Comparative study between the effect of vaginal conjugated equine estrogen cream versus vaginal hyaluronic acid injection in symptomatic vaginal atrophy of menopausal women

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Abstract:
Background: Vaginal atrophy is one of the most common features in menopause which does not improve with time and if untreated can affect the quality of life for menopausal women. Objective: To compare the effect of vaginal conjugated equine estrogen versus vaginal hyaluronic acid injection in treatment of symptomatic vaginal atrophy in menopausal women. Patients and method: A comparative clinical trial study conducted in the Department of Obstetrics and Gynecology at Al-Elwiya Maternity Teaching Hospital during the period from the first of February 2019 to the first of August 2019. The study included 50 natural postmenopausal women complaining from one or more signs or symptoms of atrophic vaginitis and then divided into two groups (Group A: 25 cases were treated by 1cc vaginal Hyaluronic acid injection and second dose two month later and (Group B: 25 cases were treated by vaginal conjugated equine estrogen cream one night dose, three week each, one week apart. The patients in both groups assessed, and vaginal PH done before and after the treatment. Results: Fifty menopausal patients enrolled in the current study between the age (45-70) years old with mean age (55±6) years and the main age group was between (51-60) years. Vaginal PH before treatment by Group A: (Hyaluronic acid injection) was (6.49±0.4) and after treatment was (5.0±0.9) with highly significant association (<0.001), while for Group B: treatment found that vaginal PH before treatment was (6.27±0.5) and after treatment was (5.4±1.8) with significant differences were found (P=0.02). Significant differences were found between Hyaluronic acid injection treatment and Improvement of vaginal dryness, loss of elasticity, and dyspareunia.

Conclusion:
Hyaluronic acid injection may be used as an alternative for menopausal women who do not want to use estrogen cream or cannot take local hormonal treatment.

**Keyword:** Vaginal atrophy, Hyaluronic acid injection, vaginal conjugated equine estrogen cream, menopausal women.

**Introduction:**

Vaginal atrophy is a common feature in menopause, which does not improve with time and, if untreated, can affect the quality of life for women. During these periods, women experience some symptoms which begin with vasomotor signs (like flushing, night sweat, etc.), changes in menstruation cycle, vaginal dryness, itching and dyspareunia and continue with temper changes, memory reduction, disorders of sexual arousal reduction, stress urinary incontinence and complaint from musculoskeletal pains. Even though some of the complications subside during the time, the symptoms of vasomotor, vaginal dryness and dyspareunia which are connected to disorder in sexual function related to lack of sexual hormones (especially Estrogen) irrespective of treatment will progress markedly and unfortunately will not be solved without treatment. As a whole, it is estimated that (10.0—40.0%) of women experience the symptoms connected with atrophy and on the other hand about 16 million women (500 thousand new cases) show such symptoms every year. (1) Hyaluronic acid (HA) is a glycosaminoglycan made up of glucuronic acid and N-acetylglucosamine residues; it is abundant in all organic tissues of mesodermal origin: vitreous humor, Wharton's jelly from the umbilical cord, etc. (2) Glycosaminoglycans are complex polysaccharides, highly acidic molecules, which have numerous negative charges and attract large amounts of sodium and at the same time water; Through this process, the turgor of the extracellular matrix increases. They are responsible for the hydration capacity of the dermis and also for the turgor and elasticity of the skin. (3) HA is different from other polysaccharides, because it does not have a defined shape, but forms meshes that are responsible for retaining a large amount of water (hydrophilicity) (1,2). It spreads randomly, occupying a very large volume due to the electrostatic repulsion of its carboxyl groups, which is why clinically each HA pillar favors the nourishment of the boundaries of the treated skin. This polysaccharide can be synthesized, purified and stabilized by biochemical methods, giving rise to a final product that can be used as filler material at the skin level. The non-animal origin of the product facilitates its use due to the almost non-existence of allergic reactions, not being necessary to carry out sensitivity tests like those that had to be carried out, for example, with purified bovine collagen. (4,5)

**Vaginal creams**
Premarin vaginal cream contains 0.625 mg conjugated equine estrogens (CEE) per gram of cream. Its composition is unique in that it does not solely contain estradiol as the active ingredient. CEE cream contains a mixture of estrogenic compounds, predominantly estrone, equilin, 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin.19 Recommended dosing is 0.5–2.0 g once daily for 21 days, followed by 7 days without treatment (repeated in a 28-day cycle) or 0.5 g twice weekly. In a randomized, placebo-controlled study, postmenopausal women with moderate to severe vaginal atrophy who received low-dose CEE cream (0.3 mg CEE, equivalent to 0.5 g Premarin vaginal cream) according to either the cyclic or the twice-weekly regimen exhibited improved VMI, improved vaginal pH, and improved most bothersome symptom scores, including those for dyspareunia, at week 12 of treatment. After the initial 12 weeks, open-label treatment was continued for 40 weeks, consistent with the patient’s prior regimen. (6)

**Aim of the study**

To compare the effect of vaginal conjugated equine estrogen cream versus vaginal hyaluronic acid injection in treatment of symptomatic vaginal atrophy in menopausal women.

**Patients and method:**

A comparative study conducted in the Department of Obstetrics and Gynecology of Al-Elwiya Maternity Teaching Hospital from 1st of February till 1st of August 2019. The study protocol was approved by scientific Council of Obstetrics and Gynecology Specialization /Iraqi Board for Medical specialization. The study included 50 natural postmenopausal women attending the outpatient clinic of Gynecology Department, complaining from one or more symptoms of vaginal atrophy (dryness, itching, redness, dyspareunia, irritation, urinary incontinence). They were informed about the nature of study and verbal consent was obtained from them.

**Inclusion criteria: -**

1. Patient at age ≥45 and agreed to participant in the study.
2. Married women (whether sexually active or not).
3. Menopausal Women with FSH level >40mIU/mL.
4. Menopausal Women with Estradiol level <0.05.

**Exclusion criteria: -**

1. Illiterate women.
2. Genital bleeding of unknown origin.
3. Hormonal dependent tumor.
4. Menopausal women due to surgical chemical or radiological causes.
5. Medical diseases such as (DM, HT, liver diseases, cardiac disease).
6. Patients using anticoagulant drugs
7. Thrombophlebitis or Thromboembolism disorder
8. Infection and inflammation (dermatitis, acne, herpes, etc.) in situ or near the zone of treatment
9. Smoker women
10. History of allergy to drugs

**Patient evaluation:**

1. **History:**
   - General, obstetrical, gynecological and drug history.
   - Detailed history about age, age of menarche, duration of menopause, parity, previous surgery, medical conditions, history of dermatological diseases.
   - History of vasomotor Symptoms (like flushing, night sweat), Symptoms of atrophic vaginitis (itching, redness, dryness, dyspareunia, burning, irritation, discharge).

2. **Examination:** Pelvic examination for vaginal pallor, petechiae, loss of rugae, fissure, loss of elasticity, urine incontinence.

3. **Investigation:**
   - The patients were also sent for full investigations including:
     - Urine analysis
     - FSH level
     - Estradiol level
     - Transvaginal U/S
     - Vaginal swab
     - Vaginal PH by PH paper (PH strip inserted into vagina)

**Preparing for treatment:**

- Needle size from 21G up to 27G was used
- Informed the patient about the indication, contraindication, possible adverse reactions.
- Local anesthesia was used.

**Procedure for treatment:**

- The skin is disinfected thoroughly with iodopovidone or chlorhexidine disinfectant
- Unscrew the syringe protection’s lid
• The needle is screwed firmly onto luer-lock connection of the syringe
• The plunger is pressed gently on in order to expel any residual air from the device
• Injected slowly by using (the retrograde sliding injection technique) 1cc of hyaluronic acid as follows; 0.66 ml in the sub mucosal layer of posterior vaginal wall and the remaining 0.33 ml in the sub dermal layer of the perineum. The injection is performed under digital control with one finger in the rectum. The important point of this step is to avoid the vascular axes of the vagina to prevent hematomas and emboli.
• Message done to the treated area gently to “distribute” the product All the cases were collected in the first two months of the study then two months later all cases of group A had second dose with reassessment by history, physical examination, vaginal PH Final reassessment of Group A two months later of second dose.
GROUP B: 25 cases were treated by vaginal conjugated equine estrogen cream (premarin vaginal cream [0.625mg.]) One night dose of vaginal conjugated equine estrogen cream (0.5-2mg) daily used for 21days, seven days apart. The patient instructed on the use of the applicator to ensure dosage accuracy. Reassessment by History, physical examination and vaginal PH two months later of using vaginal cream. Both groups were advised to keep on usual sexual life with instruction for group B during the treatment and avoid vaginal douching which effect PH.

Statistical analysis
Data of the study participants were checked for errors or inconsistency, then entered and analyzed using the statistical package for social sciences (SPSS) version 26, IBM, US, 2019. Descriptive statistics of variables presented as frequencies, proportion (%) mean and standard deviation according to the type of variables. The produced BGSM score was tested for statistical normal distribution and it did follow the normal distribution. The impact of independent variables (Age, gender, marital status, occupation, level of education, presence of comorbidities Family history of DM, duration of DM, treatment and use a glucometer) were cross tabulated against the level of BGSM as dependent variable. Significance of association between independent and dependent variables was assessed using Chi square test. Level of significance (P. value) of 0.05 or less was considered significant. Finally, results and findings presented in tables with an explanatory paragraph for each, using the Microsoft Word and excel Software version 2019.

Results:
Table (1) show that 11 patients within age group less or equal to 50 years old, 31 patients in age group between 51-60 years and 8 patients in age group > 60 years old with mean age (55±6) years.
Table 1: Age distribution of the studied group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50</td>
<td>11</td>
<td>22.0</td>
</tr>
<tr>
<td>51-60</td>
<td>31</td>
<td>62.0</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>8</td>
<td>16.0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Age (mean±SD) 55±6

As shown in table 2: no significant association were found between the studied groups A and group B among age, age of menarche, parity. (P value >0.05)

Table 2: Correlation between patient's demographic characteristics and type of treatment

<table>
<thead>
<tr>
<th></th>
<th>Type of treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A *</td>
<td>Group B **</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>55±5</td>
<td>55±7</td>
</tr>
<tr>
<td>Age of menarche</td>
<td>13±1</td>
<td>14±8</td>
</tr>
<tr>
<td>Age of menopause</td>
<td>50±5</td>
<td>49±9</td>
</tr>
<tr>
<td>Parity</td>
<td>5±2</td>
<td>6±2</td>
</tr>
</tbody>
</table>

*Group A: [Hyaluronic acid (Neauva intense rose 28 Mg)] (n=25)
**Group B [Conjugated equine estrogen cream (premarin 0.625mg)] (n=25)
Table 3 show that vaginal PH before treatment by Neauva was (6.49±0.4) and after treatment was (5.0±0.9) with highly significant association (<0.001) while for estrogen group treatment found that vaginal PH before treatment was (6.27±0.5) and after treatment was (5.4±1.8) with significant differences were found (P=0.02)

Table 3: Comparison between vaginal PH in both treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Vaginal PH before treatment</th>
<th>Vaginal PH after treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>6.49±0.4</td>
<td>5.0±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group B</td>
<td>6.27±0.5</td>
<td>5.4±1.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Itching was improved in 11/15 (73%) patients treated in group A [(Hyaluronic acid (Neauva intense rose 28 Mg)] less than 15/18 (83.3%) in Group B [ Conjugated equine estrogen cream (premarin 0.625mg)].

Irritation was improved in 7/9 (77.8%) of the patients in group A while it improved in 7/8 (45.5%) patients treated in group B.

Dryness was improved in 22/25 (88%) by group A than 15/25 (60%) patients that treated in group B, and with significant association (P=0.02).

Dyspareunia was improved in 13/17 in group A while 6/15 (40%) were improved in Group B, with significant association were found (p=0.03)

Fissure were improved in 2/3 (66.7%) patients in-group A, while 1/2 (50%) in estrogen cream. Loss of elasticity were improved in 16/18 (88.9%) treated in group A and 8/15 (53.3%) were improved in Group B, and significant association were found (P=0.02).

Redness was improved better by estrogen cream than Neauva injection [11/14 (78.6%), 8/12 (66.7%)] respectively.
For urinary incontinence, it was found that in-group A the improvement was happened in 4/8 cases (50%) while 6/9 (67.7%) cases were improved in Group B (table 4).

Table 4: Association between vaginal symptoms and type of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Itching</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>11</td>
<td>73.3</td>
<td>15</td>
</tr>
<tr>
<td>Not improved</td>
<td>4</td>
<td>26.7</td>
<td>3</td>
</tr>
<tr>
<td>Irritation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>7</td>
<td>77.8</td>
<td>7</td>
</tr>
<tr>
<td>Not improved</td>
<td>2</td>
<td>22.2</td>
<td>1</td>
</tr>
<tr>
<td>Dryness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>22</td>
<td>88.0</td>
<td>15</td>
</tr>
<tr>
<td>Not improved</td>
<td>3</td>
<td>12.0</td>
<td>10</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>13</td>
<td>76.5</td>
<td>6</td>
</tr>
<tr>
<td>Not improved</td>
<td>4</td>
<td>23.5</td>
<td>9</td>
</tr>
<tr>
<td>Fissure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>2</td>
<td>66.7</td>
<td>1</td>
</tr>
<tr>
<td>None improved</td>
<td>1</td>
<td>33.3</td>
<td>1</td>
</tr>
<tr>
<td>Loss of elasticity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>16</td>
<td>88.9</td>
<td>8</td>
</tr>
<tr>
<td>Not improved</td>
<td>2</td>
<td>11.1</td>
<td>7</td>
</tr>
<tr>
<td>Redness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>8</td>
<td>66.7</td>
<td>11</td>
</tr>
<tr>
<td>Not improved</td>
<td>4</td>
<td>33.3</td>
<td>3</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>4</td>
<td>50.0</td>
<td>6</td>
</tr>
<tr>
<td>Not improved</td>
<td>4</td>
<td>50.0</td>
<td>3</td>
</tr>
</tbody>
</table>
Discussion:

Atrophy of the vagina is a common condition in the menopausal period and the following signs characterize it: dryness and pale of vulvovaginal mucosa, with the presence, in the most severe cases, of spontaneous petechiae; disappearance of vaginal rugae, a thinning of the vaginal epithelium, elasticity loss, decreasing in secretions and lubrication. The use of hyaluronic acid treatment in vaginal atrophy with its efficacy and safety causes significant improvement in symptoms and signs of vulvovaginal atrophy. (1)

Meyer L, study reported that hyaluronic acid have a healing and hydrating properties, so play an important role in tissue regeneration process. (7) HA stimulates the healing of the VVA symptoms as: dry, irritated mucosa and several researchers have demonstrated the usefulness of applying HA gel to treat the vaginal atrophy symptoms and dryness. So considered an alternative to hormonal therapy. (8,9) Le Donne M et al compared the effect of Hyaluronic acid cream and Genestine (isoflavone) in the treatment of vaginal atrophy in which, patients received intravaginally 97 μg of genistein (group A, n = 31) or 5 mg of HA (group B, n = 31) daily for 15 days. They found no significant difference between their demographic characteristics and their result were in parallel to the result of this current study. (9)

Edwards D and M et al, mentioned that there is a long lasting effect of vaginal moisturizing of hyaluronic acid gel in relieving of Vulvovaginal symptoms, by reducing vaginal PH, and increasing vaginal mucosa moisturization, depending of the symptoms extent and the prescriptions used whether daily or every 2-3 days. (10) In Chen et al, found that the symptoms of the disease were improved when patients used hyaluronic acid vaginal gel every 3 days. (11) Vaginal pH in the level of ≥4.6 will supports the diagnosis of vulvovaginal atrophy. (12)

Ibe C, found that this change in acidity of the vaginal patients with VVA is confirmed by a decline or lack of glycogen creation with a decline of lactobacilli and an rise in the likelihood of vaginal infection developing. (13) The current study found that there is a highly significant decrease in patients treated with Hyaluronic acid(28mg/ml) and significant decrease by Conjugated equine estrogen (Premarin 0.625mg) which mean that the treatment with HA is more better than that by cream. This study was comparable to current study.

In two recent studies (Chen J et al, and Grimaldi E et al) have reported that vaginal hyaluronic acid-based moisturizers as effective in dismissing vulvovaginal symptoms as topical vaginal estrogen, and may be considered as an alternate to estrogen-based treatment. (11, 14)
Quaranta L et al, study revealed that treatment with Sinecol gel were significantly improve vulvovaginal atrophy in both subjectively (VAS) and objectively (VHI) with no adverse or unexpected effects were reported. Significant improvement found either with an overall score or in case of each single symptom. In addition, they noticed greatest efficacy for vaginal secretions and moisture. (15) Jokar A et al, study, mentioned that both Hyaluronic Acid and Permarine treatment in the vaginal atrophy will improved the symptoms, increase of cellular maturation and reduced vaginal PH; and they noticed that this improvement was occasionally were more among the group treated with Hyaluronic Acid than that treated by Permaine cream group. (1)

**Limitation of the study:** 1. Small sample size with short period of the study. 2. Evaluation methods of the patient’s conditions in the study. 3. Cost. 4. Patient self-administration of CCE (dose, time of administration, technique and abstinence) has to be fulfilled perfectly

**Conclusion:** -

Hyaluronic acid injection in solving the problem of symptoms of vulvovagina atrophy of menopausal women is revolution in aesthetic gynecology. Treatment of vaginal atrophy symptoms (Dryness, loss of elasticity and dyspareunia) is significant improvement with hyaluronic acid compare of oestrogen.

**No conflicts of interest**

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**Ethical clearance:** was taken from the scientific committee of the Iraqi Ministry of health

**References:**


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