Land (15) the results of the few clinical prospective randomised trials published, must be interpreted with extreme caution because of their methodological limitations (16, 17). Other published studies were of limited value because they were either interim analysis (18) or performed in a very small group of patients (19, 20).

The aim of our study was to evaluate the use of vacuum therapy in the treatment of acute (early treated) and chronic (late treated) full-thickness wounds. We initiated a prospective randomised clinical trial comparing vacuum therapy to the standard conventional moist gauze therapy, focusing on visual aspects, duration of healing, wound surface area, bacterial load and complications encountered.

Materials and methods

From July 1998 through October 2002, patients with a full-thickness wound that could not be closed immediately because of severely crushed tissue, infection or chronic character were included in the study after obtaining written consent. Malignant disease, superficial

bare blood vessels, deep fistulae, necrotic tissue, an unstable skin around the wound, sepsis, untreated osteomyelitis, active bleeding, uncontrolled diabetes and psychiatric disorders were considered as exclusion criteria. Wounds were sub-divided as early-treated wounds, existing less than 4 weeks prior to therapy and late-treated wounds (>4 weeks). Randomisation was performed through closed envelope assignment. Before start of the study, a power calculation was performed to determine the required sample size.

Conventional treatment consisted of standard moist gauze therapy, at least two times a day, saturated in either 0.9% saline solution, 0.2% nitrofuralam (Furacine®), 1% acetic acid solution or 2% sodium hypochlorite (Eusol). Vacuum therapy consisted of a polyurethane foam dressing with a pore size of 400-600 µm (V.A.C. ® Pack Dressing) and a continuous negative pressure of 125 mm Hg using the V.A.C. ® Classic (KCI, Houten, the Netherlands) (7). Foam dressings were changed every 48 h. All wounds were inspected every 48 h. Before start of therapy and during treatment, sharp surgical debridement of necrotic tissue took place when considered clinically needed. During both therapies, all patients were encouraged to remain as active as possible. Patients who were compelled to bed received special pressure relieving mattresses according to hospital guidelines. Nutritional status was checked and oral supplemental nutrition was given when necessary. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the Medical Ethics Committee of the Erasmus University Medical Centre.

Semi-quantitative scoring of the general wound conditions for the amount of rubor, calor, exudate production and fibrinous slough/necrotic tissue on a scale of zero to three, corresponding to none, mild, moderate or severe assessed treatment efficacy. The total score of these parameters was recorded and compared to initial values at day one. Wound surface area measurements were performed after debridement and during therapy by tracing the edge of the wound onto clear polyethylene film, covering the entire wound surface (21). After photocopying the tracing onto paper, the wound surface areas were scanned (AGFA duoscan T1200) and calculated (Adobe PhotoShop). The end-date of the trial was reached when the wound was assigned 'ready for surgical therapy' based on the above mentioned clinical wound evaluation in combination with the formation of healthy, granulating tissue.

After removing surface exudate with a sterile saline solution, tissue biopsies were performed using a scalpel removing tissue from the centre of the wound. The biopsies were taken every two to three days from the beginning of the treatment until the end of the therapy. The biopsies were sent directly to the laboratory to be weighed, homogenised, diluted and plated. The plates were cultured under both aerobe and anaerobe conditions. The total number of colony forming units (CFU) per disk were counted and calculated per gram of tissue. The data are recorded as the log of the number of CFU/gram of tissue and calculated at three different time points (i.e. (1) start of therapy; consistent with the first day after debridement, (2) ' ready for surgical therapy' and (3) the final biopsy at the end of follow-up). Bacterial count is expressed as median ± standard deviation (SD). Biopsies were processed blinded and

evaluated by a medical microbiologist. Results of the tissue biopsies were not revealed to the researchers until the end of the study.

Statistical analysis

The non-parametric Mann-Whitney U-test was used to statistically analyse differences in wound conditions within each therapy group. Wound surface area measurements were analysed by linear regression, calculating the average slope of these regression lines per treatment group. To assess if this was statistically significant within a group, Student's one-sample t-test was used. To compare between the treatment groups, Student's two-sample t-test was employed. The results of wound surface area reduction measurements are expressed after back transforming the average reduction by taking the antilog. Wound surface area reduction is expressed as mean ± standard error of the mean (SEM). The proportions of wounds 'ready for surgical therapy' were analysed using the Kaplan-Meier curve method. The null hypothesis of no difference between two treatments was tested with the Log Rank test. Patients were censored when 'ready for surgical therapy' was not reached within 30 days or when therapy was terminated before 30 days. Duration until ready for surgical therapy' is expressed as median ± SEM.

Results

Fifty-four wounds were enrolled in this study. Twenty-nine wounds were treated with vacuum therapy (12 early treated, 17 late treated) and 25 with conventional therapy (8 early treated, 17 late treated). In the vacuum-treated group 3 patients did not reach the end of the trial (defined as 'ready for surgical therapy') and therapy was stopped because of sepsis with unknown origin in one (Table 1, patient 22), lost to follow-up due to transfer to a nursing home in another (patient 23), and ischaemic pain with increased tissue necrosis in a third patient (patient 27). In the conventionally treated group, two patients did not reach the end of the trial, because of passage of the maximum follow-up limit of 30 days in one (patient 1), and refusal of further co-operation in the other (patient 13).

Prior to therapy, surgical debridement was performed in 28 out of 29 vacuum-treated wounds (97%), and in 22 out of 25 conventionally treated wounds (88%). In 4 vacuum-treated wounds, and in 3 conventionally treated wounds a second surgical debridement at the bedside had to take place. At one or more time-points during therapy, chemical debridement using sodium hypochlorite was clinically indicated in 20 out of 25 conventionally treated wounds (80%). Besides this, topical antimicrobial treatment was used at one or more occasions in 11 out of 25 conventionally treated wounds (44%).

Table 1. Demographic features and clinical data

Vacuum therapy								Conventional therapy							
no	Age	Type of wound	Stratified	A	C	Concomitant disorders	Post operative complication	no	Age	Type of wound	Stratified	A	C	Concomitant disorders	Post operative complication
1	31	Infection	early	-	-	DM I	-	2	70	Infection	early	-	+	KT	-
4	37	Infection	early	-	-	-	-	8	54	Infection	early	-	-	-	-
10	40	Infection	early	+	-	-	+	19	42	Infection	early	-	-	-	-
11	17	Infection	early	-	-	-	-	21	42	Infection	early	-	-	-	+
16	78	Infection	early	-	-	-	-	22	63	Infection	early	+	-	-	n.o
24	70	Infection	early	+	-	DM I	-	5	46	Dehiscent	early	+	-	Alcohol abuse	+
25	47	Infection	early	-	-	-	-	12	38	Dehiscent	early	+	-	-	+
28	39	Infection	early	-	-	-	-	15	52	Dehiscent	early	+	-	-	+
8	46	Dehiscent	early	+	-	Alcohol abuse	-	10	17	Infection	late	-	-	-	+
9	47	Dehiscent	early	-	-	-	+	24	46	Infection	late	+	-	Vasc	-
14	41	Trauma	early	-	-	-	-	7	66	CW	late	-	-	OM	-
21	17	Trauma	early	+	-	-	-	14	27	CW	late	+	-	Spinal cord lesion, OM	-
3	59	Infection	late	-	-	DM II, Vasc	-	20	38	CW	late	-	-	-	+
13	39	Infection	late	-	-	Sickle cell	+	1	58	PU	late	-	+	RA	n.o/stopped
5	17	CW	late	+	-	M. Crohn, OM	+	3	51	PU	late	+	+	RA	-
7	32	CW	late	+	-	OM	-	4	32	PU	late	+	-	Vasc	+
15	23	CW	late	-	-	Former operated area	+	6	45	PU	late	+	-	Former operated area	-
18	41	CW	late	+	-	OM	+	9	55	PU	late	+	-	Spinal cord lesion, OM	+
19	70	CW	late	-	-	DM I, Vasc, OM	n.o	11	27	PU	late	-	-	Spinal cord lesion	n.o.
20	43	CW	late	-	-	Former operated area	-	13	35	PU	late	-	-	Former operated area	n.o./stopped
29	53	CW	late	+	-	OM	-	16	17	PU	late	-	-	Spinal cord lesion	-
2	51	PU	late	+	+	RA	-	17	82	PU	late	+	-	Bedridden	-
6	79	PU	late	+	-	Vasculitis, OM	+	18	71	PU	late	+	+	Immunologic disorder	-
12	70	PU	late	-	-	Vasc	-	23	70	PU	late	+	-	DM I, vasc	+
22	59	PU	late	+	-	DM I, Vasc, KS	n.o./stopped	25	53	PU	late	+	-	Spinal cord lesion, OM	-
17	21	PU	late	-	-	Former operated area	-								
23	81	PU	late	+	-	Vasc, OM	n.o./stopped								
26	73	PU	late	+	-	DM II, Vasc, OM	+								
27	62	PU	late	-	+	Vasc, RF	†								
				13	2	DM:6 / Vasc: 8 / OM:8						14	4	DM:1 / Vasc:3 / OM: 4 spinal cord lesion:5	

DM I/II= Diabetes Mellitus Type I / II, Vasc = Vascular compromised, OM= Osteomyelitis, M. Crohn = Morbus Crohn, CW= Chronic Wound, PU = Pressure Ulcer , RA= Rheumatoid arthritis, KS= Karposi Sarcoma, RF= Renal Failure, † died, KT = Kidney transplant, A = Antibiotics, C =corticosteroids, n.o. = no operation.

At every dressing change, wound conditions were visually scored for amount of rubor, calor, exudate production and fibrinous slough and recorded as the cumulative score. In both treatment groups, the cumulative score of these parameters significantly decreased compared to initial values at day 1 except for days 6 and 8 in conventional therapy (Table 2). The cumulative scores were on average lower in the vacuum-treated group compared to the conventionally treated group, reaching significance on day 3, 6 and 8. Vacuum therapy seemed to be most effective in improving the wound conditions of late-treated wounds, showing a quick and steady improvement, opposed to the early-treated wounds which showed a more irregular pattern (Table 2). However, the subgroups were too small for statistical analysis. In general, the most prominent decrease was the amount of rubor and fibrinous slough, which reduced more in vacuum-treated wounds compared to conventionally treated wounds (data not shown).

Table 2. Relative wound score of all-, early-, and late treated wounds with vacuum or conventional therapy

Treatment	All wounds		Early treated		Late treated	
(day)	vacuum	conventional	vacuum	conventional	vacuum	conventional
1	100	100	100	100	100	100
3	30 *	62	29	77	32	50
4	25	57	58	-	11	58
5	20	49	10	55	29	45
6	32 *	110	38	116	25	90
7	18	42	13	53	26	40
8	26 *	69	25	56	28	78
9	13	40	3	-	21	40
10	26	57	39	49	12	62

The relative wound score is the sum of the scores of the four parameters (rubor, calor, exudate and fibrinous slough) per patient, divided by the initial value on day one X 100. * p-value < 0.05, comparing the daily score of vacuum therapy to the corresponding day in conventional therapy.

In the vacuum-treated group, 20 patients (69%) showed a healthy, granulating wound bed within 1 week compared to 14 (56%) in the conventionally-treated group. Within the next week, 5 more patients in the vacuum group showed a clean, healthy wound bed (cumulative 86%) compared to 7 in the conventionally treated group (84%). In 1 vacuum-treated patient (3%) wound healing was slow and duration of therapy exceeded 14 days compared to 3 patients in the conventional group (12%). Based on the visual aspects in combination with the formation of granulating tissue, the surgeon decided whether a wound was 'ready for surgical therapy'. Although the visual aspects improved on average faster in the vacuum-treated group, the duration until 'ready for surgical therapy' was not statistically different (6.00 ± 0.52 days for vacuum-treated wounds compared to 7.00 ± 0.81 days for conventionally-treated wounds, respectively, $p=0.19$). A shift towards a shorter duration of therapy was noticed in late treated wounds treated with vacuum therapy (6.00 ± 0.99 days versus 10.00 ± 3.78 days, $p=0.21$) (Figure 1 A). This was less obvious in the early treated wounds (5.00 ± 0.85 days and 6.00 ± 1.37 days for vacuum and conventional therapy, respectively, $p=0.70$) (Figure 1 B).

Figure 1A

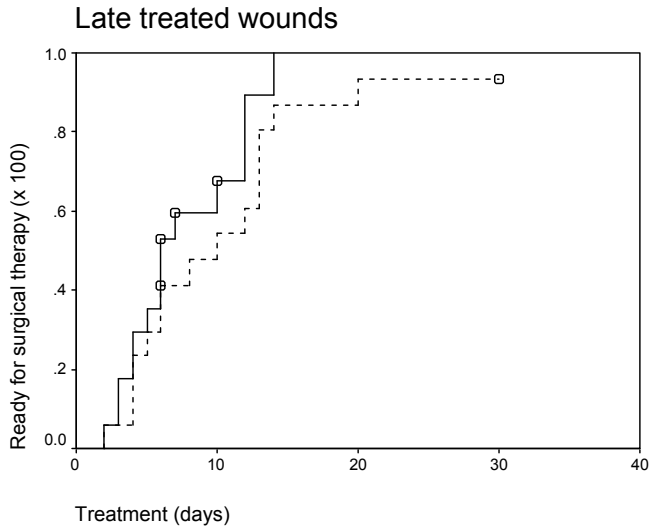

Figure 1B

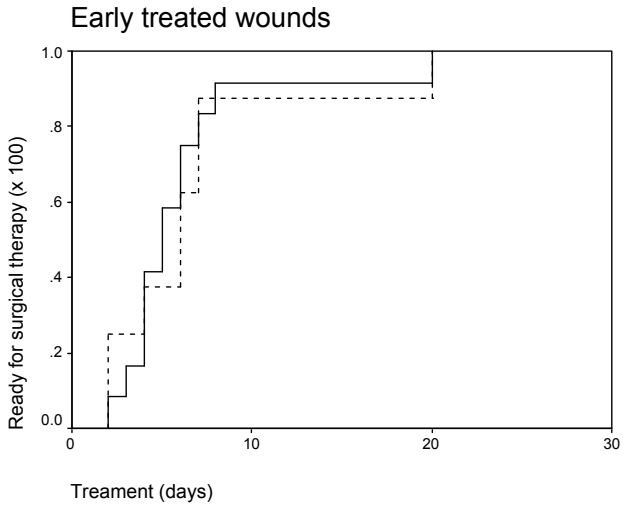

Figure 1. Kaplan-Meier cumulative survival curve. Cumulative percentage of wounds, which are 'ready for surgical therapy', depending on the number of days elapsed since beginning of therapy (Continuous line: vacuum therapy; interrupted line: conventional therapy; circles: censored patients). (A) Late-treated wounds (B) Early-treated wounds.

Wound surface area reduction was compared between 15 vacuum- and 13 conventionally treated patients. Reduction of the wound surface area was seen in 100% of the vacuum-treated patients (3.8 ± 0.5 %/day; $p<0.0001$) compared to 77% of the conventionally-treated patients (1.7 ± 0.6%/day; $p<0.05$). Both treatments gave a significant reduction in wound surface area compared to the initial wound area. However, wound surface area reduction was significantly larger in vacuum-treated wounds compared to conventionally treated wounds ($p<0.05$).

In the vacuum-treated group, two major complications (i.e. sepsis and necrosis) compelled us to terminate the therapy prematurely. This did not occur in the conventionally treated group. Minor complications encountered in the vacuum-treated group were; erosion of adjacent tissue due to increased local pressure underneath the tubing (n= 1), mild reactions of the peri-wound area (i.e. maceration and eczema) (n= 2) and sudden increase in body temperature (n= 1). In the conventionally treated group two patients experienced an allergic reaction on Furacine® and in 3 patients the wound surface area increased.

Postoperative complications were seen in 17 of 46 patients (37%) who sustained surgical closure (Table 3). In the vacuum-treated group 8 of 25 patients (32%) experienced a postoperative complication compared to nine of 21 patients (43%) in the conventionally treated group. In the vacuum-treated group, four out of eight postoperative complications were considered large (abscess (n= 2), fistula, total skin graft failure). In the conventionally treated group three out of nine postoperative complications were considered large (abscess, fistula, skin graft failure of 40%). In the vacuum-treated group, four out of eight patients with postoperative complications were diagnosed with osteomyelitis, compared to 1 in the conventionally treated group (Table 1).

Table 3. Surgical procedure and postoperative complications

TNP(n=25)			Conventional (n=21)		
No	Surgical procedure	Complications	No	Surgical procedure	Complications
2	Approximation	rest defects (n=2)	2	Approximation	rest defects (n=2)
14	Split skin graft	total graft failure (n=1)* partial loss < 20% (n=2) abscess (n=1)	11	Split skin graft	partial loss <20% (n=4) partial loss of 40% (n=1)
3	Regional flap	-	5	Regional flap	vascular problem **
6	Free flap	fistula (n=1) abscess (n=1) vascular problem **	3	Free flap	fistula (n=1) abscess (n=1)

* Split skin graft failure due to application of TNP on a non-meshed graft.

** compromised arterial perfusion not caused by the initial therapy

Seen that wound conditions improved significantly we considered that this would be reflected in a decreased bacterial load. The initial number of bacteria after debridement was approximately the same in both treatments, balancing around the level of 10^5 bacteria/g of tissue. Surprisingly, at the time point 'ready for surgical therapy' the bacterial load had not changed significantly compared to initial values. Besides this, no significant decrease of the bacterial load was found at the end of follow-up; the median bacterial count remained around the level of 10^5 bacteria per gram of tissue in both treatments (Figure 2).

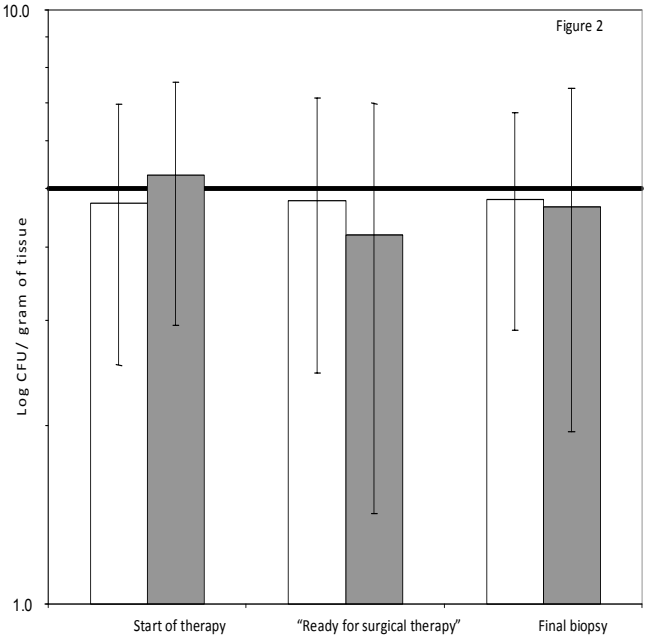

Figure 2. The total amount of bacteria, expressed as the number of CFU/g of tissue (y-axes: log scale) in biopsies of wounds treated vacuum therapy (white bars) or conventional therapy (black bars). The horizontal line represents the level of 10^5 bacteria/g of tissue. Bacterial counts are expressed as median $\pm$ sd.

Discussion

In this prospective randomised clinical trial we demonstrate that the use of vacuum therapy in an average hospital population with full thickness wounds results in improved wound healing compared to conventional moist gauze therapy. This is reflected by on average healthier wound conditions and a significant larger reduction of wound surface area compared to conventionally treated wounds. Obviously, the latter can be of major importance in plastic surgery: a smaller sized defect might result in a smaller and less complex reconstruction and secondarily could reduce donor morbidity (13).

The impetus for developing the vacuum-assisted device was initially directed towards the chronic and difficult-to-treat wounds (8). Indeed, our results demonstrate improved wound healing predominately in late-treated wounds. Nowadays, acute wounds are also treated with this therapy, however, the advantage of vacuum therapy in these wounds is less obvious (22).

One of the important advantages of vacuum therapy is the fact that healthier wound conditions were achieved without intermediate chemical debridements. In more than 3/4th of the conventionally treated patients, sodium hypochlorite was used as a chemical debrider to remove fibrinous slough. In contrast, this was not indicated in the vacuum-treated group, which might be due to decreased formation, mechanical removal during therapy or removal at sponge change of fibrinous slough. Topical antimicrobial solvents were used in the con-

ventionally treated patients in contrast to vacuum therapy where these were not indicated. These solvents can provoke a local allergic reaction and may increase multiple antimicrobial resistance (23, 24). Both chemical debriders and antimicrobial solvents are suspected cytotoxic agents, which may adversely affect wound healing (25-27).

Another major advantage of vacuum therapy is the reduction of the number of dressing changes to once every 48 h instead of twice or more every 24 h as in conventional therapy. The reduction of dressing changes leads to an improved patient compliance as the patient suffers less often pain and inconvenience. Besides this, less frequent dressing changes, result in reduced nursing time and thus reduced staff costs (€33 ± €31 and €83 ± €58 for vacuum therapy and conventional therapy, respectively; $p< 0.0001$). Also hospitalisation costs are reduced, due to on average shorter duration of therapy needed (€1788 ± €1060 and €2467 ± €1336 for vacuum therapy and conventional therapy respectively; $p< 0.05$) . These lower costs offset the high material costs of vacuum therapy, resulting in an equally expensive therapy as conventional therapy (€2235 ± €1301 and €2565 ± €1384 for vacuum therapy and conventional therapy, respectively) (28) .

We encountered some complications during vacuum therapy which were all reversible and consisted of i) erosion of adjacent tissue due to increased local pressure underneath the tubing, which can be prevented by application of pressure relieving material underneath the tubes, ii) reaction of the peri-wound area (i.e. maceration and eczema), solved by placement of alginates underneath the adhesive dressing, iii) increased body temperature due to clogging of the system due to large amounts of debris and fluid, solved by changing the foam dressings. Furthermore, in both therapies, pain during application and removal of the foam/gauze occurred, which can largely be overcome by analgesics, placement of a nonadherent dressing to the wound base or injecting a local anaesthetic (i.e. lidocaine) underneath the sponge (29). In general, the use of mechanical devices has some drawbacks. It is of great importance to have a fully compliant patient to avoid complications due to inadequate handling, e.g. reaction on alarm signalling (turning the device off) or unauthorised clamping of the tubes. We found that inadequate handling of the device occurred with patients who were difficult to confine to the department (heavy smokers). Deterioration of the wound can occur when obstruction of the system due to inadequate handling or debris remains unnoticed. Rise in body temperature, as occurred in one patient or even septicaemia, can be the consequence (30). This problem of inaccurate pressure censoring at the wound site is largely overcome with the new version of the V.A.C. ® device using pressure-sensing paths throughout the tubing up to the wound site.

We performed bacterial analysis to find out if the improved wound healing with vacuum therapy could be explained by a bacterial decrease. Although more and more debated (31, 32), levels of around 10^5 and less bacteria/g of tissue have been found to be an important determinant for successful delayed closure (33-36). Surprisingly, there was no decrease in bacterial load in either therapy. Similar findings were reported by Isago *et al.* who described healing of stage IV pressure ulcers with vacuum therapy, despite bacterial counts up to 10^6

corresponding with initial values (37). Weed *et al*. even reported a quantitative increase of bacteria during vacuum therapy, although clinically improvement of the wounds occurred in most cases (38). Seen that wound healing occurred without a decrease of bacterial load we already speculated that the combination of the different bacterial species, the nature and virulence of the species involved, and the host's ability to counter their deleterious effects is probably of more importance than the number of bacteria (39). In this previous article, we described a significant shift in bacterial species which occurred in the vacuum-treated group and not in the conventionally treated group. At this moment, further attempts are made to resolve the underlying mechanism of action of vacuum therapy by comparing wound fluid samples on composition.

Two compromising disorders (i.e. peripheral vascular disease and osteomyelitis) were found to be an underlying disease in the majority of patients with a chronic wound. Both disorders are known to be extremely difficult to treat and can cause complications during therapy and postoperatively. This became apparent in one patient with severe peripheral vascular disease, which compelled to stop vacuum therapy because of increased ischaemic pain and further deterioration of the wound. It was already suggested to treat wounds based on severe peripheral vascular disease by other modalities than vacuum therapy (40). Osteomyelitis, although recognised and treated as such, was the underlying disease in 1/3rd of all patients with postoperative complications. It has been suggested that vacuum therapy combined with instillation of antibiotics/antiseptics (6) or treatment with maggots (41) can be an effective therapeutic aid to treat wounds compromised by osteomyelitis.

There are a few limitations to this study. Firstly, we have chosen a prospective randomised setting because random allocation of patients should balance the groups for prognostic factors (such as disease severity or other predictors of good or bad prognosis). However in our study we found a larger number of diabetic, osteomyelitis and vascular compromised patients in the vacuum-treated group compared to an overrepresentation of spinal cord injuries in the conventionally treated group. This uneven distribution could have counteracted the effects of the therapies. Secondly, although it would have been optimal to blind the clinical assessment of the wounds, this was not possible because of obvious visible suction marks present in wounds treated with vacuum therapy. Thirdly, while actual surgical closure of the wound would have been the most obvious choice as an endpoint we decided to choose the moment 'ready for surgical therapy' as an endpoint. Reason for this was because the actual moment of surgical closure depended not only on the status of the wound, but more so on variables, like logistics and management.

In conclusion, we have found that vacuum therapy shows on average healthier wound conditions compared with conventional therapy especially in late-treated wounds, with a faster and larger reduction of the wound surface area. Together, with the fact that vacuum therapy is equally expensive as conventional therapy, we like to advise vacuum therapy for the treatment of full thickness wounds in the intermediate period between debridement and surgical closure.

Acknowledgement

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CHAPTER IV

An economic evaluation of the use of TNP on full-thickness wounds

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Abstract

Background: Topical negative pressure (TNP) therapy (vacuum therapy) is frequently used in the management of acute, traumatic, infected and chronic full-thickness wounds. This prospective clinical randomized trial compared the costs of TNP with conventional therapy (moist gauze) in the management of full-thickness wounds that required surgical closure.

Methods: The direct medical costs of the total number of resources needed to achieve a healthy, granulating wound bed that was 'ready for surgical therapy' were calculated.

Results: Fifty-four patients, admitted to the department of plastic and reconstructive surgery were recruited into the trial. Cost analysis showed significantly higher mean material expenses for wounds treated with TNP therapy (€ 414 ± € 229 [SD]) compared with conventional therapy (€15 ± €11; $p<0.0001$), but significantly lower mean nursing expenses (€33 ± €31 and €83 ± €58 for TNP and conventional therapy, respectively; $p<0.0001$). Hospitalization costs were lower in the TNP group (€1788 ± €1060) than in the conventional treatment group (€2467 ± €1336; $p<0.043$) due to an on average shorter duration until they were 'ready for surgical therapy'. There was no significant difference in total costs per patient between the two therapies (€2235 ± €1301 for TNP versus €2565 ± €1384 for conventional therapy).

Conclusions: TNP had higher material costs. However, these were compensated by the lower number of time-consuming dressing changes and the tendency for a shorter duration until 'ready for surgical therapy', resulting in the therapy being equally expensive therapy compared to conventional moist gauze.

Introduction

Wounds in need of reconstructive surgery are often large, with extensive soft tissue loss. Most are severely debilitating and require labour-intensive treatment. They often cannot be directly reconstructed due to contamination, their size or their chronic nature, so are treated with topical wound dressings until definite surgical closure is possible. The objective is to prevent a delay in healing, minimising the burden for the patient and practitioners and in turn minimising hospital stay and cost of therapy.

In Plastic Surgery, topical negative pressure therapy (TNP) (or vacuum therapy) has become a popular therapy to bridge the intermediate phase between debridement and definite surgical closure. Case reports and trials have described promising clinical results (1-9). In a prospective randomized trial, published in 2004, we compared TNP with conventional treatment (moist gauze) in a mixed hospital population with full-thickness wounds in need of open wound management before surgical closure. TNP appeared to be significantly more effective than conventional therapy in reducing wound surface area (10). This could decrease donor morbidity due to the need for a smaller and less complex reconstruction (8). The general condition of the TNP wounds was significantly healthier than the conventionally treated wounds, resulting in them taking less time to be 'ready for surgical therapy' (10). This paper compares the direct costs of TNP with conventional (moist gauze) therapy, as incurred in this prospective randomized trial (10).

Material and Methods

The prospective randomised trial took place between July 1998 to October 2002. Patients with an open wound that could not be closed immediately because of severely crushed tissue, infection or chronicity were included after written consent was obtained. Exclusion criteria were: malignant disease, superficial bare blood vessels, deep fistulae, necrotic tissue, an unstable skin around the wound, sepsis, untreated active osteomyelitis, active bleeding, uncontrolled diabetes and psychiatric diseases. Randomisation was performed through closed envelope assignment. A power calculation was performed to determine the required sample size. An intended total sample size of 54 patients was calculated such that a hazard ratio of 2.5 for the main endpoint could be detected with power 1-ß = 0.80 and significance level α=0.05.

Conventional treatment comprised standard moist gauze therapy, saturated in either 0.9% saline solution, or 0.2% nitrofuralam (Furacine Norgine BV), 1% acetic acid solution or 2% sodium hypochlorite (Eusol) at least twice a day. Nitrofuralam and acetic acid were only used if critical contamination, indentified using superficial swabs, was present. Eusol was used for a maximum of three days if sloughy or fibrinous tissue were present.

TNP was delivered using a device that comprises a polyurethane foam dressing with a pore size of 400-600 µm and induces a continuous negative pressure of 125 mm Hg (VAC Classic, KCI, Houten, the Netherlands) (11). The foam dressings were changed every 48 hours. The physician leading the trial scored the condition (rubor [erythema], calor [warmth], exudate production, fibrinous slough/necrotic tissue and granulation tissue) of all wounds every other day. Before and during treatment, necrotic tissue was sharp debrided when considered clinically necessary. Assessment was not blinded due to visible suction marks in wounds treated with TNP.

The number of days taken to achieve a healthy, granulating wound bed without signs of inflammation - assigned by the surgeon as 'ready for surgical therapy'-was calculated using the Kaplan-Meyer curve method. The results are described in our previous paper (10) and are reproduced in Table 1. Patients were withdrawn from the study if they were not deemed to be 'ready for surgical therapy' within 30 days of starting treatment, or if the therapy was terminated before 30 days. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, so was approved by the Medical Ethics Committee of the Erasmus University Medical Centre.

Calculations were made of the direct medical costs per patient from baseline to when the wound was 'ready for surgical therapy'. For each patient, the physician leading the trial recorded the: number and size of gauze dressings/sponges needed per dressing change, form and amount of topical solvents used, number of dressing changes given, number of

Table 1. Unit costs of wound treatment

	Unit size	**Price per Unit (€)**
VAC Classic device	Day	38.57 *
VAC Dressing Kit**	Small (10x 7.5x 3.3 cm)	25.54
	Medium (18 x 12.5 x 3.3 cm)	31.67
	Large (26 x 15 x 3.3 cm)	36.90
VAC Reservoir	300 ml	19.63
Saline 0.9%	1 litre	0.75
Nitrofuralam 0.2%***	200ml	10.38
Acetic acid 1%	100ml	0.45
Sodium hypochlorite 2%	300ml	1.90
Gauze bandage	10 x 10 cm	0.02
Absorbent bandage	10 x 10 cm	0.19
Circular fixation bandage	10 cm x 4 m	0.30
Staff/nurse	Hour	31.15
Nurse	Hour	31.15
Daily inpatient accommodation #	Day	250

* Lease costs per day for the Erasmus Medical Centre, Rotterdam

** Includes poly-urethane foam/foil and drainage tube

*** Perishable 48 hrs

Cost for a hospital bed inclusive of basic nursing care, hotel costs, doctors' visit and management costs, exclusive therapy costs (non-wound-care costs) and operation costs (12).

staff involved in each dressing change, and duration of dressing changes. The size of wounds in both groups was calculated using the three sizes of the vacuum sponges as a reference. The unit costs for staff, inpatient accommodation, and materials (2003 prices) are recorded in Table 1. Costs reflect real resource use and are in accordance with Dutch guidelines on health-care costing (12); Staff costs – average nursing wage in Dutch academic hospital, mean hospitalization costs – inpatient accommodation costs per day (12) multiplied by the number of days until 'ready for surgical therapy'. Inpatient accommodation costs per day – average costs for a hospital bed at a plastic surgery department in a Dutch academic hospital including basic nursing care, hotel costs, doctors' visit and management costs, exclusive therapy costs (costs for all treatments given excluding wound care) and operation costs. Costs of treating underlying diseases were not taken into account. Therapy costs for patients who stopped using the therapy before reaching the end point because of complications were added to the therapy costs of patients who did reached the end point, according to the equation in Table 2. This enabled us to calculate the costs of the therapy in general, including the costs of treatment failures. As a result, the mean therapy costs increased. In a sensitivity analysis we investigated whether higher or lower inpatient accommodation costs would change the difference in overall costs between both therapies. Because of the skewed cost data, statistical significance was determined using the non-parametric Mann Whitney U-test. Costs are expressed as mean ± standard deviation with the 95% confidence interval.

Table 2: Equation used to calculate therapy costs of patients who did not reach the endpoint

$$\text{Mean cost per patient, per therapy} = \frac{\text{Total cost}}{\text{(Total no. of patients)} - \text{(no. of patients not reaching endpoint)}}$$

Results

Fifty-four wounds were enrolled in this study. Twenty-nine wounds were treated with TNP and 25 with conventional therapy (Table 3). In the TNP group, therapy was stopped in two patients because of sepsis of unknown origin and a deterioration of the wound; a thirs patient was withdrawn from the study after being transferred to a nursing home. In the conventional treatment group, one patient refused further cooperation and one patient was not 'ready for surgical therapy' within 30 days. Both patient groups were similar in terms of age and wound characteristics. Before therapy, surgical debridement was performed in 28 out of 29 TNP-treated wounds (97%), and in 22 out of 25 conventionally treated wounds (88%). In four TNP-treated wounds and three conventionally treated wounds a second sharp debridement at the bedside had to take place.

In the conventional treatment group, after the first debridement an average of 17 dressing changes per wound were needed before the wounds were 'ready for surgical therapy'

Table 3. Wound characteristics

	TNP	Conventional therapy
Total number of wounds	29	25
Excluded	3	2
Acute wounds*	12	8
Chronic wounds*	17	17
Infection	12	10
Trauma	2	-
Chronic non-healing wound	7	3
Pressure ulcer	8	12
Small (< 10x 7.5x 3.3 cm)	15	17
Medium (<18 x 12.5 x 3.3 cm)	9	5
Large (26 x 15 x 3.3 cm)	5	3
Wound surface reduction	3.8 ± 0.5 % (SD) /day **	1.7 ± 0.6% /day
Median duration until "ready for surgical therapy"***	6.00 ± 0.52 (SEM) days	7.00 ± 0.81 days

* start of therapy within four weeks post-wounding (acute wounds); therapy started after four weeks post-wounding (chronic wounds)

**Larger reduction of wound surface area compared with conventional therapy ($p < 0.05$) (10)

***Duration needed to reach a healthy, granulating wound surface ($p=0.19$) (10).

(minimum: three dressing changes; maximum: 59). For every conventional dressing change, one nurse was needed, taking approximately 8.5 minutes. In the TNP group an average of two dressing changes per wound was needed to reach 'ready for surgical therapy' (minimum: zero; maximum: five). An average of 1.4 nurses was needed for each sponge change, taking approximately 29 minutes. The fewer number of dressing changes in the TNP group resulted in significantly lower mean nursing costs (€33 ± €31) than in the conventional treatment group (€83 ± €58, $p<0.0001$). However, mean material costs in the TNP group were significantly higher (€414 ± €229) than in the conventional treatment group (€15 ± €11) ($p<0.0001$) (Table 4). The average shorter duration until 'ready for surgical therapy' with TNP therapy resulted in lower hospitalization costs (€1788 ± €1060) when compared with the conventional treatment group (€2467 ± €1336) ($p<0.05$), when assuming €250 for inpatient accommodation per day.

There was no difference in the total material, nursing and hospitalization costs between the two groups (€2235 ± €1301 and €2565 ± €1384 for TNP and conventional therapy, respectively). Sensitivity analysis showed that varying the inpatient accommodation cost per day, from a minimum of €200 per day (€1878 ± €1089 and €2071 ± €1117 for TNP and conventional therapy respectively) to a maximum of €300 per day (€2593 ± €1512 and €3058 ± €1651 for TNP and conventional therapy respectively) did not have a significant effect on the total cost.

Table 4. Resource use and Mean costs of TNP and conventional therapy

	TNP n =29 (26) *	**Conventional therapy n =25 (23) ***
No. of dressing changes	57	430
No. of staff	82	430
Mean duration of changes (minutes)	29	8.5
Mean duration until ready for surgery (days)	7.2 ± (4.2)	9.9 ± (7.0)
Material (€)	414 ± (229) [326-502]	15 ± (11) [11-19]**
Nursing time (€)	33 ± (31) [21-45] **	83 ± (58) [59-106]
Hospitalization (€250/day)	1788 ± (1060) [1381-2196]***	2467 ± (1336) [2306-3616]
Therapy cost per patient (€)	2235 ± (1301) [1735-2735]	2565 ± (1384) [1999-3131]

* The costs of the five patients (three TNP and two conventional) who did not reach the end point 'ready for surgical therapy' are divided by costs for patients who reached the end point (n=26 for TNP and n=23 for conventional therapy)

** Cost nursing time= total duration of changes/60 x 31.15 Euro. $p < 0.0001$

*** $p < 0.05$.

Discussion

In a previous study we reported the positive effect of TNP on the healing of full-thickness wounds, reflected by the significantly larger reduction in wound surface area than produced by conventional therapy (moist gauze) (10). Here we compared the direct medical costs of TNP with the same conventional therapy on the same wounds.

Two previous economic evaluations have been described. One compared TNP with saline-soaked gauze in patients with trunk/trochanter pressure ulcers (13) and the other with a closed irrigation system in patients with poststernotomy mediastinitis (14). Both reported that TNP had a positive effect on wound healing, as reflected in the reduction in wound surface area in the first study and shorter hospital stay in the second, which reduced the lower overall cost. However, both studies used a non-randomized retrospective study design with a historical control group, and neither performed statistical analysis to substantiate the results. Our study is the first to compare TNP with a standard, conventional (moist gauze) therapy within a prospective randomized clinical study design.

Surprisingly, there was no significant difference in overall costs (material, nursing and hospitalisation costs) between the two therapies. While material costs were much higher in the TNP group, these were largely offset by the reduction in hospitalisation costs (in-patient accommodation). On average, patients treated with TNP were deemed fit for surgical therapy earlier, which significantly reduced hospitalisation costs. To a smaller extent the high material costs were offset by the reduction in staff costs. Although TNP dressing changes took longer and required more nurses, dressings were changed only every other day instead of two times a day or more. In addition to economic advantages, the reduction in the number of dressing changes helped improve patients concordance as the patients experienced less pain and inconvenience.

This study did not take into account the cost effects of the significantly larger reduction in wound surface area achieved with TNP. Smaller wounds will result in smaller and less complex reconstructions and, in some cases, surgical intervention might prove unnecessary (8).

Conventional moist gauze therapy is still one of the most popular wound treatments in our and many other hospitals in Europe and the USA (5, 15), although it is being replaced by less labour-intensive therapies (hydrocolloids, hydrogels and alginates). Cost-effectiveness analyses have shown that these products reduce staff costs by reducing the number of dressing changes (15, 16). It would be of interest to investigate whether TNP remains clinically and economically preferable when compared to these alternative therapies.

Conclusions

Within this comprehensive population of patients in need of wound management before definite surgical closure, TNP proved to be as expensive as conventional moist gauze therapy.

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CHAPTER V

Bacterial load in relation to Vacuum-assisted closure wound therapy: a prospective randomized trial

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In this manuscript the term Vacuum-assisted closure wound therapy (in short VAC or Vacuum therapy) is used. After introduction of other negative pressure devices besides the V.A.C. device we have decided to use the general nomenclature: Topical negative pressure therapy (TNP).

Abstract

Background: Vacuum-assisted closure has become a new technique in the challenging management of contaminated, acute, and chronic wounds. Although promising clinical results have been described, scientific proof to substantiate the mechanism of action of this therapy is scarce.

Methods: In the present study, we examined whether the positive effect on wound healing found in vacuum-assisted closure–treated wounds could be explained by an effect on the bacterial load. Fifty-four patients who needed open wound management before surgical closure were included in this study. Wounds were randomized to either vacuum-assisted closure therapy (n= 29) or treatment by conventional moist gauze therapy (n= 25). Healing was characterized by development of a clean granulating wound bed ("ready for surgical therapy") and reduction of wound surface area. To quantify bacterial load, biopsies were collected.

Results: No significant difference was found in time needed to reach "ready for surgical therapy" comparing both therapies. Wound surface area reduction was significantly larger in vacuum-assisted closure–treated wounds: 3.8 ± 0.5 percent/day (mean ± SEM) compared to conventional-treated wounds (1.7 ± 0.6 percent/day; $p < 0.05$). The total quantitative bacterial load was generally stable in both therapies. However, nonfermentative gram negative bacilli showed a significant decrease in vacuum-assisted closure–treated wounds ($p < 0.05$), whereas *Staphylococcus aureus* showed a significant increase in vacuum-assisted closure–treated wounds ($p < 0.05$).

Conclusion: This study shows a positive effect of vacuum-assisted closure therapy on wound healing, expressed as a significant reduction of wound surface area. However, this could not be explained by a significant quantitative reduction of the bacterial load.

Introduction

Wound healing and management of difficult-to-treat wounds have been the focus of many physicians to stimulate development of new techniques and wound care products. To prevent infection, extensive debridement and open wound management have been widely advocated for traumatic contaminated soft tissue defects and postoperative complications, but also for chronic, nonhealing wounds (1). In an increasing number of medical centers, vacuum-assisted closure (VAC) is used until secondary wound closure is possible.

VAC therapy comprises a sterile open-cell foam dressing covered by a transparent adhesive drape. The foam dressing is attached to a pump that provides intermittent or continuous negative pressure through a noncollapsible evacuation tube. Introduction of this negative pressure technique was described by Morykwas et al., who found in a small animal study a positive effect of VAC therapy on bacterial clearance, perfusion rate, and granulation tissue formation (2). Furthermore, soft tissue defects, infected and nonhealing wounds of the sternum, diabetic foot wounds, wounds with exposed bone, pressure ulcers, and gynecologic wounds were treated effectively with VAC therapy (3-14). In addition to these applications, VAC therapy could be used as a bolster for skin grafts, in temporal abdominal wound management and to prevent skin necroses in toxic chemotherapeutic extravasation injuries (15-17). Unfortunately, nearly all of the recommendations made for this technique are based on expert opinion rather than scientific evidence.

In a randomized prospective trial we wanted to evaluate, in a mixed hospital population, the effect of VAC therapy on wound healing compared to conventional moist gauze treatment. The aim of this study was to examine whether the increased rate of wound healing found in VAC-treated wounds could be explained by an effect on the bacterial balance. More specifically, we focused on microorganisms that are responsible for the majority of infections: gram-negative nonfermentative rods (*Pseudomonas spp.*, *Pseudomonas Aeroginosa and Acinetobacter spp.*), *Staphylococcus aureus*, gram-negative members of the family of Enterobacteriaceae (*Providencia, Proteus, Morganella, Klebsiella, Escherichia, Enterobacter, Citrobacter*) and anaerobes.

Materials and methods

Patients with a full-thickness wound that could not be closed immediately because of infection, contamination, or chronic nature were included in the study after written consent was obtained. Exclusion criteria were: Malignant disease, superficial bare blood vessels, deep fistulas, necrotic tissue, unstable skin around the wound, untreated osteomyelitis, sepsis, active bleeding, uncontrolled diabetes, and psychiatric diseases. Wounds were stratified into early treated wounds, defined as existing less than 4 weeks before hospitalization, or late treated

wounds (> 4 weeks). Patients were randomly assigned, by picking a closed envelope with the description of the therapy, to either VAC therapy or conventional moist gauze treatment. A power calculation was performed to determine the sample size before start of the study.

Wound therapy

Conventional treatment consisted of a standard moist gauze therapy two times a day or more, depending on the productivity of the wound. The following "moist" agents could be used; 0.9 percent saline, 0.2 percent nitrofuralam (Furacine® solution), 1 percent acetic acid solution or 2 percent sodium hypochlorite (Eusol). Choice of conventional moist agents depended on the degree of contamination, bacterial species, and debris. VAC therapy consisted of a polyurethane foam dressing with a pore size of 400–600 µm and a continuous negative pressure of 125 mmHg (all materials from KCI International, Houten, The Netherlands). Wounds were inspected and foam dressings were changed every 48 hours. Before the start of therapy and during treatment, debridement of necrotic tissue took place when considered clinically needed. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the Medical Ethics Committee of the Erasmus Medical Center.

Determination of "ready for surgical therapy"

Wound conditions were assessed every 48 hours and the number of treatment days necessary to achieve a clean, red, granulating wound bed ("ready for surgical therapy") was recorded.

Wound size measurements

The wound surface area was measured directly after debridement and during therapy. Measurements were done by tracing the edge of the wound onto clear polyethylene film, which was placed as a cover over the entire wound surface (18). After photocopying the tracing onto paper, the wound surface areas were scanned (AGFA Duoscan T1200, Agfa-Gavaert, Mortsel, Belgium) and calculated (Adobe Photoshop, San Jose, CA). Assessment of both clinical observations and wound surface area reduction could not be blinded, because of obvious visible suction marks present in wounds treated with VAC. Wound surface area measurements were not performed if the wound was too deep with small-sized entrances or with undermined areas beyond reach or when additional debridement had to take place during therapy.

Bacterial cultures

After removing surface exudate with a sterile saline solution, a biopsy was taken under aseptic conditions by using a scalpel, taking viable tissue from the center of the wound. The biopsies were taken at the beginning of the treatment and continued until the end of the therapy. The samples were immediately sent to the laboratory, weighed, homogenized with a sterile mortar, and diluted. A series of dilutions was plated on a Colombia blood agar, a

MacConkey agar, and a chocolate agar and incubated at 37°C in 5 percent CO_2 for 48 h. To detect anaerobes, a Brucella blood agar was cultured at anaerobic conditions for up to 5 days. The total number of colony forming units (CFU) per disk and number of CFU per species were counted and calculated per gram of tissue. Biopsies were processed blinded and evaluated by a medical microbiologist. Results of the tissue biopsies were not revealed to the researchers until the end of the study.

Statistical analysis

The proportions of wounds "ready for surgical therapy" were analyzed using the Kaplan-Meier curve method. The null hypothesis of no difference between two treatments was tested with the Log Rank test. Patients were censored when "ready for surgical therapy" was not reached within 30 days or when follow-up stopped for reasons of sepsis or refusal of further cooperation. Both wound surface area measurements and bacterial load measurements were analyzed as follows. First the measurements were logarithmically transformed. Then, a linear regression line was calculated for each patient and the average slope of these regression lines was determined per treatment group. To assess whether the average reduction was statistically significant within a group, Student's one-sample t-test was used. To compare the average reduction between the treatment groups, Student's two-sample t-test was employed. The results of wound surface area reduction are expressed after back transforming the average reduction by taking the antilog. The results of bacterial load reduction are expressed as mean regression (slope). Duration until "ready for surgical therapy" is expressed as median ± standard error of the mean (SEM), wound surface area and bacterial load reduction as mean ± SEM.

Results

Fifty-four wounds were enrolled in this study. Twenty-nine wounds were treated with VAC therapy and 25 with conventional treatment. No relevant differences in baseline characteristics were found between the treatment groups (Table 1).

'Ready for surgical therapy'analysis

Kaplan-Meier survival analysis was used to determine the effect of the treatments on the duration of therapy needed until the wound was ready for surgical closure. The median time needed to reach "ready for surgical therapy" for VAC-treated wounds was 6.00 ± 0.52 days (median ± SEM) compared to 7.00 ± 0.81 days for conventional moist-treated wounds (p= 0.19) (Figure 1 A). For early treated wounds this was 5.00 ± 0.85 days vs. 6.00 ± 1.37 days (p= 0.70), for late treated wounds 6.00 ± 0.99 days vs. 10.00 ± 3.78 days (p= 0.21).

Table 1. Baseline characteristics

	VAC (n=29)	Conventional (n=25)
Age (years)	47.7 (±19.6)	47.9 (±17.0)
Male/female	21/8	14/11
Cigarette smoker	10	11
BMI:		
<20 (underweight)	4	2
>25 (overweight)	16	12
Early treated	12	8
Late treated	17	17
Cause:		
Trauma	2	0
Infection	10	7
Dehiscence	2	3
Pressure ulcer	8	12
Miscellaneous	7	3
Comorbidity:		
Diabetes Mellitus	6	1
Vascular disease	8	3
Osteomyelitis	8	4
Spinal cord lesion	0	5
Rheumatoid arthritis	1	2
Medication:		
Corticosteroids	2	4
Antibiotics	13	14

BMI: Body Mass Index: (weight /(length^2)).

Miscellaneous wounds: chronic wounds with osteomyelitis (VAC n=5, conventional n=2) or unknown origin.

Wound surface area changes

Reduction in the wound surface area was compared in 28 patients (VAC n= 15, conventional n= 13). Reduction of the wound surface area was seen in 100 percent of the VAC-treated patients compared to 77 percent of the conventional-treated patients. Both treatments gave a significant reduction in wound surface area compared to initial wound area of 3.8 ± 0.5 percent/day ($p < 0.0001$) and 1.7 ± 0.6 percent/day ($p < 0.05$) for VAC and conventional therapy, respectively. The wound surface area reduction was significantly larger in VAC-treated wounds compared to conventional-treated wounds ($p < 0.05$; Figure 1 B).

Bacterial load reduction

In total, 222 biopsies (weight ranging from 5 mg to 270 mg) of 50 wounds (VAC n= 26, conventional n= 24) were taken during treatment; 353 isolates of 44 different species were cultured. The mean number of biopsies per patient was 4.3 ± 1.1(SD) for VAC and 4.5 ± 1.5 for conventional therapy. The quantitative bacterial load did not change significantly in both VAC and conventional therapy (slope: 0.06 ± 0.05 and – 0.05 ± 0.07; mean ± SEM; p= 0.22), respectively (Figure 2). In 11 out of 26 VAC-treated wounds (42 percent), the biopsies taken at the end of the follow-up period contained more than 10^5 bacteria compared to 10 out of 24 conventional-treated wounds (42 percent). Nine of these 21 (11 VAC, 10 conventional)

Figure 1A

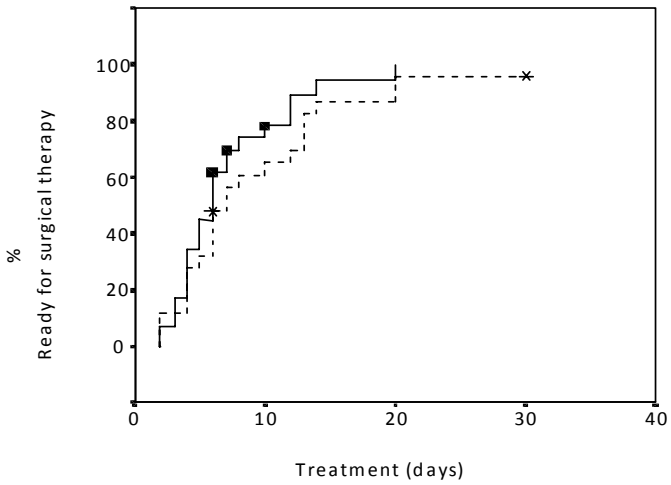

Figure 1B

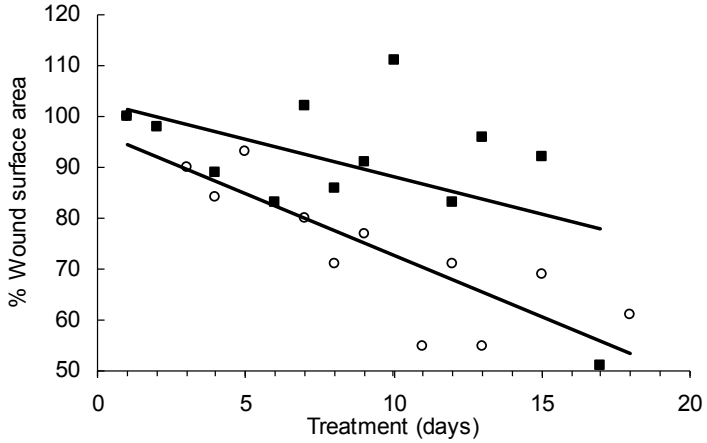

Figure 1. Assessment of "ready for surgical therapy" and reduction in wound surface area. (A) Kaplan-Meier cumulative survival curve. Cumulative percentage of wounds that are "ready for surgical therapy," depending on the number of days elapsed since beginning of therapy (continuous line: vacuum therapy; black squares: censored patients; interrupted line: conventional therapy; stars: censored patients). (B) Scatter plot of average wound surface area reduction in both therapies (open circles: vacuum therapy; black squares: conventional therapy). Inserted are the linear trend lines.

patients with a CFU count over 10^5 healed completely without any complication and one healed by secondary intention (48 percent).

Bacterial species

Further analysis of the four most frequent groups of isolates; nonfermentative negative rods, *S. aureus*, Enterobacteriaceae, and anaerobes, were done. During VAC therapy, a reduction in the number of nonfermentative negative rods was found, expressed as a negative mean

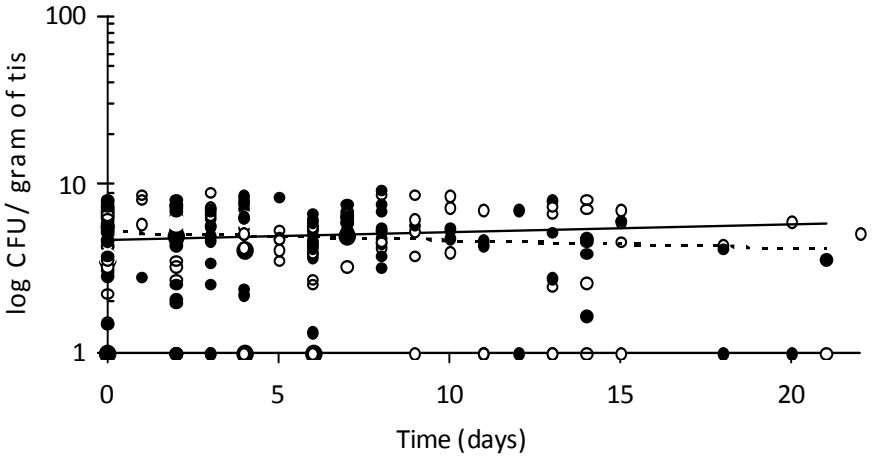

Figure 2. Logarithmic transformation of the quantitative bacterial load (CFUs/g of tissue) per patient per treatment. The black circles are the VAC therapy patients and the open circles are conventional therapy patients plotted against duration of treatment in days. Inserted are the mean linear regression lines for VAC therapy (continuous line; slope 0.06 ± 0.05) and conventional therapy (interrupted line; slope: − 0.05 ± 0.07; $p = 0.22$).

regression of – 0.15 ± 0.07 ($p < 0.05$). In conventional therapy no significant effect was observed (– 0.06 ± 0.16; p= 0.72). Comparing both therapies, no significance was found (p= 0.53). During VAC therapy an increase was seen in the number of *S. aureus*, expressed as a positive mean regression of 0.26 ± 0.11 ($p < 0.05$) vs. 0.03 ± 0.14 (p= 0.80) in conventional-treated wounds. Comparing both therapies, no significance was found (p= 0.23). The number of Enterobacteriaceae did not change significantly in VAC-treated wounds, 0.08 ± 0.07 (p= 0.25), or in conventional-treated wounds, – 0.28 ± 0.19 (p= 0.18). Also, the number of anaerobes did not significantly change in VAC- or conventional-treated wounds: 0.09 ± 0.10 (p= 0.40) and – 0.20 ± 0.11 (p= 0.12), respectively.

Discussion

This study shows that the use of VAC therapy in a mixed hospital population results in improved wound healing, reflected by a significant reduction of wound surface area in VAC-treated patients compared to conventional-treated patients. This is in line with earlier reports comparing VAC to conventional treatment in chronic nonhealing wounds (19). In the study by Joseph et al., an increase in granulation tissue formation in VAC-treated wounds was found with a subsequent decrease in wound volume. Similar results were obtained in two animal models (ischemic rabbit ear model and acute swine model) in which an increase in granulation tissue was found (2, 20). Reduction of wound surface area is a sign of improved wound healing, which could result in decreased donor morbidity due to the need of a smaller

and less complex reconstruction (9). However, we did not observe a decrease in number of treatment days needed to reach "ready for surgical therapy" compared to conventional therapy. This lack of difference might be influenced by the tendency for an overrepresentation of diabetic, osteomyelitis, and vascular compromised patients (11) to the detriment of VAC-treated wounds (see Table 1).

In the present study, we examined whether the increased rate in wound healing found in VAC-treated wounds could be explained by an effect on the bacterial balance. We could not find a significant effect of either VAC therapy or conventional therapy on the total amount of bacteria. These results differ from earlier clinical VAC studies in which a trend toward reduction of bacterial load was reported using semiquantitative superficial swabs (21-23). Our results are also in contrast with the results of an animal study in which a significant decrease in the number of bacteria was found in tissue biopsies of pigs (*S. aureus* (*n*= 3) and *Staphylococcus epidermidis* (*n*= 2) (2). The difference in outcome between our study and former mentioned clinical studies might be explained by the differences in sampling method (superficial swabs vs. biopsies) and/or method of analysis (semiquantitative vs. quantitative). With respect to the study of Morykwas et al., the observed differences could be due to the fact that theirs was an animal model in which wounds were deliberately contaminated instead of acquired (2).

Surprisingly, in our study, also the conventional-treated wounds showed no significant decrease in bacterial load. This is partly due to the difficulty in clinically assessing whether antimicrobial therapy is indicated. Furthermore, the decision to change the treatment strategy is based on the results of the superficial swab cultures, which are delayed due to the processing time. Finally, retrospective analysis of the bacteriologic data showed cases with a discrepancy in the number of bacteria determined in superficial swabs (low) compared to the later retrieved biopsies (high), giving the clinicians no reason to change the treatment strategy (data not shown). Altogether it should be noted that VAC therapy seems to have a similar effect on the quantitative bacterial load to conventional therapy, despite the fact that in VAC therapy no local antimicrobial agents are used.

Importantly, retrospective analysis showed a discrepancy between the quantitative bacterial count and the clinical evaluation of the specialist to assign a wound "ready for surgical therapy (11), because the number of bacterial colonies exceeded 10^5 bacteria in almost half of these patients. However, the arbitrary critical level of 10^5 bacteria is debatable (24-30), and is illustrated by our finding that no relation was observed between bacterial load and the number of postoperative complications. In this respect, the combination of the bacteria, the nature and virulence of the organisms involved, and the host's ability to counter their deleterious effects seem to be more important than the number of bacteria present in a wound (24, 29, 31-33).

With this in mind, the evident modulation of bacterial species we observed is of interest. A decrease in the number of nonfermentative negative rods was found in VAC-treated wounds. The reason for this decrease could be through creation of a hypoxic wound environment. In

addition, an increase in the number of *S. aureus* was found in VAC-treated wounds. In general, the risk for nosocomial colonization of wounds with *S. aureus* in hospitals is high (34). However, the presence of *S. aureus* does not necessarily indicate infection, which is particularly true in polymicrobial chronic wounds (24, 32). Furthermore, a mild contamination with *S. aureus* has been reported to stimulate wound healing (35, 36).

In addition to a shift in the bacterial species contaminating the wound, which might reflect a more favorable environment for wound healing, other mechanisms of action of VAC are still to be investigated. It is suggested that negative pressure therapy stimulates cell proliferation through the application of mechanical stress on surrounding tissue. As shown in several *in vivo* and *in vitro* studies, mechanical stress applied to cells increases the expression of certain growth factors (e.g., vascular endothelial growth factor and fibroblast growth factor-2) that are known stimulators of angiogenesis and cell proliferation (37-42). Another suggestion is that removal of excess fluid causes decompression of small vessels and thus increases local blood flow (2, 17, 41, and 43). In addition to this, active drainage of excess wound fluid containing possible inhibitory components could also result in improvement of wound environment, benefiting wound healing (44-47). The possible creation of a hypoxic environment, which has been shown in *in vitro* studies to stimulate angiogenesis, fibroblast, and epidermal cell growth might also play a role (48-50).

In conclusion, in our study we have tried to find an explanation for the improved wound healing by VAC. We found that VAC had a similar effect on the bacterial load as conventional treatment. In addition, a clear shift in bacterial species was found in VAC-treated wounds, with a significant decrease in nonfermentative negative rods to a significant increase in *S. aureus*. Part of the proposed mechanism of action behind VAC therapy could therefore be through local changes in wound environment, reflected by a modulation in bacterial species, which could be more favorable for wound healing.

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CHAPTER VI

Superficial swabs are equally reliable and less invasive than tissue biopsies for monitoring bacterial colonization in full thickness wounds: a comparative study

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CHAPTER VII

The role of Topical Negative Pressure in wound repair: Expression of biochemical markers in wound fluid during wound healing

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Abstract

Introduction: The clinical effects of topical negative pressure therapy (TNP) on wound healing are well described in numerous articles. While the mechanism(s) of action are not completely understood, it is postulated that reduction of local and interstitial tissue edema, increased perfusion of the (peri-) wound area, changed bacterial composition, and mechanical stimulation of the woundbed contribute to the clinical success. Our hypothesis is that with the removal of excessive fluid, proteolytic enzymes negatively influencing the healing process are removed.

Methods: Our aim was to assess whether the concentrations of albumin, matrixmetalloproteinase-9 (MMP-9), and tissue inhibitor of metalloproteinase (TIMP-1) were different between wounds treated with TNP and conventional gauze therapy. We analyzed wound fluid samples of 33 wounds treated with either TNP therapy (n=15) or conventional therapy (n=18) on albumin, pro- and activated MMP-9, TIMP-1, and the ratio of total MMP-9/TIMP-1.

Results: Albumin levels were found to increase significantly in acute wounds compared with chronic wounds; however, no difference could be found on comparing TNP with conventional therapy. We did find significantly lower levels of pro-MMP-9 and lower total MMP-9/TIMP-1 ratio in TNP-treated wounds during the follow-up of 10 days.

Conclusion: These data strongly suggest that TNP therapy influences the microenvironment of the wound.

Introduction

The body's response to wounding of any kind is a complex and highly orchestrated sequence of cellular and biochemical changes. Successful wound healing involves a series of overlapping phases: (i) inflammation, (ii) granulation formation and reepithelialization, and (iii) matrix formation and remodelling (1). During these phases, several enzymes are pointed out to play an important role in the maintenance of the dynamic balance of healing. For a wound to heal a balance is required between the accumulation of collagenous and noncollagenous extracellular matrix components and their remodeling by matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs) (2-4). Failure of this regulation has been suggested to affect not only wound healing (5, 6) but also other pathologic conditions such as cardiovascular disease (7), inflammatory and fibrinogenic diseases, and tumor growth and invasion (8-10).

The most described MMP in wound healing is MMP-9 (92 kDa gelatinase-B/type IV collagenase). MMP-9 has a broad range of substrate specificity for several native collagens as well as gelatin, proteoglycans, components of the basement membrane, and elastin. The finding of increased metalloproteinase levels in wound fluid in particular of MMP-2 and -9 in chronic, nonhealing wounds (11,12) has resulted in the development of wound care products that are suggested to inhibit or modulate protease expression (6,13-16). In a large series of patients with chronic wounds, Ladwig et al. (12) provided strong data supporting the hypothesis by showing a strong correlation between good healing and low ratios of total MMP-9/TIMP-1. Tarlton et al. (17) showed that in particular pro-MMP-9 and active MMP-9 measured in venous ulcers were accurate prognostic indicators of subsequent healing. They added neutrophil elastase (serine protease) to the list: whose level was significantly elevated in the region of the wound which was deteriorating vs. the regions which were improving. Improving the knowledge of this area will no doubt yield an insight that will help the clinician to better identify the mechanism involved in wound healing and thereby to intervene proactively.

The use of TNP therapy in wounds has taken an explosive flight and although many clinical studies have shown positive results, the exact mechanism of action on wound healing is still not elucidated. Experimental studies, clinical experience, and the latest randomized clinical trials have shown enhanced granulation tissue formation (18) and woundbed preparation (19), increased wound area reduction (18-20) increased cell division possibly induced by increased tension (21), decreased local and interstitial tissue edema, and increased perfusion of the (peri-) wound area (22). Recently, Stechmiller et al. published in a brief communication to the editor the alterations of proinflammatory cytokines, proteases (MMP-2 and 3), and TIMP-1 (23) during TNP therapy; however, their sample size was too small to show significant differences. Greene et al. (24) described a reduction in MMP-9/NGAL (neutrophil gelatinase-associated lipocalin), MMP-9, latent MMP-2, and active MMP-2 by 15 to 76% in three patients treated with TNP therapy.

In a prospective randomized study, exploring wound healing in wounds treated with TNP vs. wounds treated with conventional gauze therapy, we found a significant reduction of wound surface area in favor of TNP-treated patients (25). Furthermore, we found a significant modulation of bacterial species without a reduction of total bacterial load (20). To gain an insight into the possible changes of the microenvironment, we carried out biochemical analyses on wound fluids from TNP-treated and conventional gauze-treated wounds. We hypothesized that the continuous removal of exudates reduces accumulation of inhibitory factors and mechanically induces a new supply of interstitial wound fluid by means of negative pressure. The potential role of the change in bacterial species regarding the altered MMP concentrations is also an attractive factor to speculate on.

Material and methods

Wound fluid samples were collected as part of a prospective randomized clinical trial comparing wounds treated with TNP compared with conventional gauze therapy. Details of the clinical trial setup and the results have been published previously (20).

For this part of the study, 33 patients identified with a wound that could not be closed immediately because of infection or chronic character was included after written consent was obtained. Patients were randomly assigned, by picking a closed envelope with the description of the therapy, to either TNP therapy or conventional gauze treatment. Conventional gauze treatment consisted of a moist gauze therapy two times a day or more, depending on the productivity of the wound. The following "moist" agents could be used; 0.9% saline, 0.2% nitrofurazone (Furacine® solution, Norgine, Harefield, U.K.), 1% acetic acid solution, or 2% sodium hypochlorite (Eusol, The Netherlands). The choice of conventional moist agents depended on the degree of contamination, bacterial species, and debris. TNP therapy consisted of a polyurethane foam dressing with a pore size of 400–600 μm (V.A.C.® Pack Dressing) and a continuous negative pressure of 125 mmHg (V.A.C.® Classic, KCI, Houten, The Netherlands).

Before start of therapy, debridement of necrotic tissue took place in all the cases. We subdivided both therapy groups into acute and chronic wounds and problematic and nonproblematic healers. Acute wounds were defined as; existing for a short period of time before intervention (< 1 month) and acquired as a result of (i) trauma, (ii) infection, or (iii) an operative procedure. The wounds showed external manifestations of normal wound healing. Chronic wounds were defined as; existing more than 1 month before the intervention and were categorized as (i) pressure ulcers, (ii) chronic nonhealing wounds, and (iii) infected nonhealing wounds without a tendency toward normal wound healing (detailed demographic features can be found in a previous study (25) (Table1). To evaluate whether the levels of the biochemical parameters measured (i.e., albumin, pro-MMP-9, active MMP-9, and TIMP-1) can be used as prognostic indicators for wound healing, we retrospectively subdivided wounds

Table 1. Baseline characteristics

		TNP (n=15)	Conventional (n=18)	p-value
Age (years)		50.2 (±21.7)	48.3 (±18.2)	0.63
Male/female		12/3	11/7	
BMI index *	<20	1	1	0.26
	20-24	3	8	
	>25	11	9	
Wound type	Acute	6	6	0.97
	Chronic	9	12	
Location	Lower extremity	11	9	0.19
	Upper extremity	2	1	
	Trunk	2	8	
Diabetes Mellitus		3	1	0.58
Vascular disease		3	1	0.41
Osteomyelitis		3	3	0.61
Corticosteroids		-	1	0.29
Antibiotics		6	7	0.23
Duration until "RFSG" **		4.6 (± 2.0)	7.0 (± 4.4)	0.09
Problematic healer		3	7	0.41
*** Albumin (g/L)		3.5 [1.0 -6.1]	2.8 [0.8 – 5.4]	0.08
*** Pro-MMP-9 (ng/mL)		795 [52-3535]	1102 [2- 2894]	0.4
*** Active MMP-9 (ng/mL)		416 [24- 2248]	204 [28-3667]	0.9
*** TIMP-1 (ng/mL)		231 [64-2995]	272.5 [80- 3160]	0.9

* BMI index: weight/(length)^2

** "ready for surgical grafting", mean (± sd)

*** Comparison of baseline levels of variables measured at day 1, median [range]

into nonproblematic healers and problematic healers. Problematic healers needed a duration of wound therapy of more than 7 days after debridement to reach the state of "ready for surgical closure" or showed signs of impaired wound healing after surgical closure.

The study protocol was formulated conform the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Medical Ethics Committee of the Erasmus University Medical Center.

Study protocol

Wound fluid was collected daily for up to 10 days using sterile porous, polyvinylidene fluoride filters (Durapore membrane filters, Millipore®, Amsterdam, The Netherlands ∅47 mm and 0.1 µm thick), which were placed randomly across the surface of the wounds until totally saturated. No preference was made as to the location of the filters in order to require an overall view of the wound exsudate. In total, four filters per wound per dressing change were collected after full saturation and placed paired in sterile syringes. The duration of saturation depended on wound productivity, but never exceeded 20 minutes. One thousand microliters of ice-cold (4°C) phosphate-buffered saline (PBS, pH 7.4) was added. The syringes were rocked gently for 10 minutes to elute the wound fluid proteins from the filters. The filter extracts were then centrifuged at 4,000 r.p.m. for 10 minutes at 16°C, to remove particulate

matter. The supernatant of both syringes was mixed, divided over three aliquots, and stored at −20°C until analyzed.

Quantitative measurements of pro-MMP-9 and TIMP-1 protein levels were performed in duplicate using enzyme-linked immunosorbent assay (ELISA: human Biotrak Assay), according to the manufacturer's instructions (Biotrak Amersham Bioscience, Buckinghamshire, UK). The assay for pro-MMP-9 has <2.7% cross-reactivity with active MMP-9. Active MMP-9 was quantitated with the Biotrak Activity Assay System (Biotrak Amersham Bioscience). In this system, samples are incubated in microtiter wells, precoated with anti-MMP-9 antibody. Both pro-MMP-9 and active MMP-9 become bound to the anti-MMP-9 antibodies. After a wash procedure, a modified prourokinase was added where the activation sequence (normally recognized by plasmin) was replaced using protein engineering with an artificial sequence that is specifically recognized by matrix metalloproteinases. The urokinase activity, thus generated by active MMP-9 only, was detected by cleavage of a chromogenic substrate. Results were expressed as nanogram antigen per milliliter wound fluid (ng/mL) for all metalloproteinases and TIMP-1. The concentrations of albumin were expressed as gram per milliliter (g/mL) and were determined by a turbidimetric immunoassay, used for routine quantification of albumin in urine.

Statistical analysis

Therapy groups were checked for imbalance of baseline characteristics between both therapy groups. The tests performed were Fisher's exact tests for categorical variables, and the Mann–Whitney test for continuous variables as appropriate (age, body mass index, BMI) (SPSS 10 software). The longitudinal measurements of albumin, pro-MMP-9, active MMP-9, and TIMP-1 over time were analyzed using mixed-model ANOVA (random coefficient models). SAS PROC mixed (SAS Institute Inc., Cary, NC) was used in these calculations. All parameters except albumin were logarithmically transformed to obtain approximate normal distributions. Two-sided p-values<0.05 were considered to be significant in all analyses.

Results

Proteinase activity and albumin levels were measured in 33 wounds, of which 15 were treated with TNP therapy and 18 with conventional treatment. We found no relevant differences in the baseline characteristics (Table1). The baseline value (T_0) after debridement on day 1 of albumin, MMP-9, and TIMP-1 did not differ significantly between the treatment groups. The differences in levels of the biochemical markers were measured and compared longitudinally in time during 10 days of follow-up (T_0–T_{10}).

No significant difference was found on comparing albumin levels in wound fluid of TNP-treated wounds with conventionally treated wounds during 10 days of follow-up. However,

the amount of albumin in chronic wound fluid (CWF) of TNP-treated wounds had a tendency to remain higher compared with CWF of conventionally treated wounds, returning to comparable levels after 5 days (Figure 1A). On comparing wound fluid of acute wounds (AWF)

Figure 1A

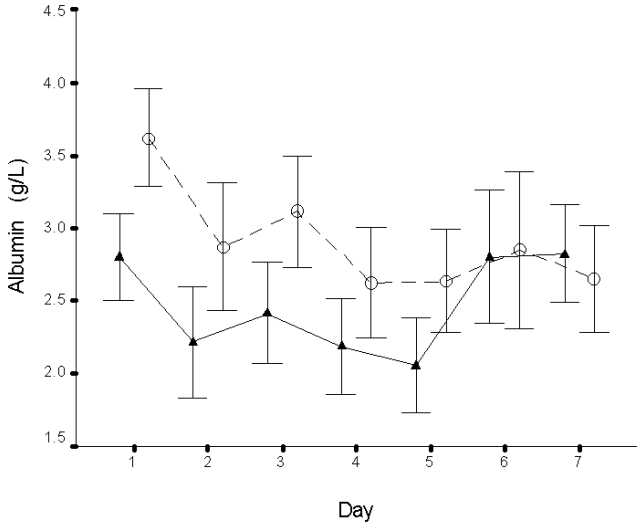

Figure 1B

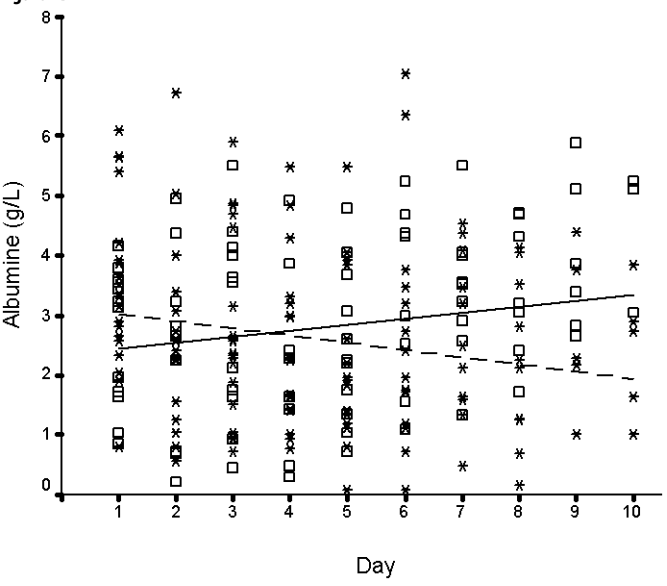

Figure 1. (A) Mean amount of albumin (g/L) in CWF treated with TNP therapy (open circle) and conventional treatment (black triangle). (B) Scatterplot displaying mean levels of albumin (g/L) in AWF (squares) and CWF (stars). The interrupted line shows a negative mean linear regression (decrease) of albumin levels in CWF, the solid line shows a positive mean linear regression (increase) of albumin levels in AWF.

with wound fluid from chronic wounds, imperative of therapy, albumin levels were found to increase with 0.10 g/L per day (95% confidence interval [CI]: 0.01–0.20) ($p<0.05$) in AWF while the albumin level of chronic wounds decreases with 0.12 g/L per day (95% CI: 0.05–0.20) ($p<0.01$). These two longitudinal lines divergate significantly from each other ($p<0.01$) (Figure 1B). Measurement of albumin levels in wound fluid might therefore be used as a relatively simple marker for the clinician to be alarmed about the tendency of the wound to become chronic.

The level of pro-MMP-9 activity showed a significant difference in the wound fluid of conventionally treated wounds compared with TNP-treated wounds. The level of pro-MMP-9 increased significantly during follow-up of 10 days in the conventionally treated group (+9.5% per day [95% CI: 2–8%]) ($p=0.01$), while TNP-treated wounds remained stable throughout the period of follow-up without a significant increase- or decrease (+0.9% per day [95% CI: −6 to 9%]) ($p=0.80$). The average difference between these lines, displayed in Figure 2, is 77% higher in conventionally treated wounds (95% CI: 14–175%) ($p=0.01$) compared with TNP-treated wounds.

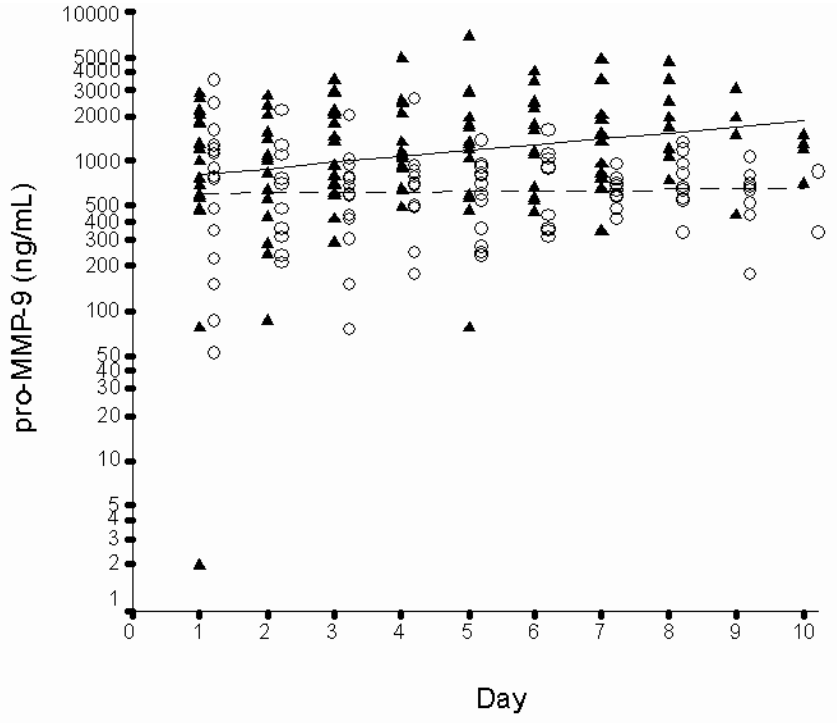

Figure 2. Scatterplot displaying mean pro-MMP-9 levels (ng/mL) in TNP treated wounds (open circle) compared to conventional treated wounds (black triangle). The linear regression analysis shows a significant increase over time in conventionally treated wounds (solid line) with mean values which are on average 77 % higher compared to a general stable linear regression in TNP treated wounds (dotted line). Horizontal axis: days post debridement. Note the logarithmically scaled vertical axis. (The single outlying observation at day 1 did not greatly affect the outcome of the regression analysis).

In both TNP-treated and conventionally treated wounds, a negative correlation between active MMP-9 and TIMP-1 was found (Figure3), which agrees with the findings in the literature. A doubling of TIMP-1 was associated with a 23% decrease (p=0.013) of active MMP-9 using conventional therapy, and with a decrease of 31% (p=0.006) using TNP. Although this correlation has a tendency to be stronger in TNP treated wounds, it is not significant.

The ratio of total MMP-9 (active MMP-9 plus pro-MMP-9) to TIMP-1 differed statistically between both treatment groups, increasing over time (p=0.02). In conventionally treated wounds, a significant increase of 12% per day was found (95% CI: 4–21%) (p<0.005), while TNP-treated wounds remained generally stable throughout the follow-up period (–2% per day [95% CI: –10 to 14%]) (p=0.60) (Figure4). This difference was mostly due to the significant difference in the level of pro-MMP-9 between both treatment groups. Active MMP-9 levels showed a tendency to remain on average lower and the level of TIMP-1 on average higher in TNP-treated wounds; however, these differences did not reach significance. Except for albumin, none of the other parameters (i.e. pro-MMP-9, active MMP-9, TIMP-1) showed a significant difference in their levels on comparing acute with chronic wounds.

In the conventionally treated group, seven patients were considered to be problematic healers, with five patients taking over 7 days until "ready for surgical closure," of whom two

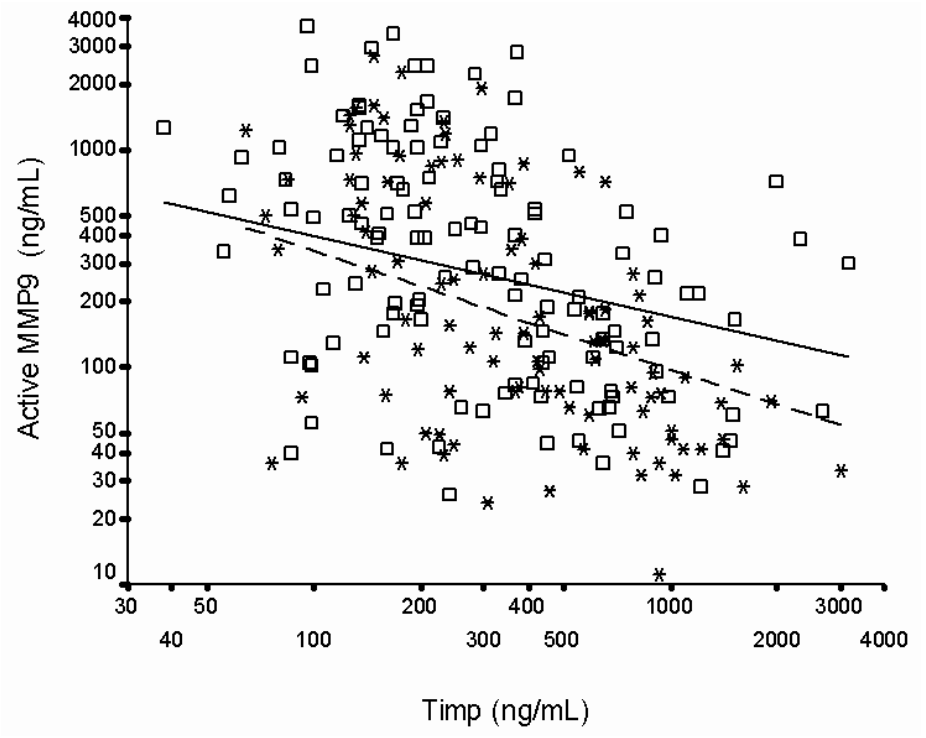

Figure 3. This figure displays the correlation between active MMP-9 and TIMP-1 in TNP treated wounds (stars, with a dotted line showing the linear regression) and conventionally treated wounds (squares, with a solid line showing the linear regression).

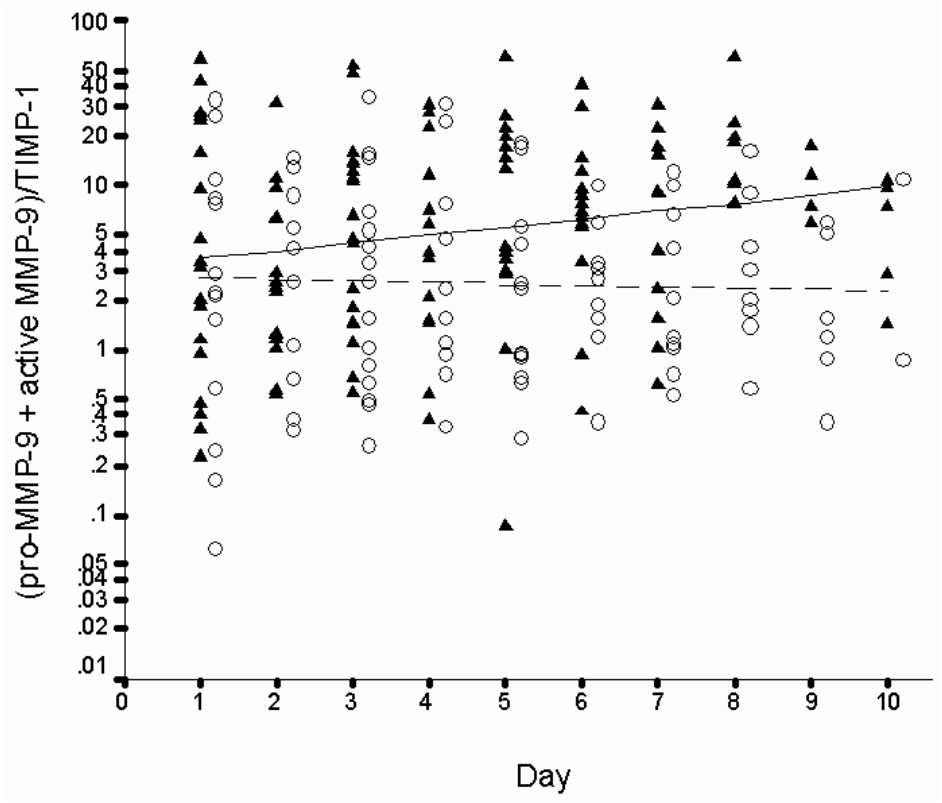

Figure 4. Scatterplot displaying Total MMP-9/TIMP-1 ratio in TNP treated wounds (open circle) compared to conventionally treated wounds (black triangle). The mean linear regression analysis shows a significant increase over time in conventionally treated wounds (solid line) compared to a general stable linear regression in TNP treated wounds (dotted line). Horizontal axis: days post debridement. Note the logarithmically scaled vertical axis.

also developed a postoperative complication (50% superficial skin graft [SSG] take and fistula formation), together with another two patients developing a complication (50–80% SSG take [n=2]). In the TNP group, three patients were considered to be problematic healers, one taking longer than 7 days and, in addition, developing a postoperative complication (<50% SSG take), together with another two patients developing a complication (fistula [n=2]). We found no significant difference between problematic healers and nonproblematic healers on comparing the various variables at day 1 post debridement nor did we find significant differences on analyzing changes in the level of the variables along time.

Discussion

Increased interest has been focused, in the last decade, on the wound environment that bathes the wound and possible clues and explanations for decreased and prolonged wound

healing in chronic wounds. Because wound fluid contains locally produced tissue products, it is suspected to provide an insight into the biochemical and cellular microenvironment of the wound bed. Sequential sampling studies using tissue biopsies or acute wound fluid (AWF) in both experimental animal and patient studies have provided information about the sequence of biochemical changes in normal wound repair (26,27). However, the role of MMPs in chronic wounds remains less clear. It is not yet evident if wound fluid samples are accurately reflecting all processes that might be present in the tissue itself (28). Previous reports provided data supporting the hypothesis that elevated levels of MMPs contribute to the failure of wounds to heal (12,27,29,30) while more recent work could not confirm any differences in expression of MMPs between acute or chronic wounds (28). These controversies could be attributed to the lack of consensus on wound fluid collection methods. A diverse range of methods have been used for the collection of wound fluid differing in both complexity and invasiveness (31) (i.e., aspiration of wound fluid from underneath occlusive film dressings, blunt end glass microcapillaries, absorbent dressing extraction, hydrophilic dextranomer beads and filters, and different sorts of draining and suction devices). No study to date has compared the effectiveness and efficiency of the collection methods. We have chosen to absorb wound fluid using hydrophilic filters, which is a rapid, noninvasive method that could be used easily in everyday practice. This also means that we recognize the difficulty of extrapolating our results to studies using the TNP suction drainage tubes (28) because this is material collected over hours of therapy.

The clinical handling/management of wounds would be improved if indicators or biochemical markers were available that could either predict or monitor progress toward healing. An important characteristic of an ideal biochemical marker would be that not only the method of collection but also the method of analysis is simple, inexpensive, robust, sensitive, and specific, using a specimen that is easy to collect in a reproducible manner and that remains stable over a longer period. The biochemical markers that we have investigated in this study (albumin, MMP-9, and TIMP-1) are relatively easy to measure in diagnostic laboratories.

We found that albumin levels of chronic wounds decreased significantly after debridement while increasing in acute wounds. James et al. and Chant (32,33) suggested that reduced levels of albumin in nonhealing chronic wounds are the consequence of capillary collapse due to capillary and tissue pressure imbalance, which reduces the protein delivery to the wound site. This could mean that with the measurement of albumin levels in wounds, one might predict the chronicity of wounds, from which earlier interventions could ensue. Although our study confirms the differences in albumin expression between acute and chronic wounds, we could not confirm the predictive value of albumin measurements in differentiating between problematic and nonproblematic healers.

We have also found significant differences in levels of proteases in wound fluid of TNP-treated wounds compared with conventionally treated wounds. The amount of pro-MMP-9 is significantly lower during the follow-up period in TNP-treated wounds compared with

conventionally-treated wounds, which could be a sign of better wound environmental conditions in TNP-treated wounds (17). Regarding the ratio of total MMP-9/TIMP-1, again a significant difference is seen in favor of TNP-treated wounds. Not only does the ratio of total MMP-9/TIMP-1 remain significantly lower in TNP-treated wounds compared with conventionally treated wounds but it also remains stable throughout the sequential sampling period. Ladwig et al. (12) provided strong data supporting the hypothesis that elevated levels of MMPs contribute to failure of wounds to heal by showing a strong correlation between good healing and low ratios of total MMP-9/TIMP-1 in a large series of patients with chronic wounds. Tarlton et al. (17) observed significant changes in levels of pro-MMP-9 in parts of wounds that did not heal compared with those that did. Although differences in levels were confirmed in our study, we could not confirm the predictive value of MMP-9 nor pro-MMP-9 measurements in differentiating between problematic and nonproblematic healers or in acute and chronic wounds.

We were surprised to find that the large difference in pro-MMP-9 levels between the two therapy groups did not lead to a significant difference in levels of activated MMP-9, especially because a number of studies, especially in eye research, have suggested that besides the MMP expression-regulating factors like cytokines and growth factors, pseudomonal elastase has also been found to be an important activator of pro-MMP-9 (34,35). We previously reported a significant decrease of the number of nonfermentative negative rods (*Pseudomonas* spp., *Pseudomonas aeroginosa*, and *Acinetobacter* spp.) in TNP-treated wounds (20). Although the significant reduction of *Pseudomonas* and *Acinetobacter* species in TNP-treated wounds might be an explanation for the low amount of active MMP-9, it does not explain the mutually low levels of active MMP-9 in conventionally treated wounds in which the significant decrease in nonfermentative negative rods was not shown. Another explanation for the low levels of active MMP-9 in both treatment groups could lie in the influence of the storage of the wound fluid samples. Samples were stored at −20°C according to the guidelines of the cellular communication assays of Biotrak Amersham Bioscience. A recent inquiry within our research department suggests, however, that fluid samples transported on dry ice, followed by storage at −70°C entail more proteolytic activity compared with samples stored at −20°C.

In this study, we could not correlate the outcome of the potential biochemical markers with clinical healing or problematic healing as compared with other investigators (12,17). An explanation could be our heterogeneous study population (in the type of wounds, duration, localization, and severity of wounding) together with the rather small group size. Another explanation could involve the difference in the collection of wound fluid compared with other studies, which we mentioned in an earlier section (31). A third explanation could be the method of analysis. We used ELISA while others have used zymography, the latter being a sensitive but not a very specific and not a truly quantitative method, together with a higher possibility of sampling contamination (36).

In summary, within this mixed hospital population significant differences have been found between biochemical analyses of wound fluid collected from wounds treated with TNP compared with conventional gauze therapy. These results might suggest that TNP influences the microenvironment of the wound most probably through continuous removal of exudate, reducing accumulation of inhibitory factors, and that in addition to the previously described effects of this dressing on wounds, the modulation of the relationship of MMPs with TIMPs is relevant and indicates that this could represent a further advantage in the treatment of wounds. To find the ultimate biochemical indicator for treatment response or prognosis of healing will be an important project for further investigation. For this, further studies with larger study samples are needed.

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CHAPTER VIII

A review of topical negative pressure therapy in wound healing: sufficient evidence?

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CHAPTER IX

Vacuum assisted closure: recommendations for use. A consensus document

Expert Working group

Principles of best practice. A World Union of Wound Healing Societies' initiative (WUWHS).

International Wound Journal 2008; 5: Suppl 4, 1-19

This article draws on the consensus opinion of an international group of experts and has been modified to fit the format of this thesis. The consensus document was supported by an unrestricted educational grant from KCI Europe Holding BV. The views expressed in this document do not necessary reflect those of KCI.

Foreword

This timely initiative draws on both the research evidence and the consensus opinion of an international group of experts (see below) to provide guidance on the successful integration of vacuum assisted closure therapy (VAC therapy*) into clinical practice. The document specifically reviews its potential use in the following selected indications: diabetic foot ulcers, complex leg ulcers, pressure ulcers, dehisced sternal wounds, open abdominal wounds and traumatic wounds. In addition, it considers quality of life and cost-effectiveness, both of which are gaining importance when evaluating treatment. This document highlights questions for future research and is designed to be practical and adaptable for local use in countries worldwide (K. Harding).

Expert working group

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* Vacuum-assisted closure wound therapy (in short VAC) also called topical negative pressure therapy (TNP).

Recommendations for use

Vacuum assisted closure (VAC) therapy has helped to improve wound care outcomes and has led to a number of dramatic changes in clinical practice over the past decade (1,2). VAC therapy must be used as part of an individualised, comprehensive treatment plan and is indicated for both acute and chronic wounds.

Planning treatment

In all situations the underlying wound etiology and comorbidities must first be addressed and treated. It is essential to optimise all aspects of the patient's physical, nutritional and psychosocial wellbeing to ensure treatment is suitable and of maximum benefit. Before starting VAC therapy it is important to define treatment aims, objectives and clinical endpoints. In some circumstances the objective will be to avoid further complications and to control symptoms, rather than to influence time to healing. Examples of clinical endpoints for VAC therapy include 50% volume reduction (3), 80% granulation tissue formation or complete closure.

In general, the key aims are to:

- Remove exudate and reduce periwound oedema
- Increase local microvascular blood flow/test vascularity
- Promote formation of granulation tissue
- Reduce complexity/size of the wound
- Optimise the wound bed prior to and following surgery
- Reduce complexity of surgical wound closure procedures (4).

In addition, the application of the VAC dressing system creates a closed, moist wound environment, which may act as a barrier to bacteria and patient/caregiver interference. VAC therapy may also help to promote patient independence, mobility and comfort.

Identifying responders to VAC therapy

In chronic wounds, it may be helpful to use the factors listed in Table 1 to assess whether the wound is likely to have a positive response to VAC therapy. It must be noted, however, that in many circumstances the patient/wound will not exhibit these attributes and yet VAC may still have an important role. A good example of this is the diabetic foot ulcer where the patient often has multiple comorbidities and the wound has a poor blood supply. For acute wounds, it is important to adequately debride the wound and follow recommended guidelines for specific wound types (e.g. dehisced sternal wounds) before commencing therapy.

Table 1. Factors that may increase success of therapy

Wound factors	Patient factors
Wound has good blood supply	Maximally medically stabilized (e.g. nutrition, blood pressure, blood glucose, fluid balance, infection
Wound has healthy, granular bed	Patient has few or well-controlled comorbidities
Wound has been freshly debrided *	Patient is comfortable (e.g. not in pain)
Wound produces high levels of exudate	Patient is adherent with therapy
Wound is greater than 2 cm wide	

*Occasionally, in some chronic wounds, surgical debridement may not be appropriate. Prior to starting VAC therapy it is important to ensure that the wound has a clean wound bed and that it does not contain necrotic tissue or excessive debris

Evaluating treatment

It is important to review progress regularly. This will involve an accurate and reproducible method of wound measurement. If there is a reduction in wound area (e.g. around 15%) after one or two weeks (5), strong consideration should be given to continuing VAC therapy with ongoing clinical evaluation. Reassess again after a further week of therapy. If there is no improvement, discontinue VAC therapy and begin an alternative treatment. VAC therapy may be reconsidered at a later stage.

In chronic wounds, an effective general assessment measure is to:

- Examine the wound margins for inflammation after the first application of VAC therapy. If there is increased inflammation consider discontinuing treatment
- Re-examine the wound margins for a thin white epithelium after the second and subsequent applications: this indicates healing
- Evaluate the overall appearance of the wound bed. A beefy, granular appearance is a positive outcome, while a dusky bed indicates inadequate tissue perfusion. Granulation tissue should increase by around 3–5% per day.

Under ideal conditions (especially in the absence of infection), well perfused wounds will respond quickly (i.e. within one week) with evidence of granulation tissue formation. This can be used to test vascularity and suitability of VAC therapy.

Adverse reactions have, on occasion, been reported (e.g. adherence to deep tissue structures). These can often be avoided by following recommendations, involving appropriately trained staff and by developing effective communication strategies. Specialist involvement will be required in certain situations.

VAC therapy and wound infection

VAC therapy is not recommended as a stand-alone treatment for wound infection (6). However, it may be used with extra caution in infected wounds as long as this is in addition to appropriate treatment of the infection (see Table 2).

Table 2. Factors to consider in the presence of infection

Debridement
Patient optimization
Antibiotic therapy
Frequent patient/wound assessment
More frequent dressing changes
Appropriate pressure settings
Periwound skin protection
Fenestrated antimicrobial dressings
Discontinue VAC therapy in case of deterioration

In the presence of persistent infection or deterioration, or in wounds exhibiting no clinical progress towards healing (i.e. odour continues or becomes apparent), perform a thorough patient and wound reassessment (including microbiological investigations), discontinue VAC therapy and change treatment. Always consider whether systemic antibiotic therapy and/or appropriate debridement is required and treat the wound infection according to local protocols. If infection develops during therapy, consider systemic antibiotic treatment and discontinue VAC therapy to allow monitoring of the wound. On specific occasions, a modification of VAC therapy may be considered for use in severely infected wounds (e.g. infected hip and knee implants and orthopaedic hardware). This involves the combination of vacuum therapy with installation of antibiotics/antiseptics into the wound bed (7, 8).

Diabetic foot ulcers

Clinicians may sometimes wrongly consider all diabetic foot ulcers to be the same for treatment purposes. In fact, there is considerable variation and the decision to use VAC therapy will depend on the wound subtype. VAC therapy can be considered for deep complex wounds, for post-surgery wounds and, occasionally, for superficial wounds in addition to standard treatments. For patients with ischemic wounds, referral to a vascular surgeon should be considered prior to VAC therapy.

Deep complex diabetic foot wounds

VAC therapy can be used in a number of ways to manage the complex diabetic foot wound:

- Reduce complexity/size –i.e. simplify the wound. In non-infected, non-ischemic, deep complex diabetic foot ulcers, VAC therapy can be used to reduce the surface area of the wound by encouraging granulation tissue formation over exposed bone, tendon or tissue. This may help to avoid the need for skin grafting and/or flaps or to reduce the complexity of the subsequent surgical closure procedure (9, 10). A special dressing technique should be used to prevent further pressure damage in plantar wounds when applying VAC therapy (11)

- Promote deep healing –Experience has shown that on occasions VAC therapy can be used for longer periods in combination with other treatment modalities (e.g. systemic antibiotics) to allow complete healing of an underlying osteomyelitis before skin closure. This avoids the problem of ulcer recurrence with residual osteomyelitis (i.e. where skin heals before the underlying bone).

In poorly perfused wounds where revascularisation is not possible, using VAC therapy for a trial period allows the clinician to observe the response to therapy and assess the viability of the tissue. Even when a positive outcome is unlikely, VAC therapy used in this way has shown unexpected and encouraging results. The clinician should strive for the most distal amputation level that achieves healing and a functional outcome (9).

Planning treatment

The planned duration of therapy for diabetic foot wounds will depend on the specific treatment goal. In many cases an initial one- to two-week period of therapy is recommended. After this time, the wound should be evaluated for progress or deterioration, and:

- If progress is good– i.e. there is a daily increase in healthy granulating tissue formation, decreasing wound depth, a good blood supply and no infection – continue VAC therapy until the treatment goal is achieved
- If progress is poor or there is deterioration, consider alternative treatments or breaks ('time-outs') in VAC therapy. During this time the clinician should re-evaluate perfusion, focus on optimising medical therapy and use other wound modalities until the tissue quality improves. Often at this time VAC therapy can be successfully reinstated.

Application to practice

- Use VAC therapy only after any underlying disease has been diagnosed and managed and after appropriate debridement of non-viable tissue
- VAC therapy can be an effective adjunct to revascularisation in diabetic foot wounds
- VAC therapy should be used only after surgical drainage of any infection with concomitant systemic antibiotic therapy according to local protocols
- VAC therapy should be combined with effective offloading and good wound care.

Post- surgery diabetic foot wounds

Randomised controlled trials (RCTs, Table 3) support the use of VAC therapy for the following:

- After open partial foot amputation (from open toe/ray/to metatarsal level) (9,12, 13)
- To aid fixation or bolstering of skin grafts (14).

Split-skin grafting and bioengineered tissue replacements, particularly acellular matrices, have been used in combination with VAC therapy as a practical alternative to flap closure in deep complex wounds (15). VAC therapy promotes vascular perfusion, which has been shown to enhance skin graft take (14).

Planning treatment

It is not always appropriate to start VAC therapy immediately following surgery and it may be beneficial to observe the wound for 1–2 days prior to application (16).
The decision to select VAC therapy will depend on:

- Viability of the skin edge and the tissue immediately below it
- Whether there is capillary bleeding
- Whether infection has been addressed and necrotic tissue has been removed
- Treatment goals and patient factors.

VAC therapy should be stopped after the clinical endpoint is achieved (e.g. an appropriate reduction in volume or adequate wound bed preparation for subsequent skin grafting).

Superficial diabetic foot wounds

VAC therapy is not recommended as a first-line treatment in superficial wounds. However it may be considered along with other advanced therapies where there has been a poor response to other treatments (i.e. effective offloading, management of infection and local dressings). Use VAC therapy with caution if the TcpO2 is between 20 and 30 mmHg and there is impaired sensation (in such cases use lower pressure settings).

Table 3. Summary of key (SIGN level 1) studies in diabetic foot ulcers

Study	Interventions	Design	Selection criteria	Clinical outcome
Armstrong DG, et al. (9)	VAC therapy vs modern moist wound therapy for 16 weeks	Multicentre, randomised, controlled trial n=162	Diabetic foot amputation to transmetatarsal level, with adequate perfusion	VAC therapy achieved wound healing in 56% vs 39 % (p=0.04) of patients with median wound bed preparation time of 42 days vs 84 days (p=0.02) compared with controls
Eginton MT, et al. (12)	VAC therapy vs conventional moist gauze dressings for 2 weeks	Randomised controlled crossover trial n=10	Large diabetic foot wounds with adequate perfusion, sharply debrided for entry	VAC therapy reduced wound volume and depth by 59% vs 0% (p<0.005) and 49% vs 8% (p=0.05)respectively, when compared with controls over the observation period
Mc Callon SK, et al. (13)	VAC therapy vs saline-moistened gauze	Randomised controlled pilot study n=10	Non-healing (>1 month) postoperative diabetic foot wounds, surgically debrided before treatment. Patients with venous disease, active infection or coagulopathy were excluded	VAC therapy produced an average decrease in wound surface area of 28% vs 9.5% increase for controls, and a average time to satisfactory healing of 22.8 days vs 42.8 days for controls. Delayed primary closure was achieved in four of five patients with VAC therapy compared with two of five controls (p values not given)

Note: Although traditional gauze has been used as the comparator in many trials, the largest of these studies (9) used a wide variety of moist wound dressings in the control group. Further studies using modern wound products vs VAC therapy have been published or are in progress. SIGN methodology complies with the criteria used by the AGREE (Appraisal of Guidelines for research and evaluation in Europe) to indentify good quality guidelines. For further information about SIGN levels of evidence visit www.sign.ac.uk.

Complex leg ulcers

It is recognised that compression therapy is regarded as the first-line treatment for venous leg ulcers (17). However, there is a role for VAC therapy in inflammatory or complex therapy-resistant leg ulcers that are unsuitable for compression (Table 4). The use of portable VAC systems may also allow ambulatory patients to be treated at home and can reduce the need for hospitalisation. For complex leg ulcers it is important to assess the wound thoroughly using bacterial culture and biopsy to confirm the diagnosis. Surgical debridement should be performed prior to the application of VAC therapy to increase the potential for success.

Inflammatory ulcers

In patients with inflammatory ulcers, VAC therapy can be used to enhance wound bed preparation before definitive surgical closure or delayed secondary healing. These patients historically have hard-to-heal wounds with high rates of skin graft failure.

Ulcers may occur in the following situations:

- Scleroderma
- Systemic lupus erythematosus
- Hypercoagulation disorders
- Rheumatoid arthritis
- Vasculitic conditions.

If the underlying clinical condition is resistant or inadequately treated, inflammatory ulcers will usually not heal despite optimal wound management. In addition, as treatment usually involves non-steroidal anti-inflammatory drugs, healing may be further impaired. In non-infected ulcers, a short trial of VAC therapy can be considered to determine whether it is likely to be beneficial. VAC therapy should be applied for 1–3 days and then removed while the response is evaluated.

Complex therapy-resistant ulcers

VAC therapy can be considered for complex therapy-resistant leg ulcers including:

- Highly exuding ulcers
- Anatomically challenging ulcers (where the application and stabilisation of dressings is difficult)

- Wounds requiring skin grafting (VAC therapy is used here for preoperative wound bed preparation and postoperative graft stabilisation).

Note: In a non-healing chronic ulcer in which other treatments have not been successful, granulation tissue may not be seen for up to two weeks when using VAC therapy.

Table 4. Summary of key (SIGN level 1) study of VAC therapy in chronic leg ulcers

Study	Interventions	Design	Selection criteria	Clinical outcome
Vuerstaek JD, et al. (18)	VAC therapy vs standard wound care and compression therapy (including surgical debridement and punch skin graft transplantation in both groups)	Randomised controlled trial n=60	Patients hospitalised with complex leg ulcers (>6 months) after failure of surgical and extensive ambulatory treatment options. Patients were followed-up for a period of 12 months	VAC therapy achieved a wound bed preparation time of 7 days vs 17 days (p=0.005), a median time to complete healing of 29 days vs 45 days (p=0.0001) and a skin graft take rate of 83% vs 70% (p=0.011) compared with controls. VAC therapy reduced total nursing time (232 mins vs 386 mins; p=0.001) and treatment costs (($3,881 vs $5,452) compared with controls

Note: Further medium and long-term follow-up studies are required to demonstrate ulcer recurrence rates, together with the durability and maintenance of stable soft tissue cover following successful VAC therapy. The role of VAC therapy in oedema management also requires clarification

Pressure ulcers

The main role of VAC therapy in pressure ulcers is in reducing the volume of a large cavity wound (19-21). VAC therapy may also have an important role in promoting comfort (e.g. reduction in dressing changes, exudate and odour), improving patient quality of life and facilitating the nursing management of these complex wounds (21). It is not generally recommended for grade/stage 2 ulcers and should not be used where there is suspected deep tissue injury under intact skin (Table 5).

Grade/stage 3 and 4 pressure ulcers

VAC therapy is recommended as a first-line treatment for grade/stage 3 and 4 pressure ulcers in certain situations (24) and should be used as part of a comprehensive treatment plan. The entire base of the wound should be visible and examined before inserting the foam. These are often complex wounds with multiple tracts; if appropriate, the wound must be debrided prior to commencing VAC therapy, with excision of bony osteomyelitis, and be fully explored to allow access to all deeper extensions.

Optimising the wound

VAC therapy can be used preoperatively to precondition wounds for reconstruction or to allow a smaller and/or less complex flap to be used. This may help to reduce the operative

time, postoperative risk and donor site morbidity. The effect of VAC therapy should be assessed continuously for a period of up to two weeks. Duration of VAC therapy will be defined by the initial wound size and the available volume of tissue for reconstruction. Post-surgery, VAC therapy may be used to manage small dehiscence as well as to improve perfusion of a marginally viable flap.

Improving mobility/symptom control

In patients who develop pressure ulcers following a major life event (e.g. a traumatic spinal cord injury in an active patient), frequent dressing changes and long-term bed rest can have a critical impact on their sense of wellbeing. VAC therapy may allow patients to mobilise in a wheelchair earlier and to return to rehabilitation programmes more quickly. Further research is required.

Some patients with pressure ulcers, such as those who have had multiple flap reconstructions, benefit from longer periods (e.g. three weeks) of VAC therapy to control symptoms. This can, for example, reduce exudate and allow a period of comfort before managing the wound with conservative measures. VAC therapy may also have a palliative role providing improved quality of life for terminally ill patients with pressure ulcers. Failure to open subcutaneous wound spaces is a frequent cause of treatment failure.

Table 5. Summary of key (SIGN level 1+2) study of VAC therapy in pressure ulcers

Study	Interventions	Design	Selection criteria	Clinical outcome
Schwien T, et al. (22)	VAC therapy vs various wound care therapies	Retrospective matched group analysis (SIGN level 2) n=60 vs n=2288	Patients with a stage 3 or 4 pressure ulcer in the home healthcare setting	Thirty-five percent of patients receiving VAC therapy were hospitalised compared with 48% in the control group ($p<0.05$). Emergent care for wound-related problems was lower in the VAC therapy group (0% vs 8%; $p<0.01$)
Joseph E, et al. (23)	VAC therapy vs saline wet-to-moist gauze dressings for 6 weeks	Randomised controlled trial (SIGN level 1) n=24	Open wounds (79% pressure ulcers) in any location that had not closed or shown signs of healing within 4 weeks despite treatment	VAC therapy achieved a mean wound volume reduction of 78% vs 30% ($p=0.38$) compared with controls. VAC therapy was associated with fewer complications (17% vs 44%; $p=0.0028$)

Note: Further high-quality, prospective studies are needed to compare VAC with other advanced therapies in this patient group

Dehisced sternal wounds

VAC therapy should be considered as a first-line treatment for dehisced sternal wounds following cardiac surgery (25, 26). This can be used as a bridge to definitive surgical closure or to achieve delayed primary closure or flap reconstruction and closure (Table 6). In addition, VAC therapy may have the following benefits:

- Stabilises the sternum
- Facilitates sternal salvage
- Facilitates drainage of the anterior mediastinum
- Enables patients to be extubated and mobilised early
- Decreases long-term mortality.

Table 6. Summary of key (SIGN level 2) study of VAC therapy in dehisced sternal wounds

Study	Interventions	Design	Selection criteria	Clinical outcome
Sjögren J, et al. (27)	VAC therapy vs conventional treatment (rewiring, open moist saline gauze dressings, closed irrigation, pectoral muscle flaps or omentum flaps)	Retrospective controlled study n=101	Patients with post-sternotomy mediastinitis (defined according to US Centers for Disease Control and Prevention (CDC) guidelines)	VAC therapy achieved 100% survival compared with 85% in controls at 90 days ($p<0.01$) and decreased the need for surgical interventions (0% vs 57.5%). Patients receiving VAC therapy had a reduced failure rate in response to first-line treatment (0% vs 37.5% failures; $p<0.001$) compared with controls
Sjögren J, et al. (28)	VAC therapy for mediastinitis post coronary artery bypass grafting (CABG) vs cases without mediastinitis post- CABG	Retrospective controlled study n=46 vs n=4781	Patients undergoing CABG divided into those developing post-sternotomy mediastinitis (defined according to US CDC guidelines) and those not developing mediastinitis	Patients with mediastinitis post- CABG, who received VAC therapy demonstrated similar early and late survival rates compared with patients without mediastinitis post-CABG (not significant)
Kutschka I, et al. (29)	VAC therapy for post-sternotomy infection	Retrospective controlled study n=10	Patients with severe post-sternotomy mediastinitis and sternal bone necrosis	Patients with mediastinitis receiving VAC therapy demonstrated increased lung function (51.3% forced expiratory volume vs 46.1%; $p=0.02$, and 48.4% vital capacity vs 42.7%; $p=0.02$) compared with controls
Fleck TM, et al. (30)	VAC therapy for mediastinitis post cardiac surgery	Retrospective controlled study n=11	Patients with mediastinitis post-cardiac surgery (CABG, aortic valve replacement, or ascending aortic replacement)	Complete healing was achieved in all 11 patients. Patients treated with pectoralis flap closure with VAC therapy had a shorter intensive care unit stay than those not receiving VAC (median 1 vs 9.5 days) (p values not given)

Note: Further high-quality, prospective studies are needed to confirm improved survival rates in this patient group

Planning treatment

In deep infected sternal wounds debridement of bone is essential before applying VAC therapy. In suspected sternal wound infection, prompt action should involve irrigation, debridement, bone biopsy, tissue cultures and antibiotic therapy. It is important to protect underlying structures using a non-adherent interposed layer and to position the foam dressing correctly to reduce complications (25, 26). VAC therapy can be carried out initially for 48 hours. The viability of the wound tissue and culture results will then guide the decision to continue. Further cultures should be taken at each dressing change. Daily levels of serum C-reactive protein may also be used to guide therapy (31). In most patients 5–12 days of VAC therapy will be appropriate.

Note: Dehisced sternal wounds are complex, involve major organs and complications can be life-threatening. Involvement of a cardiothoracic surgeon with relevant expertise is essential. VAC therapy must be combined with appropriate use of antibiotics and other treatments.

Open abdominal wounds

VAC therapy has revolutionised the treatment of open abdominal wounds, yet historically there have been obstacles to its use in this challenging group of patients (e.g. the diverse etiologies). It can be used to achieve delayed primary closure with fascia or to accelerate granulation tissue formation prior to skin grafting. VAC therapy has been applied in many studies with abdominal wall wounds (Table 7) and the following benefits were noticed:

- Improves patient survival
- Decreases number of dressing changes
- Enables a higher rate of total abdominal wall closure
- Might decrease the need for secondary surgical reconstruction
- Reduces complications (e.g. fistula, incisional hernia, infection).

The complexity of the open abdomen means VAC therapy should be used only by specialists with appropriate training and expertise (33).

Planning treatment

Training, education and experience in using VAC therapy in the open abdomen all positively affect outcomes. The frequency of dressing changes is also important. Dressings must be changed every 48–72 hours in the absence of wound infection. However, the exact frequency is dependent on the individual patient's circumstances, but ideally should not be less than three times a week.

Patients with existing fistulae should be referred to a specialist centre as special techniques are required when applying VAC therapy in this situation. These include excluding the fistula before applying negative pressure to the remaining wound, and covering a small fistula with the foam dressing. The choice of technique will be influenced by the type and volume of fluid present as well as the treatment goal. Exposed bowel must be adequately protected using a non-adherent interposed layer to prevent fistula formation or other complications. These methods have been reported only as case studies and have not been formally tested in clinical trials.

Note: It has been suggested that VAC therapy should be used with extra caution in patients with bowel anastomoses or enterotomy repairs (35); however the technique used may be important in preventing adverse events (36).

Table 7. Summary of key (SIGN level 2) studies of VAC therapy in open abdominal wounds

Study	Interventions	Design	Selection criteria	Clinical outcome
Wild T, et al. (32)	VAC abdominal dressing vs classic VAC therapy vs conventional open therapies (laparostoma)	Retrospective controlled study n=62	Patients with an open abdomen following surgery for secondary peritonitis	VAC therapy was associated with a reduced mortality rate compared with conventional open packing (14% mortality VAC abdominal dressing vs 21% classic VAC therapy vs 59% conventional therapy group; p<0.0009)
Kaplan M, et al. (33)	VAC therapy vs other techniques (e.g. polypropylene, polyglactin/polycolic, Bogotá bag and vacuum pack method)	Data compilation from published literature n=2080	Patients with open abdominal wounds or abdominal compartment syndrome	VAC therapy achieved a 79% fascial closure rate compared with 58% for the vacuum pack method (p<0.001), 34% for polypropylene and 18% for the Bogotá bag. VAC therapy had lower incidence of fistula formation (e.g. 2.6% vs 7% for the vacuum pack method (p=0.034), 13 % for the Bogotá bag and 21% for the polypropylene)
Kaplan M, et al. (34)	VAC therapy vs "vacuum pack" method*	Retrospective controlled study n=22	Patients with abdominal compartment syndrome or at high risk of abdominal compartment syndrome. Patients had their abdomen open for >48 hours	VAC therapy achieved primary closure of abdominal wall in 78% vs 12.5% patients, with a median time to wound closure of 12 vs 23 days compared with controls. VAC therapy also reduced hospital stay (30 vs 41 days) and incidence of acute respiratory distress syndrome (9% vs 50% (no p values given)

Note: Retrospective studies have shown some advantage in using VAC therapy in the management of the open abdomen. Further high-quality prospective studies are needed to confirm its role as the standard of care in this wound type. *Vacuum pack: moist towels sealed with an adhesive backed drape combined with wall suction

Traumatic wounds

One of the most important roles for VAC therapy is in the treatment of complex traumatic wounds. It should be used in combination with a comprehensive surgical assessment, exploration and debridement, which will be different for each wound type. In heavily contaminated wounds, delayed closure can be performed following repeated debridement and reapplication of VAC therapy.

Trauma wounds are diverse in relation to wound type, location, size and complexity. A multi-disciplinary approach is required, with the involvement of orthopaedic, plastic and trauma surgeons. VAC therapy is used traditionally to treat large soft tissue loss. In addition, it has an emerging role in the management of open fractures of the lower extremity, high and low-energy trauma wounds, fasciotomy wounds, degloving injuries and burns (37-39) (Table 8).

It can facilitate the following:

- Stabilisation of skin grafts and improved donor site healing (40-42)
- Stabilisation of high-energy injuries (e.g. bomb-blast, gunshot wounds) or low-energy road traffic accident injuries, either on the battlefield (in the case of war wounds) or at an emergency department, allowing safe transfer of the patient to an appropriate centre (43)
- Management of open fractures. While the role of vascularised soft tissue cover remains the gold standard treatment of lower limb fractures, VAC therapy has been used to reduce the need for complex surgery. The duration of VAC therapy is defined by the intended treatment outcome (e.g. definitive closure, volume reduction or temporising during stabilisation of the patient or underlying fracture). It also allows monitoring of open fractures to assess the viability of tissue prior to final closure by flap surgery (44-46)
- Prevention of the progression of partial-thickness burns injuries (47). It may also be used for excised full-thickness burns prior to skin grafting.

Table 8. Summary of key studies of VAC therapy in traumatic wounds

Study	Interventions	Design	Selection criteria	Clinical outcome
Stannard JP, et al. (37)	VAC therapy vs pressure dressing or standard postoperative dressing	Randomised controlled trial (SIGN Level 1) (i) n=44 and (ii) n=44	Patients with (i) traumatic injury with subsequent surgical incision or with (ii) surgical incision following a high-risk fracture after high-energy trauma	VAC therapy reduced the duration of drainage in patients with haematomas or high-risk fractures compared with controls (mean 1.6 days vs 3.1 days for haematomas; p=0.03; and 1.8 days vs 4.8 days for high-risk fractures; p=0.02)
Yang CC, et al. (38)	VAC therapy vs traditional saline-soaked wet-to-dry dressings	Retrospective controlled study (SIGN level 2) n=68	Patients undergoing fasciotomies for documented, traumatic compartment syndrome of the leg	Overall time to definitive wound closure by delayed primary closure with sutures or split-thickness skin graft coverage was 6.7 days for VAC therapy and 16.1 days for traditional dressings (p=0.0001)
Labler L, et al. (39)	VAC therapy vs standard treatment (Epigard*)	Retrospective controlled study (SIGN level 2) n=23	Patients with severe open fractures of the lower extremity (type 3A or 3B) admitted as an emergency	VAC therapy achieved a lower rate of infection than Epigard (15% vs 55%, not statistical significant)

Note: Further, high-quality, prospective studies are needed to confirm outcomes in these complex wounds.

* Epigard: is a two-layer, non medicated synthetic skin substitute

Measuring impact of VAC therapy

There is no doubt that VAC therapy can have a positive impact on a patient's quality of life (48). Table 9 identifies how VAC therapy can improve a patient's experience of living with a wound. However, in order to justify the use of this intervention in everyday practice where resources are limited, the clinician needs to be able to present a robust economic argument for its use. This is complicated by the seemingly high acquisition costs of the system. It is suggested that clinicians need to focus on using factors other than unit costs (e.g. reduction in hospital stay, staff labour and reduction in adverse events) to measure economic benefits.

Table 9. Quality of life and cost- effectiveness of VAC therapy

Quality of life (18, 48)	Advantages based on subjective experience* • Control of odour and exudate in many wound types (i.e. social benefits) with less frequent dressing changes • Able to participate in daily living activities, physical therapy and rehabilitation • Improvement in adherence/compliance (e.g. with offloading) Disadvantages ** • Noise of the VAC therapy unit (can be intrusive and difficult to tolerate) • Weight of the VAC therapy unit (mobility can be a problem, especially in older people) Other considerations • Duration of treatment • Clinician's level of expertise and confidence in using the technology • Setting in which the treatment is given (home or secondary care) • Communication (benefits need to be explained/patients' expectations assessed)
Cost-effectiveness (18, 50-52)	• Reduction in use of resources and labour • Reduction in complexity and number of surgical procedure/adverse events • Reduction in length of treatment and hospital stay/number of hospitalisations • Improvement in clinical outcome

*NB: Further prospective studies are needed to confirm these proposed advantages

** Newer generation models may help to reduce noise/mobility problems

This model has been used for the diabetic foot wound, where there is evidence that VAC therapy is associated with lower overall costs of care (49). Future practice needs to find ways of developing more user-friendly condition-specific tools for measuring quality of life and cost-effectiveness in wound care.

Future developments

Further research is needed to increase understanding of the therapeutic effects of VAC therapy to give clinicians stronger arguments to support its use (53, 54). In particular, future trials should focus on the generation of level-1 evidence and further comparative data for specific indications. This will help to clarify the potential for VAC therapy in different wound types and to enhance clinical decision making in various population groups.

For example:

- There is a small but emerging use of VAC therapy in the paediatric population. Clarification is needed on the type of foam dressing and pressure settings to be used in these patients
- Further research is needed to establish the relationship between negative pressure and blood flow and the optimal pressure for wound healing (55)
- The economic impact of VAC therapy requires further evaluation to justify the increased cost of treatment against the overall benefit of shorter healing times
- As new negative pressure devices are developed, there will be a need to compare the effectiveness of these emerging systems
- Prospective, multicentre studies with a common protocol should be performed and are needed.

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CHAPTER X

Summary and conclusions in English and Dutch

C.M. Moues

Summary and conclusions in English

The epidemiology, the etiology and the phases of wound healing are described in **Chapter one**. Successful wound healing progresses through distinct and overlapping pathophysiological stages: (i) coagulation and inflammation, (ii) cell proliferation and repair of the extra cellular matrix and (iii) the remodeling phase. Non-healing wounds often remain "arrested" in one of these phases, usually because of continued inflammation or proliferation. Progress of wound healing may be influenced by specific treatment strategies targeted at specific types of wounds in different phases of healing. The large number of factors that are involved in wound healing; the large variation in wound characteristics and the patient status all play a significant role. The underlying wound etiology and the patient's physical, nutritional and psychosocial well-being must be addressed and treated at all times in order to ensure that the proposed treatment scheme is optimal for achieving the maximum benefit. Recent advances in technology combined with a better understanding of the complex cellular and biochemical mechanisms of wound healing have resulted in the development of a myriad of advanced wound healing modalities such as hyperbaric oxygen, topical growth factors, bioengineered skin, tissue equivalents and topical negative pressure (TNP) therapy. Treatment of complex full thickness wounds has become easier by incorporating TNP therapy into wound management programs. Surgical decision taking has shifted from an acute setting towards strategically planned operations. It has become possible to treat some wounds more conservatively than initially planned while others can be closed with sophisticated flaps at a better stage in the wound healing process within this surgical plan.

In an overview article on topical wound management described in **Chapter two**, we attempted to revive the history of wound management and highlighted some of the meaningful landmarks that became the actual guidelines for major developments in wound management. The importance of integrating the best research evidence with clinical expertise and patient hallmarks for the treatment of all wounds was emphasized once again in the conclusion. The physician has a new companion, the qualified registered wound nurse for accomplishing this task. Together, they can provide selected industrial products and treatment modules, chosen from an enormous array in the patient's best interest.

We compared the clinical effect and cost effectiveness of TNP therapy with conventional moist gauze therapy for the treatment of full thickness wounds in a prospective randomized clinical trial (**Chapters three and four**). Wounds were randomized to either therapy by closed envelope assignment. Treatment efficacy was assessed by semi-quantitative scoring of the wound conditions (signs of rubor, calor, exudate production and fibrinous slough/necrotic tissue). Healing was characterized by the development of a clean granulating wound bed ('ready for surgical therapy') and reduction of wound surface area. We demonstrated that the

use of TNP therapy in an average hospital population with full-thickness wounds resulted in improved wound healing as compared with conventional moist gauze therapy. This was reflected by the average healthier wound conditions and a significantly larger reduction in wound surface area as compared with conventionally treated wounds. However, we were unable to prove a significant faster recovery in this trial according to our criterion (decrease in the number of treatment days required to achieve 'ready for surgical closure'). Furthermore, TNP therapy was noted to be as expensive as conventional moist gauze therapy within our comprehensive population of wound patients. Although, material costs were much higher in the TNP-treated group, these were largely offset by the reduction in hospitalization costs (due to a positive trend in faster recovery) and to a smaller extent by the reduction in staff costs.

In the studies presented in **Chapter five** we examined whether the positive effect on wound healing found in TNP-treated wounds could be explained by a change in the number of bacterial species or the sort of bacterial species. We could not find a significant effect of either TNP therapy or conventional moist gauze therapy on the total number of bacteria colonizing the wound (*quantitative* bacterial load). However, an important shift in bacterial species (*qualitative* bacterial load) was noted: a decrease in the number of non-fermentative negative rods (*Pseudomonas* species, *Pseudomonas aeroginosa* and *Acinetobacter* species) was observed in TNP-treated wounds together with an increase in the number of *Staphylococcus aureus*.

In the studies described in **Chapter six** we compared the most appropriate bacterial sampling method (superficial swab vs. tissue biopsy) for the prediction of significant bacterial wound contamination and prediction of post-operative complication in contaminated acute and chronic full thickness wounds after debridement and before surgical closure. We concluded that superficial swab culture and biopsy were equally reliable methods for quantifying the number and qualifying the types of viable bacteria colonizing full thickness wounds during open wound therapy. The results presented have implications for the management of patients with post-debridement surgical full thickness wounds and indicate that microbiological analysis of superficial swabs taken by a standardized method eliminates the need for the patients to undergo biopsy procedures because the additional information provided by biopsy is limited. Nonetheless, culturing must be restricted only for those wounds, which show signs of critical bacterial colonization or invasion by microorganisms. This is expressed as an enlargement of the wound, erythema extension or increased pain. In those cases topical antiseptics are indicated or in systemic infection parental or systemic antibiotic therapy.

We carried out biochemical analysis of wound fluids from TNP-treated and conventional gauze-treated wounds in studies described in **Chapter seven**. We hypothesized that continuous removal of exudate reduces the accumulation of inhibitory factors and mechanically induces a new supply of interstitial wound fluid by means of a negative pressure. Significantly

lower levels of pro-MMP-9 and lower total MMP-9/TIMP-1 ratio were observed in wound fluids from TNP-treated wounds during the follow-up of 10 days. These results might suggest that TNP influences the microenvironment of the wound most probably through continuous removal of exudate, reducing accumulation of inhibitory factors, and that in addition to the previously described effects of this dressing on wounds, the modulation of the relationship of MMPs with TIMPs is relevant and indicates that this could represent a further advantage in the treatment of wounds.

In the studies described in **Chapter eight** an analysis of peer reviewed publications was carried out, evaluating the results of basic research on the effectiveness and clinical application of TNP. More than 400 peer reviewed publications were encountered. Almost all the studies were related to the use of the commercially available V.A.C. ® device. There was a small number of studies on the use of gauze-based TNP therapy. We concluded that the mechanisms of action that can be attributed to TNP therapy were: increase of blood flow, promotion of angiogenesis, reduction of wound surface area in several wound types but not all wounds, positive modulation of inhibitory contents in wound fluid and induction of cell proliferation. We also observed that edema reduction and bacterial clearance, mechanisms that were initially attributed to TNP therapy, were not proven by basic research. It remains unknown whether gauze-based TNP therapy combining negative pressure rates of between 40-80 mm Hg with gauze and different suction tubing match these results, since the above mentioned conclusions are based on the studies using 125 mmHg TNP combined with PU or PVA sponges.

In **Chapter nine** the international consensus document on TNP therapy is presented, supported by the World Union of Wound Healing Societies, compiled by a selected group of international expert opinion leaders. The document describes the use of TNP in six different wound types; diabetic foot wounds, leg ulcers, pressure ulcers, infected sternal wounds, open abdominal wounds, and traumatic wounds. Moreover, it focuses on the cost effectiveness of TNP therapy. Clinical recommendations for TNP therapy based on randomized clinical trails and retrospective cohort studies are made in this document. Especially, chronic wounds such as diabetic foot ulcers, venous ulcers and pressure ulcers, and sternal dehiscent wounds seem to heal well with this adjunctive therapy. Future investigations should include other clinical comparative studies evaluating the additional benefits of TNP therapy, particularly in the acute wound model, management of burns and abdominal wounds.

Samenvatting en conclusies in het Nederlands

In **Hoofdstuk één** worden de epidemiologie, etiologie en de verschillende fasen van wondgenezing beschreven. Voor succesvolle wondgenezing zal de wond de verschillende en overlappende pathofysiologische stadia moeten doorlopen; (i) coagulatie en inflammatie (ii) celproliferatie en reparatie van de extra cellulaire matrix en (iii) de remodulerings fase. Wonden die niet genezen blijven vaak in één van deze fasen hangen, bij voorkeur in een voortdurende proliferatieve of ontstekings fase. Om verdere genezing van deze wonden te bewerkstelligen, zullen er specifieke behandelingsstrategieën moeten volgen, die afgestemd zijn op de verschillende types van wonden en gericht op de verschillende stadia van genezing. Dit wordt bemoeilijkt door het grote aantal verschillende factoren die tot wondheling bijdragen en de grote variabiliteit in wondkenmerken en patiëntkenmerken. In alle situaties moeten de onderliggende wondetiologie, de lichamelijke-en voedingsstatus en het psychosociale welzijn van de patiënt worden geoptimaliseerd om de beste therapie te bepalen en het maximale voordeel uit een behandeling te halen. De recente vooruitgang in technologie, die een beter begrip geeft van de complexe cellulaire en biochemische mechanismen van wondgenezing, heeft geleid tot de ontwikkeling van een verscheidenheid aan geavanceerde wondbehandelingen zoals hyperbare zuurstof therapie, groeifactoren, weefselequivalenten en negatieve druk therapie (Topical Negative Pressure, TNP). Met de integratie van TNP in wondbehandelings-programma's is het behandelen van complexe volledige diktewonden gemakkelijker geworden. Acute chirurgische indicatiestelling heeft zich verruimd van het acute moment naar een meer strategisch gepland tijdstip. Binnen de chirurgische mogelijkheden is het vervolgens mogelijk geworden om sommige wonden conservatiever te behandelen dan aanvankelijk gepland, terwijl andere wonden op een rustiger tijdstip en in een beter stadium in het wondgenezingsproces met bijvoorbeeld een tijdrovendere vrije lap kunnen worden gesloten.

In een overzichtsartikel in **Hoofdstuk twee**, is geprobeerd om de geschiedenis van topicale wondbehandeling te doen herleven en de belangrijkste hoogtepunten te benadrukken die van belang zijn geweest voor de ontwikkeling van hedendaagse richtlijnen. Wij benadrukken in de conclusie dat het voor de vorming van het kwalitatief beste behandelingsplan van belang is om wetenschappelijke kennis te combineren met klinische deskundigheid en de behoeften van de patiënt. Voor deze taak heeft de medicus een nieuwe metgezel in de strijd, namelijk de gekwalificeerde, geregistreerde wondverpleegkundige. Samen kunnen zij, uit een breed scala van industriële wondproducten, een selectie maken van het beste product en de meest passende behandelingsstrategie die het best voorzien in de behoeften van de patiënt.

In een prospectieve, klinische studie worden het klinische effect en de kosten/baten verhouding van TNP vergeleken met de conventionele vochtig gaasverband therapie **(Hoofdstuk drie en vier).** De wonden worden willekeurig verdeeld over de beide therapiemodellen. Doeltreffendheid van de behandeling wordt beoordeeld door de semi-kwantitatieve parameters van wondgenezing te scoren (tekens van rubor, calor, exudaat en fibrineus beslag en percentage granulatie weefsel). Het helen wordt gekenmerkt door ontwikkeling van een schoon, granulerend wondbed („klaar voor chirurgische therapie") en vermindering van wondoppervlakte. Wij tonen aan dat het gebruik van TNP in een gemiddelde ziekenhuisbevolking met volledige huiddikte wonden resulteert in een betere wondgenezing in vergelijking met conventionele vochtig gaasverband therapie. Dit wordt weerspiegeld door gemiddeld gezondere wondvoorwaarden en een significant grotere vermindering van het wondoppervlak in vergelijking met conventioneel behandelde wonden. Nochtans resulteerde dit niet in een sneller herstel (vermindering van het aantal benodigde behandelingsdagen om „klaar voor chirurgische sluiting " te bereiken). Voorts is TNP een even dure therapie als de conventionele vochtig gaasverband therapie. Terwijl de materiële kosten veel hoger zijn in de TNP behandelde groep, worden deze grotendeels gecompenseerd door de vermindering van ziekenhuisopnamekosten en in mindere mate door de vermindering van personeelskosten.

In **Hoofdstuk vijf** wordt onderzocht of het positieve effect gevonden in TNP behandelde wonden verklaard kon worden door een effect op de bacteriële kolonisatie. Wij kunnen geen significant effect vinden van TNP noch van conventionele therapie op de totale hoeveelheid bacteriën (*kwantitatieve* bacteriële lading). Er wordt echter wel een belangrijke verschuiving in de soort bacteriën (*kwalitatieve* bacteriële lading) gevonden in TNP behandelde wonden: namelijk een daling van het aantal niet-gistende negatieve staven (Pseudomonas soorten, Pseudomonas Aeroginosa en Acinetobacter soorten) samen met een verhoging van het aantal *Staphylococcus aureus*-bacteriën.

In **Hoofdstuk zes** wordt de doeltreffendheid van oppervlakkige wondkweken vergeleken met die van weefselbiopten voor de follow-up van klinisch niet-geïnfecteerde acute en chronische volledige huiddikte wonden en de voorspelling van postchirurgische complicaties. Wij concluderen dat de oppervlakkige wondkweek en biopten even betrouwbare methodes zijn voor de kwantificering en kwalificering van de types bacteriën die de volledige huiddikte wonden tijdens open wondtherapie koloniseren. Wij adviseren om de oppervlakkige wond kweek te verkiezen boven het weefselbiopt aangezien deze de eenvoudigste en minst invasieve methode is. Maar dan slechts in die wonden die tekenen van kritieke kolonisatie vertonen wat zich kenmerkt in uitbreiding van de wond, toename van roodheid of toename van pijn waarvoor topicale antiseptica of antibiotische therapie moet worden gestart.

In **Hoofdstuk zeven** wordt de biochemische analyse van wondvloeistoffen beschreven die zijn verzameld tijdens behandeling met TNP en conventionele vochtig gaasverband behandeling. Onze hypothese was, dat bij TNP behandelde wonden door continue afvoer van wondvocht en toevoer van vers wondvocht de accumulatie van inhiberende wondvochtfactoren wordt tegengegaan. Dit wordt aangetoond door middel van significant lagere hoeveelheden van pro-MMP-9 en totaal mmp-9/timp-1 ratio in het wondvocht van TNP behandelde wonden.

In **Hoofdstuk acht** zijn in een overzichtsartikel alle peer reviewed publicaties beschreven die het werkingsmechanisme, de doeltreffendheid en de klinische toepassing van TNP hebben weergegeven. Meer dan 450 peer reviewed publicaties werden gevonden. Veruit het grootste deel hiervan beschrijft de commerciële V.A.C. ® therapie en een klein aantal beschrijft TNP in combinatie met gaasverband. Uit deze literatuur concluderen wij dat TNP therapie een toename van doorbloeding geeft, angiogenese bevordert, het wondoppervlak verkleint van verscheidene wondtypes, inhiberende factoren in wondvloeistof vermindert en celproliferatie stimuleert. Wij vinden ook dat oedeemvermindering en bacteriële klaring, mechanismen die werden toegeschreven aan TNP therapie, niet door basisonderzoek worden bewezen. Aangezien dit op studies gebaseerd is die gebruik maken van de TNP therapie met PU en PVA sponsen en 125 mmHg negatieve druk, is het onbekend of de TNP therapie met gaasverband, lagere negatieve drukinstellingen en een ander zuigbuissysteem overeenkomstige resultaten geeft.

In **Hoofdstuk negen** wordt het internationale consensusdocument voor het gebruik van negatieve druktherapie gepresenteerd die door ons en een geselecteerde groep internationale deskundige opinieleiders werd gecompileerd. Het document beschrijft het gebruik van TNP in zes verschillende wond types: diabetes voetwonden, been ulcera, drukplekken, geïnfecteerde sternale wonden, open buikwonden en traumatische wonden. Verder concentreert het zich op artikelen welke de kosten/baten analyse of doeltreffendheid beschrijven. De aanbevelingen die gedaan worden in het consensus document zijn gebaseerd op zowel het ondersteunende bewijsmateriaal (prospectief gerandomiseerde studies en retrospectieve cohort studies) als het advies van de internationale groep deskundigen, indien er geen prospectief gerandomiseerde studieresultaten voor handen waren. Uit de studies komt naar voren dat vooral de chronische wonden (diabetes voetwonden, drukplekken en sternale wondinfecties) een betere wondgenezing laten zien met gebruik van TNP. Toekomstig onderzoek zou nieuwe klinische vergelijkende studies moeten omvatten die de bijkomende waarde van TNP therapie analyseren in acute wonden, brandwonden en abdominale wonden.

Closing remarks and future perspectives

Several meaningful changes in the principles of wound care (i.e. asepsis/antisepsis versus antibiotics, moist versus dry wound healing) have occurred over a long period of time. Based on these new insights, a wide range of wound care products were introduced on the market by the industry over the last decade. Topical negative pressure (TNP) therapy was one of these. The diversity of available products and the expansion of treatment possibilities are essential because of the increasing wound problems, linked to age of the patients and the accompanying co-morbidity. The incidence of chronic wounds is expected to increase dramatically in the future because of the increasing incidence of diabetes (1) and other health-related disorders associated with the occurrence of chronic wounds. Examining the current chronic wound care and its associated costs indicated that their global burden is considerable. The national cost for pressure ulcers (2002) alone was estimated to reach up to $2 billion, or approximately 6.6 % of the Netherlands' total health care cost (2). The cost of diseases of skin and the subcutis was calculated at € 886 million in 2005, which was 1.3% of the total health care costs (3).

Wound care, a non- fancy subject?

The signals from the growing market in wound care have been well-recognized by nurses. Internationally (WUWHS, World Union of Wound Healing Societies) and nationally (ETRS, European Tissue Repair Society; EWMA, European Wound Management Association, and EPUAP, European Pressure Ulcer Advisory Panel) various non-profit organizations were founded to promote the advancement of education and exchange of basic science and experience. Regional non-profit organizations were also founded and followed these initiatives to educate nurses in wound management skills (WCS, Wound Care Consultant Society; NOVW, Nederlandse Organisatie Voor Wondverpleegkundige). In 2004 a new training and education program for nurses with a special interest in wound care was started at the Erasmus Medical Center Rotterdam and supported by the regional organizations. After this training program of two years, including evidence-based practice, most of these nurses become a tissue viability nurse at their hospital or institution.

Unfortunately, the educational programs and congresses are predominantly attended by nurses. Needless to say that education of not only the nurses, but also the physicians is imperative for the continuation of the best practice. Wound healing education at the medical schools or at the post-graduate level has legged behind. The average Dutch medical student receives approximately 4-8 hours of didactic education (mostly frontal learning) in wound healing and tissue repair over the entire 4-year medical school curriculum (personal communication). After medical school, the education in wound care differs per specialization, most residents are only trained in basic wound care principles. Specialists confirm the lack of time to remain informed on the increasing treatment possibilities and different wound care

products. Clinically, this has resulted in a shift in the responsibility for daily wound care, from the resident and the physician specialist to the attending tissue viability nurse.

Surgical residents recognized this gap in the knowledge and decided to take the next step in self-education by organizing The Wound Healing and Wound Care Congress Rotterdam (since 1999). A second step towards increased knowledge transfer is believed to be a hands-on practical course providing instructions in wound management issues such as wound culture sampling techniques, methods of debridement, compression bandaging technique, TNP and total contact casting technique. The first hands-on course was held in June 2009. Future courses will include the integration of a skills lab using an animal model. Hopefully, these courses will eventually be a part of the standard educational program for every resident in surgery.

Research: Evidence or gut feeling

Until the late nineties of the 20th century, the application of new wound care products in every day treatment depended largely on high quality marketing, on expert opinion and gut feeling rather than on solid scientific evidence. However, evidence-based practice (EBP) has become a new paradigm in the field of medicine in the last decade. EBP refers to a decision taking process, which integrates the best available research, clinical expertise and client characteristics. The focus on using available research evidence for implementation in the practice has resulted in the development of many valuable practice guidelines (Table 2, Chapter 2). However, the use of EBP guidelines remains a challenge as individual practitioners, clinical teams and health care organizations all influence the speed and the scope of the adoption of the evidence into the daily practice.

The top of the pyramid of evidence has generally been considered to be a well-conducted and suitably powered multi-center blinded placebo controlled randomized trial. The results from these studies would then be considered Level I evidence. In wound care research, randomized controlled trials are scarce and have many limitations with respect to wound care, whereas other sources of evidence are often flawed because of the complexities of the wound healing process or are limited by their methodology. Blinding of the study is often hampered because of visible markings in the wound created by the wound product used. The large number of factors that contribute to wound healing and the high degree of variation in wound characteristics and patient status lead to numerous potential confounding factors in attempts to measure treatment efficacy. The evaluation of the healing or non-healing process is difficult because it is a dynamic process that can be interpreted in many ways.

For clinical research to adequately address this problem, a common "language" and set of tools are imperative. These tools should include a systematic and objective wound registration system; a general wound classification, a lexicon of wound descriptors, an objective measurement system and a description of wound healing end points.

Recent advances in technology of imaging and computer systems may provide the solution for the difficulty in achieving an accurate, objective wound tool. An example of this

emerging technology is enhanced digital photography. The clinician can obtain accurate and objective information on wound size, shape, outline, area and color with digital photography. The clinician defines the image areas such as the wound edge, eschar, necrotic tissue, or granulation formation and obtains measurements via the system's digital sub-pixel measuring techniques. The program then calculates the percentage of necrotic tissue, slough and granulation tissue in the wound. However, it does not provide information on the depth of the wound without additional measurements.

Research: Future studies

At present a new study has been initiated at the Department of Plastic and Reconstructive Surgery (PhD Student - Dymmie Landa, tissue viability nurse). We aim to measure wound healing in acute wounds objectively by combining digital photography with a new wound score system (alike the pressure ulcer scale for healing "PUSH tool") in this study. The current version of PUSH contains three items: length x width, exudate amount, and tissue type. The integral scores of these items are summed for a total PUSH score. The total score may range from 0 to 17, with 0 representing a healed wound. Changes in the total score over time are used to quantify the healing progress (4). Another similar system is the Pressure Sore Status Tool (PSST). The PSST is a 15-item instrument that assesses various characteristics of the wound and the surrounding tissue based on a 5-point Likert scale. The total score is followed over time to monitor the healing (5). Both the scoring systems have been used in chronic wound ulcers and pressure ulcers. No such scoring system is available for secondary healing of acute wounds. The purpose of our study is to create and validate a standardized scoring system derived from several known parameters combined with digital photography and compile an objective report that defines the type of the wound, the extent of the wound, its severity, healing or deterioration. Changes in the total score over time are used to quantify the healing progress and can be graphically displayed in an electronic patient file. We would once again like to undertake a randomized clinical trial as described in Chapter 3 of this thesis with this new objective wound tool. We hypothesize that with a better defined objective wound measurement tool, differences in wound healing between conventional and modern wound care treatment can be more adequately described and proven.

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APPENDICES

List of abbreviations
Acknowledgement
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Abbreviations

AWF	Acute wound fluid
AWMT	Advanced moist wound management
BMI	Body Mass Index
CBF	Cutaneous bloodflow
CDC	Centre of Disease Control and Prevention
CFU	Colony Forming Units
CI	Confidence interval
CWF	Chronic wound fluid
ECM	Extra Cellular Matrix
EGF	Epidermal Growth Factor
EBM	Evidence Based Medicine
EBP	Evidence Based Practice
ELISA	Enzyme-linked immunosorbent assay
ETRS	European Tissue Repair Society
EWMA	European Wound Management Association
FDA	Food and Drug Administration
FGF-2	Fibroblast Growth Factor-2
GB-TNP	Gauze-Based Topical Negative Pressure
GEE analysis	Generalized estimating equations
HBO	Hyperbaric Oxygen
Il-8	Interleukine 8
kDa	kilo Dalton
NOVW	Nederlandse organisatie voor Wondverpleegkundigen
PDGF	Platelet-derived growth factor
PBS	Phosphate buffered saline
PVA	Polyvinyl-alcohol foam dressing
PU	Polyurethane ethylene foam dressing
MMP	Matrix Metalloproteinase
RCT	Randomized Clinical Trial
rhPDGF	Recombinant human Platelet Derived Growth Factor
RST	Ready for surgical therapy
SD	Standard deviation
SEM	Standard error of the mean
SSG	Split Skin Graft
TIMP	Tissue Inhibitors of Matrix Metalloproteinase
TNP	Topical Negative Pressure

V.A.C.	Vacuum Assisted Closure
VEGF	Vascular endothelial Growth Factor
WCS	Woundcare Consultant Society
WUWHS	World Union of Wound Healing Societies

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Erasmus MC
Universitair Medisch Centrum Rotterdam

PhD Portfolio Summary

Summary of PhD training and teaching activities

C.M. Moues-Vink,
Department of Plastic, Reconstructive and Hand surgery, Erasmus MC, Rotterdam
PhD period: 2002-2004, MD residency 2004-2011

1. PhD training

	Year	Workload (Hours)
General academic skills		
Biomedical English Writing and Communication	Self taught	Full time
Conducting a clinical RCT; inclusion/sampling/follow-up	2001-2004	'02-'04
Research skills		
Inclusion of patients, sampling, analyses	2002-2004	Full time
Interpretation of results and writing	2004-2009	Part time
In-depth courses (e.g. Research school, Medical Training)		
MD residency Department of Plastic, Reconstructive and Hand surgery	2004-2011	Full time
Presentations		
Budapest, Hungary. 6th European Pressure Ulcer Advisory Panel Open Meeting, Poster	2002	40
Seattle, Washington. 13th Annual educational Symposium. Wound Healing Society (WUWHS). Young Investigator Award Session, Presentation	2003	60
Pisa, Italy. 13th European Wound Management Association (EWMA), Presentation	2003	60
Amsterdam, Netherlands. 13th Annual Meeting of the European Tissue Repair Society (ETRS), Presentation	2003	60

Rotterdam, Netherlands. Congres Wondgenezing & wondbehandeling. Invited speaker	2003	20
Paris, France. 2nd WUWHS' meeting, poster and presentation	2004	60
Galway, Ireland. Vascular society meeting. Invited speaker	2007	60
Erasmus MC, Rotterdam. Bacteriologie in een breder spectrum, Infectie preventie. Invited speaker	2008	20
Utrecht, Symposium Plastische chirurgische mogelijkheden bij de gecompliceerde wond, Invited speaker	2008	20
Toronto, Canada, 3rd WUWHS meeting, presentation	2008	60
Tjongerschans ziekenhuis, Heereveen. Regionaal wondsymposium voor extra-/en intramurale zorgverleners , invited speaker	2008	40
Hands on wound management course, Bronovo, Den Haag. Invited speaker	2009	20
WCS, wond en water management. Wondsympsium voor aandachtsvelders, invited speaker	2009	10
NVPC, najaarsvergadering, presentation	2009	10
International conferences		
Member international board of Topical negative pressure therapy group	2008	100
Seminars and workshops		
European Academy of Wound technology, France, International Seminar and practical training for wound specialists	2007	50
Chairman wound congres; "wondgenezing & wondbehandeling 2008", Rotterdam	2008	10
Scientific committee: Hands on wound management course 2009, Bronovo, Den Haag	2009	50

Didactic skills		
Bi-annual education nursing personnel plastic surgery department EMCR on wound healing	Since 2006	2 days/ annum
Other		
Coordinating an international study on pain around wound bandage changes, initiative Cardiff University	2008	30
Intranet protocol Topical negative pressure 2005/revision 2009	2005/2009	30

2. Teaching activities

	Year	Workload (Hours/ ECTS)
Lecturing		
Teacher of 4th year medical students: "Acute wounds and therapy".	2007, 2009	100
Teacher of post- HBO nurse students, opleiding wond en decubitus, EMC Rotterdam	2008, 2009	40
Supervising Master's theses		
Dymmie Landa, Tissue viability nurse, PhD student	2008 - 2014	Until now: 50
Committee		
"Sneller Beter" , Decubitus tranche 3, Erasmus MC	2006/2007	20
Post operative wound infection (POWI) project department of plastic surgery.	2008/2009	30
Werkgroep Decubitus- en wondzorg, Erasmus MC	2008/2009	50

Curriculum Vitae

Chantal Moues werd geboren op 25 juni 1974 te Leiden. Na het halen van haar HAVO en VWO diploma aan het Bonaventura College te Leiden, startte zij in 1993 met de studie geneeskunde aan de Universiteit van Utrecht. In de laatste 3 jaar van haar medische opleiding heeft zij onderzoek gedaan naar vaatverbindingen in een varkensmodel en ontstond de passie voor het “snijdende vak”. Het onderzoek waarmee zij haar artsopleiding beëindigde was een biomechanische en histologische studie naar humane gepreserveerde tarsale allograft bot-ligament-bot complexen voor reconstructie van het scapho-lunaire ligament (Prof. Dr. K.E. Bos, Plastische Chirurgie, AMC, Amsterdam). In 2000 werkte zij als AGNIO (assistent geneeskunde niet in opleiding) algemene chirurgie in het Spaarne Ziekenhuis in Haarlem. In 2001 werkte zij als AGNIO Plastische Chirurgie in het Erasmus Medisch Centrum te Rotterdam. In september 2002 werd zij voor de opleiding aangenomen, waarna zij in oktober 2004 startte met de vooropleiding algemene chirurgie in het Reinier de Graaf Gasthuis in Delft (opleider Dr. L.S. Stassen). In augustus 2005 is zij getrouwd met Frank Vink. Samen hebben zij twee kinderen; Boudewijn Julius van bijna 6 en Florent Justus van bijna 2 jaar oud. Momenteel werkt zij als arts in opleiding tot plastisch chirurg in het EMC in Rotterdam. Vanwege interesse in aangezichtschirurgie (schizis, oncologische reconstructie en esthetische chirurgie) zal zij in 2010 het Facial Surgery Fellowship (DAFPRS) gaan volgen. De opleiding tot Plastisch chirurg zal worden afgerond in januari 2011.