Case Report

Efficacy of Topical Estradiol Compared to Topical Glycolic Acid for Skin Aging Treatment in Postmenopausal Women

Shannaz Nadia Yusharyahya, Marsha Bianti

Department of Dermatology and Venereology, Faculty of Medicine, Universitas Indonesia, dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

E-mail: nadiayusharyahya@yahoo.com

Abstract

Skin aging is a complex biological process in human being, as a result from intrinsic factors (genetic, hormonal, metabolism) and extrinsic factors (UV exposure, pollution, smoking, life style). In postmenopausal women, physiologically, the amount of estrogen are decreased, causing deterioration of their skin's appearance. Along with the changes that occur, skin care require more attention. A holistic approach can increase epidermal thickness, therefore, reducing the depth of wrinkles, as well as improving skin texture and moisture. There are various treatments available to improve skin appearance due to aging. This EBCR is aimed to compare the efficacy of topical estradiol and topical glycolic acid as skin treatment in postmenopausal women. Articles were searched through Pubmed/MEDLINE, EBSCO, and Cochrane. One randomized-controlled trial by Fuchs KO, et al was obtained and critically appraised. Based on the appraisal, study by Fuchs KO, et al is considered valid, important, and applicable. Both estradiol and glycolic acid show good efficacy and safety for postmenopausal women with signs of skin aging, however estradiol is not considered to have better efficacy than glycolic acid.

Keywords: aging, efficacy, postmenopausal, topical estradiol, topical glycolic acid

Background

Skin aging is a complex biological process in human being, as a result from intrinsic factors (genetic, hormonal, metabolism) and extrinsic factors (UV exposure, pollution, smoking, life style). Skin aging may cause some alternation in skin such as: excessive dryness, thinning of epidermis, reductions in microvasculature, degradations of elastin and collagen fibers, also decreases the number of sweat and sebaceous glands.\(^1\)

Skin is one of the largest organs of the body in which aging-related changes are visible and women are concerned by the deterioration of their skin’s appearance. Hormonal changes, as in menopause, can affect skin’s appearance. Amongst many different hormones, the main ones responsible for the aging in women is estrogen. Estrogens are located on the skin surface of the face, lower limb, and genital organ area.\(^1\) Estrogens affect several skin functions and estrogen deprivation that accompanies menopause contributes to, and exacerbates, the deleterious effects of age on the skin. Skin aging due to hormonal changes occur in accordance to chronologic and photoaging.\(^2\)

Estrogen are essential for skin hydration because they increase production of glycosaminoglycan, promote an increased production of sebum, increase water retention, improve barrier function of the stratum corneum, and optimize the surface area of corneocytes. Decreased estrogen reduces the polymerization of the glycosaminoglycan, while elastin experiences granular degeneration and fragmentation, forming cystic spaces. In addition, there is a reduction in the microvasculature and thinning of the epidermis.\(^3\) Furthermore, lack of the proper blood circulation causes a decrease in the melanocyte and Langerhans cells number in the epidermis. The amount of types I and III collagen, which is the main constituent of the skin and provides the major support for skin resistance, is decreasing.
making it less resistant to external or internal factors and its permeability increases.\textsuperscript{1,2}

The skin aging process starts at the age of 25, with the appearance of first mimic wrinkles, and visible aging symptoms may be observed at the age of about 35 years. Wrinkles are caused by the loss of skin flexibility and firmness, inadequate humidity, stress, unhygienic life-style, and endo- or exogenic factors. At the age of 50s, due to endocrinological disorders, epidermal water binding function is impaired, therefore causing fixation of static wrinkles and leads to permanent damage of the skin lipid cement. The aging process occurs in all skin layers, including the appendage areas.\textsuperscript{1}

Along with those changes, the adult skin is more requiring and needs special care. A holistic approach makes it possible to increase the skin density and thickness, reduce wrinkles depth, and humidity and resilience improvement.

**Case Illustration**

A fifty two-years old-woman, had her last menorrhea 18 months ago, came to our clinic with the chief complaint increasing number of wrinkles on her face after menopause. Her skin care regimen consists of day cream, SPF 20 sunscreen, and night cream. She purchased all products from a cosmetic counter in shopping center. She denied other symptoms regarding menopause, such as hot flush, mood swing, etcetera.

On dermatologic examination, we found deep wrinkles on patient's forehead, crows feet on the angle of the eyes, and fine wrinkles under the eyes. Patient had history of retinoic acid hypersensitivity, thus alternative for aging skin treatment was preferred and glycolic acid was thought to be beneficial, and since the patient have undergone menopause, topical estrogen was also thought to have good effect for the patient.

**Clinical question**

A clinical question was formed based on the case reported above:

In postmenopausal woman with signs of skin aging, is topical estrogen therapy proven to have better efficacy compared to topical glycolic acid?

P: In postmenopausal woman with signs of skin aging
I: topical estrogen
C: topical glycolic acid
O: proven to have better efficacy

**Type of clinical question:** therapy

**Methods**

Literature search was performed in Pubmed/MEDLINE, EBSCO, and Cochrane databases on December 29\textsuperscript{th} 2016 using the keywords ‘effect’ AND ‘topical estrogen’ AND ‘topical glycolic acid’ AND ‘menopause’ along with their synonyms and related terms. (Table 1.)

**Selection**

We found a total of 2 articles from the literature search. The first step of selection is done by screening titles or abstracts, eliminating double publications. The remaining articles were reviewed using our inclusion criteria, which included suitability to the clinical question and availability of full text versions of the articles. There was one selected articles that suited the clinical question of this evidence based case report (EBCR). (Figure 1)

**Results**

We found a prospective, randomized, double-blind control trial from our literature search. In study by Fuchs KO, et al, 65 postmenopausal women were divided into three random groups. First group, consists of 22 subjects, received estradiol cream. Second group, consists of 21 subjects, received glycolic acid cream, whereas the third group received combination treatment with estradiol and glycolic acid cream. All groups were compared to placebo (vehicle cream only).

Background data were retrieved using questionnaire and subjects with history of breast cancer, skin cancer, or other severe skin diseases were excluded from this study. Smokers and users of hormon replacement therapy were not excluded. Those who qualified were randomly assigned to a group by a nurse blinded to the identity of the creams.

At the end of treatment, marked improvement of skin-aging symptoms were noted. There were statistically significant increasing epidermal thickness. In group receiving estradiol cream, the difference in epidermal thickness were 23\% (p=0.0045). In group receiving glycolic acid cream, the difference in epidermal thickness were 27\% (p=0.0046). The difference in epidermal thickness was notably greater in combination group, which was 38\% (p=0.00018)
Table 1. Results of literature search on December 29th 2016

<table>
<thead>
<tr>
<th>Database searched</th>
<th>Searching methods</th>
<th>Amount of articles retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pubmed/ MEDLINE</td>
<td>'effect' AND 'topical estrogen' AND 'topical glycolic acid' AND 'menopause'</td>
<td>2</td>
</tr>
<tr>
<td>EBSCO</td>
<td>'effect' AND 'topical estrogen' AND 'topical glycolic acid' AND 'menopause'</td>
<td>0</td>
</tr>
<tr>
<td>Cochrane</td>
<td>'effect' AND 'topical estrogen' AND 'topical glycolic acid' AND 'menopause'</td>
<td>0</td>
</tr>
</tbody>
</table>

Critical Appraisal
One relevant article by Fuchs KO, et al was reviewed by authors according to validity, importance, and applicability criteria.4

* Search was performed on December 29th 2016, 8.00PM
Are the results of this single therapeutic trial valid?

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the assignment of patients to treatments randomised?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the randomisation list concealed?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was follow-up of patients sufficiently long and complete?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients analysed in the groups to which they were randomised?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were patients and clinicians kept “blind” to treatment?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the groups treated equally, apart from the experimental treatment?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the groups similar at the start of the trial?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Are the valid results of this randomised trial important?

<table>
<thead>
<tr>
<th>% change in epidermal thickness</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (intervention)</td>
<td>Group II (control)</td>
</tr>
<tr>
<td>Fuchs KO, et al</td>
<td>23</td>
</tr>
</tbody>
</table>

Can you apply this valid, important evidence about therapy in caring for your patient?

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do these results apply to your patient?</td>
<td>No</td>
</tr>
<tr>
<td>Is the treatment feasible in your setting?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
| What are your patient’s potential benefits and harms from the therapy? | Benefits:  
- Improvement on skin thickness 
- Minimal side effects
Harms: 
- Skin punch biopsies may uncomfortable to some patients 
- Long duration of treatment may cause non-adherence in some patients |
| Are your patient’s values and preferences satisfied by the regimen and its consequences? | Yes    |
| Do your patient and you have a clear assessment of their values and preferences? | Yes    |
| Are they met by this regimen and its consequences?                      | Yes    |

**Level of Evidence: 1b**

* based on The Oxford Centre of Evidence-based Level of Evidence

Each subject was instructed to apply the creams to one side of the face and placebo cream on the opposite side. Estradiol or glycolic acid cream was applied to subject's face in the morning and at night. Those in the combination group applied the estradiol cream in the morning and the glycolic acid cream at night on one side of the face, and the vehicle cream on the other side. The application were extended to forehead border and hairline. The patients continued application for 6 months.

A 2-mm punch biopsy was obtained from the hairline of each subject’s left and right temple. The
specimens were then stained and analyzed by dermatopathologist under microscope. Both, subject and dermatopathologist, were blinded to the identity of the cream and side of application.

The rete peg pattern lengths in all treated specimens was significantly greater and more distinctly undulating than in vehicle specimens. However, statistical significance was not seen in either the estrogen or the glycolic acid group.

During the study, observed side effects were minimal. Within the first month of the study, 5 subjects withdrew from the study for personal reasons and 6 subjects withdrew secondary to skin sensitivity to the creams. Of these 6 subjects, 2 were treated with estradiol cream, 2 with glycolic acid, and 2 with combination creams. All symptoms resolved after subjects discontinued using the cream. No increase of facial pigmentation was noted in subjects. The result of 3 biopsies were not satisfactory for analysis because the epidermis was not present in the sample.

Discussion

One article is appraised from the performed literature search according to the clinical question. This study was prospective, randomized controlled trials, with double blinding so that bias can be controlled and minimized. The subject of this study was adult postmenopausal women.

Menopausal women experienced hormonal changes especially decreasing of estrogen. Estrogen affect several skin functions such as elasticity, water-holding capacity, pigmentation, and vascularity. Estrogen prevent skin aging by influencing skin thickness, skin wrinkling and skin moisture. Not only the skin, but also skin appendages are influenced by estrogen. 

Previous various studies have shown α-hydroxyl acids (AHAs) can help to reverse many signs of skin damage. AHAs can have profound effects on disorders of keratinization by diminishing corneocyte cohesion immediately above the stratum granulosum, thickening the epidermis, reversing basal cell atypia, dispersing melanin pigmentation, and maintaining a more normal rete peg pattern. Similar to AHAs, estrogen compounds have been proven effective for the treatment of aging skin. It was reported that women treated with 0.01% estradiol and 0.03% estriol compounds were found to have skin that was markedly improved in wrinkle depth, pore size, elasticity, and firmness. 

AHAs and estrogen compound both have been reported to have significant beneficial effects on the quality of aging facial skin. Fuchs et al study was conducted to clarify this findings by histologic analysis. The result were rete peg pattern return to be more undulating, as seen on younger skin. Elastic fibers were found to be more elongated, more unified, and less fragmented compared with vehicle specimens, also consistent with younger skin. Atypical cells were decreasing and collagen density were improving. 

Our study further confirmed these findings by critical appraisal. Creams containing estrogen or glycolic acid were proven to be beneficial as anti-aging treatment for postmenopausal women, and combination of both substances were proven to be statistically significant in increasing epidermal thickness as well as improvement of elasticity and firmness.

Population of this study were postmenopausal women with notable signs of skin aging, for example wrinkle. Our patient suit this population. Our patient also had history of retinoic acid hypersensitivity, thus alternative for aging skin treatment was preferred and glycolic acid was thought to be beneficial. But because patient have undergone menopause, topical estrogen was also thought to have good effect for the patient. Based on the result, estradiol and glycolic acid creams were found to be highly effective and safe in treating skin aging in postmenopausal women.

Based on the critical appraisal, the result is considered valid, important, and applicable for our patient. Although both showed marked improvement, the efficacy of topical estradiol is not superior compared to topical glycolic acid.

Conclusions and recommendations

From the critical appraisal performed, we conclude that topical estradiol is not proven to have better efficacy compared to topical glycolic acid. Further studies are still needed to support the therapy establishment.

References

2. Sevrain-Verdier S. Effect of estrogens on skin aging and the potential role of selective