A Comparative Study Evaluating the Tolerability and Efficacy of Two Topical Therapies for the Treatment of Keloids and Hypertrophic Scars

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ABSTRACT

Background: Onion extract gel (OE) and 0.5% hydrocortisone, silicone and vitamin E lotion (HSE) are two over-the-counter preparations used to enhance the cosmesis of keloids and hypertrophic scars.

Objective: To determine the tolerability and efficacy of OE versus HSE versus placebo in subjects with keloids and hypertrophic scars.

Methods: Thirty subjects (≥18 years) with keloids or hypertrophic scars were randomly assigned to one of three study preparations for 16 weeks. Scar volume was measured at baseline and weeks 4, 8, 12 and 16. Subjects and blinded investigators assessed scar parameters (induration, erythema, pigmentation alteration, pain, itching, tenderness and cosmetic appearance) and patient satisfaction at each visit using a visual analog scale (VAS). Data analysis included: mean percentage change (MPC) for subjects completing the study (n=15); the mixed model test to determine differences between the groups over time; and the Kruskal-Wallis test for the analysis of differences in subjects’ satisfaction within the three groups over 16 weeks for subjects who completed at least one follow-up visit (n=21).

Results: All three preparations were well tolerated with the exception of a mild acneiform-like eruption in one OE patient. Significant improvements were obtained with OE in volume, length, width and induration and with HSE in volume, length, induration, erythema and pigmentation alteration. There was a trend showing that a higher percentage of subjects were satisfied with OE than with HSE or placebo. The Mix Model Analysis (MMA) showed significant improvements with OE over placebo in investigator cosmetic assessment, lesion induration, pigmentation and tenderness and with HSE over placebo in investigator cosmetic assessment, lesion induration, pigmentation and erythema. Improvements in erythema and pigmentation were significantly greater in HSE than in OE.

Conclusion: Both OE and HSE were more effective than placebo in the management of hypertrophic scars and keloids.

INTRODUCTION

Keloids and hypertrophic scars are benign fibrous overgrowths of scar tissue that result from abnormal response to trauma.1 Alterations in fibroblast function lead to the production of excessive dense fibrous tissue, which extends beyond the boundaries of the original wound in keloids and remains confined to the original margins in hypertrophic scars.2 Keloids are more common in African Americans, individuals younger than 30 years of age and those with atopic symptoms.3,4 They can cause significant disfigurement and psychological distress as well as symptoms such as tenderness, pain and pruritus.5 Hypertrophic scars are raised, erythematous, pruritic, fibrous lesions associated with contractures of healing tissue and usually undergo partial spontaneous resolution over time.2 At the present time, there is no therapeutic modality considered to be universally safe and effective for the treatment of keloids.7

Current treatment options for keloids and hypertrophic scars include surgical excision, radiation, laser treatment, intralvesional corticosteroid injections, silicone gel sheeting, compression/occlusion, 5-fluorouracil and cryotherapy. It should be noted that 0.5% hydrocortisone, silicone, vitamin E lotion (HSE) (Scarguard®; Scarguard Labs (Red Rock Laboratories LLC, Great Neck, NY) and onion extract gel (OE) (Mederma®, Merz Pharmaceuticals, LLC, Greensboro, NC) are widely used over-the-counter medications for the treatment of keloids and hypertrophic scars.

HSE solution is based on occlusion therapy and a specially-formulated flexible collodion developed to improve the appearance of scars. The clear liquid formulation dries rapidly and forms a protective film after application to the skin. Many dermatologists and plastic surgeons have incorporated HSE into their post-surgical regimen. It has been anecdotally reported that the product has a beneficial effect in the stimulation of endogenous collagenase production.6 Eisen conducted an open-label pilot study with Scarguard (Scarguard Labs [Red Rock Laboratories], LLC, Great Neck, NY). After eight weeks of treatment, nine out of 12 patients reported a reduction in erythema and overall appearance, six patients reported a decrease in induration and five patients noted the scar was less raised.8
OE is a topical gel with a botanical extract derived from *Allium cepa* (Cepalin®). Patients value this remedy because of its ease of use, relatively low cost and widespread availability. OE exhibits anti-inflammatory, bacteriostatic and collagen down-regulatory properties and has been shown to improve collagen organization in a rabbit ear model. Jackson et al. found no significant differences in erythema and pruritus between pre- and post-treatment evaluations after one month of three times daily applications of OE gel for the prophylaxis of 17 Mohs microscopic surgery scars. Another double-blinded trial evaluating 97 patients with new and old scars assigned to OE gel and placebo gel control groups found the only significant difference to be patient-reported improvements of a softer, less noticeable scar at two months. No differences were noted with respect to physician-measured appearance and size and patient-measured erythema and elevation. Recently, Chung and colleagues conducted a double-blinded, split-scar study of 24 patients with new surgical wounds and found that OE gel did not improve scar appearance, erythema and hypertrophy when compared with a petroleum-based ointment. However, all the patients in this study were elderly Caucasians, a group at low risk for the development of hypertrophic scars and keloids. In this study, the authors observed the same response of subject satisfaction with OE as they found in the aforementioned study.

Patients with keloids and hypertrophic scars are frequently frustrated due to the lack of an optimal treatment modality that could offer fast results with good cosmetic outcomes, few adverse events and low recurrence rates at low cost. This issue tends to prompt patients to try over-the-counter alternatives, generating a big market for these kinds of treatments. The purpose of this study was to determine efficacy and safety of two popular over-the-counter agents (i.e., HSE and OE) in subjects with hypertrophic scars or keloids in a blinded, placebo-controlled, prospective fashion. In this study, the primary endpoint was the assessment of the target scar by the blinded-investigator and subject and the secondary endpoints included volume and color changes.

**PATIENTS, MATERIALS AND METHODS**

Subjects were recruited by a sub-investigator for this IRB-approved, principal investigator-initiated study through internal advertisements placed at hospitals and clinics within the University of Miami Miller School of Medicine and external advertisements on the Miami-Dade Metrorail. A total of 30 subjects, 18 years of age or older, with a keloid or hypertrophic scar with a diameter of 0.5 to 2.5 cm were enrolled March 2006 and March 2007. Follow-up of the last study subject was completed in June 2007. Exclusion criteria included pregnancy, breast-feeding, uncontrolled diabetes or autoimmune disorders, scar treatment within one month, plans to receive other scar treatments during the study, scars not amenable to study medications, known sensitivity to ingredients of study medications or other concomitant skin conditions that could potentially interfere with the study.

After agreeing to and signing the informed consent, subjects were evaluated in the authors’ research office and randomly assigned by another sub-investigator to receive one of three study drugs: HSE (Scarguard, Scarguard Labs, LLC, Inc. Great Neck, NY), OE (Mederma, Merz Pharmaceuticals, LLC. Greensboro, NC), or placebo (Cethaphil moisturizing lotion, Galderma Laboratories, L.P Fort Worth, TX) for 16 weeks using a computer-generated randomization list. The code was kept on a secure computer unavailable to the blinded investigators throughout the study and was not revealed until the final results were analyzed.

Subjects were instructed to apply HSE twice daily, OE three to four times daily, or placebo twice daily, according to their respective instructions as found in the package inserts. During sequential evaluations at baseline and weeks 4, 8, 12 and 16, adverse events were noted, photographs were taken and the study scar volume was measured using an alginate impression. The impressions were placed on a precision scale with a readability of 0.005 g and the scale was zeroed. Water was added until the impression was completely filled. The scale reading was converted into volume by utilizing the conversion of 1 g=1 cc based on the density of water. Subjects and the blinded investigator assessed the scar parameters (volume, length, width, height, induration, erythema, pigmentation alteration, pain, itching, tenderness and cosmetic appearance) at each visit with a visual analog scale (VAS), ranging from 0–100 (0=best and 100=worst). At each visit, subjects also assessed satisfaction to treatment with a VAS, ranging from 0–100 (0=not satisfied and 100=satisfied).

Data analysis for subjects who completed the study (n=15) was performed using two-tailed Student’s t-test. The estimated effect of the treatments was stated by the percentage changes of the means measured at week 16 compared to baseline. To ensure completeness of data analysis, the mixed model test was also used to determine differences between the groups (HSE, OE and placebo) over 16 weeks. For the mixed model test, all available observations for each subject, including those who later dropped out, were incorporated into the analysis for weeks 4, 8 and 12. In addition, the Kruskal-Wallis test was conducted for the analysis of differences in subjects’ satisfaction within the three groups over 16 weeks. The significance level used in this study was set at 95% (P<0.05).

**RESULTS**

Thirty subjects were enrolled in the study, with 10 subjects for each group. By week 4, a total of 21 subjects remained in the study, and by week 16 a total of 15 subjects (five in each study group) remained. No significant differences in gender, age or race were found between the groups. Demographic data, type of scar and scar anatomical localization in subjects who completed the study were included in the final analysis and summarized in Table 1. At week 16, HSE had a significant mean...
percentage reduction in volume ($P=0.01$), length ($P=0.02$), induration ($P<0.01$) and pigmentation alteration ($P<0.01$) compared to baseline. HSE also demonstrated a significant mean percentage improvement of the cosmetic appearance, as per the investigator evaluation ($P<0.01$) and the subject assessment ($P=0.04$). OE had a significant mean percentage reduction in volume ($P=0.01$), length ($P=0.02$), width ($P=0.02$) and induration ($P=0.03$). Data from the placebo group showed a significant mean percentage reduction in volume ($P=0.02$) and a significant mean percentage improvement in cosmetic appearance, as per the subject assessment ($P=0.01$).

The overall satisfaction of the products, defined as VAS ≥76, was positive for nine of 20 subject evaluations for HSE, 12 of 20 evaluations for OE and four of 20 evaluations for placebo over 16 weeks.

Although the difference between groups for subject satisfaction was non-statistically significant ($P=0.157$, Kruskal-Wallis test), a trend was observed where a higher percentage of subjects were satisfied with OE than HSE and placebo (Figure 1).

For the mixed model test, HSE showed significant improvement over placebo in four parameters, including investigator cosmetic assessment ($P<0.01$), lesion induration ($P<0.001$), pigmentation ($P<0.001$) and erythema ($P=0.01$). OE showed significant improvement over placebo in four parameters as well, including investigator cosmetic assessment ($P<0.01$), lesion induration ($P<0.001$), pigmentation ($P<0.001$) and tenderness ($P<0.05$).

One subject from the OE group had an acneiform-like eruption at the site of study drug application which resolved after discontinuation of the study drug. Fifteen subjects were lost to follow-up during the study.

**DISCUSSION**

The authors evaluated two popular over-the-counter agents containing HSE and OE for the treatment of keloids and hypertrophic scars. HSE combines the anti-inflammatory and anti-pruritic properties of hydrocortisone, with hydration and occlusion provided by silicone, and with the lubricant and moisturizing activity of vitamin E. In addition, silicone may also correct aberrant immunological processes, which, if left unchecked, may alter the tissue repair process and ultimately result in the formation of hypertrophic and keloid scars.21−23 The proprietary extract in OE has been shown to soften scar tissue and to improve the color, texture and overall appearance of scars in controlled studies of human wound healing.24−28

**TABLE 1.** Epidemiologic Data, Type of Scar and Anatomical Localization of the Scars in Subjects that Completed the Study and Were Included in the Final Analysis

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Race</th>
<th>Type of Scar</th>
<th>Site Of Scar</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>46</td>
<td>M</td>
<td>White</td>
<td>Hypertrophic</td>
<td>Right Shoulder</td>
</tr>
<tr>
<td>04</td>
<td>35</td>
<td>F</td>
<td>Hispanic</td>
<td>Keloid</td>
<td>Leg (posterolateral)</td>
</tr>
<tr>
<td>07</td>
<td>45</td>
<td>F</td>
<td>Black</td>
<td>Hypertrophic</td>
<td>Right Groin</td>
</tr>
<tr>
<td>15</td>
<td>48</td>
<td>F</td>
<td>Black</td>
<td>Keloid</td>
<td>Left Buttock</td>
</tr>
<tr>
<td>18</td>
<td>53</td>
<td>F</td>
<td>Black</td>
<td>Keloid</td>
<td>Right Shoulder</td>
</tr>
<tr>
<td>OE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>33</td>
<td>F</td>
<td>Black</td>
<td>Hypertrophic</td>
<td>Leg (Anterolateral)</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>M</td>
<td>Black</td>
<td>Keloid</td>
<td>Posterior Chest</td>
</tr>
<tr>
<td>16</td>
<td>45</td>
<td>F</td>
<td>Black</td>
<td>Keloid</td>
<td>Right Ear</td>
</tr>
<tr>
<td>19</td>
<td>32</td>
<td>M</td>
<td>White</td>
<td>Keloid</td>
<td>Neck (Left Side)</td>
</tr>
<tr>
<td>28</td>
<td>54</td>
<td>F</td>
<td>Black</td>
<td>Keloid</td>
<td>Right Groin</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>09</td>
<td>50</td>
<td>F</td>
<td>Hispanic</td>
<td>Keloid</td>
<td>Anterior Chest</td>
</tr>
<tr>
<td>12</td>
<td>21</td>
<td>M</td>
<td>Hispanic</td>
<td>Keloid</td>
<td>Right Ear Lobe</td>
</tr>
<tr>
<td>14</td>
<td>52</td>
<td>M</td>
<td>Black</td>
<td>Hypertrophic</td>
<td>Right Anterior Chest</td>
</tr>
<tr>
<td>23</td>
<td>26</td>
<td>F</td>
<td>Black</td>
<td>Keloid</td>
<td>Right Anterior Chest</td>
</tr>
<tr>
<td>24</td>
<td>50</td>
<td>F</td>
<td>Black</td>
<td>Keloid</td>
<td>Right Anterior Chest</td>
</tr>
</tbody>
</table>
The authors’ results showed that HSE worked better than OE and placebo, however, with the Kruskal-Wallis analysis the authors demonstrated a trend towards higher satisfaction with the use of OE than with HSE and placebo. Further studies are needed, expanding the study population in order to increase the power and elicit statistically significant differences between the groups.

CONCLUSION
Overall, the combination of 0.5% hydrocortisone, silicone and vitamin E lotion (HSE) was better than the onion extract and placebo for the treatment of keloids and hypertrophic scars. Onion extract also demonstrated in our study to be effective compared with placebo in the management of these scars. These two popular over-the-counter agents offered some degree of improvement, and they could be combined with other therapeutic modalities to increase overall efficacy and obtain better cosmetic results.

DISCLOSURES
Dr. Berman is a consultant for Red Rock Laboratories.

Drs. Perez, Viera, Patel, Konda, Amini, Huo, Zell and Tadicherla have no conflicts of interest to disclose.

REFERENCES
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