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Efficacy and mechanisms of vacuum-assisted closure (VAC) therapy in promoting wound healing: a rodent model☆

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Summary *Background:* The vacuum-assisted closure device (VAC) has revolutionised wound care, although molecular mechanisms are not well understood. We hypothesise that the VAC device induces production of pro-angiogenic factors and promotes formation of granulation tissue and healing.
Methods: A novel rodent model of VAC wound healing was established. Excisional wounds were created on rat dorsa. Wounds were dressed with Tegaderm (control group), VAC Granulofoam® and Tegaderm (special control group), or VAC Granulofoam®, T.R.A.C. PAD® with 125 mm Hg continuous negative pressure (VAC group). Wound closure rates were calculated as a percentage of initial wound sizes. Rats were sacrificed on postoperative days 3, 5 and 7; harvested tissues were processed for histology [haematoxylin & eosin (H&E), Masson's trichrome, picrosirius red] and Western blot analysis (CD31, vascular endothelial growth factor, basic fibroblast growth factor).
Results: Statistically significant wound closure rates were achieved in the experimental group at all measured time points: day 3, 28.1% (VAC) vs 8.2% (control) and 8.8% (special control) (ANOVA, $P < 0.0001$); day 5, 45.3% (VAC) vs 23.7% (control) and 22.5% (special control) (ANOVA, $P = 0.0003$); day 7, 54.4% (VAC) vs 43.0% (control) and 31.5% (special control) (ANOVA; $P < 0.0001$). Morphological evaluation by Masson's trichrome stain showed increased collagen organisation and wound maturation in the VAC group. These wounds also showed increased expression of vascular endothelial growth factor and fibroblast growth factor-2 on day 5 by Western blot analysis.

☆ Presentations
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Conclusion: A small animal VAC wound model was established. Wounds treated with a VAC device showed accelerated wound closure rates, increased pro-angiogenic growth factor production and improved collagen deposition. Further application of this model may elucidate other mechanisms.

Nearly 70% of all wounds have delayed or impaired healing from complications of an underlying disease, surgery, constant pressure, trauma, or burn injury.[1–3] Impaired wound healing leads to significant patient morbidity and mortality. The annual cost for management of these wounds is estimated to be greater than $20 billion.[4] With a rapidly ageing population that has multiple co-morbidities that predispose wound development and decreased healing efficiency, these costs are expected to escalate. The importance of reliable and efficacious treatment is crucial not only to improve patient quality of life, but also to alleviate healthcare expenditures. Traditional therapeutic approaches in the management of the most difficult wounds have been met with limited success.

One treatment modality that has proven efficacy in treating a variety of wounds is the vacuum-assisted closure (VAC) device.[5–10] This device consists of the VAC Granulofoam® (VAC foam) that is placed in the wound and covered with an occlusive dressing.[8–10] A tube connecting the dressing to a vacuum source applies sub-atmospheric pressure to the wound. In a porcine wound model, the VAC has been shown to improve wound healing by increasing blood flow, bacterial clearance, and granulation tissue formation.[8] Other purported mechanisms include removal of wound fluid and mechanical stress.[11,12] However, despite clinical success, there is a relative paucity of data regarding the exact cellular and molecular mechanism by which the VAC device accelerates wound healing.

During the normal process of wound healing, a choreographed series of molecular events allow haemostasis, removal of cellular debris, cellular proliferation, angiogenesis, deposition and contraction of new extracellular matrix, and remodelling of the scar. The smooth progression of these events leads to completion of wound closure. Successful wound healing requires coordination and precise signalling from various cells that produce an array of cytokines, growth factors, ground substance and collagen.

Previous studies have shown that mechanical stress exerted on the wound may activate signal transduction and stimulate cell proliferation.[11–13] We hypothesise that negative pressure of the VAC device promotes the production of pro-angiogenic growth factors that lead to improved angiogenesis, formation of granulation tissues and wound healing. In this study, a VAC-treated rodent wound model was established to study wound tissues. We demonstrated that VAC therapy accelerates secondary wound healing in this small animal model. Wounds treated with the VAC device show increased expression of pro-angiogenic factors and granulation tissue formation.

Materials and methods

Experimental animal model and gross wound measurement

This study was approved by the Columbia University Institutional Animal Care and Use Committee. Male rats (Lewis Strain 004; Charles River Laboratories, Wilmington, MA, USA) were obtained and housed in an approved animal care facility. Experiments were carried out on rodents aged 8–10 weeks.

Rats were anaesthetised with inhalational isofluorane. The backs were shaved and prepped with betadine solution. Under sterile conditions, 2×2 cm full-thickness wounds were created on the dorsa. The animals were divided into three groups. Wounds on the control group (CONT) were covered only with an occlusive dressing (Tegaderm). A special control (SC) group had the VAC foam and Tegaderm applied to the wound without suction. Finally, the experimental (VAC) group had wounds dressed in the standard VAC dressing (KCI Concepts, San Antonio, TX, USA), consisting of VAC foam, occlusive dressing, and a T.R.A.C.® pad connected to the VAC device and subjected to negative 125 mm Hg of continuous pressure (Figure 1) for 8 days [from day of surgery through to postoperative day (POD) 7].

Dressings were changed every 48 h under inhalational anaesthesia (isofluorane). Rats were sacrificed on PODs 3, 5 and 7. The initial wound and incremental time-point wounds were traced on to glass slides and measured using NIH Image J software. Wound closure was calculated as a percentage of the final to initial areas. At each time point, wound tissues from at least three animals for each treatment group were harvested for histological and protein analysis.

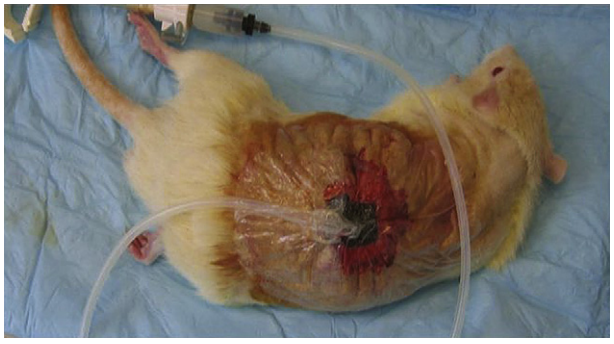

Figure 1 A modified VAC device on a rat.