Topical Timolol for Recalcitrant Wounds

Liza R. Braun, BA; Sonia A. Lamel, MD; Nicholas A. Richmond, BS; Robert S. Kirsner, MD, PhD

Report of Cases

Patient 1
A woman in her 80s with a history of venous insufficiency based on clinical presentation and vascular studies presented with multiple painful ulcerations on the bilateral ankles. She developed wounds in 1972 with subsequent trauma that led to repetitive skin breakdown. Her current wounds began 1 year ago. The patient was initially treated with multilayered elastic compression bandages (Profore; Smith & Nephew), which were changed weekly, and various foam dressings (Allevyn; Smith & Nephew; Mepilex Ag; Molnlycke Health Care). When her wound failed to heal, adjuvant therapies, including serial applications of porcine small intestine submucosa (Oasis; Healthpoint Biotherapeutics), bilayered living skin equivalent (Apligraf; Organogenesis) and an autologous split-thickness graft from the thigh were used but did not result in complete closure. After 6 months, the wound was 3.2 cm² and a β₂-adrenergic receptor (B2AR) antagonist, topical timolol, 0.5% (Timoptic; Aton Pharma), was instilled, 1 drop every 2 cm of wound edge weekly, then covered with silicone foam and 3-layer compression. All wounds, including her target ulcer, were fully epithelialized after 8 weeks of treatment, and the patient was prescribed a compression apparatus (JuxtaCure; CircAid Medical Products) to prevent recurrence.

Patient 2
A woman in her 70s with a history of venous insufficiency, rheumatoid arthritis, osteoporosis, and β-thalassemia presented with a 3-month history of ulceration on the dorsum of her right foot (Figure 1). Her wound was diagnosed as an atypical venous ulcer, given its unusual location, and initially treated with multilayered elastic compression bandages (Profore), which were changed weekly, and foam dressings (Allevyn). Her target ulcer did not close completely with standard of care or adjuvant bilayered living skin equivalent (Apligraf). Her wound was 1.0 cm² when topical timolol, 0.5% (Timoptic), was instilled, 1 drop every 2 cm of wound edge weekly, then covered with silicone foam and a 4-layer compression bandage. Her target ulcer reepithelialized after 7 weeks of treatment (Figure 2).

Patients 3 Through 5
Three additional wounds were treated with topical timolol, 0.5% (Timoptic). The clinical findings of these patients are given in the Table.

Therapeutic Challenge
Chronic, recalcitrant wounds fail to progress through the normal stages of wound healing. The most common cause of chronic wounds or ulcers include venous or arterial insufficiency, repetitive trauma from neuropathy, or prolonged pressure. Management of chronic wounds can be costly and time-consuming, necessitating selectivity of available treatment modalities to optimize care. Differential effects on keratinocyte migration and differentiation have been seen with a number of molecules, including growth factors and corticosteroids. Recent in vitro and in vivo animal research suggests catecholamines and β-adrenergic receptors may be new targets to augment the wound healing process.

Solution to the Problem
A commercially available B2AR antagonist (timolol), typically used as an intraocular glaucoma medication, was instilled in different chronic, recalcitrant wounds of 5 patients. Each patient experienced limited healing success with other modalities, including standard of care and adjuvant therapies, before switching to topical timolol. No patients included in this case series received systemic β-adrenergic antagonists at time of treatment. Patients were treated with...
topical timolol on either a daily or weekly basis, dependent on frequency of dressing changes for each specific wound, combined with standard of care. Optimal dosing is not yet known. Medication was instilled with 1 drop every 2 cm along the wound edge and allowed to dry for 2 minutes without further manipulation. Wounds were covered with foam dressings to provide fluid absorption; however, occlusive dressing selection should be determined by the treating physician. Patients received treatments for 4 to 8 weeks. Each patient improved with topical timolol, 0.5%, including 3 patients who had complete healing. The mean reduction of wound size after 7 weeks of treatment was 78.2%.

**Discussion**

β-Adrenergic receptors are present on cells in multiple organ systems, including the skin. Within skin, receptors are present on keratinocytes, fibroblasts, and melanocytes, and they may have a role in the pathophysiology of dermatologic conditions, including atopic eczema, psoriasis, and vitiligo.5 In acute partial-thickness donor site wounds, B2AR antagonists have been reported to promote wound healing, and one potential mechanism of action is via keratinocyte migration.

Keratinocyte migration occurs by the facilitation of chemotaxis, the polarization of cells, and activation of extracellular signal-related kinases essential in the signaling of promigratory pathways. The B2AR activation inhibits keratinocyte migration by activating the serine/threonine phosphatase 2A, which downregulates phosphorylation of extracellular signal-related kinases necessary for migration.2 Therefore, B2AR antagonists prevent the phosphorylation of phosphatase 2A and have the downstream effect of extracellular signal-related kinase promotion, inducing a promigratory pathway in keratinocytes.

Keratinocyte migration also occurs by galvanotaxis, a phenomenon in which cells migrate in response to electric stimuli. Keratinocytes can be stimulated to migrate with the formation of electrical poles and the application of electrical fields.2 The B2AR antagonists improve the ability of keratinocytes to respond to such migratory cues, whereas the B2AR agonists decrease keratinocytes’ ability to respond, further implicating the use of topical timolol for recalcitrant wounds.3

In the setting of burn wounds, high-stress environments exist with elevated catecholamine levels, both systemically and locally.4,6 A study4 that evaluated wounded keratinocytes in an ex vivo model demonstrated increased catecholamine-producing enzymes, tyrosine hydroxylase, and phenylethanolamine-N-methyltransferase. In a double-blinded randomized controlled trial, patients who received oral propranolol had a shorter time to healing of superficial wounds, were quicker to receive skin grafts in deeper injuries, and had shorter hospital stays compared with the placebo group.7 Previous data have indicated that B2AR antagonists may impair cellular immunity and insulin sensitivity.8,9 However, the active drug groups did not have increased incidences of sepsis or mortality.

Angiogenesis and dermal fibroblast proliferation are also regulated by B2ARs. The B2AR antagonists have been found to promote angiogenesis in chick chorioallantoic membrane assays and in vivo murine wound models. Dermal fibroblast migration is also increased (by 27%) when exposed to B2AR antagonists, and epidermal differentiation is improved with B2AR antagonists and β1- and β2-receptor antagonists.10

It is not yet clear whether catecholamines are produced endogenously by wounded keratinocytes. If keratinocytes

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>Wound Type</th>
<th>Location</th>
<th>B2AR Therapy Frequency</th>
<th>B2AR Therapy Duration, y</th>
<th>Standard of Care</th>
<th>Initial Size, cm²</th>
<th>Final Size, cm²</th>
<th>Area Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F</td>
<td>Chronic venous leg ulcer</td>
<td>Above left medial malleolus</td>
<td>Weekly</td>
<td>8</td>
<td>Foam dressing and 4-layer compression bandages</td>
<td>3.2</td>
<td>Healed</td>
<td>100</td>
</tr>
<tr>
<td>2/F</td>
<td>Chronic venous ulcer</td>
<td>Dorsal right foot</td>
<td>Weekly</td>
<td>7</td>
<td>Foam dressing and 4-layer compression bandages</td>
<td>1.0</td>
<td>Healed</td>
<td>100</td>
</tr>
<tr>
<td>3/F</td>
<td>Pressure ulcer</td>
<td>Lateral right upper thigh</td>
<td>Daily</td>
<td>4</td>
<td>Foam dressing changed daily</td>
<td>2.0</td>
<td>0.6</td>
<td>70</td>
</tr>
<tr>
<td>4/F</td>
<td>Traumatic refractory wound</td>
<td>Left midback</td>
<td>Daily</td>
<td>8</td>
<td>Foam dressing changed daily</td>
<td>4.8</td>
<td>Healed</td>
<td>100</td>
</tr>
<tr>
<td>5/M</td>
<td>Mixed origin of sickle cell and venous leg ulcer</td>
<td>Above left medial malleolus</td>
<td>Weekly</td>
<td>8</td>
<td>Foam dressing and 4-layer compression bandages</td>
<td>3.6</td>
<td>2.9</td>
<td>21</td>
</tr>
</tbody>
</table>

Abbreviation: B2AR, β2-adrenergic receptor.
are responsive to autocrine catecholamines in the absence of systemically elevated catecholamines, then other types of wounds may also be exposed to elevated levels of catecholamines produced by keratinocytes at the wound site. Extending the rationale of using systemic B2AR antagonists for burn wounds, topical B2AR antagonists may be beneficial at the site of chronic wounds. Further investigation into the presence of keratinocyte-produced catecholamines in chronic wounds or chronic wound fluid may offer further support for the use of topical B2AR antagonists.

This case series supports the use of topical timolol or other B2AR antagonists for chronic, recalcitrant wounds. The observed efficacy for several wound types suggests potential clinical benefits as an adjunct therapy. Further evaluation of treatment efficacy of B2AR antagonists in randomized controlled trials is warranted.

ARTICLE INFORMATION

Author Affiliations: Department of Dermatology and Cutaneous Surgery, University of Miami, Miller School of Medicine, Miami, Florida (Braun, Lamel, Richmond, Kirsner).

Corresponding Author: Robert S. Kirsner, MD, PhD, Department of Dermatology and Cutaneous Surgery, University of Miami, Miller School of Medicine, 1600 NW 10th Ave, Rosenstiel Medical Sciences Building, Room 2023-A, Miami, FL 33136.

Section Editor: Edward W. Cowen, MD, MHSc; Assistant Section Editors: Murad Alam, MD; Ruth Ann Vleugels, MD.

Accepted for Publication: July 23, 2013.


Author Contributions: Dr Kirsner and Ms Braun had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Braun, Richmond, Kirsner.

Acquisition of data: Braun, Richmond, Kirsner.

Analysis and interpretation of data: Braun, Lamel, Kirsner.

Drafting of the manuscript: Braun, Lamel, Richmond.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Braun, Richmond.

Administrative, technical, or material support: Braun, Kirsner.

Study supervision: Kirsner.

Conflict of Interest Disclosures: None reported.

REFERENCES


