VAC therapy: interactions in the healing process

Vacuum assisted closure (VAC) has gained widespread acceptance over recent years for the treatment of chronic or delayed wound healing. It seals the wound from the environment and stimulates healing by applying topical negative pressure to the wound surface. It is thought to act via a number of mechanisms including stimulation of blood flow, removal of bacteria, and generation of a wound environment that allows healing. This review considers the evidence on the VAC mode of action in relation to clinical results to describe a model of how it enhances the healing of difficult wounds.

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Normal dermal healing in healthy subjects restores the functional integrity of the skin. However, in some patients the healing process may be compromised by extensive tissue loss, co-morbidities, concomitant medication or other factors such as smoking, poor nutrition, or ageing. In recent years our understanding of both the healing process and the defects that occur in delayed healing has allowed the development of a number of new treatments for difficult-to-heal wounds.

Why do some wounds not heal?

Normal healing is a linear multi-step process which progresses from haemostasis through inflammation, granulation tissue formation, and re-epithelialisation, to scar formation with restoration of normal dermal function (Moore, 2001). The wound can be considered as a unique body compartment where the cells are activated to progress healing and then switched off as closure is achieved. In the wound where healing is delayed, multiple factors come into play that prevent normal cell function. These factors may be intrinsic in that they are generated locally within the wound or extrinsic in that they are systemic factors that impact on healing.

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Extrinsic factors

Advancing age is a known risk factor for impaired healing (Taylor, 2002) but although healing is slower in healthy older people, it is not defective (Eaglestein, 1989). The increased incidence of delayed healing in the aged is likely to be a consequence of medical conditions and lifestyles associated with the elderly. For instance, poor nutrition is prevalent in this group and is associated with slower healing (Himes, 1999). No definitive causal link has been established between poor nutrition and defective healing (Thomas, 2001), although many dietary components such as carbohydrates, proteins and amino acids (particularly arginine and glutamine), fats, polyunsaturated fats, zinc, vitamin A and vitamin C are required for efficient healing (Williams, 2002). Serum protein deficiency in particular has been shown to be indicative of post-surgical wound failure (Gherini, 1993).

Male gender is also associated with poor healing outcomes (Taylor, 2002) although decreased oestrogen levels in post-menopausal women may also lead to an increased incidence of leg and decubitus ulcers that can be reversed with hormone replacement therapy (Margolis et al, 2002). Topical oestrogen applied to the wound may also improve healing in both males and females (Ashcroft, 1997).

A number of co-morbidities including renal disease, hepatic failure, diabetes, peripheral vascular disease and malignancy may negatively impact on healing (Mulder, 1998). For example, uraemia may impair healing by inhibiting granulation tissue formation, and wound failure is more frequent in patients with jaundice. Multiple defects including an impaired inflammatory response and defective extracellular synthesis are found in patients with diabetes. Peripheral vascular disease leads to low oxygen levels in wound tissue and cancer chemotherapy inhibits cell division.

Intrinsic factors

Comparative analysis of wound exudates and biopsies taken from healing acute wounds and non-healing chronic wounds has allowed characterisation of defects within the non-healing wound environment. Their reversal by appropriate therapy may assist in initiating the healing of recalcitrant wounds.

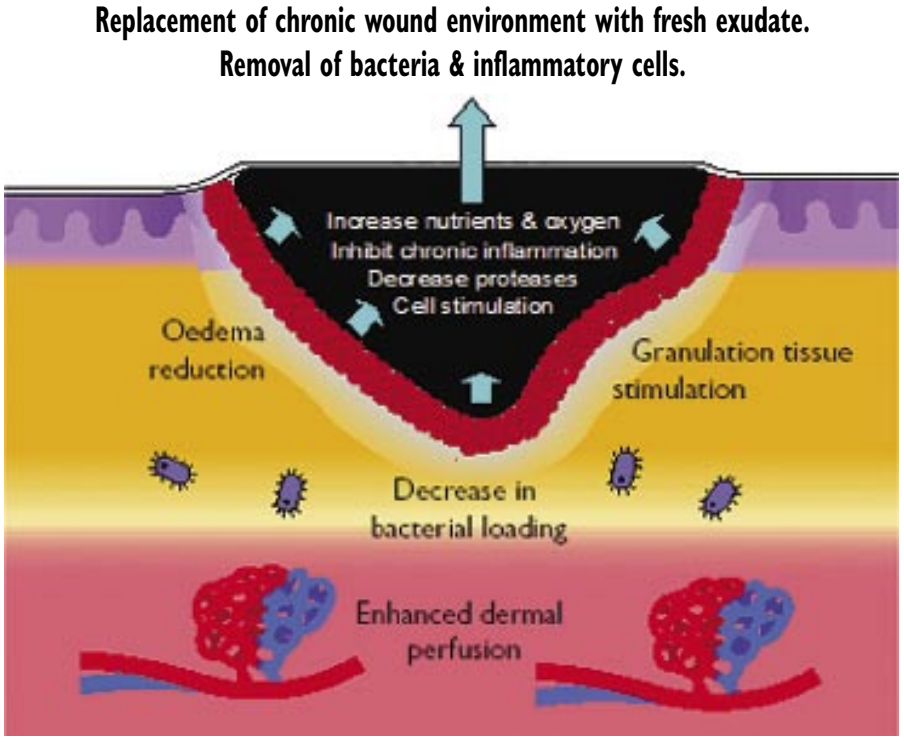

Figure 1. Effect of VAC therapy on the chronic wound microenvironment.

Wound infection is clearly deleterious to healing and requires antimicrobial therapy for healing to proceed (Loop et al, 1990). However, bacterial colonisation of wounds may not be detected clinically. With colonisation, the number of bacteria present are insufficient to generate clinical signs of infection such as erythema, cellulitis and pain, yet can still exert a deleterious effect on healing. Few dermal wounds are sterile with most wounds colonised by more than one organism. As the diversity of bacterial species within wound tissue increases, so the potential for them acting synergistically to delay healing (Trengrove, 1996).

Bacteria contribute to the high levels of proteolytic enzymes found within non-healing wounds. These enzymes are produced directly by bacteria while inflammatory cells (neutrophils and macrophages) are stimulated by bacterial products to produce them along with a range of inflammatory mediators. Proteases can also be produced by fibroblasts and keratinocytes in the wound tissue. Although present at low levels in normally healing wounds, they are elevated in chronic, and infected acute, wounds (Tarlton, 1999). This results in degradation of growth factors (Trengove, 1999) and extracellular matrix (Grinnel et al, 1992), and the inhibition of keratinocyte migration and wound re-epithelialisation (Hoffman et al, 1998).

The biological activity of chronic wound exudate is disordered when compared to exudate from healing wounds. It contains high levels of pro-inflammatory cytokines, low levels of growth factor activity (Trengove, 2000) and inhibits cell proliferation (Bucalo et al, 1993). The net effect of these factors and many others within wound exudate from non-healing wounds results in inhibition of biological processes such as re-vascularisation of the wound bed (Drinkwater, 2002), that are required before healing can be achieved.

The Vacuum Assisted Closure system

VAC is the name adopted for a commercially available system that applies topical negative pressure to promote wound healing. This is achieved by applying a reticulated, open-pore structured, polyurethane foam to the wound. After removal of necrotic tissue from the wound, the foam is cut to shape and used as a wound contact dressing and to pack any sinus or cavity. The whole wound area is then sealed with a semi-permeable film drape to effectively convert the wound to a closed system. The foam is attached via a vacuum line to a disposable container that collects exudate and to which a negative pressure is applied from a VAC pump. The pump may be set to deliver continuous or intermittent negative pressure from 50–200mmHg although it has been established that 125mmHg applied in cycles of 5 minutes on, alternating with 2 minutes off, usually gives maximum benefit (Gupta and Cho, 2004).

The foam dressings are designed to collapse when negative pressure is applied and exert suction forces with a uniform distribution throughout the wound area. Granulation tissue formation is accelerated by the treatment and there is often ingrowth to the foam dressing necessitating a change every 2 to 5 days to prevent damage to the wound bed on their removal.

Table 1
Biological activity exerted on non-healing wounds by VAC therapy

Activity	Benefit
Increase blood flow	Increase nutrient and oxygen availability
Replacement of extracellular fluid	Decrease in protease and chronic inflammatory mediators, increase in growth factor activity
Removal of bacteria	Less inflammatory stimulus Decreased protease production
Removal of inflammatory cells	Conversion from a chronic to an acute resolving inflammation
Draw wound edges together and exert mechanical stress on cells	Stimulate fibroblasts and endothelial cells
Overall activity	Stimulate granulation tissue formation

Clinical results

The VAC system has been applied successfully to a diverse range of wounds, with some randomised clinical trials and many case reports published to establish efficacy (Banwell, 2004; Gibson, 2004; Kaplan, 2004; Niezgoda, 2004; Smith, 2004; Lambert et al, 2005).

Chronic wounds

The majority of chronic wounds are reported to respond favourably to VAC therapy (Argenta and Morykwas, 1997). Pressure ulcers are frequently undermined and a VAC foam may be used to pack a sinus in contact with other foams used for an adjacent cavity. The open-pore structure allows transmission of the vacuum between adjacent foams. A study by Joesph (2000), which compared VAC therapy to traditional saline wet-to-moist treatment of chronic wounds, demonstrated a 66% decrease in wound depth over a 6-week treatment period compared to 20% for the control treatment ($p>0.0001$). Wound biopsies were taken during the course of the study to investigate how VAC therapy may exert its beneficial effect. These demonstrated greater numbers of inflammatory cells present in the wet-to-moist group and increased granulation tissue formation in the VAC group.

A rapid increase in granulation tissue formation is characteristic of the response to VAC. Treatment of a morbidly obese, hypertensive patient with a sacral pressure sore that was non-responsive to treatment with alginate dressings and a pressure-relieving mattress for 12 weeks, induced a granulation response within 2 weeks (Deva et al, 1997). Treatment was continued for 4 weeks to allow primary closure of the skin edges with permanent wound closure.

A similar initiation of healing was observed in a follow-up prospective consecutive 30 patient series (Deva, 2000). Here the mean wound duration before VAC treatment was 418 days with a mean of 35 days of treatment required to achieve an endpoint of secondary healing (6/30), direct wound closure (1/30), cavity obliteration (11/30) or graft ready (8/30).

A positive healing response has also been reported for venous leg ulcers (Sposato, 2001) and non-healing diabetic foot ulcers (McCallon, 2000). In the latter study, treatment of 10 patients with VAC after debridement produced satisfactory healing in 22.8+/- 17.4 days compared to 42.8+/- 32.5 days for the control group treated with wet-to-dry gauze.

Surgical and traumatic wounds

Traumatic wounds resulting in open fractures and large areas of skin or muscle loss have been proposed as the best responders to VAC treatment (Banwell and Teot, 2003), with special benefits in the prevention of infection. Application of VAC therapy to complex surgical wounds in patients in whom the healing potential is compromised by co-morbidity or infection is widely reported. For instance, it has been successfully applied to treat gynaecological wound failures of patients with concomitant morbid obesity, diabetes, vascular disease and malignancy (Argenta et al, 2002). As with chronic wounds, benefit was observed early in healing with a rapid initial decrease in wound volume.

Key Points

- VAC therapy produces a closed wound environment and, by applying topical negative pressure, removes wound exudate.
- It removes bacteria and chronic inflammatory cells from the wound environment.
- It stimulates blood flow to the wound bed and replaces the chronic wound environment with fresh leucocytes and plasma from the blood.
- VAC is not suitable for treating all difficult wounds and the manufacturers guidelines must be followed closely.

Retrospective comparison of sternal wounds (post-cardiac surgery) treated with VAC or traditional twice daily dressing changes, demonstrated a decrease in number of days between debridement and closure (Song, 2002). Infection of this type of wound is a particular problem and VAC therapy has been used successfully to eliminate infection in a mean of 9.3 days as defined clinically and by negative microbiological cultures (Fleck et al, 2002).

The elimination of wound infection by VAC therapy is a recurring theme in a number of publications with some studies showing a decrease in semi-quantitative bacterial cultures associated with successful healing outcome (Deva et al, 2000). However, when 54 patients were randomised to either moist gauze therapy or VAC the improved healing rate in the VAC group (3.8% reduction in wound area/day compared to 1.7%) was not related to observed changes in wound bacterial bioburden (Moues et al, 2004) as it remained unchanged in both groups.

Mode of action

Dermal wounding effectively disorders normal tissue dynamics. The continuity of the dermal barrier that protects against the ingress of bacteria and fluid loss is broken. The flow of extracellular fluid which supplies nutrients to the peripheral tissues is perturbed, and, after extravasation from capillaries, forms exudate instead of returning to the circulation via capillary re-entry or lymphatic drainage. With normal healing, temporary closure is provided by scab formation which prevents bacterial access to the tissues while granulation tissue formation proceeds with rapid re-epithelialisation. When tissue loss is large, or healing is delayed by co-morbidities, the chance of infection and delayed or inhibited healing increases.

Application of VAC therapy to an open wound immediately converts it to a closed wound system that only requires dressing changes at approximately 2 day or greater intervals. The obvious immediate benefit is a reduction in the chance of bacterial

infection. However, the application of a defined negative pressure to the wound surface has been demonstrated to exert a number of biological effects that may lead to the initiation of granulation tissue formation in previously non-healing wounds (*Table 1*).

Experimental evidence

The potential biological effects of VAC on wound tissue were determined initially in a series of experimental porcine wounds (Morykwas et al, 1997). This study demonstrated that application of negative pressure of 125mmHg gave a fourfold increase of blood flow in subcutaneous tissue and muscle. The increase was less marked with higher exerted pressures. The increase in blood flow decreased after 5 minutes continuous application of negative pressure. If negative pressure application was switched off for a recovery period of 2 minutes and then reapplied in 5 minute cycles, no decrease in blood flow was observed. While application of a continuous negative pressure of 125mmHg did increase granulation tissue formation by 63% compared to control untreated wounds, use of the '5 on / 2 off' cycle was found to stimulate granulation by 103%. Other wounds were deliberately infected with Staphylococcus bacteria and biopsies taken during treatment. After 4 days of VAC treatment, the number of bacteria fell while the control wounds did not decrease to the same level until day 11.

From the results of these experiments, a model consistent with clinical observations can be built to explain how VAC initiates the healing of chronic wounds. The increase in blood flow to capillaries underlying the wound bed will allow greater flow of fresh plasma to form extracellular fluid that will be drawn through the wound bed into the wound contact foam and then to waste. As well as supplying fresh nutrients to the wound tissue, this will also replace the existing wound environment with sterile fluid from the blood while removing bacteria and inflammatory cells (Gouttefangeas et al, 2001) from the wound bed.

As with all exuding wounds, the possible clinical significance of protein loss should be considered, and addressed as appropriate. The chronic wound environment contains high levels of proteases and disordered growth factor activity which, when removed, will allow the new population of leucocytes to be drawn into the wound bed. This will allow initiation of a resolving inflammatory response which restores the growth factor balance and is considered to be the prerequisite of initiation of healing in chronic wounds (Moore, 1999).

Application of a vacuum to wound tissue will also exert mechanical stretch forces on cells in granulation tissue as it draws the wound edges of cavity wounds inwards. This may also have a beneficial effect as stressing extracellular matrix has been shown to stimulate proliferation and functions of endothelial cells (Sumpio et al, 2002) and fibroblasts (Prajapati et al, 2000).

Practical considerations

Since its inception, VAC therapy has been found to be of considerable clinical value in the management of a wide variety of wounds. The single most important advantage is probably in its to capacity to initiate, and sustain, healing in dormant, refractory wounds.

There are, however, some disadvantages. VAC should not be regarded as a panacea in wound management. It is not suitable for all wounds, being contraindicated in wounds with fistula(e) present; necrotic tissue with eschar; untreated osteomyelitis; and, malignancy (KCI Medical, 2005). Indeed, the importance of following the manufacturer's guidelines for use cannot be over-emphasised.

While there are numerous clinical reports in the literature, there are no published randomised, controlled trials (at the time of writing, although such studies are underway: Samson et al, 2004). Thus the clinical evidence for VAC does not currently meet the highest standards (Samson et al, 2004). Costs, patient comfort and convenience, and operator skill could be disadvantageous in some circumstances. The very physical nature of the technology can be obtrusive and restrictive when compared to conventional wound treatments. However, these constraints are outweighed by the benefits in selected patients.

Conclusion

Topical negative therapy applied by VAC is one of many modalities available for the treatment of delayed or non-healing wounds. Their respective modes of action and proven efficacy on the wound environment vary significantly. Some treatments such as growth factors are highly specific and will only affect a cell which can respond to a particular factor. They can be considered as 'pushing' an indolent wound into a healing phase by cell activation. In contrast, other treatments such as interactive dressings are considered multifunctional in that they inhibit bioactivities considered deleterious to healing while still acting as a conventional dressing to generate a moist wound environment. They may be thought of as 'pulling' the wound into a healing phase by removing obstacles to healing.

VAC therapy essentially falls into the latter group of treatments by removing inhibitors of healing. It generates a moist wound environment and essentially converts an open wound into a closed system. However, in contrast to the interactive dressing, it simultaneously initiates healing in a unique non-pharmacological way. The negative pressure applied to the wound contact foam removes extracellular fluid and enhances blood flow to effectively generate a fresh wound environment that allows the healing process to be re-initiated with the generation of granulation tissue capable of supporting wound closure. WUK

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