

# Wound-Healing Technologies: Low-Level Laser and Vacuum-Assisted Closure

## Summary

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### Introduction

Chronic wounds are a major source of morbidity, lead to considerable disability, and are associated with increased mortality; therefore, they have a significant impact on public health and the expenditure of healthcare resources.<sup>1</sup>

The incidence of chronic wounds in the United States is approximately 5 to 7 million per year,<sup>1</sup> and the annual costs for management of these wounds is greater than \$20 billion.<sup>2,3</sup> In addition, chronic wounds can lead to complications, such as infections, contractures, depression or limb amputation.<sup>4</sup> These complications are associated with a need for assisted living and with higher mortality.<sup>5,6</sup>

The objective of this report is to systematically review the evidence on the outcomes of two technologies for wound healing: low-level laser therapy and vacuum-assisted closure. This report addresses the following specific questions:

1. In the treatment of chronic nonhealing wounds, what are the outcomes of low-level laser therapy for specific indications and patient types
  - as a substitute for conventional therapy? or
  - as an adjunct to conventional therapy, compared with conventional therapy alone?
2. In the treatment of acute or chronic wounds, what are the outcomes of vacuum-assisted closure for specific indications and patient types

- as a substitute for conventional dressings? and
- as an adjunct to conventional therapy, compared with conventional therapy alone?

This report also provides an overview of clinical and methodologic issues relevant to evaluating the evidence on interventions for wound healing. Many variables affect the course of wound healing; so well-controlled, randomized trials are necessary to reach conclusions on treatment efficacy.

Skin wounds are a heterogeneous and complex group of disorders with a wide variety of causes.<sup>7</sup> Approximately 70 percent are classified as pressure ulcers, diabetic ulcers, or vascular ulcers.<sup>8,9</sup> Vascular ulcers are further classified as due to arterial or venous insufficiency. Other less-frequent causes include inflammatory conditions, malignancies, burns, and radiation injuries.<sup>8</sup> Often the causes of wounds are multifactorial, such as in the diabetic patient who has both arterial insufficiency and peripheral neuropathy.<sup>8</sup> Each wound type has distinct physiologic characteristics and exists in a unique host environment with varied clinical and psychosocial factors.<sup>8</sup>

Wounds are often classified as acute or chronic. Acute wounds are generally less than 8 weeks in duration and have not yet completed the natural healing cycle. Chronic wounds are defined as wounds that have failed to proceed through an orderly and timely process that produces anatomic and functional integrity.<sup>10</sup> Chronic wounds either require a prolonged time to heal,



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do not heal completely, or recur frequently. A large number of factors can impede wound healing and may predispose a patient to the development of chronic wound(s).<sup>11,12</sup> These include both systemic factors (poor nutrition, metabolic derangements, and drugs) and local factors (tissue hypoxia, infection, and dry wound bed).<sup>13</sup>

Conventional treatment for established wounds incorporates common principles that apply to the management of all wounds, including debridement of necrotic tissue, maintenance of a moist wound bed, and control of infection. These common elements are combined with treatment modalities targeted to each type of wound and the clinical characteristics of the patient.<sup>14,15,16</sup> Optimal treatment also entails consideration of the appropriate intensity of treatment.<sup>17</sup> Unfortunately, there are no widely accepted, standardized protocols that define optimal standard treatment or the appropriate intensity of treatment delivery.

Because treatment varies widely in clinical practice, it is difficult to determine whether a patient has actually received an adequate course of treatment, and whether a nonhealing wound should truly be called “refractory.” In randomized, controlled trials, a relatively large proportion of refractory wounds heal with standard treatment (control arm). The large number of factors that contribute to wound healing, and the high degree of variability in wound characteristics, patient characteristics, and treatment delivery result in many potential confounding factors when attempting to measure treatment effect.

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 may be due to factors other than the specific intervention being tested. A concurrent control group is necessary to permit measurement of a treatment effect above that related to optimization of standard treatment or due to the natural history of wound healing. Randomized assignment to treatment group is essential in maximizing the likelihood that confounding factors are equally distributed across treatment groups. Ascertainment of outcomes should be ideally performed by an independent, blinded individual.

The U.S. Food and Drug Administration (FDA) has prepared a draft guidance document that offers information on optimal design of trials to assess wound-healing interventions, including patient selection and assessment, treatment considerations, and definition of outcomes and outcomes assessment.<sup>16</sup> The principals set forth by the FDA have been adapted in the development of the protocol for this systematic

review. In particular, outcome measurement should focus on outcomes that are quantitative and clinically meaningful.<sup>4,11</sup> The most important outcomes to be considered are (1) the percent of patients with complete healing and (2) time to complete healing. In some cases, particularly for vacuum-assisted closure, the treatment may not be expected to result in complete healing. Rather the treatment may be intended to advance the wound to a stage where healing is possible, either by continued conventional treatment or by surgical closure.

## Methods

The objective of this evidence report is to systematically review and synthesize the available evidence on the effectiveness of low-level laser treatment and vacuum-assisted closure for wound healing. Outcomes of interest were

- Primary outcomes
  - incidence of complete wound closure
  - time to complete closure
  - adverse events
- Secondary outcomes
  - facilitating surgical closure
  - need for debridement
  - infections
  - pain
  - activities of daily living
  - quality of life
  - improved cosmesis

Other secondary outcomes abstracted were change in wound size and transcutaneous oxygen tension ( $t_{c}pO_2$ ); however, these were considered to be of less clinical importance.

Electronic database searches were completed of MEDLINE<sup>®</sup> (via PubMed<sup>®</sup>), EMBASE, and the Cochrane Controlled Trials Register. The MEDLINE<sup>®</sup> search covered references entered onto the database from January 1, 1966 through June 8, 2004. The Cochrane Controlled Trials Register search was completed in 2003, through issue number 4. The EMBASE search covered references entered through June 14, 2004.

The search was limited to studies on human subjects with English-language abstracts. When abstracts were missing, the full-text article was retrieved for review if the title suggested it might possibly meet the study selection criteria. Papers published in foreign languages were reviewed if the English-language abstract appeared to meet inclusion criteria. Results of the search and study selection were reviewed by the Technical Expert Panel (TEP) for this project, in order to identify additional studies.

In addition, two companies that produce lasers used in wound healing (Microlight Corporation of America and PhotoThera), as well as the major producer of vacuum-assisted closure devices (V.A.C.<sup>®</sup>, Kinetics Concepts Inc. [KCI]), were contacted and were invited to submit evidence-based information for the review. The specific request was for “lists of published, randomized, controlled trials (RCTs), published abstracts of RCTs within the past 2 years, and published articles on study design, or protocols of any RCTs (published or in progress).”

This systematic review selected only randomized, controlled trials meeting the following criteria:

1. The trial must involve one of the following comparisons of interventions
  - a. Either low-level laser treatment or vacuum-assisted closure, compared with other wound healing interventions (alternative intervention trials).
  - b. Either low-level laser treatment or vacuum-assisted closure in addition to standard wound care, compared with standard wound care alone (incremental benefit trials).
  - c. Either low-level laser treatment or vacuum-assisted closure, compared with a sham intervention (placebo trials).
2. For low-level laser treatment, patient selection criteria must target those with chronic wounds. For vacuum-assisted closure, patient selection may address those with chronic wounds or other types of wounds.
3. The trial must report on at least one of the outcomes of interest.
4. The trial must be published as a full journal article and not merely as a conference abstract.

Titles and abstracts were screened by a single reviewer who marked each citation as either eligible for review as full-text articles or ineligible for full-text review. A second reviewer reviewed all citations marked as ineligible by the first reviewer. An eligible rating was necessary from only one reviewer to place a citation in the pool of those to be retrieved for full-text review.

In reviewing full-text articles to determine eligibility for data abstraction, a single reviewer determined whether each paper should be (1) included in systematic review, (2) excluded from systematic review, or (3) discussed with additional reviewer. One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer checked the evidence tables for accuracy.

A procedure was established in case of disagreements that could not be resolved between the two reviewers. In such cases,

the EPC Program Director was consulted and then, if necessary, the relevant members of the TEP.

This systematic review applies the general approach to grading evidence developed by the U.S. Preventive Services Task Force.<sup>18</sup> Two independent reviewers rated study quality, and disagreements in ratings were resolved by consensus.

## Results

**Low-level laser.** Eleven studies<sup>19-29</sup> met the study selection criteria for Part I of this review, nine of which were rated poor in quality,<sup>19-23, 26-29</sup> while one was rated good quality<sup>25</sup> and one was rated fair.<sup>24</sup>

Seven studies (n=262) compared standard care plus placebo with the combination of standard care and sham laser therapy.<sup>19,21,22,23,26,27,29</sup> Most of these patients had lower extremity venous ulcers. Of the three studies that reported on complete healing,<sup>19,26,27</sup> one provides weak evidence of a higher rate of healing for patients treated by machine-scanned laser versus those receiving sham laser.<sup>19</sup>

Standard treatment alone versus standard treatment plus laser was compared in three studies, which reported on a total of 151 patients with pressure ulcers.<sup>24,25,28</sup> All three studies reported on complete healing. One of these was rated as good in quality, and this higher-quality study did not show a higher probability of complete healing at 6 weeks with the addition of laser treatment,<sup>25</sup> nor did it show benefit for any of the other reported outcomes. Use of medical treatment plus ultraviolet light with medical treatment plus low-level laser therapy was compared in one study of six patients with chronic venous ulcers.<sup>20</sup> That study did not show a higher probability of complete healing at 6 weeks with the addition of laser treatment.

Overall, the quality of this body of evidence is poor, and does not permit definitive conclusions. However, the available data suggest that the addition of laser therapy does not improve wound healing, as the vast majority of comparisons in these studies do not report any group differences in the relevant outcomes. It is unlikely that the lack of significant differences is the result of a type II error, since there are no trends or patterns of outcomes that favor the laser group.

**Vacuum-assisted closure.** This body of evidence is insufficient to support conclusions about the effectiveness of vacuum-assisted closure in the treatment of wounds. There are only six trials that met the inclusion criteria for this review<sup>30-35</sup> and the included trials were of small size and poor quality. With the exception of one study of 54 patients with incomplete followup,<sup>34</sup> all studies included fewer than 25 patients. The randomization method was clearly adequate in only one study.<sup>34</sup> No study made clear that groups were comparable on all three

key baseline characteristics (age, wound duration, wound size). None provided group information about wound duration. A single study adjusted for confounders in the data analysis<sup>35</sup> and another performed an intention-to-treat analysis.<sup>32</sup>

Some outcomes in the available trials show a significant benefit for the vacuum-assisted closure group, while others do not. Only one study<sup>30</sup> gave data on the probability of complete healing, showing no significant difference between groups. A study reporting time to satisfactory healing<sup>33</sup> also found no significant difference between groups. One study found no difference between vacuum-assisted closure and control in time to readiness for surgical closure.<sup>34</sup>

Three studies reported on change in wound area,<sup>31,33,34</sup> one of which found a difference between vacuum-assisted closure and control,<sup>34</sup> while two did not.<sup>31,33</sup> Among four studies addressing change in wound volume,<sup>30,31,32,35</sup> two found a significant advantage for vacuum-assisted closure<sup>31,32</sup> and two did not achieve statistical significance.<sup>30,35</sup> One study found significant changes in wound width and depth for vacuum-assisted closure<sup>32</sup> and another found it only for depth.<sup>31</sup> It is possible that the lack of significant results in some or all of these trials result from a type II error. In most cases, the numerical results favor the vacuum-assisted closure group. Power calculations are lacking for these trials, but their small size raises the possibility that they are underpowered.

Trial protocols provided by the manufacturer of the V.A.C.<sup>®</sup> device (Kinetic Concepts, Inc., KCI) outline much larger trials that are condition-specific and address many of the quality problems found in the published studies. If implemented and completed successfully as planned, these trials will provide substantial advances in the evidence base for vacuum-assisted closure therapy, and may allow more definitive conclusions on the efficacy of vacuum-assisted closure.

## Discussion

This systematic review focused on two specific interventions for wound healing, but the issues raised in this discussion should be applied broadly. Because of the large size of populations with nonhealing and other types of wounds, the impact on healthcare expenditures is considerable. Future research should address how to improve the delivery of care, quality of care, and outcomes of treatment of wounds in various settings. There is potential to reduce the frequency of nonhealing wounds and thus the overall costs of care. New interventions have the potential to improve wound care, but outcomes must be demonstrated in well-controlled randomized trials. Strategies for reducing the occurrence of wounds in various susceptible populations also have a place in the research portfolio. Given significant costs of chronic wounds, future

comparisons of the cost-effectiveness of various strategies for preventing wounds, managing wounds, and improving quality of care would be of value to clinical decisionmakers.

## Availability of the Full Report

The full evidence report used to create this summary was prepared for the Agency for Healthcare Research and Quality by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center, under Contract No. 290-02-0026. It is expected to be available in December 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling (800)-358-9295. Inquiries should include a request for Evidence Report/Technology Assessment No. 111, *Wound Healing Technologies: Low-Level Laser and Vacuum-Assisted Closure*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Website at [www.ahrq.gov](http://www.ahrq.gov).

## Suggested Citation

Samson D, Lefevre F, Aronson N. Wound Healing Technologies: Low-Level Laser and Vacuum-Assisted Closure. Summary, Evidence Report/Technology Assessment No. 111. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center, under Contract No. 290-02-0026). AHRQ Publication No. 05-E005-1. Rockville, MD: Agency for Healthcare Research and Quality. December 2004.

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AHRQ Pub. No. 05-E005-1  
December 2004

ISSN 1530-440X