



## Efficacy and Safety of Berberex Wound Cleanser on Post-Operative Surgical Incisions

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### Abstract

**Introduction:** The skin is a natural barrier against infection, and despite this continuous and impermeable natural protection, if skin is injured by blister, splinter, cut or burn, bacteria can enter the body and cause an infection. Breaks in the skin that occurs during a surgical procedure, synonymously incisions, and present opportunities for pathogens to enter the body. *Berberex*<sup>®</sup> Wound Cleanser has been cleared by FDA for external use. *In vitro* potency has been shown against high levels of several resistant bacteria, including against MRSA, B-strep, VRE, and *E. coli*. Active ingredients allantoin and benzethonium chloride have been formulated with water, ethanol, *Aloe barbadensis* (Mill.), *Hydrastis canadensis* L., *Panax quinquefolius* L., and hydrogen peroxide. Based on the product's performance, a study was undertaken to evaluate 180 consecutive patients following spinal surgery.

**Methods:** Following IRB review, patients were evaluated from a single physician. No subjects were excluded from the study based on recognized associated risk factor(s). Patients were randomized to receive *Berberex*<sup>®</sup> Wound Cleanser (NuVision Pharmaceuticals, Atlanta, GA) post-operatively at a 1:2 proportion, and asked to apply the solution twice a day for 6 months or until wound healing had occurred. Remaining patients evaluated in this retrospective analysis were asked to follow post-operative discharge instructions common to the practice that placed limitations on lifting, and that asked the patients to wash the incision wound with soap and water. The study evaluated efficacy in terms of preventing infections, and surgical site healing with regard to pain at the site of incision, tissue cosmesis, and patient compliance.

**Results:** 66 patients were treated with the *Berberex*<sup>®</sup> Wound Cleanser; and 114 patients received the standard of care. Within the treated group there were 128 surgical levels treated, whereas 198 surgical levels were treated by the standard of care; 1.93 levels per surgical procedure for the *Berberex*<sup>®</sup>-treated and 1.73 levels for the standard-of-care patients. Over the course of the evaluation, assuring that all infections has been treated successfully – 11 patients who followed standard-of-care protocol were treated for infection, while none of the patients who received *Berberex*<sup>®</sup> for their post-operative care required any further treatment. Of those 11 patients who were treated for infection, 4 had serious infections and 7 had incidental infections. For the 4 serious infections, 3 received wound vac treatment, and 1 patient was readmitted for care. Of the 7 infections noted within the lumbar fusion group, 2 were multi-level, and within the 4 infections treated in the decompression population, another 2 were also multilevel. The severity of those requiring more aggressive treatment was not found to be correlated with the number of levels or the incidence of infection.

**Discussion:** The rate of infection in the group of 144 patients receiving standard-of-care following surgery was nearly 7.6% while the incidence in those 66 patients treated with *Berberex* were zero. Taking into consideration current observations of the effects of *Berberex*<sup>®</sup> Wound Cleanser on repair of surgical incisions that are both interventional and at the same time traumatic, this data demonstrates that incisions will heal faster with better cosmetic outcomes than under current care protocols. In this quality practice initiative, data supports clinical observation that post-operative wound dehiscence, cellulitis, seromas, low-grade infections, associated incision infections and other pathologies of the incision sites related to healing are diminished. *Berberex*<sup>®</sup> appears to be a potent agent that positively affects cosmetic healing while protecting the wound from bacterial-affected wound infection.

**Significance:** As an anti-microbial product, its effective wound management seems to be well paired with its economic benefits in minimizing the complications of post-operative surgical incision site care. As such, it may serve as a candidate for routine post-operative incision site care.

**Keywords:** *Berberex*<sup>®</sup> wound cleanser; Pathogens; Surgical incisions

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## Introduction

The skin is a natural barrier against infection, and as the largest organ in the body one of its major functions is to protect the body from infectious organisms such as parasites, bacteria and viruses that cause disease. In a greater sense however, the skin is more than a shield. In its role as an organ the skin also works to alert the immune system to the presence of harmful organisms, producing and excreting antibacterial substances, and supporting the growth of "healthy" bacteria. This is an important distinction to understand; healthy and pathogenic bacteria coexist as normal flora and maintaining the balance that is an inherent role of living tissue. If the skin is injured, bacteria can enter the body and may cause infections, or in other incidences. A reaction to injury may offset a balance of healthy and pathogenic organisms that can constitute a health risk.

The outermost layer of skin, called the epidermis, acts as a physical barrier between the inner body and the outer pathogens. The entire sciences of dermatology and immunology exist to define the skin, the wound healing process, the reconciliation of normal anatomy and regenerative repair of skin injury (Figure 1 and 2). The epidermis is a composite tissue that is 95% keratinocytes but also contains melanocytes, Langerhans cells, Merkel cells, and inflammatory cells. Keratinocytes are tightly connected to adjacent cells, so that a cobbled architecture of tightly appended cell edges assures that no bacteria can pass between them. As long as skin remains intact and healthy, bacteria and viruses are unable to penetrate the barrier. Despite this continuous and impermeable natural protection, if the skin is injured by a blister, splinter, cut or burn, bacteria can enter the body and cause an infection. This discussion centers on a separate and increasing risk-hospital-acquired infections and surgical-site infections. Breaks in the skins that occur during a surgical procedure, synonymously incisions, and present opportunities for pathogens to enter the body, and if not carefully, expose both patients and surgeons to infections.

More than 2 million people acquire serious infections with bacteria that are resistant to one or more of the antibiotics; at least 23,000 people die each year as a direct result of these antibiotic-resistant infections. A recent report [1] notes that on any given day approximately 1 of every 25 inpatients in U.S. acute care hospitals has at least one health care-associated infection. Pneumonia and surgical-site infection are the most common infection types, and *C. difficile* the most common pathogen. Infections other than those associated with central catheters, urinary catheters, and ventilators account for the majority of the U.S. burden of healthcare-associated infections.

In addition to the psychosocial stress experienced by patients, antibiotic-resistant infections add considerable costs in the form of prolonged treatments, extended hospital stays, additional physician

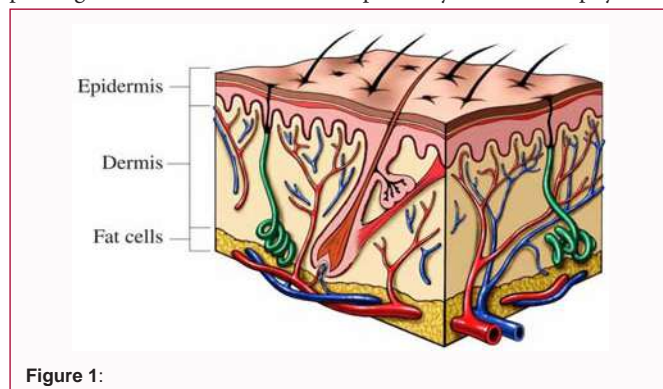


Figure 1:

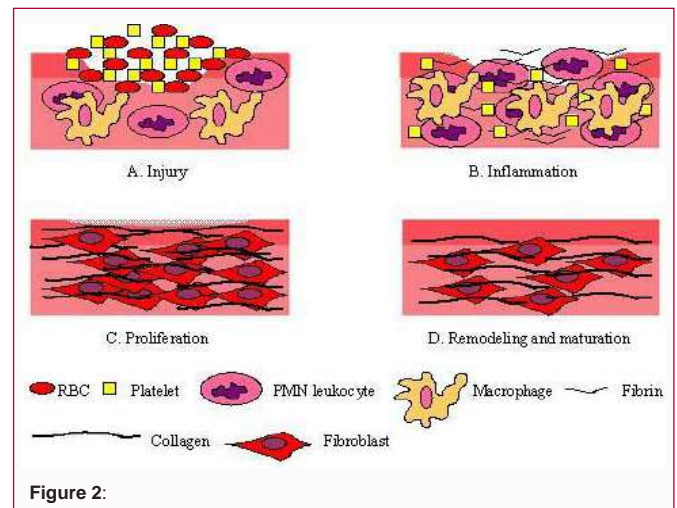


Figure 2:

visits and healthcare use, and greater incidences of disability and death relative to infections that are easily treatable with antibiotics. The total cost of antibiotic resistance to the U.S. economy, while difficult to calculate, has been estimated to vary from \$20 Billion in direct healthcare costs, to \$35 Billion when coupled to lost productivity.

Because surgical site infections (SSIs) occur on the part of the body where the surgery took place, they incur a cost and link to global responsibility for both the physician and the facility. After invasive surgery, the chances of developing an SSI are about 1 to 3 percent. When an SSI occurs it is typically within 30 days after surgery. The CDC describes three types of surgical site infections:

- **Superficial incision SSI:** This infection occurs just in the area of the skin where the surgical incision was made.
- **Deep incision SSI:** This infection occurs beneath the incision area in muscle tissue and in fascia, the tissue surrounding the muscles.
- **Organ or space SSI:** This type of infection can be in any area of the body other than skin, muscle or fascia that was involved in the surgery, such as a body organ or a space between organs.

Any SSI may cause redness, delayed healing, fever, pain, tenderness, warmth or swelling. Additional signs and symptoms specific to the type of SSI are well defined as well, and each symptom and location carries with it risks and costs associated with the complexity of the site and the virulence of the pathogen. Typically, the clinical course of action requires that the treating physician identify the pathogen(s) and define a course of antibiotic therapy to eliminate them. If the SSI occurs deep within an organ, such as after spinal surgery, the potential increases for abscess, anatomical failure, and a second surgical procedure.

While surgical environments are made as aseptic and sterile as possible, microorganism contamination can subsequently infect a surgical wound through various forms of contact such as from the touch of a contaminated caregiver or surgical instrument, through microorganisms in the air, or through microorganisms already on the body that spread into the wound. The risk is further increased by factors such as: a surgical procedure that lasts more than two hours; co-morbidities such as diabetes, cancer and depleted immune system; age; disease; obesity; tobacco use; and even emergency care. Professionally the surgeon accepts patient care regardless of each patient's attendant risks. That said, understanding the possibility

**Table 1:** Patients were followed over the course of care and the data.

	<i>Berberex</i> <sup>®</sup> Wound Cleanser	Standard Care
Patients	66	114
Number of Levels	128	198
Procedure (levels)		
Kyphosis	6 (8)	5 (5)
Lumbar Fusion [Inf]	21(38)	50(91) [7]
Laminectomy	17(29)	13(17)
Cervical Fusion	20(49)	22(41)
Decompression	2(4)	28(44) [4]
Infections [Inf]	0	11

for SSI requires that risk be not only accepted but addressed with vigilance. One of the single most efficient methods of preventing SSI has been achieved by incorporating anti-microbial wound cleansers as part of a post-surgical regimen to reduce skin flora and promote healing. A pilot study was implemented to evaluate 30 patients in a regimen of post-operative care with *Berberex*<sup>®</sup> Wound Cleanser.

*Berberex*<sup>®</sup> Wound Cleanser is a patent-pending product [2] that has been cleared by FDA as an Over-the-Counter (OTC) drug, and can be used to treat multiple pathologies such as are indicated on the product label. Its extraordinary potency against high levels of several resistant bacteria has previously been reported, including against MRSA, B-strep, VRE, and *E. coli* [3]. The active ingredients are allantoin and benzethonium chloride; the other ingredients are water, ethanol, *Aloe barbadensis* (Mill.), *Hydrastis canadensis* L., *Panax quinquefolius* L., and hydrogen peroxide. In combination the ingredients appear to have synergistic action that would not be expected from their use independently of one another. The indication is for external use only. Based on the product's clear value in post-operative care, a study was undertaken of 180 consecutive patients in treatment following spinal surgery.

## Subjects and Methods

All subjects evaluated in this retrospective trial were treated by a single physician at the *Greater Michigan Spine & Neurological Institute* in the United States. After consultation with the IRB, this analysis was deemed a quality practice improvement initiative, and not research. In part, the review and opinion indicated that the collection of data across the medical practice pertained to patient outcomes for those undergoing spinal procedures, thus patient medical data related to those procedures constituted quality improvement for the medical practice. Therefore, WIRB determined that IRB review was not required.

The patients varied in their ethnicities, and no subjects were excluded from the study based on recognized associated risk factor(s). Random patients received *Berberex*<sup>®</sup> Wound Cleanser (NuVision Pharmaceuticals, Atlanta, GA) post-operatively and were asked to apply the solution twice a day for 6 months or until wound healing had occurred. Remaining patients evaluated in this retrospective analysis were asked to follow post-operative discharge instructions common to the practice that placed limitations on lifting, and that asked the patients to wash the incision wound with soap and water. The 30 patients (16 women and 14 men) who participated in the pilot study are included among the 180 patients reported for this study. All participants received written and oral information regarding the natural and potential risks of the study and gave their informed

**Figure 3:** Incision treated by standard of care.

consent. The study was designed to evaluate *Berberex*<sup>®</sup> Wound Cleanser for safety, efficacy in terms of preventing infections, and quality of healing at the surgical site with regard to pain at the site of incision, tissue cosmesis, and patient compliance.

## Results

Patients were followed over the course of care and the data is summarized in Table 1. In all 66 patients were treated with the *Berberex*<sup>®</sup> Wound Cleanser; this was slightly less than half relative to the 114 patients who received the standard of care. Within that group of 66, in the aggregate 128 levels—indicating the number of vertebral bodies that were treated and thereby indicating the level of complexity as well—were treated and within the standard-of-care group, whereas an aggregate of 198 surgical levels were treated by the standard of care; amounting to an average of 1.93 levels per surgical procedure for the *Berberex*<sup>®</sup>-treated and an average 1.73 levels for the standard-of-care patients. Over the course of the evaluation— which was long enough to assure that all infections has been treated successfully— 11 patients who followed standard-of-care protocol were treated for infection, while none of the patients who received *Berberex*<sup>®</sup> for their post-operative care required any further treatment—i.e., there were no infections in the *Berberex*<sup>®</sup>-treated group. Of those 11 patients who were treated for infection, 4 had serious infections and 7 had incidental infections. For the 4 serious infections, 3 received wound vac treatment, and 1 patient was readmitted for care. Of the 7 infections noted within the lumbar fusion group, 2 were multi-level, and within the 4 infections treated in the decompression population, another 2 were also multilevel. The severity of those requiring more aggressive treatment was not found to be correlated with the number of levels or the incidence of infection.

It is important to recognize that the objective of surgery is to relieve pain, improve functional recovery, and in whole enhance the quality of life for the patient receiving care. Cosmesis qualifies as a key outcome of the recovery process, and in particular females being treated with spinal surgery are interested in the wound, the scar, and the reapproximation of the margins of the skin with regard to the wound. Avoiding keloid scarring, and pigmentation shifts is a goal shared by both the surgeon and the patients.

Figures 3 and 4 show the same patient with two separate incisions performed at the same time during the surgery; one was anterior and the second posterior. Both incisions are in very high stress areas. The



Figure 4: Posterior incision, *Berberex*<sup>®</sup> Treated.

patient is a construction framer who returned to work the day after surgery. Figure 3 depicts the surgical site treated under the current standard of care. Figure 4 depicts a representative surgical site treated with *Berberex*<sup>®</sup> wound cleanser. These pictures were taken two weeks postoperatively. Hyper-pigmentation of the scar, inversion at the edges, edema, swelling, and fullness at the surgical site are evident, but thermal sensitivity to touch and subcutaneous tissue may have resulted from splitting of underlying absorbable suture. The incision treated with *Berberex*<sup>®</sup> exhibits neither hyperpigmentation nor inversion of edges, and the edges remain well-approximated without swelling, edema or warmth to touch at the incision. There was no evidence of accompanying seroma.

## Discussion

As noted above *Berberex*<sup>®</sup> Wound Cleanser is based on a patented and patent-pending botanical platform that previously has been reported to have quite potent antibiotic activity. The present study evaluated its effect on healing. Addressing the mechanisms of its synergistic action for either disinfection or promotion of healing is beyond the scope of this review, as the use of berberine as a therapeutic advantage has been well documented [4-18].

Several key observations can be made from this retrospective review. First, the incidence of infection is dramatically reduced. Achieving a “zero” incidence of infection within the treatment arm of this first group of 180 patients is remarkable. In the context of a single surgeon, single practice, approximately distributed surgical procedures as to anatomy and levels within that anatomy, it is hard to detect a bias. An argument might be made that a retrospective review has statistical uncertainty—e.g., maybe the patients who were found with infection would have had that event regardless of the care. But the reverse argument of only those within the standard of care were susceptible strongly supports implementing prevention and increases the validity of the review’s conclusions.

Second, in 4 of the 11 patients treated for infection, it was severe enough to require intervention beyond a topical or oral antibiotic regimen. Of those 4 patients, 3 required wound vacuum care, and the fourth was readmitted for the infection. While the value of vacuum care is indisputable, its cost is high. In instance, KCI’s proprietary V.A.C.<sup>®</sup> Therapy System revolutionized the way in which the most serious, complex wounds have been treated. Therapy utilizes open-cell polymer foam dressing that conforms to the wound bed. When

sealed and placed under negative (vacuum) pressure, the system creates a unique wound healing environment that has been shown to promote the wound healing process, reduce edema, prepare the wound bed for closure, promote the formation of granulation tissue and remove infectious materials. Over 8 million wounds have been treated with negative pressure wound therapy (NPWT). While the exact costs of care in the 3 patients treated with NPWT technology was not available, there are a number of cost comparator evaluations that define an average cost for diabetic foot ulcer treatment ranging between \$11,984 and \$13,557 depending upon the sponge interface (47), and for readmission for surgical site infections costs can range to nearly \$30,000 for 3-month care, and up to \$111,000 for 12 month admissions [19,20]. Though all the patient care in this study was successfully concluded within the 6-month period of post-operative analysis, it is clear that readmission of 1 patient together with courses of negative pressure therapy for 3 others could approach \$200,000 in care costs as a result of the original procedure and therefore not a reimbursable expense for the facility or the physician.

Third, the regeneration of the wound and the closure of the incision not only provided a barrier to a route of infection, but also appeared to reduce the fibroblast proliferation and subsequent scarring that attend many wounds. The *Berberex*<sup>®</sup> formulation appears to be potent even in patients who have co-morbidities including diabetes. Previous work demonstrates several mechanisms that might support this therapeutic action [21-24].

A final consideration is the risk-benefit ratio for not only the patient but the surgeon. In general reimbursement is linked to outcome. Given the objective value of reducing infection, improving healing, neutralizing co-morbidities and minimizing additional costs of treatment, an investment in effective wound management following surgery is prudent. Thus the economic advantages are clear for implementation of an effective wound care program. The rate of infection in the group of 144 patients receiving standard-of-care following surgery was nearly 7.6% while the incidence in those 66 patients treated with *Berberex* were zero. If the estimates in current literature are correct in supporting a \$12,000 cost for negative pressure wound therapy, and if hospitalization requires a \$10,000 per month cost of care, then even just these 4 patients whose infections required more extensive care burdened the entire system. To demonstrate the point, those 4 patients represent 2.7% of the control group; based on national averages and studies cited (47,48), they spread an estimated cost of \$46,000 into the group of 144 patients [19,20]. The disseminated cost within this group is \$319.44 per patient. A 1% percent reduction in incidence of infection drops the extrapolated cost to \$28,962.96, and reduces the per cost risk adjustment from \$319.44 to \$201.13. Based on this study population, achieving a 1% incidence of serious infection— not merely an incident infection— had the ability to reduce the amortized risk cost by 37%. This data is critical, and though it is unlikely that any product or process will result in a net “0%” incidence, a 1% reduction would allow the entire group to be treated with a wound cleanser that costs \$118 per bottle. The low cost of achieving the reduction makes the intervention appealing.

The reduction in high costs that are not reimbursed, coupled with dose costs that are in the same range as those of other wound cleansers, would support a decision to specify *Berberex*<sup>®</sup> Wound Cleanser in improved standards of care for post-operative protocols after invasive surgery. This is further supported by improved patient outcomes and the efficacy even in the presence of difficult co-morbidities such as

diabetes. *Berberex* Wound Cleanser has HCPCS code A6260 and is reimbursed under Medicare part D and other insurance.

## Summary

Taking into consideration current observations of the effects of *Berberex* Wound Cleanser on repair of surgical incisions that are both interventional and at the same time traumatic, this data demonstrates that incisions will heal faster with better cosmetic outcomes than under current care protocols. In this quality practice initiative, data supports clinical observation that post-operative wound dehiscence, cellulitis, seromas, low-grade infections, associated incision infections and other pathologies of the incision sites related to healing are diminished. *Berberex* appears to be a potent agent that affects cosmetic healing while at the same time serving to protect the wound from bacteria. Registered by FDA as an anti-microbial product, its effective wound management seems to be well paired with its economic benefits in minimizing the complications of post-operative surgical incision site care. As such, it may serve as a candidate for routine post-operative incision site care. Characterizing the efficacy of *Berberex* would be further served by testing in a much larger population with additional surgeons and a greater number of points of care facilities. Reliable research instruments previously used for evaluating the duration of wound healing, including ultrasound grading, would further the understanding and benefits that have been discussed here.

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